Chlorodifluoromethane as a C1 Synthon in the Assembly of N-Containing Compounds

HIGHLIGHTS

- Quadruple cleavage of ClCF2H to afford a C1 synthon
- The cleavage of two stable C(sp3)-F bonds in aliphatic gem-difluoroalkanes
- Enrich C1 chemistry, green chemistry, and fluorine chemistry
- Various N-containing compounds were afforded via different role of ClCF2H

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氯二氟甲烷作为C1合成物在N-含氮化合物的组装中的应用

Xingxing Ma, Jianke Su, Xingang Zhang, and Qiuling Song

摘要

C1合成物的开发，以实现额外碳原子的添加，成为化学研究的重要主题。在过去的几十年中，C1合成物的开发取得了显著的进展，特别是在二氧化碳、一氧化碳、草酸等C1单元的开发上。此外，通过化学反应将C1合成物引入天然产物或药物分子中，以实现附加值的提升。例如，二氧化碳和草酸是最著名的C1单元，已被广泛用于各种反应过程。然而，尽管C1化学已经取得了显著的进展，但寻找新的C1合成物仍是一个值得探索的主题。本文报道了对氯二氟甲烷的四重裂解，以生成一种C1合成物，该合成物具有独特的活性，补充了现有的C1合成物，并为C1化学增添了新的价值。

引言

C1化学已经发展成为一种精致的策略，用于准备各种含碳化合物。例如，通过一氧化碳在现代化学反应中的应用（Aaresta et al., 2014; Sakakura et al., 2007; Huang et al., 2011; Yan et al., 2012; Natte et al., 2017; Wakade et al., 2017; Senadi et al., 2019）。在这些C1合成物中，CO2、CO、HCOOH和草酸是其中最著名的，它们被广泛用于各种反应过程。此外，许多化学反应在有过渡金属参与的情况下被开发出来，从而吸引了更多的化学家投身于这一领域（Aaresta et al., 2014; Sakakura et al., 2007; Aaresta et al., 2014; Huang et al., 2011; Cokoja et al., 2011）。尽管C1化学的重要性和进展，直接将额外碳原子引入到廉价和可获得的材料中，以实现产品成本的降低、实用性和可变的经济价值仍是一个热门的研究主题。特别是在合成和制药界的背景下，这些C1合成物可能会对工业产生深远的影响。

氯二氟甲烷（CICF2H）作为C1合成物，因其无毒性和工业生产成本低而广受关注。近年来，通过CICF2H的裂解研究，已经开发出多种C1合成物，以实现额外碳原子的添加。例如，对氯二氟甲烷的裂解研究揭示了在温和条件下产生重要产品的途径（Oh and Hu, 2013），以及对药物或天然产物的用途（Liu et al., 2015; Ma et al., 2018a）。目前，已知的C1合成物中，CO2、CO、草酸和草酸，可以是最著名的C1合成物，它们被广泛用于各种反应过程。此外，许多化学反应在有过渡金属参与的情况下被开发出来，从而吸引了更多的化学家投身于这一领域（Aaresta et al., 2014; Sakakura et al., 2007; Aaresta et al., 2014; Huang et al., 2011; Cokoja et al., 2011; Oh and Hu, 2013; Sordakis et al., 2018; Gibson, 1969; Enthaler et al., 2010）。尽管C1化学的重要性和进展，直接将额外碳原子引入到廉价和可获得的材料中，以实现产品成本的降低、实用性和可变的经济价值仍是一个热门的研究主题。特别是在合成和制药界的背景下，这些C1合成物可能会对工业产生深远的影响。
C-Cl bond was broken through a difluoromethyl radical pathway (Figure 1Ab) (Xu et al., 2018). Trifluoromethyl anion (CF3/C0) is readily derived from the difluorocarbene species and external fluorine source via double cleavage of ClCF2H (Figure 1Ac) (Zheng et al., 2015). Intriguingly and surprisingly, quadruple cleavage of ClCF2H to provide versatile C1 synthons, by breaking one C-Cl bond, two stable C-F bonds, and one C-H bond orderly in a single-vessel reaction (Figure 1B), has never been reported to date, probably mainly because of the high BDE of C(sp3)-F bonds (the bond dissociation energy of a single C-F bond: 485 KJ/mol) (O’Hagan, 2008).

Herein, we report a quadruple cleavage of chlorodifluoromethane as a type of C1 source to access valuable formimidamide derivatives that are widely employed as ligands or forming metal complexes as quasi-N-heterocyclic carbenes (NHCs) (Figure 1 (i) and (ii)) (Schröder et al., 2009, 2010; Bitterlich et al., 2007; Boogaerts and Nolan, 2010; Ohishi et al., 2008; Hopkinson et al., 2014). Despite the importance of these compounds, their elegant syntheses are very rare. Therefore, expanding the toolbox of methods for their synthesis will enrich diversity of this kind of compounds. Amines are very common raw materials as well as crucial building blocks with rich chirality (France et al., 2014); we envision that formimidamides could be readily generated in a single-vessel synthesis from two amines with ClCF2H as C1 source due to the special reactivity of ClCF2H. These processes represent a significant reaction modality for ClCF2H, which might promote and enrich C1 chemistry, organic fluorine chemistry (Gouverneur and Seppelt, 2015).

Figure 1. Various Transformations of ClCF2H
(A) Known transformations of ClCF2H.
(a) Double cleavage of ClCF2H to lead to difluorocarbene species.
(b) Single cleavage of ClCF2H to lead to difluoromethyl radical.
(c) Double cleavage of ClCF2H with external F− to lead to trifluoromethyl anion.
(B) Our work.
(d) Quadruple cleavage of ClCF2H as a C1 source.
2015), as well as green chemistry (Horváth, 2007). Meanwhile, ClCF2H provides a unique and alternative approach for the current known C1 sources: the control and comparison experiments with CO, CO2, and formic acid as C1 synths were performed under our standard conditions as well as the reported procedures; notably, no desired formimidamides were ever formed or obtained under those reaction conditions. These results further underscore the uniqueness and peculiarity of ClCF2H as a C1 source (for further details, see also Schemes S1 and S2).

RESULTS AND DISCUSSION
Optimization of Reaction Conditions

Our design is based on our recent discovery in which ethyl bromodifluoroacetate (BrCF2COOEt) (Ma et al., 2018b; Deng et al., 2019) could act as a C1 source and formylating reagent with amines via quadruple cleavage under basic conditions (Ma et al., 2018a, 2018c, 2018d); we postulated that the quadruple cleavage of ClCF2H could also be occurred under the similar sets since it is known that difluorocarbene could be readily accessible from ClCF2H under basic conditions. Moreover, compared with BrCF2COOEt, ClCF2H is obviously much cheaper and more atomic economical. We commenced our hypothesis by using low-cost and widely available aniline (1a) and N-methyl aniline (2a) as model substrates. To our delight, the yield of 76% of the anticipated product 3a (Zhao et al., 2005) was obtained from the reaction of 1a with 2a under the ClCF2H atmosphere without water (entry 1). More delightfully, the yield was significantly increased to 83–92% with the increase of dosage of water (entries 2-3); notably, excess water caused deteriorated effect on the reaction, since some unknown by-products were observed when the amount of water was increased to 20–30 equivalents, and the yield of the desired product was dropped to 83% (entry 2 versus entry 3, and for further details, see also Table S2). Replacing KOH with either Cs2CO3 or K2CO3 as the base resulted in lower yields (entries 4-5). To our surprise, this transformation was completely suppressed in other solvents, such as in THF and dioxane (entries 8-9) (for further details, see also Table S3). In addition, the yield of the desired product was slightly higher at the ambient temperature than at 50°C. In terms of reaction time, the longer time (36 h) led to the best result (entry 11).

Substrate Scope for Intermolecular Transformation

With the optimal reaction conditions in hand (entry 2 in Table 1), we explored the generality and limitation of this transformation (Figure 2). First, a variety of para-substituted anilines with electron-donating groups (alkoxy, phenoxy, alkyl, and N, N-dimethyl) (1b-1j), as well as electron-withdrawing groups, such as halogen (1k-1m) and nitro group (1n), delivered the desired formimidamide derivatives (3a-3n) in good to excellent yields under the standard conditions. We next examined [1,1’-biphenyl]-4-amine (1o) under this reaction condition to provide the desired product 3o in 77% yield. Besides, a large-scale (10 mmol) reaction of the N-methyl aniline (2a) has been carried out to afford 3a in 62% yield (for further details, see also Scheme S3). Similar result could be obtained for meta-substituted (m-Br) aniline (1p). Using the disubstituted 3,4-dimethylaniline (1q) and trisubstituted 2,4,6-trimethylaniline (1r), the corresponding products (3q and 3r) could be obtained in good yields (83%–85%). 5,6,7,8-Tetrahydronaphthalen-1-amine (1s) and 9H-fluoren-2-amine (1t) were carried out under the standard conditions to provide the target molecules (3s and 3t) in 80% and 76% yields, respectively. The absolute molecular structure of product 3t was unambiguously confirmed by X-ray crystallography analysis (Figure 2, and for further details, see also Table S1 and Data S1) (CCDC: 1874971). The fused polycyclic amines 9,9-diphenyl-9H-fluoren-2-amine (1u) and naphthalen-1-amine (1v) were subjected under the optimized reaction conditions, rendering the expected products (3u-3v) in moderate yields (68%–77%). Heterocyclic compounds, such as benzo[d]thiazol-2-amine (1w), were also amenable to this transformation, and the corresponding product was obtained in 62% yield. We then further investigated the scope of the N-substituted aniline derivatives with aniline (1a) under the viable reaction conditions. Delightedly, the corresponding products (3x-3z, 3aa-3ac) were obtained in good to excellent yields with good functional group tolerance. In addition, given the prevailing existence of amines in pharmaceutical molecules and natural products (Ma et al., 2018a; Brunet and Neibecker, 2001), we selected Benzocaine (1ad, local anesthetic), Amoxapine (2ae, antidepressant), 2-(piperazin-1-yl)-4-(tri-fluoromethyl)pyrimidine (2af, medical/material intermediates), and multi-functional Vildagliptin (2ag, inhibit glucagon/chiral reagent/medicinal intermediate) and exposed them under the standard conditions; the corresponding products were obtained in 59%, 76%, 61%, and 71% yields, respectively. Gratifyingly, the chiral molecule (S)-N-benzyl-1-phenylethan-1-amine (2ah) experienced the optimal reaction conditions to deliver (S,E)-N-benzyl-N’-phenyl-N-(1-phenylethyl)formimidamide (3ah) in 60% yield, which might be a potential chiral ligand to realize enantioselective-control reactions.
In addition, we found that aliphatic secondary amine is compatible under the standard conditions as well; in terms of the substrate dicyclohexylamine (4), the corresponding product 5 was acquired in 76% yield (Equation 1 in Figure 3A). It is worth mentioning that our strategy is highly regio-selective, for example, when N<sup>1</sup>-isopropyl-N<sup>3</sup>-phenylbenzene-1,3-diamine (6) was investigated under viable reaction condition, only compound 7 was afforded with diphenylamine part intact (Equation 2). In addition, when the target 3a was hydrolyzing under 1 M HCl, the two original substrates (1a and 2a) as well as two formylated compounds 1a-1 and 2a-1 were obtained, respectively (Ma et al., 2018a) (for further details, see also Scheme S4), which infers that our strategy might be a potential method for drug delayed or sustainable release when two different pharmaceutical molecules are combined by one extra carbon with our strategy (Equation 3). We carried out, therefore, correlative experiment using Benzocaine (1ad) and Vildagliptin.

Table 1. Representative Results for Optimization of the Formation of (E)-N-methyl-N,N'-diphenylformimidamide (3a)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (3 Equiv)</th>
<th>H&lt;sub&gt;2&lt;/sub&gt;O (X Equiv)</th>
<th>Solvent (2 mL)</th>
<th>T (°C)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KOH</td>
<td>0</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>r.t.</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>KOH</td>
<td>5</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>r.t.</td>
<td>92 (88)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>KOH</td>
<td>30</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>r.t.</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>5</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>r.t.</td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>5</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>r.t.</td>
<td>79</td>
</tr>
<tr>
<td>6</td>
<td>Na&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>5</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>r.t.</td>
<td>N.D.</td>
</tr>
<tr>
<td>7</td>
<td>NaHCO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>5</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>r.t.</td>
<td>N.D.</td>
</tr>
<tr>
<td>8</td>
<td>KOH</td>
<td>5</td>
<td>THF</td>
<td>r.t.</td>
<td>N.D.</td>
</tr>
<tr>
<td>9</td>
<td>KOH</td>
<td>5</td>
<td>Dioxane</td>
<td>r.t.</td>
<td>N.D.</td>
</tr>
<tr>
<td>10</td>
<td>KOH</td>
<td>5</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>50</td>
<td>70</td>
</tr>
<tr>
<td>11&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>KOH</td>
<td>5</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>r.t.</td>
<td>62&lt;sup&gt;c&lt;/sup&gt; (79)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>12&lt;sup&gt;e&lt;/sup&gt;</td>
<td>KOH</td>
<td>5</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>r.t.</td>
<td>N.D.</td>
</tr>
</tbody>
</table>

Reaction condition: aniline (1a, 1.2 equiv. 0.12 mmol), N-methylaniline (2a, 0.1 mmol), the atmosphere of chlorodifluoromethane (CICF<sub>2</sub>H) (cat. 0.3 mmol), base (3 equiv.), solvent (2 mL), for 36 h.

<sup>a</sup>GC yields.

<sup>b</sup>Isolated yields.

<sup>c</sup>For 12 h.

<sup>d</sup>For 24 h.

<sup>e</sup>No CICF<sub>2</sub>H.
Figure 2. Synthesis of Formimidamide Derivatives

(A) Scope of the primary amines.

(B) Scope of the secondary amines.

(C) Scope of R groups.

(D) Scope of the pharmaceutical molecules.

Reaction Condition 1: the primary amine (1, 0.12 mmol), the secondary amine (2, 0.1 mmol), KOH (3 equiv), H₂O (5 equiv), CH₂CN (2 mL), rt for 36 h under CF₃H atmosphere; isolated yield. ⁵ ²a 10 mmol.
(2ag) as the substrates under standard reaction condition 1; to our delight, the corresponding product 3ai was obtained in 70% yield (Equation 4). More interestingly, a highly chemoselective process was disclosed with two primary amines, in which N,N'-diphenylformimidamide and N-(difluoromethyl)-N,N'-diphenylformimidamide were obtained, respectively, by careful control of reaction conditions. Bases and additives played key roles on these two successful transformations: with K₂CO₃ as base, phenol and water as
additives (see condition 2 in Figure 3 and for further details, see also Table S4), N,N'-diphenylformimidamides (8 and 9) were obtained in moderate yields; with Cs2CO3 as the base and S8 as additive (see condition 3 in Figure 3, and for further details, see also Table S5) (Zheng et al., 2017), N-(difluoromethyl)-N,N'-diphenylformimidamides (10–15) were acquired in good yields. In the latter transformation, CICF₂H played a dual role as both C1 source and difluorocarbene source (Figure 3C).

**Substrate Scope for Intramolecular Transformation**

The success of the above-mentioned intermolecular transformation prompted us to exploit the intramolecular transformations, since the latter one always leads to cyclic compounds that are the essential skeletons in pharmaceutical and natural products (Sasaki et al., 2006; Kubo et al., 1993). Gratifyingly, when N'-methylbenzene-1,2-diamine (16) was subjected to the standard conditions for intermolecular transformation, benzimidazole 17 was obtained in 90% yield, which could be readily converted into 2-bromo-benzimidazole 18 in the presence of NBS. Then, after a series of transformation, Telmisartan, a potent angiotensin II receptor antagonist used in the treatment of essential hypertension, will be afforded (Figure 4A) (Martin et al., 2015). In addition, the transformation could be easily scaled up to 70 times from 16 to 17 without loss of the efficiency (for details, see also Scheme S6). Encouraged by this promising result, we next focused on the exploration of the formation of benzo[d]oxazoles and 1H-benzo[d]imidazoles compounds via intramolecular pattern, since it is well known that benzo[d]oxazoles and 1H-benzo[d]imidazoles are prevalent molecular scaffolds in various bioactive natural products, agrochemicals, and pharmaceuticals. After many attempts, an optimized condition was obtained (for further details, see also Tables S6 and S7). These transformations demonstrated a good functional group tolerance (Figure 4B). Different substituent groups on the benzene ring, including alkyl (19a, 19b), halo groups (19c, 19d), were all compatible, rendering the corresponding products (20a–20d) in moderate to good yield (68%–81%). Surprisingly, no desired products were detected when 2-amino-4-nitrophenol (19e) and 2-amino-5-nitrophenol (19f) underwent the same conditions, instead, the selective difluoromethylation of hydroxyl group occurred (20e' and 20f'). Good yields were achieved on various benzene-1,2-diamine compounds under the standard Reaction Condition 5 with K2CO3 as base in CH3CN (2 mL) and H2O (0.5 mL) at 100 °C for 16 h (Figure 4C). Remarkably, the products of difluoromethylation of benzimidazoles (21–29) were acquired in moderate yields via the slight adjustment of reaction condition (see reaction condition 6 for details); once again, CICF₂H played a dual role as both C1 source and difluorocarbene source in this transformation (Figure 4D).

**Mechanism Investigation**

To gain more insights into the mechanism of the aforementioned transformations, some control experiments were performed. Initially, isotope labeling experiments were conducted, 84% (3a) and 78% (20g') of D atoms were incorporated into the final products correspondingly for intermolecular and intramolecular versions, and N-H of benzimidazole was replaced by N-D completely (Figures 5A and 5B). These results suggested that the hydrogen atom attached on the extra introduced carbon (from ClCF₂H) was originated from H₂O in this process (for further details, see also Scheme S8). The trace amount of the desired product 3a was observed when benzimidazole was added into the reaction system as a difluorocarbene scavenger; instead, 1-(difluoromethyl)-1H-benzo[d]imidazole was detected by GC-MS (Figure 5C). When N-methyl-N-phenylformamide (30) or isocyanobenzene (31) was subjected to the earlier standard reaction conditions with amines, the corresponding target products 3a and 8 were not obtained (Figure 5D), indicating that the compounds 30 and 31 are not intermediates for this transformation, which is in sharp contrast to our previous results in which isocyanides are the key intermediates for those transformations with BrCF₂COOEt (Ma et al., 2018c, 2018d). To thoroughly understand the reaction sequence, two more control experiments were carried out, in which the primary amine and the secondary amine were added to the reaction mixture stepwise instead of one-pot to check which one is the first amine species interacting with CICF₂H. It turned out that primary amine might react with CICF₂H before the secondary one since 47% of the desired product was obtained in the primary-secondary amine sequence, whereas no desired product was detected with the secondary-primary amine sequence (Figures 5E and 5F). Finally, we carried out comparison experiments for CO₂, CO and HCOOH as C1 source with amines, the corresponding target products 21–29 were not obtained (Figure 5G), which further highlighted the uniqueness of CICF₂H as the C1 source in these transformations.

**Proposed Mechanism**

To thoroughly figure out the possible reactive intermediate, we carried out in situ ¹H NMR studies between 4-ethoxyaniline (1c) and CICF₂H (Figure 6A). Since isocyanides have been ruled out to be the possible
Figure 4. The Synthetic Route of the Telmisartan and the Intramolecular Reaction Scope

(A) Telmisartan synthesis with our strategy.
(B) Scope of benzoxazoles.
(C) Scope of benzimidazoles.
(D) Scope of N-difluoromethyl benzimidazoles.

* The scale of the original material 16 is 0.1 mmol; * The scale of the original material 16 is 7 mmol. (a) 1-Methylbenzimidazole (17) (5 mmol) and N-bromosuccinimide (3 equiv) in 25 mL of THF were heated under reflux for 1 h. **Condition 4:** The amine (0.2 mmol), K$_2$CO$_3$ (3 equiv), H$_2$O (5 equiv.), CH$_3$CN (2 mL), 50 °C for 12 h under the atmosphere of CICF$_3$H, isolated yield; **Condition 5:** The amine (0.2 mmol), K$_2$CO$_3$ (3 equiv), H$_2$O (0.5 mL), CH$_3$CN (2 mL), 100 °C for 16 h under the atmosphere of CICF$_3$H, isolated yield. **Condition 6:** The amine (0.1 mmol), K$_2$CO$_3$ (0.7 equiv), H$_2$O (30 μL), CH$_3$CN (2 mL), 110 °C for 48 h under the atmosphere of CICF$_3$H.
intermediates for this transformation, we envision that a type of intermediate $3c'$ might be formed in this transformation. To our delight, in situ $^1$H NMR studies indeed indicated the formation of (E)-N-(4-ethoxyphenyl)formimidoyl fluoride ($3c'$), which was increased continually at the first 6 h, whereafter it started to decline probably owing to its volatile property and the existence of various nucleophiles in the reaction system, such as H$_2$O and amines. The intermediate $3c'$ was totally consumed after 18 h or during the process of striping the solvent (for further details, see also Schemes S9–S11). To validate its presence, various nucleophiles (phenols, alcohols, amines, and carboxylic acids) were added into the system after 2 h, and the corresponding desired products were detected in GC-MS (Equation 1 in Figure 6B, and for further details, Scheme S12). In addition, one more control experiment was carried out with a ClCF$_2$H balloon for 5 h;
Figure 6. In situ $^1$H NMR, the Capture of Reaction Intermediates and the Proposed Mechanism

(A) In situ $^1$H NMR studies.

(B) The capture of reaction intermediates.

(C) The plausible reaction mechanism.
the product 32, isocyanide 33, and N-(4-ethoxyphenyl)formamide (34) were obtained in 15%, 27%, and 38% yields, respectively (Equation 2 in Figure 6B), suggesting that the intermediate is a chemically active compound, which will further decompose into isocyanide by one more C-F bond cleavage easily. We have carried out the control experiments in the presence of radical scavengers; the reactions proceeded smoothly at room temperature to afford desired products in moderate yields. Those results suggest that the single electron transfer (SET) pathway could not be involved in this transformation (for further details, see also Scheme S13). On the basis of the above-mentioned results, a proposed mechanism for the reaction of CICF₂H as a C₁ source is depicted in Figure 6C. The base coordinates with CICF₂H to generate difluorocarbene first. Then the primary amine traps the in situ generated difluorocarbene affording intermediate I, which is very sensitive under basic conditions to lead to monofluorouimine species via the cleavage of one C-F bond; subsequent inter- or intramolecular nucleophilic attack on the imine species (II and III) eventually delivers products 3, 5, 7, and 20 by SN₂Ar substitution (path a) or nucleophilic addition (path b) (Ma et al., 2018a). As either R² or R³ is H, the product could embark on capturing one more in situ generated difluorocarbene unceasingly to render the products (10–15). The products 21–29 were obtained in one-pot synthesis when compound 20 (X = NH) meets with excess CICF₂H in basic conditions as a difluorocarbene scavenger.

Conclusion
In summary, we have disclosed a C₁ source generated from chlorodifluoromethane (CICF₂H). This method allows the synthesis of a broad range of the formimidamides and benzo[d]oxazoles, benzo[d]imidazole derivatives via intermolecular and intramolecular reactions with good efficiency as well as high regio- and chemoselectivity under mild reaction condition. To our knowledge, this is the first example that CICF₂H proceeds quadruple cleavage to act as a C₁ synthon and the valuable products were fabricated from readily available starting materials under transition-metal-free conditions. This process might enrich C₁ chemistry, green chemistry, and fluorine chemistry as well as might partially solve the problem of the disposition of ODS. Preliminary mechanistic studies revealed that (E)-N-phenylformimidoyl fluoride intermediate is involved in this process, which is a distinct intermediate from BrCF₂COOEt case. Further studies toward the detailed mechanism and transformations and applications as well as exploration on more intriguing methodologies with this unusual C₁ source are under way in our laboratory.

Limitation of the Study
Primary aliphatic amines showed poor or no reactivity toward this reaction system. In addition, reactive intermediate (e.g., 3c’) was not isolated owing to its high reactivity.

METHODS
All methods can be found in the accompanying Transparent Methods supplemental file.

DATA AND CODE AVAILABILITY
The structures of 3t reported in this article have been deposited in the Cambridge Crystallographic Data Centre under accession numbers CCDC: 1874971.

SUPPLEMENTAL INFORMATION
Supplemental Information can be found online at https://doi.org/10.1016/j.isci.2019.07.005.

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AUTHOR CONTRIBUTIONS
X.M. and J.S. performed the experiments and developed the reactions. X.Z. checked the manuscript and came up with suggestions for this transformation. Q.S. designed and directed the project and wrote the manuscript with the feedback of X.M.
REFERENCES


Supplemental Information

Chlorodifluoromethane as a C1 Synthon in the Assembly of N-Containing Compounds

Xingxing Ma, Jianke Su, Xingang Zhang, and Qiuling Song
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Transparent Methods

General Methods for Experiments

All chemicals were purchased from Adamas Reagent, Energy chemical company, Bide Pharmatech Ltd and Shang Fluoro company (ClCF₂H). Unless otherwise stated, all experiments were conducted in a sealed tube under ClCF₂H atmosphere. Reactions were monitored by TLC or GC-MS analysis. Flash column chromatography was performed over silica gel (200-300 mesh).

¹H-NMR and ¹³C-NMR spectra were recorded in CDCl₃ and DMSO-d₆ on a Bruker Avance III 500 MHz NMR spectrometer (500 MHz ¹H, 125 MHz ¹³C (CPD), 470 MHz ⁹F (CPD)) at room temperature. Chemical shifts were reported in ppm on the scale relative to CDCl₃ (δ = 7.26 for ¹H-NMR, δ = 77.00 for ¹³C-NMR) as an internal reference. Coupling constants (J) were reported in Hertz (Hz).

General Procedure for the Transformations of CO₂, CO and HCOOH as C₁ sources.

![Chemical structures and reaction conditions]

**Reaction Condition 1:** the amine (1a, 0.12 mmol), N-methyl amine (2a, 0.1 mmol), KOH (3 equiv), H₂O (5 equiv), CH₃CN (2 mL), (HCOOH 3 equiv) rt for 36 h under CO₂/CO atmosphere.

**Reaction condition 2:** the amine (1a, 0.12 mmol), N-methyl amine (2a, 0.1 mmol), K₂CO₃ (3 equiv), phenol (10 mol%), H₂O (5 equiv), CH₃CN (2 mL), (HCOOH 3 equiv) 80 °C for 12 h under CO₂/CO atmosphere.

**Reaction condition 3:** the amine (1a, 0.12 mmol), N-methyl amine (2a, 0.1 mmol), Cs₂CO₃ (3 equiv), S₈ (5 mol%), CH₃CN (5 mL), (HCOOH 3 equiv) 80 °C for 26 h under CO₂/CO atmosphere.

**Reaction Condition 4:** the amine (1a, 0.12 mmol), N-methyl amine (2a, 0.1 mmol), K₂CO₃ (3 equiv), H₂O (5 equiv.), CH₃CN (2 mL), (HCOOH 3 equiv) 50 °C for 12 h under CO₂/CO atmosphere.

**Reaction Condition 5:** the amine (1a, 0.12 mmol), N-methyl amine (2a, 0.1 mmol), K₂CO₃ (3 equiv), H₂O (0.5
mL), CH₃CN (2 mL), (HCOOH 3 equiv) 100 °C for 16 h under the atmosphere of ClCF₂H, isolated yield.

**Reaction Condition 6:** the amine (1a, 0.12 mmol), N-methyl amine (2a, 0.1 mmol), K₂CO₃ (5 equiv), H₂O (30 mL), CH₃CN (2 mL), (HCOOH 3 equiv) 110 °C for 48 h under CO₂/CO atmosphere.

**Scheme S1.** The transformations of CO₂, CO and HCOOH as C₁ sources, related to Figure 1

No desired product 3a was obtained when we carried out many experiments by using CO₂, CO and HCOOH as C₁ sythons under reaction conditions 1/2/3/4/5/6.

**Scheme S2.** the transformation for CO₂ and CO as C₁ sources under transition metals, related to Figure 1

In addition, various transformations for using CO₂ and CO as C₁ sources in presence of transition metals (TM = Pd, Rh, Ni, Zn, Al) were also carried out according to the reported literature procedures (Tlili et al., 2015; Huang et al., 2011), unfortunately, no desired product 3a was detected.

**General Procedure for Large-scale Reaction of the N-methyl Aniline (2a).**

**Scheme S3.** Large-scale reaction of the N-methyl aniline (2a), related to Figure 2

**Large-scale reaction of the N-methyl aniline**

In a dried Schlenk round flask (1500 mL) were placed amine 1a (12 mmol, 1.2 equiv, 1.1 g), N-methyl amine 2a (10 mmol, 1 equiv, 1.07 g) and KOH (30 mmol, 3 equiv, 1.7 g). Then the flask was filled with ClCF₂H. Whereafter the solvent was added into Schlenk tube by injector. The resulting mixture was stirred at room temperature for 4 days. Upon completion of the reaction, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatograph (silica gel, Petroleum ether : Ethyl acetate = 50:1, v/v) to give the desired product 3a (62%, 1.31 g).
General Procedure for the Experiment for the Decomposition of Target Product.

Scheme S4. The experiment for the decomposition of target product, related to Figure 3B

The Decomposition of Target Product 3a
To a mixture of (E)-N-methyl-N,N'-diphenyl-formimidamide 3a (0.2 mmol) in MeOH (2 mL), 1 M HCl was added to the seal tube. The resulting mixture was stirred at 80 °C for 3 h. Upon completion of the reaction, the compounds 1a, 2a, 1a-1 and 2a-1 were detected via TLC and GC-MS.

General Procedure for the synthesis of 3, 8-9 and 10-15.

Scheme S5. General process for the synthesis of 3, 8-9 and 10-15, related to Figure 2, Figure 3C and Figure 3D.

Preparations of target product 3
In a dried Schlenk tube were placed the primary amines 1 (0.12 mmol, 1.2 equiv), the secondary aniline 2 (0.1 mmol), KOH (0.3 mmol, 3 equiv) and H2O (0.5 mmol, 5 equiv). Then the tube was vacuumized for removing the air. Subsequently, chlorodifluoromethane and CH3CN (2 mL) were added into the mixtures via an injector. The resulting mixture was stirred at room temperature for 36 h. Upon completion of the reaction, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, Petroleum ether : Ethyl acetate = 80:1, v/v) to give the desired product (3).

Preparations of target product 8 and 9
In a dried Schlenk tube were placed the anilines 1 (0.2 mmol, 1.2 equiv), K2CO3 (0.6 mmol, 3 equiv), phenol (0.02 mmol, 10 mol%) and H2O (1 mmol, 5 equiv), Then the tube was vacuumized for removing the air. Subsequently, chlorodifluoromethane and CH3CN (2 mL) were added into the mixtures via an injector. The resulting mixtures
was stirred at 80 °C for 12 h. Upon completion of the reaction, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, Petroleum ether: Ethyl acetate = 50:1, v/v) to give the desired product (8-9).

**Preparations of target product 10-15**

In a dried Schlenk tube were placed the aniline 1 (0.2 mmol), Cs₂CO₃ (0.6 mmol, 3 equiv), S₈ (0.02 mmol, 10 mol%) and H₂O (1 mmol, 5 equiv), Then the tube was vacuumized for removing the air. Subsequently, chlorodifluoromethane and CH₃CN (5 mL) is added into the mixtures via an injector. The resulting mixture was stirred at 80 °C for 26 h. Upon completion of the reaction, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, Petroleum ether: Ethyl acetate = 100:1, v/v) to give the desired product (10-15).

**General Procedure for the Large-scale Synthesis of 18**

![Scheme S6. General process for the large-scale synthesis of 18, related to Figure 4A.](image)

**Preparations of target product 17**

In a dried Schlenk tube were placed N⁴-methylbenzene-1,2-diamine 16 (7 mmol), KOH (21 mmol, 3 equiv) and H₂O (35 mmol, 5 equiv), Then the tube was vacuumized for removing the air. Subsequently, chlorodifluoromethane and solvent is added into the mixtures via an injector. The resulting mixture was stirred at room temperature for 48 h. Upon completion of the reaction, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, Petroleum ether: Ethyl acetate = 10:1, v/v) to give the desired product 17 in 78% yield.

**Preparations of target product 18**

Methylbenzimidazole (17) (5 mmol) and N-bromosuccinimide (15 mmol) in 30 mL of THF were heated under reflux for 1 h. The solvent was removed by a rotary evaporator, and the residue was recrystallized from EtOAc to afford 18 in 90% yield as a white solid.
General process for the synthesis of 20 and 21-29.

Scheme S7. General process for the synthesis of 20 and 21-29, related to Figure 4B-4D.

Preparations of target products 20a-20d, 20e′ and 20f′
In a dried Schlenk tube were placed 2-aminophenol compounds (19a-19f) (0.2 mmol), K₂CO₃ (0.6 mmol, 3 equiv) and H₂O (1 mmol, 5 equiv). Then the tube was vacuumized for removing the air. Subsequently, chlorodifluoromethane and CH₃CN (2 mL) is added into the mixtures via an injector. The resulting mixture was stirred at 50 °C for 12 h. Upon completion of the reaction, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, Petroleum ether : Ethyl acetate = 100:1, v/v) to give the desired product.

Preparations of target products 20g-20o
In a dried Schlenk tube were placed benzene-1,2-diamine compounds (0.2 mmol), K₂CO₃ (0.6 mmol, 3 equiv) and H₂O (0.5 mL). Then the tube was vacuumized for removing the air. Subsequently, chlorodifluoromethane and CH₃CN (2 mL) is added into the mixtures via an injector. The resulting mixture was stirred at 100 °C for 16 h. Upon completion of the reaction, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, Petroleum ether : Ethyl acetate = 10:1, v/v) to give the desired product.

Preparations of target products 21-29
In a dried Schlenk tube were placed benzene-1,2-diamine compounds (0.1 mmol), K₂CO₃ (0.5 mmol, 5 equiv) and H₂O (0.5 mL). Then the tube was vacuumized for removing the air. Subsequently, chlorodifluoromethane and CH₃CN (2 mL) is added into the mixtures via an injector. The resulting mixture was stirred at 100 °C for 48 h. Upon completion of the reaction, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, Petroleum ether : Ethyl acetate = 50:1, v/v) to give the desired product 21-29.
The experiment for H-scrambling of the target product 3a

\[
\begin{align*}
3a, & \ 2 \text{ mmol} \\
\rightarrow \ & \begin{array}{c}
\text{KOH (3 equiv)} \\
\text{D}_2\text{O (5 equiv)} \\
\text{CH}_3\text{CN (2 mL)} \\
\text{RT, 24 h}
\end{array} \\
\rightarrow \ & \begin{array}{c}
\text{H/D} > 99\%
\end{array}
\end{align*}
\]

Scheme S8. The experiment for H-scrambling of the target product 3a, related to Figure 5a-5b

We carried out a H-scrambling experiment by exposing the product 3a to the standard condition in the presence of D$_2$O. No corresponding deuterium-labeling product 3a-D was detected (Scheme S8).

**In-situ $^1$H NMR of 3c’**

\[
\begin{align*}
\text{EtO-} & \begin{array}{c}
\text{NH}_2
\end{array} \\
\rightarrow \ & \begin{array}{c}
\text{KOH (3 equiv)} \\
\text{CD}_3\text{CN (2 mL)}
\end{array} \\
\rightarrow \ & \begin{array}{c}
\text{3c’}
\end{array}
\end{align*}
\]

Scheme S9. In-situ $^1$H NMR of 3c’, related to Figure 6A.

**General Procedure for In-situ $^1$H NMR of 3c’**

There still is plentiful ClCF$_2$H dissolved in solvent (CD$_3$CN) in the first couple of hours, which caused a problem to detect compound 3c’ by NMR analysis (Scheme S9-S11). In order to see $^1$H peak of compound 3c’ more clearly, we carried out an experiment for about 1 hour and stripped the excess ClCF$_2$H at low temperature, the
resulting mixture was analyzed by in situ NMR. The below figure has shown the change of possible reactive intermediate at different time.

Scheme S10. In-situ $^1$H NMR of 3c’, related to Figure 6A.

Scheme S11. the change of possible reactive intermediate at different time, related to Figure 6A.
The experiments for capturing of reaction intermediate 3c’

![Scheme S12](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophiles</th>
<th>Desired product</th>
<th>MW (GC-MS)</th>
<th>HRMS (+H)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtO-(\text{phenol})</td>
<td>EtO-(\text{3c’})</td>
<td>241</td>
<td>242.1180(^a) (242.1181)(^b)</td>
</tr>
<tr>
<td>2</td>
<td>EtO-(\text{1,1,2,3,3,3-hexafluoropropan-1-ol})</td>
<td>EtO-(\text{3c’})</td>
<td>329</td>
<td>330.0929(^a) (330.0929)(^b)</td>
</tr>
<tr>
<td>3</td>
<td>EtO-(\text{benzoic acid})</td>
<td>EtO-(\text{3c’})</td>
<td>269</td>
<td>270.1123(^a) (270.1130)(^b)</td>
</tr>
<tr>
<td>4</td>
<td>EtO-(\text{hexanoic acid})</td>
<td>EtO-(\text{3c’})</td>
<td>263</td>
<td>264.1592(^a) (264.1600)(^b)</td>
</tr>
<tr>
<td>5</td>
<td>EtO-(\text{diphenylmethanol})</td>
<td>EtO-(\text{3c’})</td>
<td>331</td>
<td>332.1654(^a) (332.1651)(^b)</td>
</tr>
</tbody>
</table>

\(^a\) HRMS (ESI, m/z) found; \(^b\) HRMS (ESI, m/z) calc'd

**Scheme S12. Various nucleophiles for capturing 3c’, related to Figure 6B.**

**General Procedure for various nucleophiles for capturing 3c’**

In order to validate the presence of the compound 3c’, various nucleophiles, such as phenols, 1,1,2,3,3,3-hexafluoropropan-1-ol, benzoic acid, hexanoic acid and diphenylmethanol were added into the system after 2 h (entries 1-5), the corresponding desired products were detected by GC-MS (MW: 241, 329, 269, 263 and 331). In addition, we conducted the tests of HRMS (ESI, m/z). Delightedly, we detected corresponding m/z of various anticipated products (Scheme S12).
The experiments for capturing of radical

We have carried out the control experiments in presence of radical scavengers (TEMPO, BHT, ethene-1,1-diyldibenzene and (1-cyclopropylvinyl)benzene), the reactions proceeded smoothly at room temperature to afford desired products in moderate yields. Those results suggest the SET pathway could not be involved in this transformation.

Characterization data for products

\((E)-N\text{-}methyl-N,N'\text{-}diphenylformimidamide\) (3a) (CAS number: 32189-59-6)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (19 mg, 88%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta \) 8.11 (s, 1H), 7.41 – 7.35 (m, 2H), 7.34 – 7.29 (m, 2H), 7.20 – 7.12 (m, 3H), 7.11 – 7.00 (m, 3H), 3.52 (s, 3H).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta \) 151.5, 151.2, 145.1, 129.5, 129.1, 124.1, 123.4, 121.3, 119.9, 34.1.

\((E)-N'\text{-}(4\text{-}methoxyphenyl)-N\text{-}methyl-N\text{-}phenylformimidamide\) (3b)

The reaction was performed following the general
procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (20 mg, 82%).\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.09 (s, 1H), 7.37 (dd, \(J = 8.6, 7.4\) Hz, 2H), 7.18 – 7.11 (m, 3H), 7.01 – 6.96 (m, 2H), 6.86 (d, \(J = 8.9\) Hz, 2H), 3.80 (s, 3H), 3.50 (s, 3H). \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 156.1, 150.7, 145.2, 144.8, 129.5, 123.9, 121.9, 119.7, 114.4, 55.5, 34.0.

HRMS (ESI, m/z) calcd for C\(_{15}\)H\(_{16}\)N\(_2\)O[M+H]: 241.1335; found: 241.1337

\((E)-N'^{-}(4\text{-ethoxyphenyl})-N\text{-methyl-}N\text{-phenylformimidamide (3c)}\)

![Diagram of (E)-N'- (4-ethoxyphenyl)-N-methyl-N-phenylformimidamide (3c)]

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (24 mg, 81%).\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.11 (s, 1H), 7.41 – 7.35 (m, 2H), 7.34 – 7.28 (m, 2H), 7.19 – 7.13 (m, 3H), 7.09 – 6.96 (m, 7H), 3.52 (s, 3H). \(^1^3\)C NMR (125MHz, CDCl\(_3\)) \(\delta\) 158.22 (s), 1529, 151.0, 147.4, 145.1, 129.6, 124.2, 122.6, 122.2, 120.3, 119.9, 118.0, 34.1.

HRMS (ESI, m/z) calcd for C\(_{20}\)H\(_{19}\)N\(_2\)O[M+H]: 303.1492; found: 303.1491

\((E)-N\text{-methyl-}N'^{-}(4\text{-phenoxyphenyl})-N\text{-phenylformimidamide (3d)}\)

![Diagram of (E)-N-methyl-N'- (4-phenoxyphenyl)-N-phenylformimidamide (3d)]

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (24 mg, 81%).\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.14 (s, 1H), 7.41 – 7.35 (m, 2H), 7.34 – 7.28 (m, 2H), 7.19 – 7.13 (m, 3H), 7.09 – 6.96 (m, 7H), 3.52 (s, 3H). \(^1^3\)C NMR (125MHz, CDCl\(_3\)) \(\delta\) 158.22 (s), 1529, 151.0, 147.4, 145.1, 129.6, 124.2, 122.6, 122.2, 120.3, 119.9, 118.0, 34.1.

HRMS (ESI, m/z) calcd for C\(_{20}\)H\(_{19}\)N\(_2\)O[M+H]: 303.1492; found: 303.1491

\((E)-N\text{-methyl-}N'^{-}(4\text{-methylthio)phenyl})-N\text{-phenylformimidamide (3e)}\)

![Diagram of (E)-N-methyl-N'- (4-methylthio)phenyl)-N-phenylformimidamide (3e)]

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (21 mg, 83%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.08 (s, 1H), 7.38 (dd, \(J = 8.6, 7.4\) Hz, 2H), 7.26 – 7.22 (m, 2H), 7.19 – 7.12 (m, 3H), 7.03 – 6.95 (m, 2H), 3.51 (s, 3H), 2.47 (s, 3H). \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 151.0, 149.3, 145.0, 132.1, 129.5, 128.8, 124.3, 121.8, 120.0, 34.2, 17.2.
HRMS (ESI, m/z) cale for C_{15}H_{17}N_{2}[M+H]^+: 257.1107; found: 257.1109.

**(E)-N-methyl-N-phenyl-N’-(p-tolyl)formimidamide (3f)**

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (19 mg, 86%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.10 (s, 1H), 7.42 – 7.33 (m, 2H), 7.20 – 7.06 (m, 5H), 7.00 – 6.90 (m, 2H), 3.51 (s, 3H), 2.33 (s, 3H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 150.9, 149.0, 145.2, 132.8, 129.7, 129.5, 124.0, 121.0, 119.8, 34.1, 20.9.

HRMS (ESI, m/z) cale for C_{15}H_{17}N_{2}[M+H]^+: 225.1386; found: 225.1388.

**(E)-N’-(4-ethylphenyl)-N-methyl-N-phenylformimidamide (3g)**

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (20 mg, 83%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.11 (s, 1H), 7.41 – 7.30 (m, 2H), 7.20 – 7.08 (m, 5H), 7.03 – 6.92 (m, 2H), 3.51 (s, 3H), 2.63 (q, \(J\) = 7.6 Hz, 2H), 1.24 (t, \(J\) = 7.6 Hz, 3H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 150.9, 149.1, 145.2, 139.3, 129.5, 128.5, 124.0, 121.1, 119.8, 34.1, 28.3, 15.8.

HRMS (ESI, m/z) cale for C_{16}H_{19}N_{2}[M+H]^+: 239.1543; found: 239.1543.

**(E)-N’-(4-(tert-butyl)phenyl)-N-methyl-N-phenylformimidamide (3h)**

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (21 mg, 79%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.12 (s, 1H), 7.41 – 7.29 (m, 4H), 7.20 – 7.09 (m, 3H), 7.03 – 6.91 (m, 2H), 3.51 (s, 3H), 1.33 (s, 9H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 150.9, 148.8, 146.2, 145.2, 129.5, 126.0, 123.9, 120.7, 119.7, 34.3 34.0, 31.5.

HRMS (ESI, m/z) cale for C_{18}H_{23}N_{2}[M+H]^+: 267.1856; found: 267.1853.

**(E)-N’-(4-isopropylphenyl)-N-methyl-N-phenylformimidamide (3i)**

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (22 mg, 86%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.11 (s, 1H), 7.41 – 7.32 (m, 2H), 7.19 – 7.10 (m, 5H), 7.01 – 6.93 (m, 2H), 3.51 (s, 3H), 2.89 (dt, \(J\))
= 13.8, 6.9 Hz, 1H), 1.25 (d, J = 6.9 Hz, 6H). \( ^{13}C \) NMR (125 MHz, CDCl\(_3\)) \( \delta \) 150.9, 149.2, 145.2, 143.9, 129.4, 127.0, 123.9, 121.0, 119.7, 34.0, 33.5, 24.2. HRMS (ESI, m/z) calcd for C\(_{17}H_{21}N_2\)[M+H\(^+\)]: 253.1699; found: 253.1701.

(E)-N’-(4-(dimethylamino)phenyl)-N-methyl-N-phenylformimidamide (3j)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (19 mg, 77%). \(^1H\) NMR (500 MHz, CDCl\(_3\)) \( \delta \) 8.12 (s, 1H), 7.39 – 7.31 (m, 2H), 7.18 – 7.07 (m, 3H), 7.02 – 6.94 (m, 2H), 6.79 – 6.64 (m, 2H), 3.50 (s, 3H), 2.92 (s, 6H). \(^{13}C\) NMR (125 MHz, CDCl\(_3\)) \( \delta \) 150.9, 148.8, 146.2, 145.2, 129.5, 126.0, 123.9, 120.7, 119.7, 34.3, 34.0, 31.5. HRMS (ESI, m/z) calcd for C\(_{19}H_{20}N_3\)[M+H\(^+\)]: 254.1652; found: 254.1655.

(E)-N’-(4-fluorophenyl)-N-methyl-N-phenylformimidamide (3k)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (17 mg, 75%). \(^1H\) NMR (500 MHz, CDCl\(_3\)) \( \delta \) 8.05 (s, 1H), 7.46 – 7.31 (m, 2H), 7.15 (dd, \( J = 10.9, 4.2 \) Hz, 3H), 7.06 – 6.87 (m, 4H), 3.50 (s, 3H). \(^{13}C\) NMR (125 MHz, CDCl\(_3\)) \( \delta \) 160.6, 158.6, 151.2, 147.6, 145.1, 129.5, 124.2, 122.2, 120.0, 115.7, 115.5, 34.2. HRMS (ESI, m/z) calcd for C\(_{14}H_{13}F_3N_2\)[M+H\(^+\)]: 229.1136; found: 229.1137.

(E)-N’-(4-chlorophenyl)-N-methyl-N-phenylformimidamide (3l)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (19 mg, 77%). \(^1H\) NMR (500 MHz, CDCl\(_3\)) \( \delta \) 8.05 (s, 1H), 7.44 – 7.34 (m, 2H), 7.29 – 7.22 (m, 2H), 7.20 – 7.10 (m, 3H), 7.04 – 6.91 (m, 2H), 3.50 (s, 3H). \(^{13}C\) NMR (125 MHz, CDCl\(_3\)) \( \delta \) 151.3, 150.1, 145.0, 129.5, 129.1, 128.5, 124.4, 122.5, 120.1, 34.3. HRMS (ESI, m/z) calcd for C\(_{14}H_{14}ClN_2\)[M+H\(^+\)]: 245.8040; found: 245.8038.

(E)-N’-(4-bromophenyl)-N-methyl-N-phenylformimidamide (3m)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (21 mg,
71%. $^1$H NMR (500 MHz, CDCl$\text{3}$) $\delta$ 8.06 (s, 1H), 7.44 – 7.35 (m, 4H), 7.21 – 7.14 (m, 3H), 6.98 – 6.88 (m, 2H), 3.51 (s, 3H).$^{13}$C NMR (125 MHz, CDCl$\text{3}$) $\delta$ 151.3, 150.6, 144.9, 132.0, 129.5, 124.5, 123.0, 120.1 116.2, 34.3.

HRMS (ESI, m/z) calcd for C$_{14}$H$_{14}$BrN$_2$[M+H]$^+$: 289.0335; found: 289.0336.

$(E)$-$N$-$methyl-N'-$(4$-nitrophenyl)$-$N$-$phenylformimidamide (3n)

The reaction was performed following the general procedure. The residue was purified by flash chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (15 mg, 77%).$^1$H NMR (500 MHz, CDCl$\text{3}$) $\delta$ 8.22 – 8.13 (m, 2H), 8.10 (s, 1H), 7.46 – 7.37 (m, 2H), 7.22 (dd, $J$ = 17.7, 7.7 Hz, 3H), 7.13 – 7.05 (m, 2H), 3.55 (s, 3H).$^{13}$C NMR (125 MHz, CDCl$\text{3}$) $\delta$ 152.1, 144.4, 143.5, 129.7, 125.3, 121.4, 120.7, 34.7.

HRMS (ESI, m/z) calcd for C$_{20}$H$_{19}$N$_2$[M+H]$^+$: 289.1081; found: 289.1079.

$(E)$-$N'-$([1,1'$'$-biphenyl]-4-$y$l)$-$N$-$methyl-N$-$phenylformimidamide (3o)

The reaction was performed following the general procedure. The residue was purified by flash chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (22 mg, 77%).$^1$H NMR (500 MHz, CDCl$\text{3}$) $\delta$ 8.17 (s, 1H), 7.61 (dd, $J$ = 7.3, 1.0 Hz, 2H), 7.57 (dt, $J$ = 9.0, 1.8 Hz, 2H), 7.41 (dt, $J$ = 19.8, 7.7 Hz, 4H), 7.32 (td, $J$ = 7.5, 1.1 Hz, 1H), 7.22 – 7.10 (m, 5H), 3.87 (s, 2H), 3.77 (d, $J$ = 0.7 Hz, 3H).$^{13}$C NMR (125 MHz, CDCl$\text{3}$) $\delta$ 151.1, 150.8, 145.1, 141.0, 136.2, 129.5, 128.7, 127.8, 126.7, 124.2, 121.6, 120.0, 34.2.

HRMS (ESI, m/z) calcd for C$_{20}$H$_{19}$N$_2$[M+H]$^+$: 289.1543; found: 289.1544.

$(E)$-$N'-$(3$-bromophenyl)$-$N$-$methyl-N$-$phenylformimidamide (3p)

The reaction was performed following the general procedure. The residue was purified by flash chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (21 mg, 71%).$^1$H NMR (500 MHz, CDCl$\text{3}$) $\delta$ 8.05 (s, 1H), 7.43 – 7.34 (m, 2H), 7.23 – 7.11 (m, 6H), 7.03 – 6.92 (m, 1H), 3.50 (s, 3H).$^{13}$C NMR (125 MHz, CDCl$\text{3}$) $\delta$ 153.0, 151.5, 144.8, 130.3, 129.5, 126.1, 124.6, 124.1, 1227, 120.3, 34.3.

HRMS (ESI, m/z) calcd for C$_{14}$H$_{13}$BrN$_2$[M+H]$^+$: 289.0335; found: 289.0333.

$(E)$-$N'-$(3,4$'$-dimethylphenyl)$-$N$-$methyl-N$-$phenylformimidamide (3q)

The reaction was performed following the general procedure. The residue was purified by flash chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (20
mg, 83%). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.11 (s, 1H), 7.37 (dd, $J = 8.6, 7.4$ Hz, 2H), 7.19 – 7.10 (m, 3H), 7.07 (d, $J = 7.9$ Hz, 1H), 6.86 (d, $J = 2.0$ Hz, 1H), 6.80 (dd, $J = 7.9, 2.3$ Hz, 1H), 3.51 (s, 3H), 2.25 (d, $J = 8.3$ Hz, 6H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 150.8, 149.3, 145.2, 137.2, 131.5, 130.3, 129.4, 123.9, 122.6, 119.8, 118.3, 34.0, 19.9, 19.1.

HRMS (ESI, m/z) calcd for C$_{16}$H$_{18}$N$_2$[M+H]$^+$: 239.1543; found: 239.1546.

**(E)-N'-mesityl-N-methyl-N-phenylformimidamide (3r)**

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (22 mg, 85%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.84 (s, 1H), 7.35 (dd, $J = 8.6, 7.5$ Hz, 2H), 7.16 – 7.04 (m, 3H), 6.92 – 6.81 (m, 2H), 3.54 (s, 3H), 2.26 (s, 3H), 2.16 (s, 6H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 151.2, 146.9, 145.1, 131.7, 129.4, 129.0, 128.6, 123.5, 119.2, 33.6, 20.7, 18.7.

HRMS (ESI, m/z) calcd for C$_{17}$H$_{21}$N$_2$[M+H]$^+$: 253.1699; found: 253.1704.

**(E)-N-methyl-N-phenyl-N'-(5,6,7,8-tetrahydronaphthalen-1-yl)formimidamide (3s)**

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (21 mg, 80%). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.03 (s, 1H), 7.42 – 7.32 (m, 2H), 7.20 – 7.09 (m, 3H), 7.05 (t, $J = 7.6$ Hz, 1H), 6.84 (d, $J = 7.6$ Hz, 1H), 6.64 (d, $J = 7.6$ Hz, 1H), 3.52 (s, 3H), 2.79 (dt, $J = 12.7, 6.2$ Hz, 4H), 1.86 – 1.74 (m, 4H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 150.0, 149.5, 145.2, 137.9, 130.7, 129.4, 125.7, 124.4, 123.6, 119.3, 116.0, 33.7, 29.9, 25.4, 23.4, 23.4.

HRMS (ESI, m/z) calcd for C$_{18}$H$_{21}$N$_2$[M+H]$^+$: 265.1699; found: 265.1702.

**N-methyl-N-phenylformimidamide (3t)**

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (23 mg, 76%). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.20 (s, 1H), 7.73 (t, $J = 7.1$ Hz, 2H), 7.52 (d, $J = 7.4$ Hz, 1H), 7.45 – 7.33 (m, 3H), 7.26 (dd, $J = 11.1, 3.7$ Hz, 2H), 7.22 – 7.13 (m, 3H), 7.09 (dd, $J = 8.0, 1.9$ Hz, 1H), 3.89 (s, 2H), 3.56 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 151, 150.6, 1452, 144.6, 143.0, 141.9, 137.3, 129.5, 126.7, 125.8 124.9, 124.1, 120.3, 120.0, 119.3, 117.8, 37.0, 34.2.

HRMS (ESI, m/z) calcd for C$_{21}$H$_{19}$N$_2$[M+H]$^+$: 299.1543; found: 299.1547.
(E)-\(N'\)-(9H-fluoren-2-yl)-(E)-\(N'\)-(9,9-diphenyl-9H-fluoren-2-yl)-N-methyl-N-phenylformimidamide (3u)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (31 mg, 68%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.09 (s, 1H), 7.73 (dd, \(J = 7.8, 4.5\) Hz, 2H), 7.38 (ddd, \(J = 14.9, 7.4, 6.1\) Hz, 4H), 7.30 – 7.11 (m, 16H), 7.06 (dd, \(J = 8.0, 1.9\) Hz, 1H), 3.52 (s, 3H).\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 152.5, 151.3, 151.1, 150.9, 146.1, 145.1, 140.3, 135.7, 129.8, 128.2 127.4, 126.8, 126.5, 126.1, 124.2, 120.7, 120.4, 120.0, 119.5, 65.5, 34.5. HRMS (ESI, m/z) calcd for C\(_{21}\)H\(_{19}\)N\(_2\)[M+H]: 299.1543; found: 299.1541.

(E)-\(N'\)-methyl-\(N'\)-(E)-\(N\)-methyl-\(N'\)-(naphthalen-1-yl)-N-phenylformimidamide (3v)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (20 mg, 77%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.24 (s, 1H), 7.78 (dd, \(J = 18.2, 8.3\) Hz, 3H), 7.46 – 7.29 (m, 6H), 7.24 – 7.10 (m, 3H), 3.58 (s, 3H).\(^{13}\)C NMR (125MHz, CDCl\(_3\)) \(\delta\) 151.4, 149.3, 145.1, 134.6, 130.7, 129.5, 128.78, 127.6 127.11, 126.1, 124.2, 123.0, 120.0, 116.4, 34.3. HRMS (ESI, m/z) calcd for C\(_{18}\)H\(_{16}\)N\(_2\)[M+H]: 261.1386; found: 261.1383.

(E)-\(N'\)-(benzo[d]thiazol-2-yl)-N-methyl-N-phenylformimidamide (3w)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (17 mg, 62%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.80 (s, 1H), 7.73 (dd, \(J = 22.2, 8.0\) Hz, 2H), 7.43 (t, \(J = 7.9\) Hz, 2H), 7.39 – 7.35 (m, 1H), 7.28 (dd, \(J = 8.6, 0.8\) Hz, 3H), 7.22 (t, \(J = 7.6\) Hz, 1H), 3.59 (s, 3H).\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 172.9, 155.2, 151.9, 143.9, 133.7, 129.7, 126.2, 125.9, 123.3, 121.5 121.4, 121.2, 35.3. HRMS (ESI, m/z) calcd for C\(_{15}\)H\(_{13}\)N\(_3\)S[M+H]: 268.0903; found: 268.0902.

(E)-\(N'\)-methyl-\(N'\)-phenyl-\(N\)-(p-toly)formimidamide (3x)

The reaction was performed following the general procedure. The residue was purified by flash
column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (19 mg, 85%).\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 8.05 (s, 1H), 7.31 (t, \(J = 7.8\) Hz, 2H), 7.18 (d, \(J = 8.2\) Hz, 2H), 7.13 – 6.95 (m, 5H), 3.49 (s, 3H), 2.35 (s, 3H).\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 151.6, 151.3, 142.7, 134.0, 130.0, 129.1, 123.2, 121.3, 120.2, 34.3, 20.7.

HRMS (ESI, m/z) calcd for C\textsubscript{15}H\textsubscript{17}N\textsubscript{2}[M+H]\textsuperscript{+}: 225.1386; found: 225.1390.

**\((E)-N-(4-chlorophenyl)-N-methyl-N'-phenylformimidamide (3y)\)**

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (20 mg, 83%).\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 8.04 (s, 1H), 7.35 – 7.28 (m, 4H), 7.11 – 7.06 (m, 3H), 7.06 – 7.00 (m, 2H), 3.49 (s, 3H).\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 151.2, 150.6, 143.7, 129.4, 129.1, 123.6, 121.2, 120.9, 34.2.

HRMS (ESI, m/z) calcd for C\textsubscript{14}H\textsubscript{13}ClN\textsubscript{2}[M+H]\textsuperscript{+}: 245.0840; found: 245.0836.

**\((E)-N-methyl-N'-phenyl-N-(\alpha-tolyl)formimidamide (3z)\)**

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (15 mg, 68%).\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.73 (s, 1H), 7.32 – 7.24 (m, 5H), 7.17 (dd, \(J = 6.8, 2.1\) Hz, 1H), 7.06 (t, \(J = 8.0\) Hz, 3H), 3.39 (s, 3H), 2.35 (s, 3H).\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 152.8, 151.6, 134.8, 131.5, 129.0, 127.3, 127.0, 123.0, 121.3, 31.5, 18.2.

HRMS (ESI, m/z) calcd for C\textsubscript{15}H\textsubscript{17}N\textsubscript{2}[M+H]\textsuperscript{+}: 225.1386; found: 25.1389.

**\((E)-N-ethyl-N,N'-diphenylformimidamide (3aa)\)**

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (18 mg, 82%).\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.98 (s, 1H), 7.41 – 7.34 (m, 2H), 7.33 – 7.27 (m, 2H), 7.20 – 7.13 (m, 3H), 7.10 – 7.00 (m, 3H), 4.09 (q, \(J = 7.1\) Hz, 2H), 1.31 (d, \(J = 7.1\) Hz, 3H).\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 151.7, 150.5, 144.0, 129.5, 129.1, 124.4, 123.2, 121.3, 121.1, 41.9, 12.8.

HRMS (ESI, m/z) calcd for C\textsubscript{15}H\textsubscript{17}N\textsubscript{2}[M+H]\textsuperscript{+}: 225.1386; found: 225.1390.

**\((E)-N-ethyl-N'-phenyl-N-(p-tolyl)formimidamide (3ab)\)**

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (19 mg,
80%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.92 (s, 1H), 7.29 (dd, $J = 8.1, 7.5$ Hz, 2H), 7.17 (d, $J = 8.1$ Hz, 2H), 7.09 – 7.00 (m, 5H), 4.05 (q, $J = 7.1$ Hz, 2H), 2.35 (s, 3H), 1.30 – 1.28 (m, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 151.9, 150.7, 141.6, 134.3, 130.0, 129.0, 123.0, 121.6, 121.3, 42.0, 20.8, 12.8.

HRMS (ESI, m/z) caled for C$_{16}$H$_{18}$N$_2$[M+H]$^+$: 239.1543; found: 239.1542.

(E)-N-butyl-N,N'-diphenylformimidamide (3ac)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (19 mg, 76%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.99 (s, 1H), 7.40 – 7.34 (m, 2H), 7.29 (t, $J = 7.8$ Hz, 2H), 7.16 (dd, $J = 12.0, 7.6$ Hz, 3H), 7.10 – 6.99 (m, 3H), 4.13 – 3.93 (m, 2H), 1.70 (tt, $J = 7.7, 6.7$ Hz, 2H), 1.44 – 1.35 (m, 2H), 0.94 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 155.3, 151.8, 150.9, 144.3, 129.4, 129.0, 124.9, 123.1, 121.3, 46.5, 29.5, 20.2, 13.9.

HRMS (ESI, m/z) caled for C$_{16}$H$_{18}$N$_2$[M+H]$^+$: 239.1543; found: 239.1544.

Ethyl (E)-4-(((methyl(phenyl)amino)methylene)amino)methylene)amino)benzoate (3ad)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (17 mg, 59%). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.13 (s, 1H), 8.07 – 7.98 (m, 2H), 7.47 – 7.36 (m, 2H), 7.21 (dd, $J = 7.7, 4.8$ Hz, 3H), 7.12 – 7.00 (m, 2H), 4.38 (q, $J = 7.1$ Hz, 2H), 3.55 (s, 3H), 1.41 (t, $J = 7.1$ Hz, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 166.7, 155.7, 151.6, 144.8, 130.9, 129.6, 125.2, 124.7, 121.1, 120.4, 60.7, 34.4, 14.4.

HRMS (ESI, m/z) caled for C$_{17}$H$_{18}$N$_2$O$_2$[M+H]$^+$: 283.1441; found: 283.1442.

(E)-1-(4-(2-chlorodibenzo[bf][1,4]oxazepin-11-yl)piperazin-1-yl)-N-phenylmethanimine (3ae)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (32 mg, 76%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.59 (s, 1H), 7.42 (dd, $J = 8.7, 2.6$ Hz, 1H), 7.36 (d, $J = 2.6$ Hz, 1H), 7.32 – 7.27 (m, 2H), 7.23 – 7.16 (m, 2H), 7.12 (ddd, $J = 13.6, 5.3, 3.7$ Hz, 2H), 7.08 – 6.97 (m, 4H), 3.59 (s, 8H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ
(E)-N-phenyl-1-((4-(4-(trifluoromethyl)pyrimidin-2-yl)piperazin-1-yl)methanimine (3af)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (20.5 mg, 61%).$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.53 (d, $J = 4.8$ Hz, 1H), 7.61 (s, 1H), 7.28 (t, $J = 7.8$ Hz, 2H), 7.04 (t, $J = 7.3$ Hz, 1H), 6.99 (d, $J = 7.4$ Hz, 2H), 6.82 (d, $J = 4.8$ Hz, 1H), 3.99 – 3.94 (m, 4H), 3.60 (s, 4H).$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 161.4, 160.3, 156.8, 156.5, 156.2, 155.9, 152.3, 151.4, 129.1, 123.0, 121.1, 119.9, 119.4, 118.9, 105.2, 43.6. HRMS (ESI, m/z) calcd for C$_{18}$H$_{25}$F$_3$N$_5$[M+H]$^+$: 336.1431; found: 336.1430.

(E)-N-(2-((S)-2-cyanopyrrolidin-1-yl)-2-oxoethyl)-N-((1R,3R,5R,7S)-3-hydroxyadamantan-1-yl)-N’-phenylformimidamide compound with I1-methane and methane (1:1:2) (3ag)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a yellow oil (29 mg, 71%).$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.92 (s, 1H), 7.25 (dd, $J = 14.9$, 7.3 Hz, 2H), 7.01 (dt, $J = 14.7$, 7.4 Hz, 1H), 6.87 (dd, $J = 16.8$, 7.5 Hz, 2H), 5.69 – 4.72 (m, 1H), 4.34 (dd, $J = 28.7$, 15.6 Hz, 1H), 4.07 (t, $J = 14.5$ Hz, 1H), 3.82 – 3.47 (m, 2H), 2.41 – 1.81 (m, 15H), 1.71 (s, 4H).$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 169.5, 168.9, 152.0, 151.6, 149.7, 149.6, 129.1, 129.0, 122.8, 122.6, 121.3, 121.2, 119.4, 118.6, 69.5, 69.4, 59.2, 58.8, 49.9, 49.7, 47.5, 46.8, 46.6, 46.2, 45.0, 44.4, 43.8, 41.1, 41.1, 34.6, 32.3, 30.7, 29.9, 29.7, 25.4, 23.2.

(S,E)-N-benzyl-N’-phenyl-N-((1-phenylethyl)formimidamide (3ah)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (19 mg, 60%).$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.97 (s, 1H), 7.57 – 7.15 (m, 12H), 7.05 (ddd, $J = 9.5$, 5.2, 1.0 Hz,
3H), 4.90 (s, 1H), 4.51 (d, J = 65.1 Hz, 2H), 1.59 (d, J = 7.1 Hz, 3H).$^{13}$C NMR (125 MHz, CDCl$_3$) δ 152.3, 151.9, 141.6, 138.4, 129.1, 128.7, 128.6, 128.3, 127.7, 127.1, 126.90 – 125.52 (m), 122.7, 121.4, 58.3, 48.5, 20.6. HRMS (ESI, m/z) calcd for C$_{22}$H$_{22}$N$_2$[M+H]$^+$: 315.1856; found: 315.1858.

(E)-$N_2N$-dicyclohexyl-$N'$-phenylformimidamide (5)

![Image](image)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (22 mg, 76%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.70 (s, 1H), 7.28 (dd, J = 10.8, 4.8 Hz, 2H), 7.02 – 6.93 (m, 3H), 1.77 (dd, J = 69.6, 11.6 Hz, 11H), 1.58 – 1.31 (m, 9H), 1.19 – 1.10 (m, 2H), 0.89 (dt, J = 12.6, 6.5 Hz, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 153.3, 150.6, 128.9, 122.0, 121.3, 29.7, 25.6. HRMS (ESI, m/z) calcd for C$_{19}$H$_{10}$N$_2$[M+H]$^+$: 285.2325; found: 285.2321.

(Z)-$N$-isopropyl-$N'$-phenyl-$N$-(3-(phenylamino)phenyl)formimidamid (7)

![Image](image)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 80:1, v/v) to give the product as a yellow oil (18 mg, 54%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.73 (s, 1H), 7.35 – 7.28 (m, 4H), 7.13 – 6.99 (m, 10H), 5.84 (s, 1H), 1.28 (d, J = 6.8 Hz, 7H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 153.0, 152.1, 142.6, 142.4, 133.9, 129.8, 129.5, 129.0, 123.5, 122.6, 121.6, 121.3, 118.4, 117.4, 114.8, 23.1, 21.1.

4-(((E)-((2-((S)-2-cyanopyrrolidin-1-yl)-2-oxoethyl)((1r,3R,5R,7S)-3-hydroxyadamantan-1-yl)amino)methylene)amino)benzoate (3ai)

![Image](image)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 20:1, v/v) to give the product as a yellow oil (33.5 mg, 70%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.92 (s, 1H), 7.88 (dd, J = 8.4, 4.6 Hz, 2H), 6.84 (dd, J = 16.5, 8.5 Hz, 2H), 5.48 – 4.63 (m, 1H), 4.38 – 4.18 (m, 3H), 4.15 – 3.93 (m, 2H), 3.78 – 3.66 (m, 2H), 3.62 – 3.34 (m, 1H), 2.59 (d, J = 138.4 Hz, 1H), 2.37 – 2.07 (m, 7H), 2.03 – 1.98 (m, 1H), 1.98 – 1.80 (m, 6H), 1.67 (s, 4H), 1.56 – 1.47 (m, 2H), 1.33 (t, J = 7.1 Hz, 3H), 1.24 – 1.12 (m, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 171.2, 171.1, 168.9, 168.4,
166.8, 166.7, 156.3, 155.9, 150.1, 150.0, 130.9, 130.8, 124.3, 121.0, 120.9, 119.1, 118.5, 74.6, 69.3, 69.2, 67.1, 60.6, 60.5, 60.4, 59.6, 59.2, 56.7, 49.7, 49.5, 47.4, 46.8, 46.6, 46.2, 45.0, 44.5, 43.6, 41.0, 41.0, 34.6, 34.5, 32.3, 30.6, 29.9, 25.4, 23.2, 21.1, 21.0, 16.2, 14.4, 14.2.

(E)-N,N’-diphenylformimidamide (8)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 50:1, v/v) to give the product as a yellow oil (11 mg, 53%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.20 (s, 1H), 7.31 (t, $J = 7.8$ Hz, 4H), 7.24 – 6.64 (m, 6H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 129.4, 123.4, 118.9.

HRMS (ESI, m/z) calcd for C$_{13}$H$_{13}$N$_2$[M+H]$^+$:197.1073; found: 197.1076.

(E)-N,N’-di-p-tolylformimidamide (9)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 50:1, v/v) to give the product as a yellow oil (11 mg, 48%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.17 (s, 1H), 7.11 (d, $J = 8.1$ Hz, 4H), 6.94 (d, $J = 8.0$ Hz, 4H), 2.33 (s, 6H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 149.3, 132.8, 129.9, 119.5, 118.9, 29.7, 20.7.

HRMS (ESI, m/z) calcd for C$_{15}$H$_{17}$N$_2$[M+H]$^+$:225.1386; found: 225.1389.

(E)-N-(difluoromethyl)-N,N’-diphenylformimidamide (10)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 100:1, v/v) to give the product as a yellow oil (17 mg, 67%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.84 (t, $J = 2.8$ Hz, 1H), 7.57 (t, $J = 52.5$ Hz, 1H), 7.45 (dd, $J = 6.9$, 1.6 Hz, 2H), 7.42 – 7.37 (m, 3H), 7.32 (dd, $J = 10.7$, 5.0 Hz, 2H), 7.14 (t, $J = 7.4$ Hz, 1H), 7.06 – 7.00 (m, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 149.4, 149.1, 136.4, 129.5, 129.2, 128.2, 127.4, 124.6, 121.1 110.2 (s, $J = 243.75$Hz). $^{19}$F NMR (470 MHz, CDCl$_3$) $\delta$ -97.8, -102.8.

HRMS (ESI, m/z) calcd for C$_{14}$H$_{13}$F$_2$N$_2$[M+H]$^+$:247.1041; found: 247.1042.

(E)-N-(difluoromethyl)-N,N’-di-p-tolylformimidamide (11)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 100:1, v/v) to give the product as a yellow oil (17 mg, 61%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.82 (t, $J =
2.8 Hz, 1H), 7.55 (dd, J = 67.5, 54.9 Hz, 1H), 7.17 – 7.11 (m, 2H), 6.94 (d, J = 8.2 Hz, 2H), 2.42 (s, 3H), 2.35 (s, 3H).\(^{13}\text{C}\) NMR (125 MHz, CDCl\(_3\)) \(\delta\) 149.0, 147.0, 138.2, 134.1, 133.7, 130.1, 129.7, 127.5, 120.9, 110.2 (s, J = 237.5Hz), 21.1, 20.8.\(^{19}\text{F}\) NMR (470 MHz, CDCl\(_3\)) \(\delta\) -97.8, -103.0.

HRMS (ESI, m/z) caleed for C\(_{16}\)H\(_{12}\)F\(_{2}\)N\(_{2}\)[M+H]\(^{+}\):275.1354; found: 275.1356.

**(E)-N-(difluoromethyl)-N',N'-bis(4-ethylphenyl)formimidamide (12)**

![Image](https://via.placeholder.com/150)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 100:1, v/v) to give the product as a yellow oil (18 mg, 59%).\(^{1}\text{H}\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.81 (t, \(J = 2.8\) Hz, 1H), 7.53 (t, \(J = 61.2\) Hz, 1H), 7.27 (s, 4H), 7.14 (d, \(J = 8.4\) Hz, 2H), 6.98 – 6.91 (m, 2H), 2.69 (q, \(J = 7.6\) Hz, 2H), 2.63 (q, \(J = 7.6\) Hz, 2H), 1.26 (s, 3H), 1.23 (t, \(J = 7.6\) Hz, 3H).\(^{13}\text{C}\) NMR (125 MHz, CDCl\(_3\)) \(\delta\) 149.0, 147.1, 144.4, 140.6, 133.9, 128.9, 128.5, 127.5, 121.0, 110.2 (s, \(J = 242.5\)Hz), 28.5, 28.3, 15.7, 15.4.

\(^{19}\text{F}\) NMR (470 MHz, CDCl\(_3\)) \(\delta\) -98.5, -103.0.

HRMS (ESI, m/z) caleed for C\(_{18}\)H\(_{14}\)F\(_{2}\)N\(_{2}\)[M+H]\(^{+}\):303.1667; found: 303.1668.

**(E)-N-(difluoromethyl)-N',N'-bis(4-isopropylphenyl)formimidamide (13)**

![Image](https://via.placeholder.com/150)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 100:1, v/v) to give the product as a yellow oil (21 mg, 62%).\(^{1}\text{H}\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.81 (t, \(J = 2.8\) Hz, 1H), 7.55 (t, \(J = 61.2\) Hz, 1H), 7.28 (s, 4H), 7.20 – 7.13 (m, 2H), 7.00 – 6.90 (m, 2H), 2.92 (ddt, \(J = 30.5, 13.8, 6.9\) Hz, 2H), 1.28 (s, 3H), 1.26 (s, 3H), 1.24 (s, 3H), 1.23 (s, 3H).\(^{13}\text{C}\) NMR (125 MHz, CDCl\(_3\)) \(\delta\) 149.0, 147.2, 145.2, 134.0, 127.4, 127.1, 120.9, 110.2 (s, \(J = 247.5\)Hz), 33.8, 33.6, 24.1, 23.9. \(^{19}\text{F}\) NMR (470 MHz, CDCl\(_3\)) \(\delta\) -98.0, -103.0.

HRMS (ESI, m/z) caleed for C\(_{20}\)H\(_{22}\)F\(_{2}\)N\(_{2}\)[M+H]\(^{+}\):331.1980; found: 331.1986.

**(E)-N',N'-bis(4-(tert-butyl)phenyl)-N-(difluoromethyl)formimidamide (14)**

![Image](https://via.placeholder.com/150)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 100:1, v/v) to give the product as a yellow oil (23 mg, 65%). \(^{1}\text{H}\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.85 (t, \(J = 2.8\) Hz, 1H), 7.59 (t, \(J = 55.2\) Hz, 1H), 7.55 (dd, \(J = 67.5, 54.9\) Hz, 1H), 7.17 – 7.11 (m, 2H), 6.94 (d, \(J = 8.2\) Hz, 2H), 2.42 (s, 3H), 2.35 (s, 3H).\(^{13}\text{C}\) NMR (125 MHz, CDCl\(_3\)) \(\delta\) 149.0, 147.0, 138.2, 134.1, 133.7, 130.1, 129.7, 127.5, 120.9, 110.2 (s, \(J = 237.5\)Hz), 21.1, 20.8. \(^{19}\text{F}\) NMR (470 MHz, CDCl\(_3\)) \(\delta\) -97.8, -103.0.

HRMS (ESI, m/z) caleed for C\(_{16}\)H\(_{12}\)F\(_{2}\)N\(_{2}\)[M+H]\(^{+}\):275.1354; found: 275.1356.
Hz, 1H), 7.48 – 7.44 (m, 2H), 7.44 – 7.28 (m, 5H), 7.03 – 6.94 (m, 2H), 1.37 (s, 9H), 1.34 (s, 9H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 151.2, 149.1, 147.5, 146.8, 133.7, 126.9, 126.4, 126.0, 120.7, 110.2 (t, $J = 242.5$ Hz), 34.7, 34.4, 31.38, 31.1. $^{19}$F NMR (470 MHz, CDCl$_3$) δ -98.1, -102.9.

(E)-$N,N'$-bis(4-bromophenyl)-$N$-(difluoromethyl)formimidamide (15)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a yellow oil (23 mg, 57%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.78 (t, $J = 2.4$ Hz, 1H), 7.66 (t, $J = 38.0$ Hz, 1H), 7.59 – 7.56 (m, 2H), 7.43 – 7.40 (m, 2H), 7.26 – 7.23 (m, 2H), 6.91 – 6.84 (m, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 148.6, 135.0, 132.8, 132.2, 129.1, 122.8, 117.9 (t, $J = 571.3$ Hz), 100.0. $^{19}$F NMR (470 MHz, CDCl$_3$) δ -99.5, -102.9.

1-methyl-1H-benzo[d]imidazole (17) (CAS number:1632-83-3)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a yellow oil (12 mg, 90%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.86 (s, 1H), 7.81 (dd, $J = 7.1$, 1.2 Hz, 1H), 7.39 (dd, $J = 7.0$, 1.1 Hz, 1H), 7.35 – 7.26 (m, 2H), 3.84 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 143.7, 143.5, 122.94 (s), 122.1, 120.3, 109.3, 31.0.

6-methylbenzo[d]oxazole (20a) (CAS number:10531-80-3)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 100:1, v/v) to give the product as a colourless oil (21 mg, 81%). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.03 (s, 1H), 7.65 (d, $J = 8.1$ Hz, 1H), 7.39 (s, 1H), 7.18 (dd, $J = 8.1$, 0.7 Hz, 1H), 2.50 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 152.1, 150.3, 137.8, 136.1, 125.9, 119.9, 111.1, 21.8.

5-methylbenzo[d]oxazole (20b) (CAS number:10531-78-9)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 100:1, v/v) to give the product as a colourless oil (21 mg, 77%). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.07 (s, 1H), 8.07 (s, 1H), 7.40 (d, $J = 8.2$ Hz, 1H), 7.40 (d, $J = 8.2$ Hz, 1H), 7.27 (t, $J = 7.8$ Hz, 1H), 7.27 (t, $J = 7.8$ Hz, 1H), 7.16 (d, $J = 7.5$ Hz, 1H), 7.16 (d, $J = 7.5$ Hz, 1H), 2.64 (s, 3H), 2.64 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 151.8, 149.7, 139.2, 131.0, 125.3, 125.1, 108.2, 16.5.
5-chlorobenzo[d]oxazole (20c) (CAS number:17200-29-2)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 100:1, v/v) to give the product as a colourless oil (22 mg, 70%). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.11 (s, 1H), 7.77 (d, $J_1$ = 2.0 Hz, 1H), 7.51 (d, $J_2$ = 8.7 Hz, 1H), 7.36 (dd, $J_3$ = 8.7, 2.0 Hz, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 153.7, 148.5, 141.1, 130.2, 126.1, 120.6, 111.8.

5-bromobenzo[d]oxazole (20d) (CAS number:132244-31-6)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 100:1, v/v) to give the product as a colourless oil (25 mg, 68%). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.09 (s, 1H), 7.93 (d, $J_1$ = 1.7 Hz, 1H), 7.49 (dt, $J_2$ = 20.0, 5.2 Hz, 2H).

19F NMR (470 MHz, CDCl$_3$) δ -81.0.

2-(difluoromethoxy)-5-nitroaniline (20e')

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 100:1, v/v) to give the product as a colourless oil (36 mg, 89%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.63 (d, $J_1$ = 2.7 Hz, 1H), 7.59 (dd, $J_2$ = 8.8, 2.7 Hz, 1H), 7.12 (d, $J_3$ = 8.8 Hz, 1H), 6.58 (t, $J_4$ = 72.8 Hz, 1H), 4.20 (s, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 145.7, 142.3, 139.0, 117.8 (s, J=261.25Hz), 113.5, 110.6. $^{19}$F NMR (470 MHz, CDCl$_3$) δ -81.0.

2-(difluoromethoxy)-4-nitroaniline (20f')

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 100:1, v/v) to give the product as a colourless oil (34 mg, 84%). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.03 – 7.90 (m, 2H), 6.76 (d, $J_1$ = 8.8 Hz, 1H), 6.57 (t, $J_2$ = 72.9 Hz, 1H), 4.66 (s, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 145.1, 138.2, 136.0, 118.1, 116.1,116.0(s,J=262.5Hz) 114.0. $^{19}$F NMR (470 MHz, CDCl$_3$) δ -80.8.

benzo[d]oxazole (20g) (CAS number:51-17-2)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (20 mg, 86%). $^1$H NMR (500 MHz,
6-methylbenzo[d]oxazole (20h) (CAS number: 4887-83-6)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (24 mg, 92%). $^1$H NMR (500 MHz, DMSO) $\delta$ 12.47 (s, 1H), 8.18 (s, 1H), 7.39 (d, $J = 7.6$ Hz, 1H), 7.07 (t, $J = 7.6$ Hz, 1H), 6.98 (d, $J = 7.2$ Hz, 1H), 2.52 (s, 3H). $^{13}$C NMR (125 MHz, DMSO) $\delta$ 141.77 (s), 122.16 (s), 17.24 (s).

5-fluoro-1H-benzo[d]imidazole (20i) (CAS number: 1977-72-6)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (21 mg, 78%). $^1$H NMR (500 MHz, DMSO) $\delta$ 12.56 (s, 1H), 8.25 (s, 1H), 7.58 (dd, $J = 8.4$, 4.9 Hz, 1H), 7.42 – 7.36 (m, 1H), 7.07 – 7.01 (m, 1H). $^{13}$C NMR (125 MHz, DMSO) $\delta$ 159.9, 158.0, 143.8, 110.5.

7-chloro-1H-benzo[d]imidazole (20j) (CAS number: 16931-35-4)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (26 mg, 86%). $^1$H NMR (500 MHz, DMSO) $\delta$ 12.80 (s, 1H), 8.32 (s, 1H), 7.53 (s, 1H), 7.30 – 7.17 (m, 2H). $^{13}$C NMR (125 MHz, DMSO) $\delta$ 143.3, 123.5, 121.6, 111.4.

5-bromo-1H-benzo[d]imidazole (20k) (CAS number: 4887-88-1)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (29 mg, 75%). $^1$H NMR (500 MHz, DMSO) $\delta$ 12.63 (s, 1H), 8.26 (s, 1H), 7.79 (s, 1H), 7.55 (s, 1H), 7.32 (d, $J = 8.2$ Hz, 1H). $^{13}$C NMR (125 MHz, DMSO) $\delta$ 143.8, 100.0.

6-nitro-1H-benzo[d]imidazole (20l) (CAS number: 94-52-0)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a yellow solid (14 mg, 42%). $^1$H NMR (500 MHz, DMSO) $\delta$ 8.63 – 8.41 (m, 2H), 8.17 – 7.97 (m, 1H), 7.75 (ddd, $J = 8.4$, 7.5, 1.8 Hz, 1H). $^{13}$C NMR (125 MHz, DMSO) $\delta$ 143.8, 100.0.
1H). $^1$C NMR (126 MHz, DMSO) δ 147.17 (d, $J = 9.3$ Hz), 143.09 (s), 118.00 (d, $J = 9.4$ Hz), 115.29 (s), 113.18 (s).

5-5,6-dimethyl-1H-benzo[d]imidazole (20m) (CAS number: 582-60-5)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (23mg, 79%). $^1$H NMR (500 MHz, DMSO) δ 8.05 (s, 1H), 7.34 (s, 2H), 2.29 (s, 6H). $^1$C NMR (125 MHz, DMSO) δ 141.4, 130.5, 115.8, 20.4.

5,6-difluoro-1H-benzo[d]imidazole (20n) (CAS number: 78581-99-4)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (24mg, 77%). $^1$H NMR (500 MHz, DMSO) δ 12.65 (s, 1H), 8.28 (s, 1H), 7.64 (d, $J = 22.7$ Hz, 2H). $^1$C NMR (125 MHz, DMSO) δ 144.5.

5,6-dichloro-1H-benzo[d]imidazole (20o) (CAS number: 6478-73-5)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (28mg, 75%). $^1$H NMR (500 MHz, DMSO) δ 12.75 (s, 1H), 8.35 (s, 1H), 7.88 (s, 2H). $^1$C NMR (125 MHz, DMSO) δ 145.2

1-(difluoromethyl)-1H-benzo[d]imidazole (21)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (11.4 mg, 61%). $^1$H NMR (500 MHz, CDCl₃) δ 8.12 (s, 1H), 7.93 – 7.76 (m, 1H), 7.61 (dd, $J = 5.4$, 3.6 Hz, 1H), 7.37 (ddd, $J = 85.8$, 55.8, 43.2 Hz, 3H). $^1$C NMR (125 MHz, CDCl₃) δ 143.9, 139.1, 130.6, 124.8, 124.2, 121.0, 111.1, 109.0 (t, $J = 248.8$ Hz) $^{19}$F NMR (470 MHz, CPD, CDCl₃) δ -93.7.

1-(difluoromethyl)-5(6)-methyl-1H-benzo[d]imidazole (22)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (11 mg, 58%). $^1$H NMR (500 MHz, CDCl₃) δ 8.05 (d, $J = 11.4$ Hz, 1H), 7.71 (d, $J = 8.3$ Hz, 1H), 7.62 (s, 1H), 7.48 (d, $J = 8.3$ Hz, 1H), 7.41 (d, $J = 4.1$ Hz, 1H), 7.29 (s, 1H), 7.20 (d, $J = 11.8$, 4.5 Hz, 1H), 7.17 (s, 1H), 2.50 (d, $J = 8.8$ Hz, 3H). $^1$C NMR (125 MHz, CDCl₃) δ 144.2, 142.0,
139.1, 138.6, 135.6, 134.1, 130.7, 128.5, 126.2, 125.7, 120.7, 120.4, 110.98 (d,  \( J = 5.5 \) Hz), 110.56 (s), 108.97 (s), 106.99 (s), 21.79 (s), 21.51 (s).\(^{19}\)F NMR (470 MHz, CDCl\(_3\)) \( \delta \) -93.6, -93.7.

### 1-(difluoromethyl)-4,7-dimethyl-1\(H\)-benzo[d]imidazole (23)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (11 mg, 63%).\(^{1}\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 8.13 (d,  \( J = 27.9 \) Hz, 1H), 7.69 (d,  \( J = 8.1 \) Hz, 1H), 7.61 (s, 1H), 7.49 (s, 1H), 7.45 – 7.38 (m, 1H), 7.37 (s, 1H), 7.33 – 7.26 (m, 1H), 7.18 (t,  \( J = 6.0 \) Hz, 1H), 2.66 (d,  \( J = 18.6 \) Hz, 3H).\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 143.2, 139.7, 138.1, 131.1, 130.3, 124.7, 124.5, 124.1, 121.6, 118.7, 110.9, 109.0, 108.4, 19.2, 16.6.\(^{19}\)F NMR (471 MHz, CDCl\(_3\)) \( \delta \) -87.3, -93.8.

### 1-(difluoromethyl)-5(6)-fluoro-1\(H\)-benzo[d]imidazole (24)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (10 mg, 53%).\(^{1}\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 8.11 (d,  \( J = 20.5 \) Hz, 1H), 7.78 (dd,  \( J = 8.9, 4.7 \) Hz, 1H), 7.56 (dd,  \( J = 8.9, 4.5 \) Hz, 1H), 7.52 (dd,  \( J = 8.9, 2.4 \) Hz, 1H), 7.41 (d,  \( J = 9.8 \) Hz, 1H), 7.35 – 7.27 (m, 1H), 7.15 (m,  \( J = 13.5, 9.1, 2.2 \) Hz, 1H).\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) 161.5 (d,  \( J = 46.3 \) Hz), 159.5 (d,  \( J = 37.5 \) Hz), 140.5, 139.5, 122.8 (d,  \( J = 10.0 \) Hz), 112.9 (d,  \( J = 47.5 \) Hz), 112.6 (t,  \( J = 113.8 \) Hz), 98.4 (d,  \( J = 28.8 \) Hz).\(^{19}\)F NMR (470 MHz, CDCl\(_3\)) \( \delta \) -93.7, -94.0, -115.6, -118.0.

### 5(6)-chloro-1-(difluoromethyl)-1\(H\)-benzo[d]imidazole (25)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (12 mg, 58%).\(^{1}\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 8.14 (s, 1H), 7.85 (d,  \( J = 1.8 \) Hz, 1H), 7.56 (d,  \( J = 8.7 \) Hz, 1H), 7.45 (s, 1H), 7.40 (dd,  \( J = 8.6, 1.9 \) Hz, 1H), 7.33 (s, 1H), 7.21 (s, 1H).\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 144.8, 140.2, 129.9, 129.1, 125.4, 120.9, 112.0, 108.8 (\( J = 248.75 \) Hz, ).\(^{19}\)F NMR (470 MHz, CDCl\(_3\)) \( \delta \) -93.8.

### 5(6)-bromo-1-(difluoromethyl)-1\(H\)-benzo[d]imidazole (26)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (15 mg, 60%).\(^{1}\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 8.09 (d,  \( J = 7.1 \) Hz, 1H), 7.97 (d,  \( J = 0.6 \) Hz, 1H), 7.77 (s, 1H), 7.68 (d,  \( J = 8.6 \) Hz, 1H), 7.52 – 7.45 (m, 2H), 7.43 (d,  \( J = 6.2 \) Hz, 1H),...
7.31 (d, J = 6.1 Hz, 1H), 7.19 (d, J = 6.1 Hz, 1H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\))  145.2, 142.9, 140.1, 139.6, 131.4, 129.4, 128.0, 127.7, 123.9, 122.2, 118.2, 117.3, 114.4, 112.4, 108.9 (t, J = 250.0 Hz), 108.8 (t, J = 250.0 Hz). \(^{19}\)F NMR (470 MHz, CDCl\(_3\))  -93.8.

1-(difluoromethyl)-5,6-dimethyl-1H-benzo[d]imidazole (27)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (13 mg, 69%). \(^1\)H NMR (500 MHz, CDCl\(_3\))  7.99 (s, 1H), 7.99 (s, 4H), 7.59 (s, 4H), 7.38 (s, 1H), 7.38 (d, J = 5.7 Hz, 5H), 7.37 (s, 4H), 7.26 (s, 2H), 7.26 (d, J = 2.0 Hz, 3H), 7.14 (s, 1H), 7.14 (s, 1H), 2.38 (d, J = 8.9 Hz, 25H), 2.38 (d, J = 8.9 Hz, 25H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\))  142.5, 138.3, 134.2, 133.2, 129.0, 120.9, 111.24, 109.00 (t, J = 247.5Hz), 20.5, 20.3. \(^{19}\)F NMR (470MHz, CDCl\(_3\))  -93.6.

1-(difluoromethyl)-5,6-difluoro-1H-benzo[d]imidazole (28)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (10 mg, 51%). \(^1\)H NMR (500 MHz, CDCl\(_3\))  8.11 (s, 1H), 7.62 (dd, J = 10.0, 7.2 Hz, 1H), 7.44 (dd, J = 9.3, 6.8 Hz, 1H), 7.41 (s, 1H), 7.29 (s, 1H), 7.17 (s, 1H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\))  150.15 (d, J = 15.5 Hz), 149.80 (d, J = 14.8 Hz), 148.19 (d, J = 15.5 Hz), 147.86 (d, J = 15.0 Hz), 140.44 (s), 139.35 (d, J = 9.0 Hz), 125.7, 108.8, 108.7 (t, J = 228.8Hz), 108.5, 106.8, 100.0, 99.8. \(^{19}\)F NMR (470MHz, CDCl\(_3\))  -94.0, -137.9, -138.0, -140.3, -140.3.

5,6-dichloro-1-(difluoromethyl)-1H-benzo[d]imidazole (29)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (13 mg, 55%). \(^1\)H NMR (500 MHz, CDCl\(_3\))  8.11 (s, 1H), 7.95 (s, 1H), 7.75 (s, 1H), 7.40 (s, 1H), 7.28 (s, 1H), 7.16 (s, 1H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\))  143.2, 140.7, 129.3, 128.8, 122.3, 112.9, 110.7(t, J = 228.8Hz). \(^{19}\)F NMR (470 MHz, CDCl\(_3\))  -93.9.

(E)-N,N'-bis(4-ethoxyphenyl)formimidamide (32)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a white solid (8.5 mg, 15%). \(^1\)H NMR (500 MHz, CDCl\(_3\))  8.02 (s, 1H), 6.97 (d, J = 8.6 Hz, 4H), 6.89 – 6.81 (m, 4H), 4.01
(q, J = 7.0 Hz, 4H), 1.40 (t, J = 7.0 Hz, 6H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 155.4, 120.2, 115.3, 63.8, 14.9.

1-ethoxy-4-isocyanobenzene (33)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a colourless oil (8 mg, 27%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.29 (d, J = 8.9 Hz, 2H), 6.87 – 6.82 (m, 2H), 4.03 (q, J = 7.0 Hz, 2H), 1.42 (t, J = 7.0 Hz, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 162.3, 159.3, 127.8, 115.0, 63.9, 14.7.

N-(4-ethoxyphenyl)formamide (34)

The reaction was performed following the general procedure. The residue was purified by flash column chromatography (silica gel, Petroleum ether: AcOEt = 10:1, v/v) to give the product as a colourless oil (8 mg, 27%). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.50 (d, J = 11.5 Hz, 0.49 H), 8.31 (d, J = 1.8 Hz, 0.49 H), 8.09 (s, 0.46 H), 7.47 – 7.35 (m, 1.42 H), 7.06 – 6.96 (m, 1H), 6.90 – 6.81 (m, 2H), 4.00 (qd, J = 7.0, 4.3 Hz, 2H), 1.40 (q, J = 6.9 Hz, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 163.1, 158.9, 157.0, 156.1, 129.8, 129.4, 121.8, 121.7, 115.5, 114.8, 63.8, 63.7, 14.8.

References
