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Cu-Catalyzed Arylation of Bromo-Difluoro-Acetamides by Aryl Boronic Acids, Aryl Trialkoxysilanes and Dimethyl-Aryl-Sulfonium Salts: New Entries to Aromatic Amides

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Abstract: We describe a mechanism-guided discovery of a synthetic methodology that enables the preparation of aromatic amides from 2-bromo-2,2-difluoroacetamides utilizing a copper-catalyzed direct arylation. Readily available and structurally simple aryl precursors such as aryl boronic acids, aryl trialkoxysilanes and dimethyl-aryl-sulfonium salts were used as the source for the aryl substituents. The scope of the reactions was tested, and the reactions were insensitive to the electronic nature of the aryl groups, as both electron-rich and electron-deficient aryls were successfully introduced. A wide range of 2-bromo-2,2-difluoroacetamides as either aliphatic or aromatic secondary or tertiary amides were also reactive under the developed conditions. The described synthetic protocols displayed excellent efficiency and were successfully utilized for the expeditious preparation of diverse aromatic amides in good-to-excellent yields. The reactions were scaled up to gram quantities.

Keywords: fluorine; amides; copper; catalysis; C-C-coupling; boronic acids; aryl trialkoxysilanes; dimethyl-aryl-sulfonium salts

1. Introduction

The amide functional group is abundant in peptides and numerous natural products and is also ubiquitous in a vast range of biologically active compounds, marketed drugs, and a broad spectrum of agrochemicals [1–7]. The presence of the amide motif or its isosteres condition biological activity of many privileged scaffolds [7]. By recent estimates, almost a quarter of all marketed pharmaceuticals possesses an amide bond, making this functional group the most encountered in medicinal chemistry. Amides are prevalent in advanced materials [7,8], and many life science relevant substances; amides also play pivotal roles in supramolecular chemistry [9,10], molecular recognition [9–11], and catalysis [12,13]. The amide functional group can be tuned electronically and conformationally to gain desired structural, physical, and biological properties. The chemistry of amide group is vast, and by its virtue amides can be transformed into many other functional groups [14–20]. Due to the omnipresence and profound importance of the amide functionality, the development of principally new synthetic routes aiming at installation of the
amide structural moiety is of current importance in both modern organic and medicinal chemistry. In this context, many new synthetic routes were elaborated [21–24]. Among those, it is important to mention such game-changing strategy as aminocarbonylations of aryl halides utilizing CO [25–27].

One conceptually underexplored strategy to prepare new amides was the installation of the amide structural unit by attaching an appropriate substituent onto the prefunctionalized CO-N structural motif bearing a tuned leaving group on the amide carbon. Analysis of the literature revealed that this tactic has been realized using C-N synthons bearing Cl [28] and CHal (Hal = Cl, Br, I) as a leaving group [29–31]. These strategies were predominately used for the construction of aromatic amides with different substituents on the nitrogen atom. Another method was developed that is based upon the transition-metal-catalyzed arylation of N-substituted formamides by different aryl-containing reagents, predominantly aryl halides [32–34].

Based on a mechanistic consideration, we considered that 2-bromo-2,2-difluoroacetamides 1 would be particularly attractive for the formation of aryl-amides by activation using transition-metal catalysis. Combining the halogens in this particular fashion on the trihaloacetamide enables us to harness the attractive features of copper catalysis and fluoride-mediated catalysis. We set out to explore 2-bromo-2,2-difluoroacetamides 1 in coupling reactions with aryl boronic acids 2 and (aryl)trialkoxy silanes 3 arylation agents as donors of aryl or heteroaryl substituents (Scheme 1a). We hypothesized (Scheme 1b) that using transition-metal-assisted catalysis, a 2-bromo-2,2-difluoroacetamide unit could undergo an oxidative addition on an appropriately tuned by ligands metal nuclei, forming an organometallic intermediate (structure 6) [35–37], followed by a rearrangement possibly via a CF$_2$-carbene complex 7, which undergoes loss of difluorocarben and simultaneous exchange of Br versus F giving rise to an organometallic (intermediate 8) capable of undergoing reaction with aryl boronic acids or aryl trialkoxysilanes to deliver a new intermediate (9), which after the reductive elimination would result in the formation of a new C-C bond to yield the desired aryl amide (5). An alternative mechanistic pathway could be via copper-intermediate 11 (Scheme 1c), as a result of the reaction between a fluorinated transition-metal catalyst and an aryl boronic acid (or aryl trialkoxysilane). This species could react with a carbon-centered radical 10 to form the species 9, which then decomposes into the final amide product 5. The formation of the radical species 10 would be unusual from the mechanistic point of view. A similar mechanism has, however, been suggested on the instance of palladium-catalyzed carboxylate-assisted ethoxycarboxylation of aromatic acids by ethyl bromodifluoroacetate in a very recent study [38,39]. It is worth noting that the concept of F versus B(OR)$_2$ (or Si(OR)$_3$) exchange on the copper nuclei, which we are postulating here, was suggested by Giri and Brawn for the mechanism in their copper-catalyzed Suzuki–Miyaura C-C couplings. These protocols were operational not only for boronic esters, but also for a broad range of trialkoxysilanes [40–42]. Based on the assumption of a fluoride-bearing Ar-Cu-F intermediate being active (similar to structure 8), and in a view of the recent literature on copper-supported C-C coupling protocols, we envisioned the use of copper catalysts. We also envisioned the preparation of aromatic amides as a result of the C-C coupling between aryl boronic acids, aryl trialkoxysilanes, or sulphonium salts with 2-bromo-2,2-difluoroacetamides according to the general synthetic scenario depicted in the Scheme 1.
than those using metalorganic reagents, thus enabling the creation larger amide structural diversities.

Scheme 1. (a) Synthetic scenario, (b,c) Proposed reaction mechanisms.

We first considered the use of 2-bromo-2,2-difluoroacetamides as a source of the -CO-NR₂ synthon. The only literature example known to date where ethoxycarboxylation of aromatic acids occurs using ethyl bromodifluoroacetate was described recently by Zhao et al. [38]. Similar access was proposed by Shi and co-workers in an alkoxycarbonylation of benzamides utilizing chloroformates [28]. Trifluoroacetamide has been used for the construction of aromatic and aliphatic amides via C(O)-CF₃ bond cleavage utilizing the reaction with Grignard reagents [43]. The routes proposed by us utilize commercially or readily available reagents aryl donors and are visibly more atom economic and efficient than those using metalorganic reagents, thus enabling the creation larger amide structural diversities.

2. Results and Discussion

We selected three model reactions and performed a set of trial experiments to identify the trends and generalities depicted in Scheme 2 and Tables 1–3. After testing numerous reaction parameters, among which are catalysts, ligands, solvents, and bases, we noticed that some of the copper salts in combination with nitrogen-containing ligands (not indicated in the optimization Tables), in particular solvents, facilitate the expected C-C-coupling reaction and thus the formation of the desired aromatic amide. Furthermore, we succeeded in establishing the optimal reaction conditions for synthetic protocols (a) and (b), which were identical and consisted in the use of CuBr₂ (0.1 equiv.), KF (2 equiv.), MgCl₂ (1 equiv.) with hexafluoropropanol as the solvent, where all reactions were conducted in ACE pressure tubes at 70 °C for 8 h. One crucial aspect appeared to be the addition of calix[4]arene derivatives, which most probably act as ligands for the copper salt. The best efficiency was observed for the corresponding calix[4]arene L₁. The magnesium salt, due to the high affinity of Mg²⁺ towards electron rich fluoride ion (hardness of Mg²⁺ in terms of the Pearson Hard-Soft acid-base theory), is most probably involved in the activation of one of the C-Hal bonds, like the corresponding C-F bond, by the coordination onto fluorine.
(where the fluoride ion in turn is a hard base, as per the Pearson Hard-Soft acid-base theory) and formation of the Mg-haloalkane complex [44,45]. The optimized reaction conditions allowed the efficient preparation of the model amide compound 5a in 87% and 90%, respectively (Tables 1 and 2). This success encouraged further exploration of the scope and limitation of these two new protocols. We set out to test the scope and limitations of these coupling reactions by selecting twenty-two 2-bromo-2,2-difluoroacetamides 1 and reacting those with a range of aryl boronic acids 2 (twenty-three different substrates) and aryltrialkoxyasilanes 3 (seventeen substrates). In a result of this study, we successfully prepared thirty-one amide derivativities 5 in good-to-excellent yields.

### Table 1. Prepared Amide Derivatives 5

| Entry | Reagent (Equiv)/Catalyst/Ligand/Additive | Time | Solvent | Yield (%) |
|-------|----------------------------------------|------|---------|-----------|
| 1a    | 1 boronic acid (1.5)/CuI (0.1)/KF (2.0) | 0    | DMF     | 90%       |
| 5b    | 2 boronic acid (1.5)/CuBr2 (0.1)/KF (2.0) | Trace | DMF     | 90%       |
| 5c    | 3 boronic acid (1.5)/CuI (0.1)/KF (2.0) | 0    | DMF     | 90%       |
| 5d    | 4 boronic acid (1.5)/CuI (0.1)/KF (2.0) | 0    | DMF     | 90%       |
| 5e    | 5 boronic acid (1.5)/CuCl2 (0.1)/L1 (0.2)/KF (2.0) | 0    | DMF     | 90%       |
| 5f    | 6 boronic acid (1.5)/CuCl2 (0.1)/L1 (0.2)/KF (2.0) | 0    | DMF     | 90%       |
| 5g    | 7 boronic acid (1.5)/CuF2 (0.1)/L1 (0.2)/KF (2.0) | 0    | DMF     | 90%       |
| 5h    | 8 boronic acid (1.5)/CuI (0.1)/KF (2.0) | 0    | DMF     | 90%       |
| 5i    | 9 boronic acid (1.5)/CuI (0.1)/KF (2.0) | 0    | DMF     | 90%       |
| 5j    | 10 boronic acid (1.5)/CuI (0.1)/KF (2.0) | 0    | DMF     | 90%       |
| 5k    | 11 boronic acid (1.5)/CuI (0.1)/KF (2.0) | 0    | DMF     | 90%       |
| 5l    | 12 boronic acid (1.5)/CuI (0.1)/KF (2.0) | 0    | DMF     | 90%       |
| 5m    | 13 boronic acid (1.5)/CuI (0.1)/KF (2.0) | 0    | DMF     | 90%       |
| 5n    | 14 boronic acid (1.5)/CuI (0.1)/KF (2.0) | 0    | DMF     | 90%       |
| 5o    | 15 boronic acid (1.5)/CuI (0.1)/KF (2.0) | 0    | DMF     | 90%       |
| 5p    | 16 boronic acid (1.5)/CuI (0.1)/KF (2.0) | 0    | DMF     | 90%       |
| 5q    | 17 boronic acid (1.5)/CuI (0.1)/KF (2.0) | 0    | DMF     | 90%       |

### Scheme 2. Model reactions for reaction conditions optimization: (a) Reaction of 2-bromo-2,2-difluoro-N-phenylacetamide with (4-(trifluoromethyl)phenyl)boronic acid, (b) Reaction of 2-bromo-2,2-difluoro-N-phenylacetamide with trimethoxy(4-(trifluoromethyl)phenyl)asilane, (c) Reaction of 2-bromo-2,2-difluoro-N-phenylacetamide with dimethyl[4-(trifluoromethyl)phenyl)sulfonyl]triflate.

Focusing first on the reactions utilizing aryl boronic acids and aryltrialkoxyasilanes, these synthetic protocols were tolerant to numerous functional groups placed on both coupling partners. In particular, both methodologies allowed the coupling of aryl substrates bearing a vast range of electron-withdrawing and electron-donating substituents placed in ortho-, meta-, and para- positions, respectively; among those are alkyl groups, alkoxy groups, Ph, halogens including fluorine, as well as C_{2}F_{3}, C_{2}F_{3}O, and C_{2}F_{3}S groups. Substrates bearing 1-naphthyl, 1-thiophenyl, and 3-pyridyl moieties also showed excellent efficiency with some discrepancy for the formation of the thionyl derivative 5n (Scheme 3). Interestingly, both protocols were operational for aryl substrates bearing diverse ortho substituents (Me, F, Cl, Br, C_{2}F_{3}, C_{2}F_{3}O). Of note, highly fluorinated boronic acids and aryltrialkoxyasilanes were prone to enter those protocols readily delivering the corresponding amides 5g, 5o, 5q. Regarding the reactivity of 2-bromo-2,2-difluoroacetamide counterparts 1, we did not observe any influence on the reaction efficiency of the substituents placed on the amide nitrogen—both alkyl and aryl groups as well as mixed derivatives exerted excellent tolerability within the developed protocols (Scheme 3). These reactions were not affected by changing a substitution pattern on the 2-bromo-2,2-difluoroacetamides: Species with alkyl as well as aryl substituents on the amide motif were equally effective within both synthetic protocols (Scheme 2). To further demonstrate the synthetic utility of these methodologies, the gram-scale reactions were successfully performed using 10 mmol of the 2-bromo-2,2-difluoroacetamides, which yielded the expected products in high yields.
Table 1. Optimization of the reaction conditions for synthetic protocol (a).

| Reaction (a) b | Entry | Reagent (Equiv)/Catalyst/Ligand/Additive | Solvent/Temperature/Time | Yield (%) 5a a |
|---------------|-------|----------------------------------------|--------------------------|----------------|
|               | 1     | boronic acid (1.5)/CuI (0.1)/KF (2.0)  | DMF/100 °C/12 h          | 0              |
|               | 2     | boronic acid (1.5)/CuBr₂ (0.1)/KF (2.0) | DMF/100 °C/12 h          | Trace          |
|               | 3     | boronic acid (1.5)/CuI (0.1)/KF (2.0), MgCl₂ (1.0) | (CF₃)₂CHOH/70 °C/12 h | 12             |
|               | 4     | boronic acid (1.5)/Cu (0.1)/L₁ (0.2)/KF (2.0), MgCl₂ (1.0) | (CF₃)₂CHOH/70 °C/12 h | 38             |
|               | 5     | boronic acid (1.5)/CuF₂ (0.1)/L₁ (0.2)/KF (2.0), MgCl₂ (1.0) | (CF₃)₂CHOH/70 °C/12 h | 49             |
|               | 6     | boronic acid (1.5)/CuCl₂ (0.1)/L₁ (0.2)/KF (2.0), MgCl₂ (1.0) | (CF₃)₂CHOH/70 °C/12 h | 67             |
|               | 7     | boronic acid (1.5)/CuBr₂ (0.1)/L₁ (0.2)/KF (2.0), MgCl₂ (1.0) | (CF₃)₂CHOH/70 °C/12 h | 88             |
|               | 8     | boronic acid (1.3)/CuBr₂ (0.1)/L₁ (0.2)/KF (2.0), MgCl₂ (1.0) | (CF₃)₂CHOH/70 °C/8 h   | 87             |
|               | 9     | boronic acid (1.3)/CuBr₂ (0.1)/L₁ (0.2)/KF (2.0), MgCl₂ (1.0) | DMF/70 °C/8 h           | 11             |
|               | 10    | boronic acid (1.3)/CuBr₂ (0.1)/L₁ (0.2)/KF (2.0), MgCl₂ (1.0) | (CF₃)₂CHOH/70 °C/8 h   | 18             |
|               | 11    | boronic acid (1.3)/L₁ (0.2)/KF (2.0), MgCl₂ (1.0) | (CF₃)₂CHOH/70 °C/8 h   | 0              |
|               | 12    | boronic acid (1.3)/CuBr₂ (0.1)/L₁ (0.2)/KF (2.0), MgCl₂ (1.0) | (CF₃)₂CHOH/70 °C/8 h   | 27             |
|               | 13    | boronic acid (1.3)/CuBr₂ (0.1)/L₁ (0.2)/KF (2.0), MgCl₂ (1.0)/TEMPO (2.0) | CF₃₂CHOH/70 °C/8 h | 75             |
|               | 14    | boronic acid (1.3)/CuBr₂ (0.1)/L₁ (0.2)/KF (2.0), MgCl₂ (1.0)/TEMPO (3.0) | (CF₃)₂CHOH/70 °C/8 h | 60             |
|               | 15    | boronic acid (1.3)/CuBr₂ (0.1)/L₁ (0.2)/KF (2.0), MgCl₂ (1.0)—in dark | (CF₃)₂CHOH/70 °C/8 h | 84             |

a Isolated yield. b All reactions were conducted in inert atmosphere.

Table 2. Optimization of the reaction conditions for synthetic protocol (b).

| Reaction (b) b | Entry | Reagent (Equiv)/Catalyst/Ligand/Additive | Solvent/Temperature/Time | Yield (%) 5a a |
|---------------|-------|----------------------------------------|--------------------------|----------------|
|               | 1     | aryl trialkoxysilane (1.4)/CuBr₂ (0.1)/L₁ (0.2)/KF (2.0), MgCl₂ (1.0) | (CF₃)₂CHOH/70 °C/8 h   | 90             |
|               | 2     | aryl trialkoxysilane (1.4)/CuBr₂ (0.1)/L₁ (0.2)/KF (2.0), MgCl₂ (1.0) | DMF/70 °C/8 h           | 22             |
|               | 3     | aryl trialkoxysilane (1.4)/CuBr₂ (0.1)/KF (2.0), MgCl₂ (1.0) | (CF₃)₂CHOH/70 °C/8 h   | 21             |
|               | 4     | aryl trialkoxysilane (1.4)/L₁ (0.2)/KF (2.0), MgCl₂ (1.0) | (CF₃)₂CHOH/70 °C/8 h   | 0              |
|               | 5     | aryl trialkoxysilane (1.4)/CuBr₂ (0.1)/L₁ (0.2)/KF (2.0) | (CF₃)₂CHOH/70 °C/8 h   | 25             |
|               | 6     | aryl trialkoxysilane (1.4)/CuBr₂ (0.1)/L₁ (0.2)/KF (2.0), MgCl₂ (1.0)/TEMPO (2.0) | (CF₃)₂CHOH/70 °C/8 h | 72             |
Table 2. Cont.

| Reaction (b) b | Entry | Reagent (Equiv)/Catalyst/Ligand/Additive | Solvent/Temperature/Time | Yield (%) 5a a |
|---------------|-------|------------------------------------------|--------------------------|----------------|
|               | 7     | aryl trialkoxysilane (1.4)/CuBr₂ (0.1)/L₁ (0.2)/KF (2.0), MgCl₂ (1.0)/TEMPO (3.0) (CF₃)₂CHOH/70 °C/8 h | | 58 |
|               | 8     | aryl trialkoxysilane (1.4)/CuBr₂ (0.1)/L₁ (0.2)/KF (2.0), MgCl₂ (1.0)—in dark (CF₃)₂CHOH/70 °C/8 h | | 91 |

a Isolated yield. b All reactions were conducted at room temperature in inert atmosphere.

Table 3. Optimization of the reaction conditions for synthetic protocol (c).

| Reaction (c) b | Entry | Reagent (Equiv)/Catalyst/Ligand/Additive | Solvent/Temperature/Time | Yield (%) 5a a |
|---------------|-------|------------------------------------------|--------------------------|----------------|
|               | 1     | sulphonium salt (1.4)/CuBr₂ (0.1)/L₁ (0.2)/KF (2.0), MgCl₂ (1.0) (CF₃)₂CHOH/70 °C/12 h | | 47 |
|               | 2     | sulphonium salt (2)/CuCl₂ (0.1), L₁ (0.2)/KF (2.0), MgCl₂ (1.0) (CF₃)₂CHOH/70 °C/12 h | Trace | |
|               | 3     | sulphonium salt (2)/Cul (0.1), L₁ (0.2)/KF (2.0), MgCl₂ (1.0) (CF₃)₂CHOH/70 °C/12 h | Trace | |
|               | 4     | sulphonium salt (1.6)/CuBr₂ (0.3), Pd(OAc)² (0.2)/L₁ (0.25)/KF (2.0), MgCl₂ (1.0) (CF₃)₂CHOH/70 °C/12 h | 17 | |
|               | 5     | sulphonium salt (1.6)/CuBr₂ (0.3)/L₂ (0.25)/KF (2.0), MgCl₂ (1.0) (CF₃)₂CHOH/70 °C/12 h | 29 | |
|               | 6     | sulphonium salt (1.6)/CuBr₂ (0.3), PdCl₂ (0.2)/L₂ (0.25)/KF (2.0), MgCl₂ (1.0) (CF₃)₂CHOH/70 °C/12 h | 48 | |
|               | 7     | sulphonium salt (1.6)/CuBr₂ (0.3), Pd(OAc)² (0.2)/L₂ (0.25)/KF (2.0), MgCl₂ (1.0) (CF₃)₂CHOH/70 °C/12 h | 53 | |
|               | 8     | sulphonium salt (1.6)/CuBr₂ (0.3), [Ru(p-cymene)Cl₂]₂ (0.2)/L₂ (0.25)/KF (2.0), MgCl₂ (1.0) (CF₃)₂CHOH/70 °C/11 h | 84 | |
|               | 9     | sulphonium salt (1.6)/CuBr₂ (0.3), [Ru(p-cymene)Cl₂]₂ (0.2)/KF (2.0), MgCl₂ (1.0) (CF₃)₂CHOH/70 °C/11 h | 27 | |
|               | 10    | sulphonium salt (1.6)/[Ru(p-cymene)Cl₂]₂ (0.2)/L₂ (0.25)/KF (2.0), MgCl₂ (1.0) (CF₃)₂CHOH/70 °C/11 h | 0 | |
|               | 11    | sulphonium salt (1.6)/CuBr₂ (0.3), [Ru(p-cymene)Cl₂]₂ (0.2)/L₂ (0.25)/KF (2.0) (CF₃)₂CHOH/70 °C/11 h | 18 | |
|               | 12    | sulphonium salt (1.6)/CuBr₂ (0.3), [Ru(p-cymene)Cl₂]₂ (0.2)/L₂ (0.25)/KF (2.0), MgCl₂ (1.0)/TEMPO (2.0) (CF₃)₂CHOH/70 °C/11 h | 69 | |
|               | 13    | sulphonium salt (1.6)/CuBr₂ (0.3), [Ru(p-cymene)Cl₂]₂ (0.2)/L₂ (0.25)/KF (2.0), MgCl₂ (1.0)/TEMPO (3.0) (CF₃)₂CHOH/70 °C/11 h | 55 | |
|               | 14    | sulphonium salt (1.6)/CuBr₂ (0.3), [Ru(p-cymene)Cl₂]₂ (0.2)/L₂ (0.25)/KF (2.0), MgCl₂ (1.0)—in dark (CF₃)₂CHOH/70 °C/11 h | 86 | |

a Isolated yield. b All reactions were conducted at room temperature in inert atmosphere.
Scheme 3. (a) Reactions of 2-bromo-2,2-difluoro-acetamides with aryl boronic acid, (b) Reactions of 2-bromo-2,2-difluoro-acetamides with aryl trialkoxysilanes, (c) Reactions of 2-bromo-2,2-difluoro-acetamides with dimethyl-aryl-sulfonium triflates. Product scope of amides using developed synthetic protocols.
To the general scope and limitations, it is also important to note: (1) Within both described syntactic protocols we tried numerous other N-substituted and N-unsubstituted derivatives of 2-bromo-2,2-difluoroacetic acid, for instance: 2-bromo-2,2-difluoroethanethioamides, 2-bromo-2,2-difluoroacetimidamides, 2-bromo-2,2-difluoroacetoxyhydrazonamides; all these substrates were not prone to enter the developed arylation protocols; (2) Aryl pinacol borates as well as aryl trifluoroborates in the form of potassium salts act as arylation agents in the frames of both synthetic protocols (2 and 4 examples respectively, Scheme 3); (3) 2,2-Difluoro-2-idoacetamides exerted similar activity as the corresponding bromo derivatives (2 examples, Scheme 3).

As the final accord of this work, we turned our attention to aryl sulphonium salts 4. These are donors of aryl groups and are often considered as equivalents of aryl halides, possessing low reduction potentials [46–48]. We assumed that those species might have capacity to enter the title synthetic protocol (Scheme 2c). These compounds did not react well under previously optimized reaction conditions, where the model compound 5a was obtained in 47% yield (Table 3, Entry 1). Thus, we embarked once more on the search for new operational reaction conditions for the model reaction. It is worthwhile to note that in the case of this reaction, we had to increase the amount of copper salt to 0.3 equiv. and add 0.2 equiv. of [Ru(p-cymene)Cl₂]₂, which was superior to other TM co-catalysts (Table 3). Finally, by employing CuBr₂ (0.3 equiv.), [Ru(p-cymene)Cl₂]₂ (0.2 equiv.), KF (2 equiv.), MgCl₂ (1 equiv.) and 0.25 equiv. of calix[5]arene derivative (L₂), in hexafluoropropanol, the model amide 5a was prepared in 84% yield. Further study of the scope resulted in the preparation of ten amides in total (Scheme 3c).

To gain the insight to the reaction mechanism, we performed several control experiments: (a) Reactions without addition of calixarenes; (b) reactions without CuBr₂ and MgCl₂; (c) reactions in the dark and (d) reactions with 2 equiv. and 3 equiv. of TEMPO, which led to the modest decrease of the yield of title model amid compound. All these experiments are depicted in the Tables 1–3.

3. Materials and Methods

Commercially available starting materials, reagents, catalysts, anhydrous, and degassed solvents were used without further purification. Flash column chromatography was performed with Merck Silica gel 60 (230–400 mesh). The solvents for column chromatography were distilled before the use. Thin layer chromatography was carried out using Merck TLC Silica gel 60 F254 and visualized by short-wavelength ultraviolet light or by treatment with potassium permanganate (KMnO₄) stain. ¹H, ¹³C, and ¹⁹F-NMR spectra were recorded on a Bruker 250 and 500 MHz at 20 °C. All ¹H-NMR spectra are reported in parts per million (ppm) downfield of TMS and were measured relative to the signals for CHCl₃ (7.26 ppm) and DMSO (2.50 ppm). All ¹³C{¹H}-NMR spectra were reported in ppm relative to residual CHCl₃ (77.00 ppm) or DMSO (39.70 ppm) and were obtained with ¹H decoupling. Coupling constants, J, are reported in Hertz (Hz). Gas chromatographic analyses was performed on Gas Chromatograph Mass Spectrometer GCMS-QP2010 Ultra instrument.

The optimal reaction conditions were identified by microscale high-throughput experimentation screening. Parallel synthesis was accomplished in an MBraun glovebox operating with a constant Ar-purge (oxygen and water <5 ppm). Screening reactions were carried out in 10 mL vials using suitable heating blocks. Liquid chemicals were dosed using gas tight micro syringes. Isolation of obtained compounds was achieved by column chromatography on Silica gel.

All used boronic acids 2 and some aryl trialkoxyssilanes 3 are commercially available and were purchased from appropriate vendors. 2-Bromo-2,2-difluoroacetamides [49–57], 1, 2-iodo-2,2-difluoroacetamides [54], aryl trialkoxyssilanes 3 [58–64], sulfonium salts 4 [65–67], and calixarenes L₁, L₂ [68,69] are known compounds in the literature and were prepared according to the known literature, and the spectral data are identical with the corresponding literature. Copies ¹H and ¹³C-NMR spectra are placed in Supplementary Materials.
General procedure for the synthesis of amides 5 by the reaction of 2-bromo-2,2-difluoroacetamides 1 with aryl boronic acids 2.

Under inert atmosphere (glovebox operating with a constant Ar-purge), to an 18 mL ACE pressure tube equipped with a stir bar, consequently, an appropriate 2-bromo-2,2-difluoroacetamide (1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl₂ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate aryl boronic acid (1.3 mmol, 1.3 equiv.), the L₁ (0.2 mmol, 0.2 equiv.), and finally CuBr₂ (0.1 mmol, 0.1 equiv.) were placed; then the hexafluoropropanol (0.12 mmol/mL) was added and the reaction vessel was properly capped by Teflon stopper. Finally, the reaction vessel was removed from the glovebox and subjected to heating under vigorous stirring for 8 h. The progress of the reaction was controlled by TLC. After completion, the reaction mixture was evaporated until it reached dryness using a rotary evaporator, the content of the flask was generously treated with distilled water, filtered, and finally properly dried in vacuum. The resulting crude was directly subjected to gradient flash chromatography on silica gel using a mixture of hexane/ethyl acetate as eluent to isolate the desired amide derivative.

The gram scale synthesis was performed on 10 mmol of the starting 2-bromo-2,2-difluoroacetamide.

General procedure for the synthesis of amides 5 by the reaction of 2-bromo-2,2-difluoroacetamides 1 with trialkoxysilanes 3.

Under inert atmosphere (glovebox operating with a constant Ar-purge), to an 18 mL ACE pressure tube equipped with a stir bar, an appropriate 2-bromo-2,2-difluoroacetamide (1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl₂ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate trialkoxysilane (1.4 mmol, 1.4 equiv.), the L₁ (0.2 mmol, 0.2 equiv.), and finally CuBr₂ (0.1 mmol, 0.1 equiv.) was consequently placed; then the hexafluoropropanol (0.12 mmol/mL) was added and the reaction vessel was properly capped by Teflon stopper. Finally, the reaction vessel was removed from the glovebox and subjected to heating under vigorous stirring for 8 h. The progress of the reaction was controlled by TLC. After completion, the reaction mixture was evaporated until it reached dryness using a rotary evaporator, the content of the flask was generously treated with distilled water, filtered, and finally properly dried in vacuum. The resulting crude was directly subjected to gradient flash chromatography on silica gel using a mixture of hexane/ethyl acetate as eluent to isolate the desired amide derivative.

The gram scale synthesis was performed on 10 mmol of the starting 2-bromo-2,2-difluoroacetamide.

General procedure for the synthesis of amides 5 by the reaction of 2-bromo-2,2-difluoroacetamides 1 with (aryl)dimethylsulfonium salts 4.

Under inert atmosphere (glovebox operating with a constant Ar-purge), to an 18 mL ACE pressure tube equipped with a stir bar, an appropriate 2-bromo-2,2-difluoroacetamide (1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl₂ (95 mg, 1.0 mmol, 1.0 equiv.), aryl sulphonium salt (1.6 mmol, 1.6 equiv.), the L₂ (0.25 mmol, 0.25 equiv.), [Ru(p-cymene)Cl₂]₂ (0.2 mmol, 0.2 equiv.), and finally CuBr₂ (0.3 mmol, 0.3 equiv.) was consequently placed; then the hexafluoropropanol (0.12 mmol/mL) was added and the reaction vessel was properly capped by Teflon stopper. Finally, the reaction vessel was removed from the glovebox and subjected to heating under vigorous stirring for 11 h. The progress of the reaction was controlled by TLC. After completion, the reaction mixture was evaporated until it reached dryness using a rotary evaporator, the content of the flask was generously treated with distilled water, filtered, and finally properly dried in vacuum. The resulting crude was directly subjected to gradient flash chromatography on silica gel using a mixture of hexane/ethyl acetate as eluent to isolate the desired amide derivative.

The gram scale synthesis was performed on 10 mmol of the starting 2-bromo-2,2-difluoroacetamide.

N-phenyl-4-(trifluoromethyl)benzamide 5a. The title compound was prepared, starting with 2-bromo-2,2-difluoroacetamide 1a (250 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl₂ (95 mg, 1.0 mmol, 1.0 equiv.), aryl boronic acid 2n (247 mg, 1.3 mmol, 1.3 equiv.), L₁ (130 mg, 0.2 mmol, 0.2 equiv.), CuBr₂ (22.3 mg, 0.1 mmol, 0.1 equiv.),
and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide $5a$ (231 mg, 0.87 mmol, 87%). The gram scale synthesis was performed on 10 mmol of the starting 2-bromo-2,2-difluoroacetamide $1a$ and the amide $5a$ was prepared in 80% yield (2.12 g, 8 mmol).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide $1a$ (250 mg, 1.0 mmol, 1.0 equiv.), MgCl$_2$ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate trialkoxysilane $3k$ (372 mg, 1.4 mmol, 1.4 equiv.), the $L1$ (130 mg, 0.2 mmol, 0.2 equiv.), CuBr$_2$ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide $5a$ (222 mg, 0.84 mmol, 84%). The gram scale synthesis was performed on 10 mmol of the starting 2-bromo-2,2-difluoroacetamide $1a$ and the amide $5a$ was prepared in 77% yield (2.04 g, 7.7 mmol).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide $1a$ (250 mg, 1.0 mmol, 1.0 equiv.), MgCl$_2$ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate potassium trifluoro(4-(trifluoromethyl)phenyl)borate (328 mg, 1.3 mmol, 1.3 equiv.), the $L1$ (130 mg, 0.2 mmol, 0.2 equiv.), CuBr$_2$ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide $5a$ (222 mg, 0.84 mmol, 84%). The gram scale synthesis was performed on 10 mmol of the starting 2-bromo-2,2-difluoroacetamide $1a$ and the amide $5a$ was prepared in 79% yield (1.93 g, 7.3 mmol).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide $1a$ (250 mg, 1.0 mmol, 1.0 equiv.), MgCl$_2$ (95 mg, 1.0 mmol, 1.0 equiv.), MgCl$_2$ (584 mg, 1.6 mmol, 1.6 equiv.), the $L2$ (202 mg, 0.25 mmol, 0.25 equiv.), [Ru(p-cymene)Cl$_2$$_2$] (122 mg, 0.2 mmol, 0.2 equiv.), CuBr$_2$ (67 mg, 0.3 mmol, 0.3 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide $5a$ (222 mg, 0.84 mmol, 84%). The gram scale synthesis was performed on 10 mmol of the starting 2-bromo-2,2-difluoroacetamide $1a$ and the amide $5a$ was prepared in 73% yield (1.93 g, 7.3 mmol).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide $1a$ (250 mg, 1.0 mmol, 1.0 equiv.), MgCl$_2$ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate 4,4,5,5-tetramethyl-2-(4-(trifluoromethyl)phenyl)-1,3,2-dioxaborolane (354 mg, 1.3 mmol, 1.3 equiv.), the $L1$ (130 mg, 0.2 mmol, 0.2 equiv.), CuBr$_2$ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide $5a$ (222 mg, 0.84 mmol, 84%). The gram scale synthesis was performed on 10 mmol of the starting 2-bromo-2,2-difluoroacetamide $1a$ and the amide $5a$ was prepared in 73% yield (1.93 g, 7.3 mmol).

Alternatively, the title compound was prepared starting with an appropriate 2,2-difluoro-2-ido-N-phenylacetamide (297 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl$_2$ (247 mg, 2.0 mmol, 2.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl$_2$ (247 mg, 2.0 mmol, 2.0 equiv.), MgCl$_2$ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate aryl sulphonium salt $4a$ (28.6 mg, 0.1 mmol, 0.1 equiv.), the $L2$ (202 mg, 0.25 mmol, 0.25 equiv.), [Ru(p-cymene)Cl$_2$$_2$] (122 mg, 0.2 mmol, 0.2 equiv.), CuBr$_2$ (67 mg, 0.3 mmol, 0.3 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide $5a$ (222 mg, 0.84 mmol, 84%). The gram scale synthesis was performed on 10 mmol of the starting 2-bromo-2,2-difluoroacetamide $1a$ and the amide $5a$ was prepared in 73% yield (1.93 g, 7.3 mmol).

Alternatively, the title compound was prepared starting with an appropriate 2,2-difluoro-2-ido-N-phenylacetamide (297 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl$_2$ (247 mg, 2.0 mmol, 2.0 equiv.), MgCl$_2$ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate 4,4,5,5-tetramethyl-2-(4-(trifluoromethyl)phenyl)-1,3,2-dioxaborolane (354 mg, 1.3 mmol, 1.3 equiv.), the $L1$ (130 mg, 0.2 mmol, 0.2 equiv.), CuBr$_2$ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide $5a$ (222 mg, 0.84 mmol, 84%). The gram scale synthesis was performed on 10 mmol of the starting 2-bromo-2,2-difluoroacetamide $1a$ and the amide $5a$ was prepared in 73% yield (1.93 g, 7.3 mmol).

Flash column chromatography was performed using a mixture of hexane/ethyl acetate 3:1 as an eluent to provide the corresponding amide product.

White solid, mp 184–185 °C. $^1$H-NMR (500 MHz, DMSO-$d_6$): $\delta$ 7.12 (t, 1H, $^3$J = 7.3 Hz, CH$_A$), 7.37 (t, 2H, $^3$J = 8.3 Hz, CH$_A$), 7.80 (d, 2H, $^3$J = 7.6 Hz, CH$_A$), 7.89 (d, 2H, $^3$J = 8.2 Hz, CH$_A$), 8.16 (d, 2H, $^3$J = 8.1 Hz, CH$_A$), 10.5 (s, 1H, NH).

$^{13}$C($^1$H)-NMR (126 MHz, DMSO-$d_6$): $\delta$ 120.5, 123.9 (q, $^1$J$_{CF}$ = 273.8 Hz, CF$_3$), 124.0, 125.4 (d, $^1$J$_{CF}$ = 3.1 Hz), 128.6, 128.7, 131.4 (q, $^1$J$_{CF}$ = 30.3 Hz, CCF$_3$), 138.8 (d, $^1$J$_{CF}$ = 11.3 Hz), 164.4.
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1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl$_2$ (95 mg, 1.0 mmol, 1.0 equiv.). The title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1e (300 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl$_2$ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate aryl boronic acid 3a (231 mg, 1.3 mmol, 1.3 equiv.), the L1 (130 mg, 0.2 mmol, 0.2 equiv.), CuBr$_2$ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5b (245 mg, 0.81 mmol, 81%).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1e (300 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl$_2$ (95 mg, 1.0 mmol, 1.0 equiv.), the L1 (130 mg, 0.2 mmol, 0.2 equiv.), CuBr$_2$ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5b (245 mg, 0.80 mmol, 80%).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1e (300 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl$_2$ (95 mg, 1.0 mmol, 1.0 equiv.), the L2 (202 mg, 0.25 mmol, 0.25 equiv.), CuBr$_2$ (122 mg, 0.2 mmol, 0.2 equiv.), CuBr$_2$ (67 mg, 0.3 mmol, 0.3 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5b (233 mg, 0.77 mmol, 77%).

Flash column chromatography was performed using a mixture of hexane/ethyl acetate 3:1 as an eluent to provide the corresponding amide product.

White solid, mp 146–147 °C. $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 3.80 (s, 9H, tBu), 7.46–7.51 (m, 5H, CH$_2$Ar), 7.72 (d, 1H, $^3J = 8.4$ Hz, CH$_3$Ar), 7.87–7.90 (m, 3H, CH$_2$Ar), 7.92 (s, 1H, CH$_3$Ar), 7.97 (br. s, 1H, CH$_3$Ar), 8.33 (s, 1H, NH).

$^{13}$C($^1$H)-NMR (126 MHz, CDCl$_3$): $\delta$ 31.2, 35.0, 120.79, 120.80, 121.2, 125.7, 125.9, 126.3, 127.1, 127.5, 127.51, 128.7, 131.9, 132.5, 134.1.

HRMS (TOF MS ES+): Calcd for C$_{14}$H$_{13}$NOF$_3$ (M+H) 296.0901. Found 296.0898.

$N$-(2,4-difluorophenyl)-3-methylbenzamide 5d. The title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1f (286 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl$_2$ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate aryl boronic acid 2b (177 mg, 1.3 mmol, 1.3 equiv.), the L1 (130 mg, 0.2 mmol,
of 2 equiv.), CuBr$_2$ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5d (217 mg, 0.88 mmol, 88%).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoracetamide 1j (207 mg, 0.84 mmol, 84%).

Flash column chromatography was performed using a mixture of hexane/ethyl acetate 4:1 as an eluent to provide the corresponding amide product.

White solid, mp 106–107 °C. $^1$H-NMR (500 MHz, CDCl$_3$): δ 2.41 (s, 3H, Me), 6.85–6.90 (m, 2H, CH$_Ar$), 7.35–7.36 (m, 2H, CH$_Ar$), 7.63–7.65 (m, 1H, CH$_Ar$), 7.68 (s, 1H, CH$_Ar$), 8.02 (br s, 1H, NH), 8.29–8.33 (m, 1H, CH$_Ar$).

$^{13}$C($^1$H)-NMR (126 MHz, CDCl$_3$): δ 21.4, 103.4 (d, $J_{CF} = 26.5$ Hz), 103.6 (d, $J_{CF} = 26.5$ Hz), 111.2 (dd, $J_{CF} = 21.7$ Hz, $J_{CF} = 3.6$ Hz), 122.6 (dd, $J_{CF} = 10.5$ Hz, $J_{CF} = 3.7$ Hz), 123.1 (d, $J_{CF} = 9.3$ Hz), 124.0, 127.8, 128.6, 132.9, 134.1, 138.7, 152.9 (dd, $J_{CF} = 246.4$ Hz, $J_{CF} = 11.9$ Hz), 158.6 (dd, $J_{CF} = 246.5$ Hz, $J_{CF} = 11.4$ Hz), 165.7.

HRMS (TOF MS ES+): Calcd for C$_{14}$H$_{12}$NO$_2$F$_3$ (M + H) 248.0894. Found 248.0898.

3-chloro-N-(3,4-dimethoxyphenyl)benzamide 5e. The title compound was prepared starting with an appropriate 2-bromo-2,2-difluoracetamide 1g (310 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl$_2$ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate aryl boronic acid 2a (203 mg, 1.3 mmol, 1.3 equiv.), CuBr$_2$ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5e (242 mg, 0.83 mmol, 83%).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoracetamide 1g (310 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl$_2$ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate trialkoxysilane 2 (326 mg, 1.4 mmol, 1.4 equiv.), the L1 (130 mg, 0.2 mmol, 0.2 equiv.), CuBr$_2$ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5e (239 mg, 0.82 mmol, 82%).

Flash column chromatography was performed using a mixture of hexane/ethyl acetate 4:1 as an eluent to provide the corresponding amide product.

Light purple, solid mp 127–128 °C. $^1$H-NMR (500 MHz, CDCl$_3$): δ 3.79 (s, 3H, OMe), 6.77 (d, 1H, $J_{3} = 8.4$ Hz, CH$_Ar$), 7.02 (dd, 1H, $J_{3} = 8.7$ Hz, $J_{4} = 2.1$ Hz, CH$_Ar$), 7.32 (t, 1H, $J_{3} = 7.9$ Hz, CH$_Ar$), 7.36–7.37 (m, 1H, CH$_Ar$), 7.44 (dd, 1H, $J_{3} = 8.0$ Hz, $J_{4} = 1.0$ Hz, CH$_Ar$), 7.70 (d, 1H, $J_{3} = 7.0$ Hz, CH$_Ar$), 7.81 (s, 1H, CH$_Ar$), 8.26 (s, 1H, NH).

$^{13}$C($^1$H)-NMR (126 MHz, CDCl$_3$): δ 55.7, 55.9, 105.2, 111.1, 112.6, 125.1, 127.3, 129.9, 131.1, 131.6, 134.7, 146.1, 148.8, 164.5.

HRMS (TOF MS ES+): Calcd for C$_{15}$H$_{15}$NO$_3$Cl (M + H) 292.0738. Found 292.0740.

3-methoxy-N-phenylbenzamide 5f. The title compound was prepared starting with an appropriate 2-bromo-2,2-difluoracetamide 1a (250 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl$_2$ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate trialkoxysilane 3 (378 mg, 1.4 mmol, 1.4 equiv.), the L1 (130 mg, 0.2 mmol, 0.2 equiv.), CuBr$_2$ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5f (207 mg, 0.91 mmol, 91%).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoracetamide 1a (250 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl$_2$ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate trialkoxysilane 3 (378 mg, 1.4 mmol, 1.4 equiv.), the L1 (130 mg, 0.2 mmol, 0.2 equiv.), CuBr$_2$ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5f (200 mg, 0.88 mmol, 88%).
Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1a (250 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl₂ (95 mg, 1.0 mmol, 1.0 equiv.), aryloxonium salt 4b (410 mg, 1.6 mmol, 1.6 equiv.), the L₂ (202 mg, 0.25 mmol, 0.25 equiv.), [Ru(cyclohexene)Cl₂]₂ (122 mg, 0.2 mmol, 0.2 equiv.), CuBr₂ (67 mg, 0.3 mmol, 0.3 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5f (204 mg, 0.90 mmol, 90%).

Flash column chromatography was performed using a mixture of hexane/ethyl acetate 4:1 as an eluent to provide the corresponding amide product.

White solid, mp 116–117 °C. ¹H-NMR (500 MHz, CDCl₃): δ 3.78 (s, 3H, OMe), 7.02 (dd, 1H, ²J = 8.2 Hz, ¹J = 2.5 Hz, CH₃), 7.13 (t, 1H, ³J = 7.5 Hz, CH₃), 7.28–7.40 (m, 5H, CH₂, CH₃), 7.64 (d, 2H, ³J = 7.9 Hz, CH₂), 8.23 (s, 1H, NH).

¹³C[¹H]-NMR (126 MHz, CDCl₃): δ 55.3, 112.3, 117.9, 118.8, 120.3, 124.5, 128.9, 129.6, 136.3, 137.9, 159.8, 165.8.

HRMS (TOF MS ES⁺): Calcd for C₁₄H₁₄NO₂ (M + H) 228.1025. Found 228.1025. 

4-fluoro-N-(m-tolyl)-3-(trifluoromethyl)benzamide 5g. The title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1c (264 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl₂ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate aryl boronic acid 2p (270 mg, 1.3 mmol, 1.3 equiv.), the L₁ (130 mg, 0.2 mmol, 0.2 equiv.), CuBr₂ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5g (267 mg, 0.90 mmol, 90%).

Flash column chromatography was performed using a mixture of hexane/ethyl acetate 5:1 as an eluent to provide the corresponding amide product.

Colorless solid, mp 121–122 °C. ¹H-NMR (500 MHz, DMSO-d₆): δ 2.31 (s, 3H, Me), 6.94 (d, 1H, ³J = 7.4 Hz, CH₃), 7.24 (d, 1H, ³J = 8.2 Hz, CH₃), 7.56 (d, 2H, ³J = 8.3 Hz, CH₂), 7.60 (s, 1H, CH₃), 8.33–8.36 (m, 2H, CH₂, CH₃), 10.36 (s, 1H, NH).

¹³C[¹H]-NMR (126 MHz, DMSO-d₆): δ 21.2, 116.5 (d, ¹JCF = 33.5 Hz, JCF = 12.1 Hz), 117.5 (d, ¹JCF = 20.8 Hz), 117.7, 121.1, 122.4 (q, ¹JCF = 272.3 Hz, CF₃), 124.8, 126.9, 128.5, 131.7 (d, ¹JCF = 3.1 Hz), 135.1 (d, ¹JCF = 9.4 Hz), 137.9, 138.7, 160.6 (d, ¹JCF = 257.0 Hz), 163.0.

HRMS (TOF MS ES⁺): Calcd for C₁₃H₁₂NO₃F (M + H) 298.0861. Found 298.0855.

N-(p-tolyl)-2-(trifluoromethoxy)benzamide 5h. The title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1b (264 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl₂ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate aryl boronic acid 2q (268 mg, 1.3 mmol, 1.3 equiv.), the L₁ (130 mg, 0.2 mmol, 0.2 equiv.), CuBr₂ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5h (218 mg, 0.74 mmol, 74%).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1b (264 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl₂ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate trialkoxysilane 3m (395 mg, 1.4 mmol, 1.4 equiv.), the L₁ (130 mg, 0.2 mmol, 0.2 equiv.), CuBr₂ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5h (221 mg, 0.75 mmol, 75%).

Flash column chromatography was performed using a mixture of hexane/ethyl acetate 5:1 as an eluent to provide the corresponding amide product.

White solid, mp 108–109 °C. ¹H-NMR (500 MHz, CDCl₃): δ 2.35 (s, 3H, Me), 7.18 (d, 2H, ³J = 8.0 Hz, CH₃), 7.32 (d, 1H, ³J = 8.0 Hz, CH₃), 7.42 (t, 1H, ³J = 7.5 Hz, CH₃), 7.51–7.55 (m, 3H, CH₃), 8.04 (d, 1H, ³J = 7.7 Hz, CH₃), 8.30 (s, 1H, NH).

¹³C[¹H]-NMR (126 MHz, CDCl₃): δ 20.9, 120.3 (q, ¹JCF = 261.0 Hz, OF₃), 120.4, 121.2, 124.3, 129.6, 131.9, 132.6, 134.6, 135.0, 145.7, 162.1.

HRMS (TOF MS ES⁺): Calcd for C₁₃H₁₃NO₃F₃ (M + H) 312.0847. Found 312.0848.

N-(4-methoxyphenyl)-2-(trifluoromethoxy)benzamide 5i. The title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1f (280 mg, 1.0 mmol,
1.4 equiv.), the \( {L_1} \) \( {135.7, 137.4, 139.0, 165.7}. \)

\( {J_{125.7, 126.4 (q, 1.4 \text{ equiv})}} \), the \( {L_1} \) \( {122.2, 127.6, 128.3, 130.6, 131.8, 132.5, 145.7, 156.8, 162.1}. \)

10 mmol of the starting 2-bromo-2,2-difluoroacetamide \( 1f \) (172 mg, 0.70 mmol, 70%).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide \( 1c \) (95 mg, 1.0 mmol, 1.0 equiv.), appropriate trialkoxysilane \( 2 \) (95 mg, 1.0 mmol, 1.0 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide \( 5i \) (224 mg, 0.72 mmol, 72%).

Flash column chromatography was performed using a mixture of hexane/ethyl acetate 6:1 as an eluent to provide the corresponding amide product.

Pink solid, mp 117–118 °C. \(^1H\)-NMR (500 MHz, CDCl\(_3\)) : \( \delta \) 3.81 (s, 3H, OMe), 6.88–6.92 (m, 2H, CH\(_2\)), 7.32 (d, 1H, J\(_{3} =7.8 \text{ Hz, CH}\(_2\)_Ar), 7.42 (dt, 1H, J\(_{2} =7.8 \text{ Hz, CH}\(_2\)_Ar), 7.51–7.54 (m, 3H, CH\(_3\)_Ar), 8.02 (dd, 1H, J\(_{1} =1.7 \text{ Hz, CH}\(_2\)_Ar), 8.25 (s, 1H, NH).

\(^{13}C\)\(^{(1)}\)-NMR (126 MHz, CDCl\(_3\)) : \( \delta \) 55.5, 114.2, 120.3 (q, J\(_{CF} =260.4 \text{ Hz, OCF}_3\)), 121.2, 122.2, 127.6, 128.3, 130.6, 131.8, 132.5, 145.7, 156.8, 162.1.

HRMS (TOF MS ES\(^+\)) : Calcd for C\(_{15}\)H\(_{13}\)NO\(_2\)F\(_3\) (M + H) 296.0940. Found 296.0898.

\( N-(m\text{-tolyl})-2\text{-}(trifluoromethyl)benzamide \ 5j \). The title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide \( 1c \) (264 mg, 1.0 mmol, 1.0 equiv.), \( \text{KF} \) (116 mg, 2.0 mmol, 2.0 equiv.), \( \text{MgCl}_2 \) (95 mg, 1.0 mmol, 1.0 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide \( 5j \) (239 mg, 0.65 mmol, 65%).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide \( 1c \) (264 mg, 1.0 mmol, 1.0 equiv.), \( \text{KF} \) (116 mg, 2.0 mmol, 2.0 equiv.), \( \text{MgCl}_2 \) (95 mg, 1.0 mmol, 1.0 equiv.), appropriate trialkoxysilane \( 3m \) (395 mg, 1.4 mmol, 1.4 equiv.), the \( L_1 \) (130 mg, 0.2 mmol, 0.2 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide \( 5j \) (224 mg, 0.67 mmol, 67%).

Flash column chromatography was performed using a mixture of hexane/ethyl acetate 5:1 as an eluent to provide the corresponding amide product.

Colorless solid, mp 120–121 °C. \(^1H\)-NMR (500 MHz, CDCl\(_3\)) : \( \delta \) 2.35 (s, 3H, Me), 6.98 (d, 1H, J\(_{3} =7.57 \text{ Hz, CH}\(_2\)_Ar), 7.22 (t, 1H, J\(_{2} =8.1 \text{ Hz, CH}\(_2\)_Ar), 7.33 (d, 1H, J\(_{2} =7.6 \text{ Hz, CH}\(_2\)_Ar), 7.44 (s, 1H, CH\(_3\)_Ar), 7.54–7.57 (m, 3H, CH\(_2\)_Ar), 7.69–7.71 (m, 3H, NH, CH\(_3\)_Ar).

\(^{13}C\)\(^{(1)}\)-NMR (126 MHz, CDCl\(_3\)) : \( \delta \) 21.4, 117.3, 120.8, 123.7 (q, J\(_{CF} =276.1 \text{ Hz, CF}_3\)), 125.7, 126.4 (q, J\(_{CF} =5.2 \text{ Hz, CF}_3\)), 127.1 (q, J\(_{2} =31.5 \text{ Hz, CF}_3\)), 128.5, 128.9, 130.0, 132.1, 135.7, 137.4, 139.0, 165.7.

HRMS (TOF MS ES\(^+\)) : Calcd for C\(_{15}\)H\(_{13}\)NO\(_2\)F\(_3\) (M + H) 280.0957. Found 280.0949.

\( N-(4\text{-chlorophenyl})-2\text{-methylbenzamide} \ 5k \). The title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide \( 1h \) (285 mg, 1.0 mmol, 1.0 equiv.), \( \text{KF} \) (116 mg, 2.0 mmol, 2.0 equiv.), \( \text{MgCl}_2 \) (95 mg, 1.0 mmol, 1.0 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide \( 5k \) (172 mg, 0.70 mmol, 70%).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide \( 1h \) (285 mg, 1.0 mmol, 1.0 equiv.), \( \text{KF} \) (116 mg, 2.0 mmol, 2.0 equiv.), \( \text{MgCl}_2 \) (95 mg, 1.0 mmol, 1.0 equiv.), appropriate trialkoxysilane \( 3c \) (297 mg, 1.4 mmol, 1.4 equiv.), the \( L_1 \) (130 mg, 0.2 mmol, 0.2 equiv.), and hexafluoropropanol (0.12 mmol/mL).
and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5k (182 mg, 0.74 mmol, 74%).

Flash column chromatography was performed using a mixture of hexane/ethyl acetate 3:1 as an eluent to provide the corresponding amide product.

White solid, mp 136–138 °C. 1H-NMR (500 MHz, CDCl3): δ 2.41 (s, 3H, Me), 7.17 (t, 1H, J = 7.2 Hz, CHAr), 2.70 (d, 1H, J = 7.2 Hz, CHAr), 7.25 (d, 2H, J = 8.7 Hz, CHAr), 7.31 (dt, 2H, J = 7.6 Hz, J′ = 0.8 Hz, CHAr), 7.36 (d, 1H, J = 7.2 Hz, CHAr), 7.50 (d, 1H, J = 8.4 Hz, CHAr), 7.87 (br s, 1H, NH).

13C{1H}-NMR (126 MHz, CDCl3): δ 19.7, 121.2, 125.8, 126.6, 129.0, 129.4, 130.3, 131.2, 135.9, 136.3, 136.5, 168.2.

HRMS (TOF MS ES+): Calcd for C15H13NOF 246.0690. Found 246.0686.

2-bromo-N-(3,4-dimethoxyphenyl)benzamide 5l. The title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1g (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5l (185 mg, 0.55 mmol, 55%). Flash column chromatography was performed using a mixture of hexane/ethyl acetate 2:1 as an eluent to provide the corresponding amide product.

Purple solid, mp 140–141 °C. 1H-NMR (500 MHz, CDCl3): δ 3.83 (s, 3H, OMe), 3.84 (s, 3H, OMe), 6.79 (d, 1H, J = 8.7 Hz, CHAr), 7.00 (dd, 1H, J = 8.4 Hz, J′ = 2.6 Hz, CHAr), 7.22–7.26 (m, 1H, CHAr), 7.29–7.32 (m, 1H, CHAr), 7.41 (d, 1H, J = 2.3 Hz, CHAr), 7.51 (dd, 1H, J = 7.6 Hz, J′ = 1.6 Hz, CHAr), 7.55 (d, 1H, J = 8.3 Hz, CHAr), 7.96 (s, 1H, NH).

13C{1H}-NMR (126 MHz, CDCl3): δ 55.8, 56.0, 104.8, 111.2, 112.0, 119.2, 127.5, 129.4, 131.2, 131.4, 133.3, 137.7, 146.0, 148.9, 165.5.

HRMS (TOF MS ES+): Calcd for C15H13NOF 246.0690. Found 246.0684.

N-(4-fluorophenyl)nicotinamide 5m. The title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1i (268 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl2 (95 mg, 1.0 mmol, 1.0 equiv.), appropriate aryl boronic acid 2t (95 mg, 1.0 mmol, 1.0 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5m (173 mg, 0.80 mmol, 80%).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1i (268 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl2 (95 mg, 1.0 mmol, 1.0 equiv.), appropriate trialkoxysilane 3o (277 mg, 1.4 mmol, 1.4 equiv.), the L1 (130 mg, 0.2 mmol, 0.2 equiv.), CuBr2 (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5m (166 mg, 0.77 mmol, 77%).

Flash column chromatography was performed using a mixture of hexane/ethyl acetate 1:1 as an eluent to provide the corresponding amide product.

White solid, mp 130–131 °C. 1H-NMR (500 MHz, CDCl3): δ 7.02 (t, 2H, J = 8.7 Hz, CHAr), 7.34–7.37 (m, 1H, CHAr), 7.55–7.58 (m, 2H, CHAr), 8.15 (d, 1H, J = 8.3 Hz, CHAr), 8.66 (dd, 1H, J = 4.7 Hz, J′ = 1.4 Hz, CHAr), 8.80 (s, 1H, NH), 9.03 (s, 1H, CHAr).

13C{1H}-NMR (126 MHz, CDCl3): δ 115.7 (d, JCF = 22.2 Hz), 122.5 (d, JCF = 7.0 Hz), 123.7, 130.6, 133.5, 135.9, 152.2, 159.7 (d, JCF = 244.1 Hz), 164.1.

HRMS (TOF MS ES+): Calcd for C15H12NOF3Na (M + Na) 302.0769. Found 302.0769.

N-(m-tolyl)thiophene-2-carboxamide 5n. The title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1c (264 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl2 (95 mg, 1.0 mmol, 1.0 equiv.), appropriate aryl boronic acid 2u (166 mg, 1.3 mmol, 1.3 equiv.), the L1 (130 mg, 0.2 mmol, 0.2 equiv.), CuBr2 (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification
of the dry crude performed by column chromatography on silica gel provides the amide 5n (169 mg, 0.78 mmol, 78%).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1c (264 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl₂ (95 mg, 1.0 mmol, 1.0 equiv.), CuBr₂ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5o (233 mg, 0.88 mmol, 88%).

Flash column chromatography was performed using a mixture of hexane/ethyl acetate 8:1 as an eluent to provide the corresponding amide product.

Brownish solid, mp 105–106 °C. ¹H-NMR (500 MHz, CDCl₃): δ 2.32 (s, 3H, Me), 6.94 (t, 1H, 3J = 7.8 Hz, CH₂Ar), 7.01–7.08 (m, 1H, Thiophene), 7.21 (t, 1H, 3J = 7.8 Hz, CH₃Ar), 7.39 (d, 1H, 3J = 8.1 Hz, CH₂Ar), 7.47 (s, 1H, CH₂Ar), 7.51 (d, 1H, 3J = 4.8 Hz, Thiophene), 7.64 (d, 1H, 3J = 3.6 Hz, Thiophene).

¹³C¹H-NMR (126 MHz, CDCl₃): δ 21.4, 117.4, 121.0, 125.4, 127.8, 128.4, 128.8, 130.7, 137.5, 138.9, 139.4, 160.1.

HRMS (TOF MS ES⁺): Calcd for C₁₂H₁₂NOS (M + H) 240.1157. Found 240.1155.

3,4-difluoro-N-isopropylbenzamide 5o. The title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1k (216 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl₂ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate aryl boronic acid 2g (205 mg, 1.3 mmol, 1.3 equiv.), the L1 (130 mg, 0.2 mmol, 0.2 equiv.), CuBr₂ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5o (238 mg, 0.90 mmol, 90%).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1k (216 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl₂ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate trialkoxysilane 3p (286 mg, 1.4 mmol, 1.4 equiv.), the L1 (130 mg, 0.2 mmol, 0.2 equiv.), CuBr₂ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5p (263 mg, 0.91 mmol, 91%).
Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 11 (258 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl₂ (95 mg, 1.0 mmol, 1.0 equiv.), MgCl₂ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate trialkoxysilane 3h (326 mg, 1.4 mmol, 1.4 equiv.), the L1 (130 mg, 0.2 mmol, 0.2 equiv.), CuBr₂ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5p (266 mg, 0.92 mmol, 92%).

Flash column chromatography was performed using a mixture of hexane/ethyl acetate 8:1 as an eluent to provide the corresponding amide product.

White solid, mp 129–130 °C. ¹H-NMR (500 MHz, CDCl₃): δ 1.15 (s, 6H, Me), 1.48 (s, 6H, Me), 3.58 (m, 2H, 2xCH₃), 7.24 (dt, 2H, 3J = 8.5 Hz, 4J = 2.0 Hz, CH₂Ar), 7.34 (dt, 2H, 3J = 8.3 Hz, 4J = 1.7 Hz, CH₂Ar).

¹³C(¹H)-NMR (126 MHz, CDCl₃): δ 20.7, 212.7, 128.7, 134.6, 137.2, 169.9.

HRMS (TOF MS ES+): Calcd for C₁₃H₁₉NOCl (M + H) 240.1157. Found 240.1155.

2,3,4-trifluoro-N,N-diisopropylbenzamide 5q. Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 11 (258 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl₂ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate aryl boronic acid 2i (263 mg, 1.3 mmol, 1.3 equiv.), the L1 (130 mg, 0.2 mmol, 0.2 equiv.), CuBr₂ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5q (215 mg, 0.83 mmol, 83%).

Flash column chromatography was performed using a mixture of hexane/ethyl acetate 11:1 as an eluent to provide the corresponding amide product.

White solid, mp 45–46 °C. ¹H-NMR (500 MHz, CDCl₃): δ 1.10 (m, 6H, 2xMe), 1.52 (s, 3H, NCH), 3.50–3.53 (m, 1H, NCH), 3.65–3.68 (m, 1H, NCH), 6.97–7.00 (m, 1H, NCH), 6.97–7.00 (m, 1H, NCH), 7.24 (dt, 2H, 3J = 2.7 Hz, CH₂Ar), 7.34 (dt, 2H, 3J = 1.7 Hz, CH₂Ar).

¹³C(¹H)-NMR (126 MHz, CDCl₃): δ 20.5 (m), 46.2, 51.3, 112.9 (dd, JCF = 18.0 Hz, 3JCF = 3.3 Hz), 121.3 (m), 124.3 (dd, JCF = 6.5 Hz, 3JCF = 2.2 Hz), 139.7 (dt, 1JCF = 253.7 Hz, 3JCF = 15.2 Hz), 147.2 (ddd, 1 JCF = 249.8 Hz, 3JCF = 10.9 Hz, 4JCF = 3.1 Hz), 151.2 (ddd, 1JCF = 251.3 Hz, 3JCF = 9.8 Hz, 4JCF = 2.4 Hz), 163.5.

HRMS (TOF MS ES+): Calcd for C₁₃H₁₇NOF (M + H) 260.1262. Found 260.1262.

N-cyclohexyl-2-fluorobenzamide 5r. The title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1p (258 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl₂ (95 mg, 1.0 mmol, 1.0 equiv.), MgCl₂ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate aryl boronic acid 2i (203 mg, 1.3 mmol, 1.3 equiv.), the L1 (130 mg, 0.2 mmol, 0.2 equiv.), CuBr₂ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5r (188 mg, 0.85 mmol, 85%).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1p (258 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl₂ (95 mg, 1.0 mmol, 1.0 equiv.), MgCl₂ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate potassium trifluoro(2-fluorophenyl)borate (263 mg, 1.3 mmol, 1.3 equiv.), the L1 (130 mg, 0.2 mmol, 0.2 equiv.), CuBr₂ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5r (192 mg, 0.87 mmol, 87%).

Flash column chromatography was performed using a mixture of hexane/ethyl acetate 10:1 as an eluent to provide the corresponding amide product.

Colorless solid, mp 45–46 °C. ¹H-NMR (500 MHz, CDCl₃): δ 1.19–1.29 (m, 3H, Cy), 1.36–1.46 (m, 2H, Cy), 1.58–1.62 (m, 1H, Cy), 1.69–1.73 (m, 2H, Cy), 1.98–2.01 (m, 2H, Cy), 3.98–4.00 (m, 1H, Cy), 6.61 (s, 1H, NH), 7.04–7.08 (m, 1H, CH₂Ar), 7.19–7.22 (m, 1H, CH₂Ar), 7.38–7.42 (m, 1H, CH₂Ar), 8.03 (dd, 1H, 3J = 7.9 Hz, 4J = 1.8 Hz, CH₂Ar).

¹³C(¹H)-NMR (126 MHz, CDCl₃): δ 24.7, 25.5, 32.9, 48.5, 115.8 (d, JCF = 23.6 Hz), 121.5 (d, JCF = 11.0 Hz), 124.6 (d, JCF = 2.7 Hz), 131.9, 133.0 (d, JCF = 9.0 Hz), 160.4 (d, JCF = 246.0 Hz, CF), 162.1 (d, JCF = 2.4 Hz).

HRMS (TOF MS ES+): Calcd for C₁₃H₁₇NOF (M + H) 222.1294. Found 222.1294.
N-cyclohexyl-N-methyl-[1,1'-biphenyl]-4-carboxamide 5s. The title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1O (270 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl2 (95 mg, 1.0 mmol, 1.0 equiv.), appropriate aryl boronic acid 2e (442 mg, 1.4 mmol, 1.4 equiv.), the L1 (130 mg, 0.2 mmol, 0.2 equiv.), CuBr2 (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5s (243 mg, 0.83 mmol, 83%).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1O (270 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl2 (95 mg, 1.0 mmol, 1.0 equiv.), appropriate trialkoxysilane 3e (424 mg, 1.4 mmol, 1.4 equiv.), the L1 (130 mg, 0.2 mmol, 0.2 equiv.), CuBr2 (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5s (243 mg, 0.83 mmol, 83%).

Flash column chromatography was performed using a mixture of hexane/ethyl acetate 8:1 as an eluent to provide the corresponding amide product.

Colorless solid, mp 105 - 106 °C. 1H-NMR (500 MHz, CDCl3): δ 1.07–1.09 (m, 2H, Cy), 1.47–1.56 (m, 4H, Cy), 1.72–1.82 (m, 4H, Cy), 2.83, 3.00 (s, 3H, Me cis/trans), 3.54, 4.51 (s, 1H, Cy cis/trans), 7.33–7.36 (m, 1H, CHAr), 7.42–7.45 (m, 4H, CHAr), 7.60–7.61 (m, 4H, CHAr).

13C(1H)-NMR (126 MHz, CDCl3): δ 25.0, 25.3, 25.4, 27.4, 29.4, 29.5, 30.7, 31.9, 52.7, 58.1, 126.5 126.7, 126.9, 127.1, 127.2, 127.5, 128.7, 135.8, 140.1, 141.8, 171.4.

HRMS (TOF MS ES+): Calcd for C20H20NO (M + H) 294.1856. Found 294.1858.

N-benzyl-3-methoxybenzamide 5t. The title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1u (264 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl2 (95 mg, 1.0 mmol, 1.0 equiv.), appropriate aryl boronic acid 2w (198 mg, 1.3 mmol, 1.3 equiv.), the L1 (130 mg, 0.2 mmol, 0.2 equiv.), CuBr2 (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5t (217 mg, 0.90 mmol, 90%).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1u (264 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl2 (95 mg, 1.0 mmol, 1.0 equiv.), appropriate trialkoxysilane 3j (378 mg, 1.4 mmol, 1.4 equiv.), the L1 (130 mg, 0.2 mmol, 0.2 equiv.), CuBr2 (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5t (210 mg, 0.87 mmol, 87%).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1u (264 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl2 (95 mg, 1.0 mmol, 1.0 equiv.), aryl sulphonium salt 4b (410 mg, 1.6 mmol, 1.6 equiv.), the L2 (202 mg, 0.25 mmol, 0.25 equiv.), [Ru(p-cymene)Cl2]2 (122 mg, 0.2 mmol, 0.2 equiv.), CuBr2 (67 mg, 0.3 mmol, 0.3 equiv.), and hexafluoropropanol (0.17 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5t (202 mg, 0.84 mmol, 84%).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1u (264 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl2 (95 mg, 1.0 mmol, 1.0 equiv.), appropriate potassium trifluoro(3-methoxyphenyl)borate (278 mg, 1.3 mmol, 1.3 equiv.), the L1 (130 mg, 0.2 mmol, 0.2 equiv.), CuBr2 (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5t (193 mg, 0.80 mmol, 80%).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1u (264 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl2 (95 mg, 1.0 mmol, 1.0 equiv.), appropriate 2-(3-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (304 mg, 1.3 mmol, 1.5 equiv.), the L1 (130 mg, 0.2 mmol, 0.2 equiv.), CuBr2 (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The
purification of the dry crude performed by column chromatography on silica gel provides the amide 5t (200 mg, 0.83 mmol, 83%).

Alternatively, the title compound was prepared starting with an appropriate N-benzyl-2,2-difluoro-2-iodoacetamide (311 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl$_2$ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate aryl boronic acid 2n (247 mg, 1.3 mmol, 1.3 equiv.), CuBr$_2$ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5u (281 mg, 0.81 mmol, 81%).

Flash column chromatography was performed using a mixture of hexane/ethyl acetate 7:1 as an eluent to provide the corresponding amide product.

White solid, mp 77–78 °C. $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 2.36 (s, 3H, Me), 4.60 (d, 2H, $^3J = 5.6$ Hz, CH$_2$), 6.78 (br s, 1H, NH), 7.26–7.33 (m, 7H, CH$_{Ar}$), 7.57 (d, 1H, $^3J = 7.2$ Hz, CH$_{Ar}$), 7.63 (s, 1H, CH$_{Ar}$).

$^{13}$C($^1$H)-NMR (126 MHz, CDCl$_3$): $\delta$ 21.2, 43.9, 123.9, 127.4, 127.7, 127.8, 128.3, 128.6, 132.1, 134.2, 138.3, 167.6.

HRMS (TOF MS ES+): Calcd for C$_{14}$H$_{16}$NO (M + H) 226.1234. Found 226.1232.

$N$-cyclohexyl-$N$-phenyl-4-(trifluoromethyl)benzamide 5u. The title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1n (332 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl$_2$ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate trialkoxysilane 3k (372 mg, 1.4 mmol, 1.4 equiv.), CuBr$_2$ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5u (312 mg, 0.90 mmol, 90%).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1n (332 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl$_2$ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate aryl sulphonium salt 4a (584 mg, 1.6 mmol, 1.6 equiv.), the L1 (130 mg, 0.2 mmol, 0.2 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5u (281 mg, 0.81 mmol, 81%).

Flash column chromatography was performed using a mixture of hexane/ethyl acetate 8:1 as an eluent to provide the corresponding amide product.

Colorless solid, mp 195–196 °C. $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 0.97 (tq, 1H, $^3J = 13.4$ Hz, $^4J = 2.9$ Hz, Cy), 1.22 (dq, 2H, $^3J = 12.9$ Hz, $^4J = 2.9$ Hz, Cy), 1.45 (d, 2H, $^3J = 12.4$ Hz, Cy), 1.61 (d, 1H, $^3J = 13.3$ Hz, Cy), 1.78 (d, 2H, $^3J = 13.3$ Hz, Cy), 1.96 (d, 2H, $^3J = 11.1$ Hz, Cy), 4.72 (s, 1H, Cy), 7.00 (d, 2H, $^3J = 6.9$ Hz, CH$_{Ar}$), 7.19–7.20 (m, 3H, CH$_{Ar}$), 7.31 (d, 2H, $^3J = 7.3$ Hz, CH$_{Ar}$), 7.36 (d, 2H, $^3J = 6.9$ Hz, CH$_{Ar}$).

$^{13}$C($^1$H)-NMR (126 MHz, CDCl$_3$): $\delta$ 25.3, 25.8, 31.5, 55.3, 123.7 (q, $^1J_{CF} = 271.2$ Hz, CF$_3$), 124.6, 127.8, 128.3, 128.6, 130.4 (q, $^2J_{CF} = 28.0$ Hz, CF$_3$), 130.6, 139.2, 140.8, 169.1.

HRMS (TOF MS ES+): Calcd for C$_{20}$H$_{21}$NO$_3$F (M + H) 348.1581. Found 348.1575.

$N$-((1s,3s)-adamantan-1-yl)-4-(trifluoromethyl)benzamide 5v. The title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1q (308 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl$_2$ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate aryl boronic acid 2n (247 mg, 1.3 mmol, 1.3 equiv.), CuBr$_2$ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5v (281 mg, 0.87 mmol, 87%).
Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1q (308 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl₂ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate trialkoxysilane 3i (326 mg, 1.4 mmol, 1.4 equiv.), the L₁ (130 mg, 0.2 mmol, 0.2 equiv.), CuBr₂ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5v (291 mg, 0.90 mmol, 90%).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1q (308 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl₂ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate potassium trifluoro(4-(trifluoromethyl)phenyl)borate (328 mg, 1.3 mmol, 1.3 equiv.), the L₁ (130 mg, 0.2 mmol, 0.2 equiv.), CuBr₂ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5v (271 mg, 0.84 mmol, 84%).

Flash column chromatography was performed using a mixture of hexane/ethyl acetate 1:1 as an eluent to provide the corresponding amide product.

White solid, mp 158–159 °C. ¹H-NMR (500 MHz, CDCl₃): δ 1.70 (s, 6H, Adam), 2.11 (s, 9H, Adam), 5.91 (s, 1H, NH), 7.61 (d, 2H, J = 8.6 Hz, CH₆), 7.78 (d, 2H, J = 7.9 Hz, CH₄).

³¹C[¹H]-NMR (126 MHz, CDCl₃): δ 29.4, 36.2, 41.5, 52.6, 123.7 (q, J_CF = 273.6 Hz, CF₃), 125.4 (m), 132.6 (q, J_CF = 31.1 Hz, CCF₃), 139.3.

HRMS (TOF MS ES+): Calcd for C₁₃H₂₁NOF₃ (M + H) 324.1573. Found 324.1575.

3-chloro-N-cyclopropylbenzamide 5w. The title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1r (214 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl₂ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate aryl boronic acid 2k (203 mg, 1.3 mmol, 1.3 equiv.), the L₁ (130 mg, 0.2 mmol, 0.2 equiv.), CuBr₂ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5w (127 mg, 0.65 mmol, 65%).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1r (214 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl₂ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate trialkoxysilane 3i (326 mg, 1.4 mmol, 1.4 equiv.), the L₁ (130 mg, 0.2 mmol, 0.2 equiv.), CuBr₂ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5w (125 mg, 0.64 mmol, 64%).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1r (214 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl₂ (95 mg, 1.0 mmol, 1.0 equiv.), aryl sulphonium salt 4d (516 mg, 1.6 mmol, 1.6 equiv.), the L₂ (202 mg, 0.25 mmol, 0.25 equiv.), [Ru(p-cymene)Cl₂]₂ (122 mg, 0.2 mmol, 0.2 equiv.), CuBr₂ (67 mg, 0.3 mmol, 0.3 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5w (113 mg, 0.58 mmol, 58%).

Flash column chromatography was performed using a mixture of hexane/ethyl acetate 7:1 as an eluent to provide the corresponding amide product.

Colorless solid, mp 142–143 °C. ¹H-NMR (500 MHz, CDCl₃): δ 0.83–0.86 (m, 2H, CH₂), 1.06–1.09 (m, 2H, CH₂), 1.48–1.53 (m, 1H, CH), 7.04 (d, 1H, J = 7.9 Hz, CH₆), 7.20 (t, 1H, J = 8.7 Hz, CH₂), 7.32 (d, 1H, J = 7.9 Hz, CH₆), 7.63 (br. s, 1H, CH₆), 7.74 (s, 1H, NH).

³¹C[¹H]-NMR (126 MHz, CDCl₃): δ 8.2, 15.7, 17.7, 19.9, 124.0, 129.9, 134.6, 139.2, 172.3.

HRMS (TOF MS ES+): Calcd for C₁₃H₁₁NOCl (M + H) 196.0532. Found 196.0529.

[1,1′-biphenyl]-4-yl(pyrrolidin-1-yl)methanone 5x. The title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1s (228 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl₂ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate aryl boronic acid 2e (257 mg, 1.3 mmol, 1.3 equiv.), the L₁ (130 mg, 0.2 mmol, 0.2 equiv.), CuBr₂ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification
of the dry crude performed by column chromatography on silica gel provides the amide 5x (236 mg, 0.91 mmol, 91%).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1s (228 mg, 1.0 mmol, 1.0 equiv.), DF 1.4 equiv.), the L1 (202 mg, 0.25 mmol, 0.25 equiv.), CuBr2 (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5x (223 mg, 0.89 mmol, 89%).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1s (228 mg, 1.0 mmol, 1.0 equiv.), DF 1.4 equiv.), the L1 (202 mg, 0.25 mmol, 0.25 equiv.), [Ru(p-cymene)Cl3], aryl sulphonium salt 4e (582 mg, 1.6 mmol, 1.6 equiv.), the L2 (202 mg, 0.25 mmol, 0.25 equiv.), CuBr2 (22.3 mg, 0.1 mmol, 0.1 equiv.), CuBr2 (67 mg, 0.3 mmol, 0.3 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5x (206 mg, 0.82 mmol, 82%).

Flash column chromatography was performed using a mixture of hexane/ethyl acetate 8:1 as an eluent to provide the corresponding amide product.

White solid, mp 139–140 °C. 1H-NMR (500 MHz, CDCl3): δ 1.86 (m, 4H, Pyrr), 3.39 (s, 2H, Pyrr), 3.58 (s, 2H, Pyrr), 7.34 (t, 1H, J = 7.7 Hz, CHAr), 7.43 (t, 2H, J = 7.7 Hz, CHAr), 7.57 – 7.59 (m, 6H, CHAr).

13C{1H}-NMR (126 MHz, CDCl3): δ 24.3, 26.3, 46.1, 49.5, 126.7, 127.0, 127.6, 128.7, 135.8, 140.1, 142.4, 169.3.

HRMS (TOF MS ES+): Calcld for C17H18NO (M + H) 252.1391. Found 252.1388.

N-phenethyl-1-naphthamide 5y. The title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1t (203 mg, 1.0 mmol, 1.0 equiv.), DF 1.4 equiv.), the L1 (130 mg, 0.2 mmol, 0.2 equiv.), CuBr2 (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5y (212 mg, 0.77 mmol, 77%). The gram scale synthesis was performed on 10 mmol of the starting 2-bromo-2,2-difluoroacetamide 1t and the amide 5y was prepared in 70% yield (1.93 g, 7.8 mmol).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1t (278 mg, 1.0 mmol, 1.0 equiv.), DF 1.4 equiv.), the L1 (130 mg, 0.2 mmol, 0.2 equiv.), CuBr2 (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5y (212 mg, 0.77 mmol, 77%). The gram scale synthesis was performed on 10 mmol of the starting 2-bromo-2,2-difluoroacetamide 1t and the amide 5y was prepared in 70% yield (1.93 g, 7.8 mmol).

Flash column chromatography was performed using a mixture of hexane/ethyl acetate 5:1 as an eluent to provide the corresponding amide product.

White solid, mp 117–118 °C. 1H-NMR (500 MHz, CDCl3): δ 3.00 (t, 2H, J = 6.1 Hz, CH2), 3.80 (q, 2H, J = 7.2 Hz, CH2), 6.13 (s, 1H, NH), 7.27–7.28 (m, 3H, CHAr), 7.33–7.37 (m, 2H, CHAr), 7.40–7.43 (m, 1H, CHAr), 7.48–7.54 (m, 3H, CHAr), 7.86–7.88 (m, 1H, CHAr), 7.89 (d, 1H, J = 8.0 Hz, CHAr), 8.20–8.22 (m, 1H, CHAr).

13C{1H}-NMR (126 MHz, CDCl3): δ 35.6, 41.0, 124.6, 124.85, 125.3, 126.3, 126.5, 127.0, 128.2, 128.7, 128.8, 130.0, 130.4, 133.6, 134.3, 138.7.

HRMS (TOF MS ES+): Calcld for C19H18NO (M + H) 276.1396. Found 276.1398.

N-benzyl-3-chlorobenzamide 5z. The title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1u (264 mg, 1.0 mmol, 1.0 equiv.), DF 1.4 equiv.), the L1 (130 mg, 0.2 mmol, 0.2 equiv.), CuBr2 (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry
crude performed by column chromatography on silica gel provides the amide 5z (209 mg, 0.85 mmol, 85%).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1u (264 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl₂ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate trialkoxysilane 3i (372 mg, 1.4 mmol, 1.4 equiv.), the L1 (130 mg, 0.2 mmol, 0.2 equiv.), CuBr₂ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5z (194 mg, 0.79 mmol, 79%).

Flash column chromatography was performed using a mixture of hexane/ethyl acetate 2:1 as an eluent to provide the corresponding amide product.

Yellowish solid, mp 93–94 °C. ¹H-NMR (500 MHz, CDCl₃): δ 4.57 (d, 2H, ³J = 5.5 Hz, CH₂), 6.77 (s, 1H, NH), 7.27–7.35 (m, 6H, CH₄Ar), 7.44 (dd, 1H, ³J = 8.0 Hz, ⁴J = 1.0 Hz, CH₃Ar), 7.64 (d, 1H, ³J = 1.8 Hz, CH₄Ar), 7.77 (d, 1H, ³J = 1.8 Hz, CH₄Ar).

¹³C(¹H)-NMR (126 MHz, CDCl₃): δ 44.1, 125.1, 127.3, 127.6, 127.8, 128.7, 129.8, 131.5, 134.7, 136.1, 137.8, 166.1.

HRMS (TOF MS ESI+): Calcd for C₁₃H₁₃NOF (M + H) 244.1143. Found 244.1138.

N-(4-fluorobenzyl)-2-methylbenzamide 5aa. The title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1v (202 mg, 0.25 mmol, 0.25 equiv.), [Ru(p-cymene)Cl₂]Ar (158 mg, 0.60 mmol, 60%), CuBr₂ (174 mg, 0.72 mmol, 72%).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1v (202 mg, 0.25 mmol, 0.25 equiv.), [Ru(p-cymene)Cl₂]Ar (158 mg, 0.60 mmol, 60%), CuBr₂ (174 mg, 0.72 mmol, 72%).

Yellowish solid, mp 119–120 °C. ¹H-NMR (500 MHz, CDCl₃): δ 2.36 (s, 3H, Me), 4.46 (d, 2H, ³J = 5.7 Hz, CH₂), 6.40 (s, 1H, NH), 6.97 (t, 2H, ³J = 8.7 Hz, CH₄Ar), 7.11–7.17 (m, 2H, CH₄Ar), 7.23–7.28 (m, 4H, CH₄Ar).

¹³C(¹H)-NMR (126 MHz, CDCl₃): δ 19.7, 42.9, 115.4 (d, JCF = 22.0 Hz), 125.6, 126.6, 129.3 (d, JCF = 8.9 Hz), 129.9, 130.9, 134.1 (d, JCF = 2.3 Hz), 136.0 (d, JCF = 2.7 Hz), 126.1 (d, JCF = 243.3 Hz), 169.9.

HRMS (TOF MS ESI+): Calcd for C₁₃H₁₃NOCl (M + H) 246.0686. Found 246.0686.

N-(4-fluorobenzyl)-2-methylbenzamide 5aa. The title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1v (202 mg, 0.25 mmol, 0.25 equiv.), [Ru(p-cymene)Cl₂]Ar (158 mg, 0.60 mmol, 60%), CuBr₂ (174 mg, 0.72 mmol, 72%).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1v (202 mg, 0.25 mmol, 0.25 equiv.), [Ru(p-cymene)Cl₂]Ar (158 mg, 0.60 mmol, 60%), CuBr₂ (174 mg, 0.72 mmol, 72%).

Colorless solid, mp 119–120 °C. ¹H-NMR (500 MHz, CDCl₃): δ 0.85 (m, 6H, CH₃), 4.57 (d, 2H, ³J = 8.7 Hz, CH₂), 7.23–7.28 (m, 4H, CH₄Ar), 7.64 (d, 1H, ³J = 1.8 Hz, CH₄Ar), 7.77 (d, 1H, ³J = 1.8 Hz, CH₄Ar).

¹³C(¹H)-NMR (126 MHz, CDCl₃): δ 44.1, 125.1, 127.3, 127.6, 127.8, 128.7, 129.8, 131.5, 134.7, 136.1, 137.8, 166.1.

HRMS (TOF MS ESI+): Calcd for C₁₃H₁₃NOCl (M + H) 246.0686. Found 246.0686.

N,N-dibenzyl-4-fluorobenzamide 5ab. The title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1m (354 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl₂ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate trialkoxysilane 3i (372 mg, 1.4 mmol, 1.4 equiv.), the L1 (130 mg, 0.2 mmol, 0.2 equiv.), CuBr₂ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5ab (290 mg, 0.91 mmol, 91%). The gram scale synthesis was performed on 10 mmol of the
starting 2-bromo-2,2-difluoroacetamide 1m and the amide 5ab was prepared in 83% yield (2.65 g, 8.3 mmol).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1m (354 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl\(_2\) (95 mg, 1.0 mmol, 1.0 equiv.), appropriate trialkoxysilane 3f (361 mg, 1.4 mmol, 1.4 equiv.), the L1 (130 mg, 0.2 mmol, 0.2 equiv.), CuBr\(_2\) (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5ab (287 mg, 0.90 mmol, 90%). The gram scale synthesis was performed on 10 mmol of the starting 2-bromo-2,2-difluoroacetamide 1m and the amide 5ab was prepared in 78% yield (2.45 g, 7.8 mmol).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1m (354 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl\(_2\) (354 mg, 1.0 mmol, 1.0 equiv.), appropriate 2-(4-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (289 mg, 1.3 mmol, 1.3 equiv.), the L1 (130 mg, 0.2 mmol, 0.2 equiv.), CuBr\(_2\) (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5ab (284 mg, 0.89 mmol, 89%).

Flash column chromatography was performed using a mixture of hexane/ethyl acetate 3:1 as an eluent to provide the corresponding amide product.

White solid, mp 86–87 °C. \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \(\delta\) 4.20 (s, 2H, CH\(_2\)), 4.71 (s, 2H, CH\(_2\)), 7.07 (t, 2H, J = 7.6 Hz, CH\(_{Ar}\)), 7.15 (br. s, 2H, CH\(_{Ar}\)), 7.30–7.33 (m, 4H, CH\(_{Ar}\)), 7.36–7.39 (m, 4H, CH\(_{Ar}\)), 8.50–8.53 (m, 2H, CH\(_{Ar}\)).

\(^{13}\)C\(^{1}\)H-NMR (126 MHz, CDCl\(_3\)): \(\delta\) 47.2, 51.6, 115.6 (d, J\(_{CF}\) = 22.2 Hz), 126.8 (m), 127.7 (m), 128.4 (m), 128.7 (m), 128.9, 129.0, 132.0 (m), 136.5 (d, J\(_{CF}\) = 67.9 Hz), 163.3 (d, J\(_{CF}\) = 247.5 Hz), 171.3.

HRMS (TOF MS ES+): Calcld for C\(_{21}\)H\(_{19}\)NOF (M + H) 320.1455. Found 320.1451.

N,N-dibenzyl-4-(trifluoromethyl)thiobenzamide 5ac. The title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1m (354 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl\(_2\) (95 mg, 1.0 mmol, 1.0 equiv.), appropriate arylic boronic acid 2s (289 mg, 1.3 mmol, 1.3 equiv.), the L1 (130 mg, 0.2 mmol, 0.2 equiv.), CuBr\(_2\) (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5ac (337 mg, 0.84 mmol, 84%).

Flash column chromatography was performed using a mixture of hexane/ethyl acetate 3:1 as an eluent to provide the corresponding amide product.

Colorless solid, mp 68–70 °C. \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \(\delta\) 4.39 (s, 2H, CH\(_2\)), 4.74 (s, 2H, CH\(_2\)), 7.13 (d, 2H, J = 6.9 Hz, CH\(_{Ar}\)), 7.30–7.34 (m, 4H, CH\(_{Ar}\)), 7.37–7.40 (m, 4H, CH\(_{Ar}\)), 7.54 (d, 2H, J = 8.1 Hz, CH\(_{Ar}\)), 7.67 (d, 2H, J = 8.1 Hz, CH\(_{Ar}\)).

\(^{13}\)C\(^{1}\)H-NMR (126 MHz, CDCl\(_3\)): \(\delta\) 47.1, 51.5, 127.1 (q, J\(_{CF}\) = 258.2 Hz, SCF\(_3\)), 126.9, 127.7, 128.2, 128.4, 128.8, 129.0, 135.9, 136.2, 136.5, 138.6, 170.8.

HRMS (TOF MS ES+): Calcld for C\(_{22}\)H\(_{19}\)NO\(_2\)F\(_3\)S (M + H) 402.1141. Found 402.1139.

N,N-dibenzyl-2-(trifluoromethyl)benzamide 5ad. The title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1m (354 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl\(_2\) (95 mg, 1.0 mmol, 1.0 equiv.), appropriate arylic boronic acid 2o (287 mg, 1.3 mmol, 1.3 equiv.), the L1 (130 mg, 0.2 mmol, 0.2 equiv.), CuBr\(_2\) (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL).
The purification of the dry crude performed by column chromatography on silica gel provides the amide 5ac (247 mg, 0.67 mmol, 67%).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1m (354 mg, 1.0 mmol, 1.0 equiv.), KF (116 mg, 2.0 mmol, 2.0 equiv.), MgCl₂ (95 mg, 1.0 mmol, 1.0 equiv.), appropriate trialkoxysilane 3l (372 mg, 1.4 mmol, 1.4 equiv.), the L1 (130 mg, 0.2 mmol, 0.2 equiv.), CuBr₂ (22.3 mg, 0.1 mmol, 0.1 equiv.), and hexafluoropropanol (0.12 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5ab (229 mg, 0.62 mmol, 62%).

Flash column chromatography was performed using a mixture of hexane/ethyl acetate 4:1 as an eluent to provide the corresponding amide product.

Colorless solid, mp 135–136 °C. 1H-NMR (500 MHz, CDCl₃): δ 4.11 (t, 2H, J = 15.3 Hz, CH₂), 4.25 (d, 1H, J = 15.8 Hz, CH₂), 5.33 (d, 1H, J = 14.8 Hz, CH₂), 7.11 (m, 2H, J = 7.1 Hz, CH₆), 7.29–7.37 (m, 8H, CH₆), 7.47–7.51 (m, 2H, CH₆), 7.56 (t, 1H, J = 7.1 Hz, CH₆), 7.71 (d, 1H, J = 7.8 Hz, CH₆).

13C(1H)-NMR (126 MHz, CDCl₃): δ 46.4, 51.1, 123.7 (q, J CF = 274.8 Hz, CF₃), 126.6 (m), 127.3, 127.4, 127.7, 127.8, 128.5, 128.8, 129.1, 129.1, 132.1, 135.0, 135.5, 136.1, 169.2.

HRMS (TOF MS ES+): Calcd for C₁₉H₁₄O₂N₂F₄ (M + H) 370.1422. Found 370.1419.

N1,N1,N3,N3-tetrabenzylisophthalamide 5ae. The title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1m (885 mg, 2.5 mmol, 2.5 equiv.), KF (232 mg, 2.0 mmol, 2.0 equiv.), MgCl₂ (190 mg, 2.0 mmol, 2.0 equiv.), appropriate aryl boronic acid 2v (166 mg, 1.0 mmol, 1.0 equiv.), the L1 (260 mg, 0.4 mmol, 0.4 equiv.), CuBr₂ (44.6 mg, 0.2 mmol, 0.2 equiv.), and hexafluoropropanol (0.08 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5ae (445 mg, 0.85 mmol, 85%).

Alternatively, the title compound was prepared starting with an appropriate 2-bromo-2,2-difluoroacetamide 1m (885 mg, 2.5 mmol, 2.5 equiv.), KF (232 mg, 4.0 mmol, 4.0 equiv.), MgCl₂ (190 mg, 2.0 mmol, 2.0 equiv.), appropriate trialkoxysilane 3q (318 mg, 1.0 mmol, 1.0 equiv.), the L1 (260 mg, 0.4 mmol, 0.4 equiv.), CuBr₂ (44.6 mg, 0.2 mmol, 0.2 equiv.), and hexafluoropropanol (0.08 mmol/mL). The purification of the dry crude performed by column chromatography on silica gel provides the amide 5ae (419 mg, 0.80 mmol, 80%).

Flash column chromatography was performed using a mixture of hexane/ethyl acetate 1:2 as an eluent to provide the corresponding amide product.

White solid, mp 172–173 °C. 1H-NMR (500 MHz, CDCl₃): δ 4.39 (s, 4H, 2xCH₂), 4.71 (s, 4H, 2xCH₂), 7.12 (d, 4H, J = 6.8 Hz, CH₆), 7.28–7.37 (m, 16H, CH₆), 7.53 (s, 4H, CH₆).

13C(1H)-NMR (126 MHz, CDCl₃): δ 46.9, 51.4, 126.8, 126.9, 127.6, 127.7, 128.4, 128.7, 128.9, 136.0, 136.6, 137.4, 171.3.

HRMS (TOF MS ES+): Calcd for C₃₆H₃₃N₂O₂ (M + H) 525.2540. Found 525.2539.

4. Conclusions

Summing up, basing on the mechanism assumption, we described three new mechanism-guided copper-catalyzed protocols for the direct arylation of 2-bromo-2,2-difluoroacetamides using aryl boronic acids, aryl trialkoxysilanes, and aryl sulphonium salts as the aryl donors. The deployment of the scope of the reactions showcased the unique tolerance of the developed methodologies towards vast range of structural patterns and substituents on all coupling parts. These methods offer rapid entry to structurally diverse aromatic amides from simple and commercially availed precursors. Noteworthily, all methodologies were prone for scale-up to gram quantities.

Supplementary Materials: Scheme S1: List of 2-bromo-2,2-difluoroacetamides 1 used for preparation of amides 5; Scheme S2: List of aryl boronic acids 2 used for preparation of amides 5; Scheme S3: List of (aryl)trialkoxysilanes 3 used for preparation of amides 5; Scheme S4: List of (aryl)dimethylsulphonium salts 4 used for preparation of amides 5; Copies 1H and 13C-NMR spectra.
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