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Rearrangement of 4-Amino-3-halo-pyridines by Nucleophilic Aromatic Substitution

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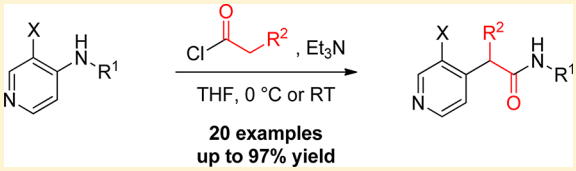
Supporting Information

ABSTRACT: The reaction of 3-halo-4-aminopyridines with acyl chlorides and triethylamine is described. The pyridin-4-yl α-substituted acetamide products were obtained in moderate to high yields. The presented rearrangement reaction, in which the presumed *N*-acylated intermediate reacts intramolecularly via nucleophilic aromatic substitution, results in a formal two-carbon insertion.

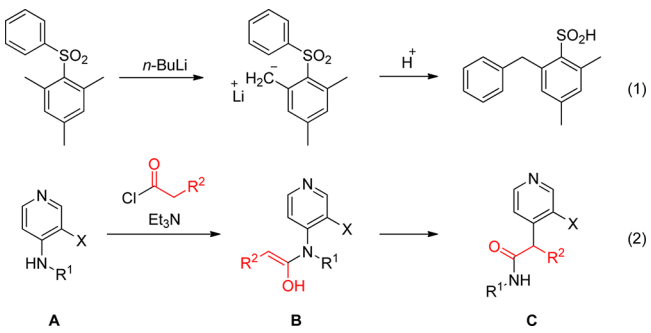


Rearrangements are especially elegant reactions, leading to nonobvious products via intramolecular bond breakage and formation.[1,2] Through atom or atom group migration they can provide access to complex molecules and are valuable transformations in natural product synthesis, heterocyclic chemistry, and industrial processes.[3−8] The Smiles rearrangement is an intramolecular nucleophilic substitution in which an aromatic system shifts from one heteroatom to another via a spirocyclic intermediate. Usually, the nucleophilic heteroatom of phenols or anilines intramolecularly attacks a second aromatic ring, which is activated by electron-withdrawing substituents ortho or para to the attacked position.[9−13]

In the Smiles−Truce rearrangement, an extended variant of the Smiles rearrangement, the nucleophilic attack is carried out by a carbanion and leads to the formation of a new C−C bond, making it an attractive reaction for synthetic chemists (Scheme 1).[2,12,14,15]

In this study, we wish to report the facile synthesis of pyridin-4-yl α-substituted acetamides. The rearrangement of *in situ* generated intermediate **B** leads to the insertion of a two carbon unit into the C−N bond of 4-aminopyridine **A**. We suggest that intramolecular nucleophilic attack by the enol (**B**) leads to the breakage of a C−N bond and the formation of a new C−C bond (Scheme 1). The obtained pyridin-4-yl α-substituted acetamide products (**C**) constitute synthetically useful products for the synthesis of functionalized molecules.[16,17] The herein described pyridin-4-yl α-substituted acetamides are synthetically demanding synthons and to our best knowledge have not been reported previously in the literature.

Scheme 1. C−C Bond-Forming Rearrangements: (1) Smiles−Truce rearrangement, (2) *N*-Acyl Aminopyridine Rearrangement



In the original attempt to *N*-acylate **1a**, adding triethylamine (7 equiv) and chloro acetyl chloride (7 equiv) in THF at room temperature, the starting material **1a** was consumed overnight, and 2-chloro-2-(3-chloropyridin-4-yl)-*N*-(2,4-dimethoxybenzyl) acetamide **2a** was isolated in 79% yield (Table 1, entry 1). However, the isolated product proved not to be the anticipated *N*-acylated compound. Single-crystal X-ray analysis confirmed the formation of the unexpected rearrangement product **2a** (Figure 1).

Motivated by the potential scope and applicability of this reaction, we decided to further investigate our initial findings. Examination of the reaction conditions found that excess and/or repeated addition of reactants was crucial for complete turnover of the starting material (not achieved for every substrate). We propose that triethylamine promotes dehydrohalogenation of chloro acetyl chloride to generate a ketene *in situ* (ketenes are known to form under the given conditions), which subsequently reacts with **1a**.[18] As reported by Sauer and others,[19−21] the high reactivity of ketenes often leads to dimerization and polymerization byproducts and could explain the requirement for an excess of reagents. For strongly exothermic reactions, lowering the temperature to 0 °C

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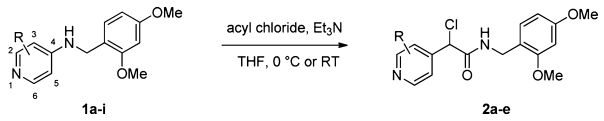
Table 1. Rearrangement of 3-Substituted 4-Amino-pyridines



1a-i 2a-e

			product		
entry	substrate	R	rearranged	*N*-acylated	yield [%]
1	**1a**	3-Cl	**2a**		79
2	**1b**	3-F	**2b**	**3a**	12/3
3	**1c**	3-Br	**2c**		84
4	**1d**	3-I	**2d**		29
5	**1e**	3-Me	**2e**		10
6	**1f**	3-CN		**3b**	14
7	**1g**	3-CO_2Me			
8	**1h**	2-Cl		**3c**	47
9	**1i**	2-CN		**3d**	98

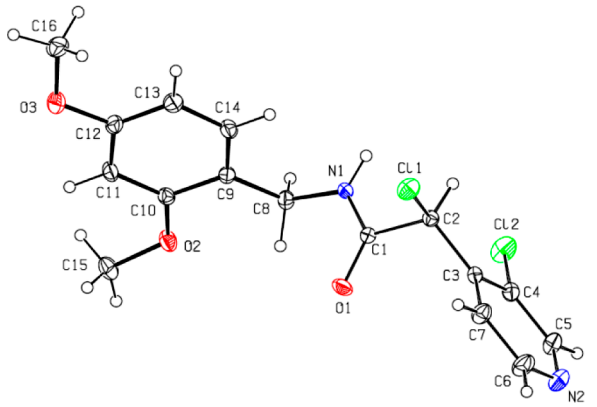


Figure 1. Crystal structure of **2a**.

increased the isolated yields. Overall, the reaction appeared to be cleaner in THF than in CH_2Cl_2 or toluene, and thus THF became the solvent of choice for further studies.

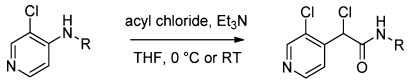
We subjected various substituted 4-aminopyridines to the optimized conditions and found that halogen (**1a–d**) and methyl (**1e**) substituents in the 3-position were tolerated, whereas introduction of a nitrile (**1f**) or methyl acetate group (**1g**) led to *N*-acylation or no reaction (Table 1). Interestingly, subjecting *N*-(2,4-dimethoxybenzyl)-3-fluoropyridin-4-amine (**1b**) to the standard reaction conditions resulted in a mixture of the rearranged and the *N*-acylated products **2b** and **3a** in a 2.5:1 ratio. However, the same substrate (**1b**) gave solely the rearranged product *N*-(2,4-dimethoxybenzyl)-2-(3-fluoropyridin-4-yl)-2-phenoxyacetamide (**2r**) when treated with phenoxyacetyl chloride.

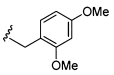
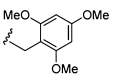
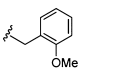
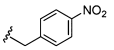
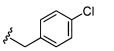
Electron-withdrawing halides in the 3-position seem to enable the nucleophilic attack at the pyridine's ipso-carbon (C-4). A comparable activation of an aromatic substrate is observed in the Smiles rearrangement, where ortho- or para-activating substituents are required in the migrating aryl moiety.[1,2] Despite the electron-withdrawing character of nitrile and methyl ester substituents, decoration of the pyridine with these moieties did not allow substrates **1f** and **1g** to rearrange. Surprisingly, methyl substitution in the 3-position yielded the rearranged product.

The para-position of the ring nitrogen with respect to the reactive center proved to be essential for the reaction, since moving the heteroatom to another position in the ring did not allow the substrates 5-bromo-2-chloro-*N*-(2,4-dimethoxybenzyl)pyridin-3-amine and 3-chloro-*N*-(2,4-dimethoxybenzyl)pyridin-2-amine to undergo rearrangement. In addition to the importance of the substituents in the 3-position, the pyridine nitrogen further withdraws electron density from the aromatic ring and thus increases the electrophilicity of the reacting ipso-carbon.

Substitution in the 2-position (**1h** and **1i**) led to *N*-acylated products (**3c,d**). No substitution of the pyridine ring (*N*-(2,4-dimethoxybenzyl)pyridin-4-amine) gave an unstable product that could not be isolated. Multiple substituents on the pyridine core were not tolerated as substrates for this reaction (methyl 3-chloro-4-((2,4-dimethoxybenzyl)amino)picolinate and (3-chloro-4-((2,4-dimethoxybenzyl)amino)pyridin-2-yl)-methanol). We then turned our attention to the amino-substituent and explored its influence on the rearrangement reaction (Table 2). Although this position appeared to accept a

Table 2. Influence of the Nitrogen Substituent on the Rearrangement



entry	subst.	R	product	yield [%]
1	**1a**		**2a**	79
2	**1j**		**2f**	63
3	**1k**		**2g**	69
4	**1l**		**2h**	34
5	**1m**		**2i**	53
6	**1n**		**2j**	54
7	**1o**		**2k**	53
8	**1p**		**2l**	35
9	**1q**		**2m**	32

wide range of substituents from benzylic (**1a**, **1j–n**) and aromatic (**1o**) to aliphatic (**1p,q**) residues (Table 2), the 2,4-dimethoxybenzyl group afforded the best yield.

To further illustrate the synthetic value of this method, we investigated the applicability of various acyl chlorides. A focused set was employed for the generation of mono- or disubstituted ketenes, which all afforded the rearranged product in excellent yields ranging from 79% to 97% (Table 3). Only introduction of a second substituent at the α-carbon led to a slightly lower yield of 63% for **2n**. The methyl substituent probably sterically hinders the nucleophilic attack on the pyridine's γ-carbon. When acetyl chloride or bromo acetyl bromide were used as acylating agents, no product could be isolated, although consumption of the starting material was observed.

For the presented rearrangement reaction the following mechanism is proposed (Scheme 2). First the ketene, which is formed *in situ* by dehydrohalogenation of an acyl chloride with

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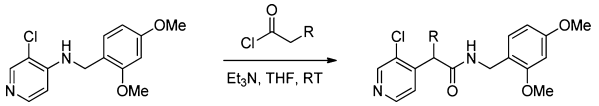
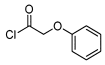
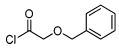
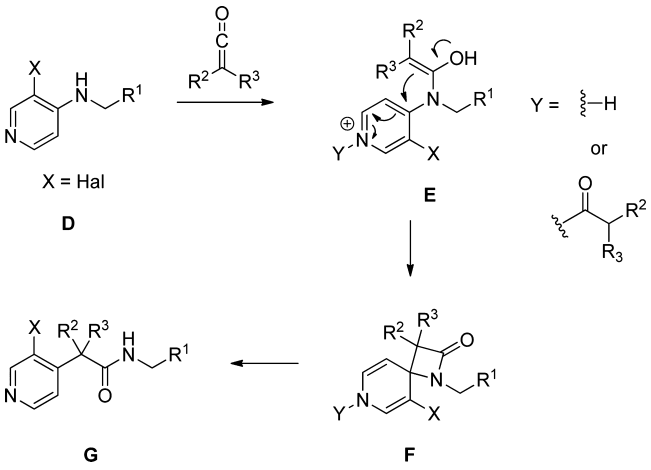
Table 3. Various Acyl Halides Employed in the Rearrangement



entry	acyl chloride	product	R	yield [%]
1		**2a**	Cl	79
2		**2n**	Cl, Me	63
3		**2o**	OMe	97
4		**2p**	OPh	92
5		**2q**	OBn	83

Scheme 2. Proposed Mechanism for the Rearrangement of 4-Amino-3-halo-pyridines



triethylamine, is attacked on its electrophilic carbon by the amine nitrogen of substrate **D** to form the intermediate **E**. Then, intramolecular π-orbital interaction between the enolate α-carbon and the pyridine ipso-carbon results in the formation of the four-membered spiro-β-lactam transition state **F**. Finally, rearomatization of the pyridine leads to breakage of the weaker C−N bond of the spiro-β-lactam and results in formation of the pyridin-4-yl α-substituted acetamide **G**. The nucleophilic attack on the pyridine γ-carbon by the enol is possibly facilitated by ortho substitution with an electron-withdrawing halide. Moreover, the electronegative nitrogen of the pyridine ring lowers the energy of the π-system's LUMO and increases the electrophilicity of the γ-position.[3−8] This effect could be enhanced by either catalytic acylation (excess of acyl chloride) or protonation (via the trialkylammonium salts resulting from the ketene formation, which can act as Brønsted acid catalysts)[18] of the pyridine nitrogen atom. This might further decrease the electron density of the aromatic ring and ultimately lead to a higher susceptibility of the γ-carbon toward a nucleophile. A phenyl analogue of the pyridine precursor **1a**, *N*-benzyl-2-chloro-4-nitroaniline, whose γ-carbon is highly activated through strongly electron-withdrawing *o*-chloro and *p*-nitro substituents, does not undergo the rearrangement under the applied standard reaction conditions.

Anand and co-workers have recently reported a [2 + 2] cycloaddition of cyclohexanone imines and ketenes leading to the formation of spiro-β-lactams.[22] The corresponding analogues cannot be isolated from our rearrangement reactions since rearomatization of the pyridine ring induces cleavage of the C−N bond and leads to the open structure. However, the formation of these spirocyclic-β-lactams by an analogous pathway provides further evidence for the inclusion of transition state **F** in our proposed mechanism.[23]

In summary, we have described the rearrangement of 3-halo-4-amino-pyridines when treated with triethylamine and acyl chlorides, to yield pyridin-4-yl-acetamides. The mild reaction conditions and the simple workup allow a straightforward and scalable synthesis (on a multigram scale **2a** was obtained in 50% yield) of pyridin-4-yl α-substituted acetamides. These molecules represent promising precursor molecules for the synthesis of branched aryl acetamides, which might be employed in future biological screening campaigns and are yet to be exploited structures.

EXPERIMENTAL SECTION

General Information. NMR spectra were recorded on a 500 MHz spectrometer (500 MHz ^{1}H, 125 MHz ^{13}C) at 25 °C. Chemical shifts are reported in ppm (δ) referenced to the NMR solvent, and coupling constants (J) are in hertz.[24] Flash column chromatography was performed on silica gel (60 Å mesh). High-resolution mass spectrometry (HRMS) was conducted using a quadrupole-time-of-flight (QTOF) hybrid mass spectrometer system coupled with an ultraperformance liquid chromatography (UPLC) system. Microwave reactions were carried out in the microwave reactor Biotage Initiator Eight (single-mode reactor, temperature control via IR).

General Procedure A for the Synthesis of 2,4-Dimethoxybenzyl-pyridin-4-amines. The reductive aminations were conducted according to literature using the corresponding aminopyridine (1 equiv), benzaldehyde (3 equiv), acetic acid (3 equiv), sodium triacetoxyborohydride (3 equiv), and DCE (20 mL).[25,26] Some reactions required refluxing at 80 °C. The crude product was purified by silica gel flash chromatography (1−8% MeOH/CH_2Cl_2 or 10−80% EtOAc/hexanes).

General Procedure B for the Synthesis of 2,4-Dimethoxybenzyl-pyridin-4-amines. The copper-catalyzed amination of aryl halides was conducted according to literature.[27] Alternatively, some products were obtained through irradiation in a microwave reactor at 100 °C for 60 min at the absorption level "High". The crude product was purified by silica gel flash chromatography (1−8% MeOH/CH_2Cl_2 or 10−80% EtOAc/hexanes).

General Procedure C for the Rearrangement Reaction of Pyridin-4-amines. A 5 mL reaction vial was charged with the corresponding secondary pyridin-4-amine (0.25 mmol), TEA (3 equiv), and THF (2 mL). Then, the corresponding acyl chloride was added dropwise (the more exothermic reactions required cooling to 0 °C), and the reaction mixture was stirred at rt. If LC−MS indicated incomplete reaction, TEA (5 equiv) and the acyl chloride (2 equiv) were added in intervals of 1 h twice, and the reaction mixture was stirred overnight before it was diluted with EtOAc and saturated $NaHCO_3$ (aq). The aqueous layer was extracted with EtOAc (3×), and the combined organic layers were concentrated and purified by silica gel flash chromatography (1−8% MeOH/CH_2Cl_2 or 10−80% EtOAc/hexanes).

3-Chloro-*N*-(2,4-dimethoxybenzyl)pyridin-4-amine (1a). Procedure A; yellow oil (9.47 g, 83%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.97 (d, J = 5.6 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.73 (t, J = 6.1 Hz, 1H), 6.58 (d, J = 2.4 Hz, 1H), 6.48−6.45 (m, 2H), 4.32 (d, J = 6.2 Hz, 2H), 3.84 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.7, 157.7, 148.9, 148.2, 147.5, 128.0, 117.7, 115.7, 106.2, 104.6, 98.4, 55.4, 55.1, 39.9. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{14}H_{16}ClN_2O_2$ ([M + H]$^+$): 279.0900, found 279.0892.

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***N*-(2,4-Dimethoxybenzyl)-3-fluoropyridin-4-amine (1b).** Procedure A; colorless oil (0.452 g, 37%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.08 (d, J = 3.8 Hz, 1H), 7.88 (d, J = 5.4 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.91 (t, J = 6.2 Hz, 1H), 6.57 (d, J = 2.3 Hz, 1H), 6.52−6.45 (m, 2H), 4.26 (d, J = 6.2 Hz, 2H), 3.83 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.7, 157.7, 148.6 ($^1J_{C-F}$ = 245 Hz), 146.2 ($^4J_{C-F}$ = 4.4 Hz), 142.0 ($^3J_{C-F}$ = 9.9 Hz), 134.7 ($^4J_{C-F}$ = 19 Hz), 128.2, 118.0, 106.7, 104.5, 98.3, 55.4, 55.1, 39.6. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{14}H_{16}FN_2O_2$ ([M + H]$^+$): 263.1196, found 263.1187.

3-Bromo-*N*-(2,4-dimethoxybenzyl)pyridin-4-amine (1c). Procedure A; colorless oil (0.491 g, 50%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.26 (s, 1H), 7.99 (d, J = 5.6 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.58 (d, J = 2.4 Hz, 1H), 6.51 (t, J = 6.1 Hz, 1H), 6.48−6.44 (m, 2H), 4.32 (d, J = 6.2 Hz, 2H), 3.84 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.8, 157.7, 150.2, 149.8, 148.7, 128.1, 117.6, 106.6, 104.6, 98.4, 55.5, 55.1, 40.2. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{14}H_{16}BrN_2O_2$ ([M + H]$^+$): 323.0395, found 323.0396.

***N*-(2,4-Dimethoxybenzyl)-3-iodopyridin-4-amine (1d).** Procedure A; colorless oil (427 mg, 51%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.41 (s, 1H), 7.97 (d, J = 5.6 Hz, 1H), 7.04 (d, J = 8.3 Hz, 1H), 6.58 (d, J = 4.2 Hz, 1H), 6.46 (dd, J = 2.4, 8.3 Hz, 1H), 6.40 (d, J = 5.7 Hz, 1H), 6.11 (t, J = 6.0 Hz, 1H), 4.33 (d, J = 6.1 Hz, 2H), 3.84 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.8, 157.8, 155.9, 152.2, 149.0, 128.3, 117.6, 106.2, 104.5, 98.4, 83.3, 55.5, 55.1, 40.6. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{14}H_{16}IN_2O_2$ ([M + H]$^+$): 371.0257, found 371.0241.

***N*-(2,4-Dimethoxybenzyl)-3-methylpyridin-4-amine (1e).** Procedure A; colorless oil (1.28 g, 25%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.89 (s, 1H), 7.87 (s, 1H), 7.02 (d, J = 8.3 Hz, 1H), 6.57 (d, J = 2.4 Hz, 1H), 6.50 (dd, J = 2.4, 8.4 Hz, 1H), 6.26−6.21 (m, 2H), 4.27 (d, J = 6.1 Hz, 2H), 3.84 (s, 3H), 3.72 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.5, 157.6, 151.5, 148.7, 147.9, 127.9, 118.4, 116.7, 104.4, 104.2, 98.3, 55.4, 55.1, 14.4. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{15}H_{19}N_2O_2$ ([M + H]$^+$): 259.1447, found 259.1437.

4-((2,4-Dimethoxybenzyl)amino)nicotinonitrile (1f). Procedure B; white solid (328 mg, 32%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.48 (s, 1H), 8.17 (d, J = 6.3 Hz, 1H), 7.71 (t, J = 5.8 Hz, 1H), 7.07 (d, J = 8.3 Hz, 1H), 6.60−6.58 (m, 2H), 6.48 (dd, J = 2.4, 8.3 Hz, 1H), 4.37 (d, J = 6.4 Hz, 2H), 3.83 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.9, 157.7, 154.3, 152.7, 150.9, 128.3, 117.0, 116.1, 106.2, 104.7, 98.4, 92.7, 55.5, 55.2, 40.2. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{15}H_{16}N_3O_2$ ([M + H]$^+$): 270.1243, found 270.1230.

Methyl 4-((2,4-Dimethoxybenzyl)amino)nicotinate (1g). Procedure A; white solid (596 mg, 20%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.72 (s, 1H), 8.49 (bs, 1H), 8.19 (d, J = 6.3 Hz, 1H), 7.71 (d, J = 8.3 Hz, 1H), 7.17 (d, J = 8.2 Hz, 1H), 6.80 (d, J = 6.4 Hz, 1H), 6.48 (dd, J = 2.3, 8.3 Hz, 1H), 4.40 (d, J = 5.9 Hz, 2H), 3.83 (s, 6H), 3.73 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.1, 160.2, 158.0, 154.2, 150.5, 150.3, 129.2, 117.2, 106.8, 106.7, 104.6, 98.6, 55.5, 55.2, 51.9, 40.7. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{16}H_{19}N_2O_4$ ([M + H]$^+$): 303.1345, found 303.1331.

2-Chloro-*N*-(2,4-dimethoxybenzyl)pyridin-4-amine (1h). Procedure A; pale yellow oil (0.631 g, 55%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.78 (d, J = 5.9 Hz, 1H), 7.19 (t, J = 5.5 Hz, 1H), 7.11 (d, J = 8.3 Hz, 1H), 6.58 (d, J = 2.4 Hz, 1H), 6.51−6.48 (m, 3H), 4.16 (d, J = 5.8 Hz, 2H), 3.81 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.0, 158.0, 155.9, 150.9, 148.8, 129.1, 117.8, 107.3, 105.1, 104.5, 98.4, 55.4, 55.2, 40.1. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{14}H_{16}ClN_2O_2$ ([M + H]$^+$): 279.0900, found 279.0893.

4-((2,4-Dimethoxybenzyl)amino)picolinonitrile (1i). Procedure B; colorless crystals (504 mg, 26%); mp 119−121 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.09 (d, J = 5.9 Hz, 1H), 7.38 (t, J = 5.6 Hz, 1H), 7.13 (d, J = 8.3 Hz, 1H), 7.05 (d, J = 1.9 Hz, 1H), 6.72 (bs, 1H), 6.59 (d, J = 2.4 Hz, 1H), 6.49 (dd, J = 2.4, 8.3 Hz, 1H), 4.19 (d, J = 5.6 Hz, 2H), 3.81 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.1, 158.1, 153.9, 150.5, 132.7, 129.3, 126.3, 122.0, 118.2, 117.4, 104.5, 98.5, 55.4, 55.2, 40.1. HRMS m/z (ESI$^+$-QTOF) calcd for $C_{15}H_{16}N_3O_2$ ([M + H]$^+$): 270.1243, found 270.1231.

3-Chloro-*N*-(2,4,6-trimethoxybenzyl)pyridin-4-amine (1j). Procedure A; white solid (81 mg, 3%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.15−8.07 (m, 2H), 6.83 (d, J = 5.5 Hz, 1H), 6.26 (s, 2H), 5.69 (t, J = 5.8 Hz, 1H), 4.30 (d, J = 6.0 Hz, 2H), 3.83 (s, 6H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.8, 158.9, 148.7, 148.4, 147.5, 115.7, 106.1, 105.5, 91.0, 55.9, 55.3, 35.0. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{15}H_{18}ClN_2O_3$ ([M + H]$^+$): 309.1006, found 309.1013.

3-Chloro-*N*-(2-methoxybenzyl)pyridin-4-amine (1k). Procedure A; white solid (1.32 g, 55%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.21 (s, 1H), 8.00 (d, J = 5.6 Hz, 1H), 7.27 (m, 1H), 7.13 (dd, J = 7.4, 1.3 Hz, 1H), 7.06 (d, J = 8.1 Hz, 1H), 6.92 (td, J = 7.4, 0.6 Hz, 1H), 6.87 (t, J = 6.1 Hz, 1H), 6.47 (d, J = 5.7 Hz, 1H), 4.45 (d, J = 6.1 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 157.6, 149.9, 149.2, 148.5, 129.1, 127.9, 126.5, 121.2, 116.6, 111.6, 107.1, 56.3, 41.1. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{13}H_{14}ClN_2O$ ([M + H]$^+$): 249.0795, found 249.0791.

3-Chloro-*N*-(4-nitrobenzyl)pyridin-4-amine (1l). Procedure A; off-white solid (53 mg, 3%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.22−8.20 (m, 3H), 7.97 (d, J = 5.6 Hz, 1H), 7.59 (d, J = 8.7 Hz, 2H), 7.26 (t, J = 6.1 Hz, 1H), 6.48 (d, J = 5.5 Hz, 1H), 4.61 (d, J = 6.3 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 148.7, 148.3, 147.8, 147.0, 146.6, 127.9, 123.6, 115.9, 106.3, 44.6. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{12}H_{11}ClN_3O_2$ ([M + H]$^+$): 264.0540, found 264.0533.

3-Chloro-*N*-(4-chlorobenzyl)pyridin-4-amine (1m). Procedure A; white solid (328 mg, 15%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.96 (dd, J = 0.5, 5.7 Hz, 1H), 7.40−7.33 (m, 4H), 7.13 (t, J = 6.3 Hz, 1H), 6.49 (d, J = 5.6 Hz, 1H), 4.45 (d, J = 6.3 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 148.8, 148.2, 147.7, 137.8, 131.4, 128.7, 128.4, 115.8, 106.3, 44.3. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{12}H_{11}Cl_2N_2$ ([M + H]$^+$): 253.0289, found 253.0299.

***N*-benzyl-3-chloropyridin-4-amine (1n).** Procedure A; white solid (422 mg, 22%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.15 (s, 1H), 7.95 (d, J = 5.6 Hz, 1H), 7.32 (d, J = 4.4 Hz, 4H), 7.21−7.25 (m, 1H), 7.09 (t, J = 6.3 Hz, 1H), 6.50 (d, J = 5.6 Hz, 1H), 4.46 (d, J = 6.3 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 149.0, 148.2, 147.6, 138.7, 128.4, 126.9, 126.7, 115.7, 106.4, 45.0. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{12}H_{12}ClN_2$ ([M + H]$^+$): 219.0689, found 219.0691.

3-Chloro-*N*-phenylpyridin-4-amine (1o). See ref 28.

3-Chloro-*N*-propylpyridin-4-amine (1p). Procedure A; yellow oil (740 mg, 53%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.16 (s, 1H), 8.03 (d, J = 5.6 Hz, 1H), 6.63 (d, J = 5.6 Hz, 1H), 6.30 (t, J = 5.6 Hz, 1H), 3.17−313 (m, 2H), 1.58−1.51 (m, 2H), 0.88 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 149.0, 148.3, 147.6, 115.5, 105.7, 48.4, 21.4, 11.1. HRMS (ESI$^+$-QTOF) m/z calcd for $C_8H_{12}ClN_2$ ([M + H]$^+$): 171.0689, found 171.0678.

***N*-(But-3-en-1-yl)-3-chloropyridin-4-amine (1q).** Procedure B; yellow oil (128 mg, 32%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.14 (s, 1H), 8.05 (d, J = 5.7 Hz, 1H), 6.68 (d, J = 5.7 Hz, 1H), 6.23 (t, J = 5.6 Hz, 1H), 5.87−5.75 (m, 1H), 5.13−5.08 (m, 1H), 5.06−5.03 (m, 1H), 3.27 (q, J = 6.1, 6.9 Hz, 2H), 2.34−2.29 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 148.8, 148.3, 147.6, 135.7, 116.7, 115.6, 105.8, 41.0, 32.5. HRMS (ESI$^+$-QTOF) m/z calcd for $C_9H_{12}ClN_2$ ([M + H]$^+$): 183.0689, found 183.0681.

2-Chloro-2-(3-chloropyridin-4-yl)-*N*-(2,4-dimethoxybenzyl)-acetamide (2a). Procedure C; white solid (3.8 g, 79%); mp 145−147 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.87 (t, J = 5.7 Hz, 1H), 8.68 (s, 1H), 8.61 (d, J = 5.1 Hz, 1H), 7.70 (d, J = 5.1 Hz, 1H), 7.10 (d, J = 8.3 Hz, 1H), 6.55 (d, J = 2.4 Hz, 1H), 6.49 (dd, J = 2.4, 8.3 Hz, 1H), 5.92 (s, 1H), 4.27−4.18 (m, 2H), 3.76 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.8, 160.0, 157.8, 149.1, 148.6, 142.9, 130.0, 129.2, 124.2, 117.8, 104.3, 98.3, 55.4, 55.2, 54.8, 37.9. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{16}H_{17}Cl_2N_2O_3$ ([M + H]$^+$): 355.0616, found 355.0600.

2-Chloro-*N*-(2,4-dimethoxybenzyl)-2-(3-fluoropyridin-4-yl)-acetamide (2b). Procedure C; purification by preparative HPLC (5−95% MeCN/H_2O, 15 min); white solid (8 mg, 12%); mp 119−122 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (d, J = 1.4 Hz, 1H), 8.44 (d, J = 5.0 Hz, 1H), 7.37−7.36 (m, 2H), 7.19 (d, J = 8.1 Hz, 1H), 6.50 (d, J = 2.5 Hz, 1H), 6.45 (dd, J = 2.5, 8.1 Hz, 1H), 5.56 (s, 1H), 4.50−4.41

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(m, 2H), 3.87 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.66, 161.18, 158.90, 157.22 (d, $^1J_{C-F}$ = 259.5 Hz, 1C), 145.45 (d, $^4J_{C-F}$ = 5.4 Hz, 1C), 138.0 (d, $^2J_{C-F}$ = 24.5 Hz, 1C), 134.7 (d, $^3J_{C-F}$ = 10.9 Hz, 1C), 130.9, 124.0, 117.7, 104.3, 99.0, 55.7, 55.6, 52.9 (d, $^3J_{C-F}$ = 1.8 Hz, 1C), 40.4. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{16}H_{17}ClFN_2O_3$ ([M + H]$^+$): 339.0912, found 339.0905.

2-(3-Bromopyridin-4-yl)-2-chloro-*N*-(2,4-dimethoxybenzyl)-acetamide (2c). Procedure C; recrystallization (CH_2Cl_2/hexanes); off-white solid (59 mg, 84%); mp 155−157 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.90 (d, J = 5.6 Hz, 1H), 8.78 (s, 1H), 8.62 (d, J = 5.2 Hz, 1H), 7.69 (d, J = 4.9 Hz, 1H), 7.10 (d, J = 8.3 Hz, 1H), 6.55 (d, J = 2.4 Hz, 1H), 6.48 (dd, J = 2.4, 8.3 Hz, 1H), 5.84 (s, 1H), 4.27−4.18 (m, 2H), 3.76 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 160.0, 157.8, 151.7, 149.0, 144.5, 129.2, 124.6, 121.1, 117.8, 104.3, 98.3, 57.1, 55.4, 55.2, 37.9. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{16}H_{17}BrClN_2O_3$ ([M + H]$^+$): 399.0111, found 399.0103.

2-Chloro-*N*-(2,4-dimethoxybenzyl)-2-(3-iodopyridin-4-yl)-acetamide (2d). Procedure C; recrystallization (MeOH); off-white solid (24 mg, 29%); mp 158−160 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.94 (s, 1H), 8.92 (t, J = 5.5 Hz, 1H), 8.58 (d, J = 5.0 Hz, 1H), 7.64 (d, J = 5.0 Hz, 1H), 7.11 (d, J = 8.3 Hz, 1H), 6.55 (d, J = 2.5 Hz, 1H), 6.48 (dd, J = 2.4, 6.0 Hz, 1H), 5.66 (s, 1H), 4.27−4.18 (m, 2H), 3.76 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 159.9, 157.8, 157.4, 149.2, 147.7, 129.2, 124.4, 117.8, 104.3, 99.1, 98.3, 61.4, 55.4, 55.2, 37.8. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{16}H_{17}IClN_2O_3$ ([M + H]$^+$): 446.9972, found 446.9974.

2-Chloro-*N*-(2,4-dimethoxybenzyl)-2-(3-methylpyridin-4-yl)-acetamide (2e). Procedure C; clear oil (12 mg, 10%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.68 (d, J = 5.5 Hz, 1H), 8.44 (d, J = 5.1 Hz, 1H), 8.42 (s, 1H), 7.48 (d, J = 5.1 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.54 (d, J = 2.1 Hz, 1H), 6.47 (dd, J = 2.1, 8.3 Hz, 1H), 5.79 (s, 1H), 4.25−4.16 (m, 2H), 3.75 (s, 3H), 3.73 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.0, 160.5, 158.4, 151.4, 148.2, 144.2, 131.6, 129.8, 122.5, 118.4, 104.8, 98.8, 56.1, 55.9, 55.7, 38.4, 15.9. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{17}H_{20}ClN_2O_3$ ([M + H]$^+$): 335.1162, found 335.1150.

2-Chloro-2-(3-chloropyridin-4-yl)-*N*-(2,4,6-trimethoxy-benzyl)acetamide (2f). Procedure C; off-white solid (19 mg, 63%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.70 (s, 1H), 8.61 (d, J = 5.1 Hz, 1H), 8.37 (t, J = 4.6 Hz, 1H), 7.70 (d, J = 5.1 Hz, 1H), 6.24 (s, 2H), 5.85 (s, 1H), 4.29−4.18 (m, 2H), 3.78 (s, 3H), 3.75 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.2, 160.8, 159.1, 149.1, 148.5, 143.0, 130.1, 124.1, 104.8, 90.7, 55.7, 55.3, 54.7, 32.2. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{17}H_{19}Cl_2N_2O_4$ ([M + H]$^+$): 385.0722, found 385.0720.

2-Chloro-2-(3-chloropyridin-4-yl)-*N*-(2-methoxybenzyl)-acetamide (2g). Procedure C; yellow solid (91 mg, 69%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.96 (m, 1H), 8.68 (s, 1H), 8.61 (d, J = 5.1 Hz, 1H), 7.70 (d, J = 5.1 Hz, 1H), 7.26 (m, 1H), 7.18 (dd, J = 7.4, 1.6 Hz, 1H), 6.99 (d, J = 8.2 Hz, 1H), 6.91 (td, J = 7.4 Hz, 0.9, 1H), 5.95 (s, 1H), 4.30 (m, 2H), 3.75 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.0, 156.7, 149.1, 148.6, 142.8, 130.0, 128.4, 128.0, 125.6, 124.2, 120.1, 110.6, 55.3, 54.9, 38.1. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{15}H_{15}Cl_2N_2O_2$ ([M + H]$^+$): 325.0511, found 325.0496.

2-Chloro-2-(3-chloropyridin-4-yl)-*N*-(4-nitrobenzyl)-acetamide (2h). Procedure C; white solid (10 mg, 34%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.37 (t, J = 5.8 Hz, 1H), 8.70 (s, 1H), 8.62 (d, J = 5.1 Hz, 1H), 8.22 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 5.0 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 6.00 (s, 1H), 4.49 (d, J = 6.1 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.5, 149.2, 148.7, 146.6, 146.5, 142.8, 130.0, 128.3, 124.3, 123.5, 55.1, 42.4. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{14}H_{12}Cl_2N_3O_3$ ([M + H]$^+$): 340.0256, found 340.0255.

2-Chloro-*N*-(4-chlorobenzyl)-2-(3-chloropyridin-4-yl)-acetamide (2i). Procedure C; white solid (43 mg, 53%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.20 (t, J = 5.8 Hz, 1H), 8.68 (s, 1H), 8.60 (d, J = 5.2 Hz, 1H), 7.67 (d, J = 5.2 Hz, 1H), 7.41−7.38 (m, 2H), 7.30−7.27 (m, 2H), 5.94 (s, 1H), 4.33 (d, J = 6.1 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.2, 149.2, 148.6, 142.8, 137.5, 131.6, 130.0, 129.2, 128.3, 124.3, 55.0, 42.2. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{14}H_{12}Cl_3N_2O$ ([M + H]$^+$): 329.0015, found 329.0009.

***N*-Benzyl-2-chloro-2-(3-chloropyridin-4-yl)acetamide (2j).** Procedure C; white solid (44 mg, 54%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.18 (t, J = 5.6 Hz, 1H), 8.68 (s, 1H), 8.61 (d, J = 5.1 Hz, 1H), 7.69 (d, J = 5.1 Hz, 1H), 7.35−7.24 (m, 5H), 5.94 (s, 1H), 4.35 (d, J = 6.1 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.5, 150.1, 148.5, 143.6, 137.2, 131.6, 129.1, 128.2, 128.15, 123.8, 56.1, 44.6. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{14}H_{13}Cl_2N_2O$ ([M + H]$^+$): 295.0394, found 295.0394.

2-Chloro-2-(3-chloropyridin-4-yl)-*N*-phenylacetamide (2k). Procedure C; white solid (43 mg, 53%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.74 (s, 1H), 8.71 (s, 1H), 8.64 (d, J = 5.0 Hz, 1H), 7.77 (d, J = 5.1 Hz, 1H), 7.60−7.57 (m, 2H), 7.37−7.33 (m, 2H), 7.15−7.11 (m, 1H), 6.06 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.5, 149.1, 148.7, 142.3, 138.0, 130.0, 128.9, 124.4, 124.1, 119.6, 55.7. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{13}H_{11}Cl_2N_2O$ ([M + H]$^+$): 281.0248, found 281.0234.

2-Chloro-2-(3-chloropyridin-4-yl)-*N*-propylacetamide (2l). Procedure C; colorless oil (63 mg, 35%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.65 (d, J = 5.6 Hz, 1H), 8.60 (d, J = 5.0 Hz, 1H), 7.68 (d, J = 5.0 Hz, 1H), 5.84 (s, 1H), 3.09 (q, J = 5.9, 6.7 Hz, 2H), 1.49−1.42 (m, 2H), 0.84 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.8, 149.1, 148.6, 143.0, 129.2, 124.2, 55.0, 41.0, 20.9, 11.2. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{10}H_{13}Cl_2N_2O$ ([M + H]$^+$): 247.0405, found 247.0395.

***N*-(But-3-en-1-yl)-2-chloro-2-(3-chloropyridin-4-yl)-acetamide (2m).** Procedure C; colorless oil (24 mg, 32%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.66 (t, J = 6.0 Hz, 1H), 8.60 (d, J = 5.0 Hz, 1H), 7.66 (d, J = 5.0 Hz, 1H), 5.84 (s, 1H), 5.80−5.72 (m, 1H), 5.05 (dq, 1.6, 2.0, 17.0 Hz, 1H), 5.02−4.99 (m, 1H), 3.22−3.18 (m, 2H), 2.22−2.19 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.9, 149.1, 148.6, 143.0, 136.9, 130.0, 124.2, 116.5, 55.0, 39.7, 33.9. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{11}H_{13}Cl_2N_2O$ ([M + H]$^+$): 259.0405, found 259.0395.

2-Chloro-2-(3-chloropyridin-4-yl)-*N*-(2,4-dimethoxybenzyl)-propanamide (2n). Procedure C; white solid (99 mg, 63%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.62 (s, 1H), 8.60 (d, J = 5.2 Hz, 1H), 8.38 (t, J = 5.9 Hz, 1H), 7.79 (d, J = 5.2 Hz, 1H), 7.11 (d, J = 8.3 Hz, 1H), 6.54 (d, J = 2.8 Hz, 1H), 6.48 (dd, J = 2.3, 8.3 Hz, 1H), 4.24 (m, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.3, 159.7, 157.6, 150.1, 148.6, 146.9, 130.2, 128.5, 122.8, 118.3, 104.2, 98.1, 68.8, 55.3, 55.1, 38.0, 28.5. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{17}H_{19}Cl_2N_2O_3$ ([M + H]$^+$): 369.0773, found 369.0768.

2-(3-Chloropyridin-4-yl)-*N*-(2,4-dimethoxybenzyl)-2-methoxyacetamide (2o). Procedure C; white solid (194 mg, 97%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.63 (s, 1H), 8.55 (d, J = 4.9 Hz, 1H), 8.47 (t, J = 6.0 Hz, 1H), 7.46 (d, J = 4.9 Hz, 1H), 7.05 (d, J = 8.3 Hz, 1H), 6.54 (d, J = 2.4 Hz, 1H), 6.46 (dd, J = 2.4, 8.3 Hz, 1H), 5.09 (s, 1H), 4.21 (d, J = 6.0 Hz, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 3.34 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.3, 159.8, 157.7, 149.0, 148.2, 144.2, 130.8, 128.7, 123.3, 118.4, 104.2, 98.2, 79.2, 57.6, 55.3, 55.2, 37.1. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{17}H_{20}ClN_2O_4$ ([M + H]$^+$): 351.1112, found 351.1096.

2-(3-Chloropyridin-4-yl)-*N*-(2,4-dimethoxybenzyl)-2-phenoxyacetamide (2p). Procedure C; off-white solid (196 mg, 92%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.81 (t, J = 5.7 Hz, 1H), 8.67 (s, 1H), 8.54 (d, J = 5.0 Hz, 1H), 7.55 (d, J = 5.0 Hz, 1H), 7.29 (t, J = 8.1 Hz, 2H), 6.85−7.05 (m, 4H), 6.53 (d, J = 2.3 Hz, 1H), 6.44 (dd, J = 2.3, 8.3 Hz, 1H), 6.06 (s, 1H), 4.18−4.30 (m, 2H), 3.75 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ166.1, 159.8, 157.7, 156.4, 149.2, 148.3, 143.3, 130.5, 129.6, 128.8, 123.3, 122.0, 118.2, 115.5, 104.2, 98.2, 75.2, 55.4, 55.2, 37.3. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{22}H_{22}ClN_2O_4$ ([M + H]$^+$): 413.1268, found 413.1263.

2-(Benzyloxy)-2-(3-chloropyridin-4-yl)-*N*-(2,4-dimethoxybenzyl)acetamide (2q). Procedure C; white solid (159 mg, 83%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.63 (s, 1H), 8.56 (d, J = 4.9 Hz, 1H), 8.49 (t, J = 5.9 Hz, 1H), 7.54 (d, J = 4.9 Hz, 1H), 7.40−7.25 (m, 5H), 7.07 (d, J = 8.5 Hz, 1H), 6.55 (d, J = 2.2 Hz, 1H), 6.46 (dd, J = 2.2 Hz, J = 8.5 Hz, 1H), 5.75 (CH_2Cl_2), 5.30 (s, 1H), 4.65−4.50 (m, 2H), 4.26 (m, 2H), 3.76 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (125 MHz,

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DMSO-d_6) δ 167.3, 159.8, 157.7, 149.0, 148.2, 144.3, 137.1, 130.8, 128.7, 128.3, 128.2, 127.9, 127.9, 127.7, 123.4, 118.5, 104.2, 98.3, 77.2, 71.5, 55.3, 55.2, 37.3. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{15}H_{15}Cl_2N_2O_2$ ([M + H]$^+$): 325.0511, found 325.0496. HRMS m/z calcd for $C_{23}H_{24}ClN_2O_4$ ([M + H]$^+$): 427.1425, found 427.1405.

***N*-(2,4-Dimethoxybenzyl)-2-(3-fluoropyridin-4-yl)-2-phenoxyacetamide (2r).** Procedure C; preparative HPLC (5−95% MeCN/H_2O, 15 min); white solid (6 mg, 14%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.76 (t, J = 5.8 Hz, 1H), 8.62 (d, J = 1.4 Hz, 1H), 8.47 (d, J = 5.0 Hz, 1H), 7.60 (t, J = 5.5 Hz, 1H), 7.32−7.28 (m, 2H), 7.03−6.98 (m, 4H), 6.53 (d, J = 2.4 Hz, 1H), 6.43 (dd, J = 2.4, 8.3 Hz, 1H), 6.09 (s, 1H), 4.27−4.20 (m, 2H), 3.74 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.5, 159.8, 157.6, 156.8 (d, $^1J_{C-F}$ = 257.2 Hz, 1C), 156.4, 146.1 (d, $^4J_{C-F}$ = 5.0 Hz, 1C), 138.0 (d, $^2J_{C-F}$ = 23.7 Hz, 1C), 132.7 (d, $^3J_{C-F}$ = 11.7 Hz, 1C), 129.6, 128.6, 123.1, 122.0, 118.2, 115.6, 104.2, 98.2, 72.5, 55.3, 55.2, 37.2. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{22}H_{22}FN_2O_4$ ([M + H]$^+$): 397.1564, found 397.1545.

2-Chloro-*N*-(2,4-dimethoxybenzyl)-*N*-(3-fluoropyridin-4-yl)-acetamide (3a). Procedure C; 1:2.5 mixture of **3a** and the rearranged product **2b**. The ^{1}H NMR of the mixture was collected and confirms identity of **3a**, however the product could not be isolated.

2-Chloro-*N*-(3-cyanopyridin-4-yl)-*N*-(2,4-dimethoxybenzyl)-acetamide (3b). Procedure C; colorless oil (14 mg, 14%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.94 (s, 1H), 8.47 (d, J = 6.1 Hz, 1H), 7.17 (d, J = 6.3 Hz, 1H), 6.82 (d, J = 8.6 Hz, 1H), 6.48 (d, J = 8.5 Hz, 1H), 6.32 (dd, J = 8.3, 8.6 Hz, 1H), 5.53 (s, 2H), 5.43 (s, 2H), 3.92 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.6, 159.4, 157.7, 150.0, 145.8, 144.7, 143.1, 128.6, 116.2, 110.4, 109.9, 104.9, 102.9, 98.7, 55.8, 55.6, 40.6. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{17}H_{17}ClN_3O_3$ ([M + H]$^+$): 346.0958, found 346.0946.

2-Chloro-*N*-(2-chloropyridin-4-yl)-*N*-(2,4-dimethoxybenzyl)-acetamide (3c). Procedure C; brown oil (33 mg, 47%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.36 (d, J = 5.4 Hz, 1H), 7.53 (d, J = 1.7 Hz, 1H), 7.34 (dd, J = 1.85, 4.4 Hz, 1H), 7.10 (d, J = 8.3 Hz, 1H), 6.47 (d, J = 2.2 Hz, 1H), 6.43 (dd, J = 2.3, 8.5 Hz, 1H), 4.85 (s, 2H), 4.39 (s, 2H), 3.71 (s, 3H), 3.62 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.4, 160.2, 158.0, 151.2, 150.7, 150.5, 130.2, 122.3, 121.5, 115.6, 104.5, 98.3, 55.2, 55.1, 47.3, 42.9. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{16}H_{17}Cl_2N_2O_3$ ([M + H]$^+$): 355.0616, found 355.0618.

2-Chloro-*N*-(2-cyanopyridin-4-yl)-*N*-(2,4-dimethoxybenzyl)-acetamide (3d). Procedure C; off-white solid (63 mg, 98%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.69 (d, J = 5.4 Hz, 1H), 8.08 (d, J = 2.1 Hz, 1H), 7.65 (dd, J = 2.1, 5.4 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 6.47 (d, J = 2.5 Hz, 1H), 6.43 (dd, J = 2.4, 8.4 Hz, 1H), 4.88 (s, 2H), 4.44 (ss, 2H), 3.71 (s, 3H), 3.61 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.5, 160.3, 158.0, 152.2, 149.8, 133.4, 130.3, 127.2, 125.8, 117.1, 115.5, 104.5, 98.3, 55.2, 55.1, 47.4, 43.0. HRMS (ESI$^+$-QTOF) m/z calcd for $C_{17}H_{17}ClN_3O_3$ ([M + H]$^+$): 346.0958, found 346.0955.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Crystallographic data (in CIF format) for **2a** and **2c** and ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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