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Cu-Catalyzed Aerobic Oxidative Cyclization of Guanidylpyridines and Derivatives

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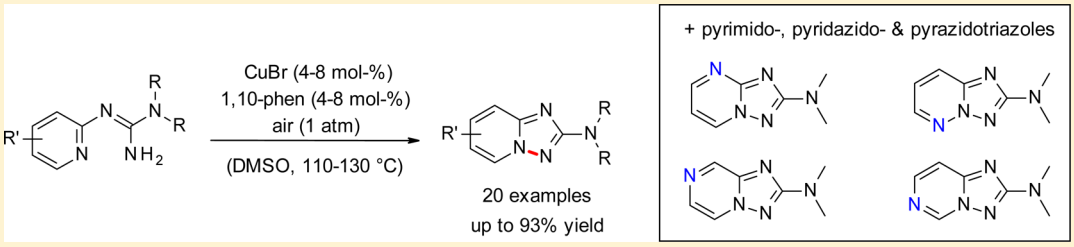
Supporting Information



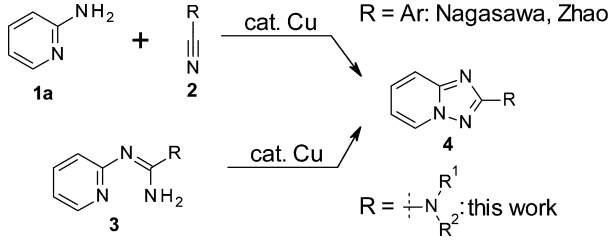
ABSTRACT: A new method for the straightforward synthesis of 2-amino-[1,2,4]triazolo[1,5-*a*]pyridines and derivatives is presented. The target products are synthesized in high yields from guanidylpyridines and analogues via copper-catalyzed N−N coupling. The present methodology shows a wide scope, tolerating not only different substituents on the pyridine ring but also different heterocylic rings such as pyrazines, pyrimidines, and pyridazines.

2-Amino-[1,2,4]triazolo[1,5-*a*]pyridine scaffolds have acquired increased relevance in medicinal chemistry in the past few years.[1] Compounds containing this core structure have shown biological activity in a variety of therapeutic domains spanning from oncology to inflammatory diseases. Synthetic access to 2-amino-[1,2,4]triazolo[1,5-*a*]pyridines typically involves multistep reaction sequences with low atom efficiency,[2] with 2-alkyl amino derivatives posing significant challenges.[2d−f] In the past few years, metal-catalyzed N−N coupling has emerged as a promising tool to construct 1,2-diazaheterocycles.[3] Nevertheless, the scope of this novel methodology is still quite narrow, as witnessed by the paucity of available related literature.[4]

Inspired by a report from Ueda and Nagasawa[3a] and internal work[3b] on the synthesis of 2-*aryl*-[1,2,4]triazolo[1,5-*a*]pyridines (Scheme 1, top), we hoped to employ the N−N disconnection approach for the 2-amino derivatives. Unfortunately, application of the Nagasawa methodology to aminopyridine **1a** and dimethylcyanamide only afforded the desired product **4a** in moderate yield.[5] We speculated that a possible issue was the low reactivity of cyanamide under the reaction conditions.[6] Reasoning that guanidine **3** (Scheme 1, bottom, R = NR^1R^2) would be a more suitable starting material,[7] we hence embarked on the development of an efficient catalytic system for its oxidative N−N bond coupling.[8]

We started our investigations by testing various solvents with 5 mol % CuBr and 5 mol % phenanthroline **5a** (Figure 1) at 130 °C, using model substrate **3a**. We were pleased to observe full conversion and 92% yield using DMSO as the most suitable solvent (Table 1, entry 1).[9] It is worth noting that neither additives nor chlorinated solvents were required for the reaction to proceed in high yield, rendering the present

Scheme 1. Approaches to 2-Amino-[1,2,4]triazolo[1,5-*a*]pyridine via Oxidative N−N Bond Formation



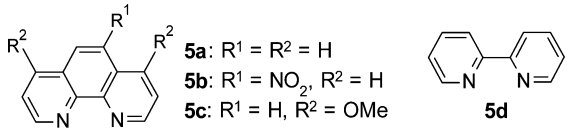


Figure 1. Ligands.

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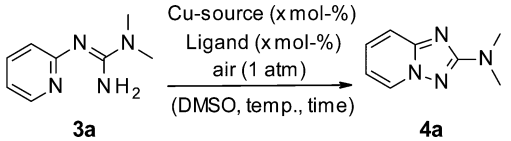
Table 1. Optimization of Reaction Conditions[a]



3a 4a

Entry	Cu-source	Ligand	x	T (°C)	t (h)	Conv. (%)[b]	Yield (%)[b]
1	CuBr	**5a**	5	130	3	>99	92
2	CuI	**5a**	5	130	6	>99	99
3	CuCl	**5a**	5	130	6	91	90
4[c]	Cu	**5a**	5	130	18	93	85
5	CuBr	**5b**	5	130	21	>99	92
6	CuBr	**5c**	5	130	6	85	44
7	CuBr	**5d**	5	130	22	>99	95
8	CuBr	**5a**	5	110	21	>99	97
9	CuBr	**5a**	4	110	22	99	90[d]
10	CuBr	**5a**	2.5	110	22	53	44
11	CuBr	-	4	110	22	57	42

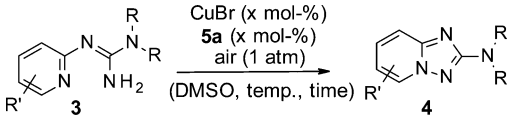
[a]All reactions run on a 0.3 g scale at a concentration of 0.6 M. [b]By HPLC using internal standard. [c]Cu powder used. [d]Isolated yield: 87% (average of two runs).

methodology very attractive from both an economic and ecologic point of view.

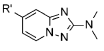
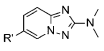
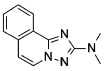
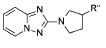
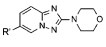
Various Cu-containing catalyst precursors were tested, which revealed that Cu(I) sources generally give better results than Cu(II).[9] Copper halides generally showed very good activities with CuBr > CuI > CuCl (entries 1−3). Cu powder performed also very well (entry 4). On the other hand, variations on the ligand were less tolerated. Among the various ligands tested,[9] **5b** and **5d** proved the most effective, although much longer reaction times were needed in comparison to **5a** to reach full conversion (entries 5 and 7). The presence of a methoxy group on the phenanthroline (ligand **5c**) dramatically reduced the reaction selectivity (entry 6). When the copper/ligand loading and the temperature were reduced to 4 mol % and 110 °C, respectively, the best catalyst combination proved to be CuBr and **5a** (entries 8−9).[9] Notably, the reaction also worked in the absence of a ligand, although the conversion is much lower (entry 11).[10] The reaction can also be carried out using a mixture of 5% v/v oxygen in nitrogen as oxidative agent, albeit with longer reaction times.[11]

Next, we explored the substrate scope of the reaction. Substitutions at all four positions of the pyridine fragment were tolerated, as well as a variety of functional groups (Table 2). Interestingly, while 3- and 6-chloro derivatives cyclize in good yield (entries 1 and 12), the corresponding bromo analogues **3y** and **3z** showed no conversion. If the halogen is iodine, CuI had to be used in place of CuBr in order to avoid halogen scrambling on the aromatic ring (entry 9).[12] Furthermore, we investigated the scope of substitutions at the guanidine fragment. Besides the dimethylamino group, cyclic five- (entries 16−17) and six-membered rings (entries 18−19) as well as a diethylamino group (entry 14) were tolerated, albeit the latter with a moderate yield. If steric bulk was increased even further to a diisopropylamino group, only traces of product could be

Table 2. Substrate Scope



3 4

Entry	Product			x	T (°C)	t (h)	Yield[a] (%)
1		**4b**	R‘ = Cl	8	110	29	79
2		**4c**	R‘ = Me	4	110	23	86
3		**4d**	R‘ = Cl	6	110	40	78
4		**4e**	R‘ = Me	8	130	18	55
5		**4f**	R‘ = OMe	8	110	23	80
6		**4g**	R‘ = Cl	8	110	41	82
7		**4h**	R‘ = F	4	110	23	74
8		**4i**	R‘ = Br	4	110	46	67
9[b]		**4j**	R‘ = I	8	110	20	83
10		**4k**	R‘ = Me	4	110	43	79
11		**4l**	R‘ = Ph	4	110	46	77
12		**4m**		4	110	23	77
13		**4n**		8	110	40	83
14		**4o**	R = Et	8	130	24	45
15		**4p**	R = iPr	8	130	40	traces
16		**4q**	R‘‘ = H	8	130	16	93
17		**4r**	R‘‘ = OH	6	130	22	57
18		**4s**	R‘ = H	4	110	25	70
19		**4t**	R‘ = F	4	110	46	59

[a]Isolated yield, average of two runs on a 0.3 g scale. [b]CuI used as catalyst precursor.

detected (entry 15).[13] To our delight, the cyclization also occurred with an unprotected hydroxy group as substituent (entry 17), thus expanding the functional group tolerability.

Remarkably, bis-azaheterocyclic substrates such as 2-guanidyl pyrimidine, pyridazine, and pyrazine can also be transformed into the corresponding fused triazolo heterocycles in moderate to good yields (Table 3).

The mechanism of the reaction is still unclear. As shown in Table 1, a ligand acceleration effect was detectable, but not as pronounced as in other Cu-catalyzed couplings.[14] Moreover, reaction performance was nearly independent of the Cu/ligand ratio.[9] On the other hand, the replacement of the phenanthroline with poorly coordinating bases such as 2,6-lutidine or DBU strongly inhibited the reaction, suggesting that phenanthroline is unlikely to act simply as a base.[9,15] Detailed kinetic experiments as well as efforts to isolate catalytically relevant Cu complexes are currently ongoing in our laboratories.

In summary, a straightforward synthesis of 2-amino-[1,2,4]-triazolo[1,5-*a*]pyridines has been reported. The present

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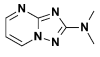
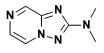
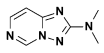
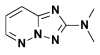
Table 3. Pyrimidyl-, Pyridazyl-, and Pyrazylguanidines as Substrates[a]

Entry	Product		T (°C)	t (h)	Yield[b] (%)
1		**4u**	130	19	77
2		**4v**	130	41	78
3		**4w**	130	46	67
4		**4x**	130	43	40

[a]Reaction conditions: substrate (0.3 g), CuBr (8 mol %), **5a** (8 mol %), air (1 atm), DMSO. [b]Isolated yield, average of two runs.

methodology has demonstrated wide substrate scope. Of note, each and every position of the ring can be decorated with halogens, thus allowing further derivatizations via coupling chemistry. Additionally, a fourth nitrogen can be introduced in the six-membered ring, giving access to the pyrimidine, pyridazine, and pyrazine analogues. The method runs with catalytic amounts of an inexpensive copper salt and readily available oxygen as the oxidation agent. These features render the reaction attractive for future applications.

EXPERIMENTAL SECTION

General Experimental Details. Sodium hydride (NaH) was purchased as a 60% suspension in mineral oil. Prior to use, the suspension was washed three times with hexane to remove the mineral oil. Amounts refer to the 60% suspension. *N*-(Pyridin-2-yl)guanidine (see ref 13) was purchased as a bis hydrochloride salt. The free base was liberated using sodium carbonate prior to use. All other commercially available starting materials were used as received. HPLC spectra were recorded using analytical methods reported in brackets and specified in the Supporting Information. High-resolution mass spectra (HRMS) were recorded in Q-TOF mode. NMR spectra were recorded using 400 and 600 MHz instruments at ambient temperature with $CDCl_3$ as the solvent. Chemical shifts (δ in ppm) are reported relative to tetramethylsilane as internal standard in the following format: chemical shift in ppm (peak form, *coupling constant if applicable*, integral). NMR abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; quint, quintuplet; sext, sextuplet; hept, heptuplet; m, multiplet; br, broad. Melting points were recorded on a melting point apparatus (compounds **3/4a−c**, **3/4f**, **3/4h−j**, **3/4l−n**, **3/4s−t**, **3y**, **3z**) or on a differential scanning calorimetry (DSC) instrument using a temperature program heating from 30−400 °C at a rate of 2.5 K/min (compounds **3/4d−e**, **3/4g**, **3/4k**, **3/4o−r**, **3/4u−x**).

General Procedure A. Under a stream of argon sodium *tert*-butoxide (1.1 equiv) was added to a well stirred solution of substrate (1.00 equiv) in dimethyl sulfoxide (DMSO, *C* = 0.1 g/mL). The mixture was stirred for 15 min at room temperature (RT). Then, *N,N*-dimethylcyanamide (1.18 equiv) was added dropwise. The solution was stirred for 30 min at RT and then heated at 50 °C until full conversion (3−21 h). The reaction was quenched with cold water and then extracted three times with dichloromethane (DCM). The organic phases were collected, dried with sodium sulfate, and evaporated to dryness. The product was purified by column chromatography. The column chromatography was performed using prepacked silica columns that were neutralized with the respective eluent enriched with 1−10% of triethylamine.

1,1-Dimethyl-3-pyridin-2-yl-guanidine (***3a***). Under a stream of argon, sodium hydride (5.00 g, 125 mmol, 1.18 equiv) was added to a well stirred solution of pyridin-2-amine (10 g, 106 mmol, 1.00 equiv) in DMSO (100 mL) at 10 °C. Then, *N,N*-dimethylcyanamide (10 mL, 126 mmol, 1.18 equiv) was added and the mixture was stirred at RT for 90 min. The reaction was quenched with 200 mL of cold water and then extracted three times with 200 mL of ethyl acetate (AcOEt). The organic phases were dried with sodium sulfate and filtered, and the solvent was evaporated. The crude product was dissolved in 50 mL of DCM, and 50 mL of water was added. The aqueous phase was extracted twice with 50 mL of DCM. The organic phases were collected and dried with sodium sulfate, and the solvent was then evaporated. After purification by column chromatography (eluent: DCM/MeOH 98:2), the product was obtained as a yellow oil in 62% yield (10.98 g). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.10 (dd, J = 5.0, 2.1 Hz, 1 H), 7.46−7.44 (m, 1 H), 7.40 (s broad, 2 H), 6.87 (dt, J = 8.2, 1.0 Hz, 1 H), 6.66−6.64 (m, 1 H), 3.06 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 163.2, 156.6, 145.6, 137.1, 120.1, 114.6, 36.8; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_8H_{13}N_4$: 165.1134, found 165.1152; HPLC (method A): t_R = 1.9−2.2 min.

3-(3-Chloropyridin-2-yl)-1,1-dimethyl-guanidine (***3b***). The general procedure A was followed on 1 g (7.78 mmol) of 3-chloropyridin-2-amine. Since, after 5 h, the reaction was not completed, 0.4 equiv of sodium *tert*-butoxide were added and the reaction was stirred for 16 more hours. After purification by column chromatography (eluent: DCM/heptane 70:30), the product was obtained as a yellow oil in 63% yield (0.98 g). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.99 (dd, J = 5.2, 1.8 Hz, 1 H), 7.57 (dd, J = 7.6, 1.8 Hz, 1 H), 7.36 (s broad, 2 H), 6.59 (dd, J = 7.6, 4.9 Hz, 1 H), 3.12 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 158.7, 156.4, 143.7, 137.0, 125.0, 114.4, 36.7; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_8H_{12}ClN_4$: 199.0745, found 199.0757; HPLC (method A): t_R = 6.4 min.

1,1-Dimethyl-3-(3-methylpyridin-2-yl)guanidine (***3c***). Under a stream of argon, NaH (517 mg, 12.9 mmol, 1.4 equiv) was added to a well stirred solution of 3-methylpyridin-2-amine (930 μL, 9.23 mmol, 1.00 equiv) in DMSO (10 mL). The mixture was stirred for 45 min RT. Then, *N,N*-dimethylcyanamide (880 μL, 11.0 mmol, 1.2 equiv) was added dropwise and the solution was heated at 50 °C for 2.5 h. The reaction was quenched with 50 mL of cold water and then extracted three times with 50 mL of DCM. The organic phases were collected, dried with sodium sulfate, and evaporated to dryness. After purification by column chromatography (eluent: DCM/heptane 90:10), the product was obtained as a yellow oil in 82% yield (1.35 g). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.97 (dd, J = 5.0, 2.0 Hz, 1 H), 7.38 (s broad, 2 H), 7.34−7.32 (m, 1 H), 6.59 (dd, J = 7.1, 5.0 Hz, 1 H), 3.07 (s, 6 H), 2.27 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 161.3, 155.6, 142.8, 136.9, 127.7, 114.2, 36.7, 18.5; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_9H_{15}N_4$: 179.1291, found 179.1312; HPLC (method A): t_R = 3.3 min.

3-(4-Chloro-2-pyridyl)-1,1-dimethyl-guanidine (***3d***). The general procedure A was followed on 4-chloropyridin-2-amine (1.00 g, 7.78 mmol, 1.00 equiv), sodium *tert*-butoxide (897 mg, 9.33 mmol, 1.2 equiv), and *N,N*-dimethylcyanamide (754 μL, 7.78 mmol, 1.00 equiv). After purification by column chromatography (eluent: DCM/heptane 80:20), the product was obtained as a light brown solid in 75% yield (1.26 g). mp 50−51 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.97 (d, J = 5.6 Hz, 1 H), 7.38 (br s, 1 H exch.), 6.88 (d, J = 1.9 Hz, 1 H), 6.64 (d, J = 2.1 Hz, 1 H), 3.06 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 164.0, 156.7, 146.2, 143.7, 119.4, 114.6, 36.8; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_8H_{12}ClN_4$: 199.0745, found 199.076; HPLC (method B): t_R = 4.0 min.

1,1-Dimethyl-3-(4-methyl-2-pyridyl)guanidine (***3e***). The general procedure A was followed on 4-methylpyridin-2-amine (2.5 g, 23.1 mmol, 1.00 equiv), sodium *tert*-butoxide (3.11 g, 32.4 mmol, 1.4 equiv), and *N,N*-dimethylcyanamide (2.11 g, 30.1 mmol, 1.3 equiv). After purification by column chromatography (eluent: DCM/heptane 80:20), the product was obtained as a light yellow oil in 44% yield (1.82 g). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.97 (d, J = 5.4 Hz, 1 H), 7.38 (br s, exch., 2 H), 6.71 (s, 1 H), 6.49 (dd, J = 1.3, 5.4 Hz, 1 H), 3.00 (s, 6 H), 2.21 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 162.9, 156.4, 147.6, 145.0, 120.0, 115.9, 36.6, 20.7; HRMS (ESI-QTOF) $m/$

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z: $[M + H]^+$ Calcd for $C_9H_{15}N_4$: 179.1291, found 179.131; HPLC (method B): t_R = 2.7 min.

3-(4-Methoxypyridin-2-yl)-1,1-dimethyl-guanidine (**3f**). Under a stream of argon, NaH (452 mg, 11.3 mmol, 1.4 equiv) was added to a well stirred solution of 4-methoxypyridin-2-amine (1 g, 8.06 mmol, 1.00 equiv) in DMSO (10 mL). The mixture was stirred for 45 min at RT. Then, *N*,*N*-dimethylcyanamide (770 μL, 9.67 mmol, 1.2 equiv) was added dropwise and the solution was heated at 50 °C for 2 h. The reaction was quenched with 50 mL of cold water and then extracted three times with 50 mL of DCM. The organic phases were collected, dried with sodium sulfate, and evaporated to dryness. The product was obtained as a yellow oil in 90% yield (1.41 g). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.92 (d, *J* = 5.9 Hz, 1 H), 7.42 (s broad, 2 H), 6.39 (d, *J* = 2.4 Hz, 1 H), 6.30 (dd, *J* = 5.9, 2.5 Hz, 1 H), 3.80 (s, 3 H), 3.06 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 166.6, 164.9, 156.6, 146.3, 104.4, 102.0, 54.7, 36.7; HRMS (ESI-QTOF) *m*/*z*: $[M + H]^+$ Calcd for $C_9H_{15}N_4O$: 195.1240, found 195.1243; HPLC (method A): t_R = 4.1−4.5 min.

3-(5-Chloro-2-pyridyl)-1,1-dimethyl-guanidine (**3g**).[16] The general procedure A was followed on 5-chloropyridin-2-amine (4.0 g, 31.1 mmol, 1.00 equiv), sodium *tert*-butoxide (3.89 g, 40.4 mmol, 1.3 equiv), and *N*,*N*-dimethylcyanamide (3.016 mL, 31.1 mmol, 1.00 equiv). After purification by two column chromatographies (eluent: DCM/heptane 80:20), the product was obtained as a light brown solid in 32% yield (2.00 g). mp 62−63 °C (Lit. [16]: 58−61 °C (ligroine)); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04 (dd, *J* = 0.6, 3.0 Hz, 1 H), 7.39 (dd, *J* = 3.0, 8.9 Hz, 1 H), 7.25 (br s, exch., 2 H), 6.81 (dd, *J* = 0.8, 8.6 Hz, 1 H), 3.06 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 161.4, 156.4, 143.8, 136.9, 121.3, 121.1, 36.8; HRMS (ESI-QTOF) *m*/*z*: $[M + H]^+$ Calcd for $C_8H_{12}ClN_4$: 199.0745, found 199.076; HPLC (method B): t_R = 3.6 min.

3-(5-Fluoropyridin-2-yl)-1,1-dimethyl-guanidine (**3h**). Under a stream of argon, sodium *tert*-butoxide (950 mg, 9.89 mmol, 1.11 equiv) was added to a well stirred solution of 5-fluoropyridin-2-amine (1 g, 8.92 mmol, 1.00 equiv) in DMSO (10 mL). The mixture was stirred for 15 min at room temperature. Then, *N*,*N*-dimethylcyanamide (850 μL, 10.7 mmol, 1.20 equiv) was added dropwise. The solution was heated at 50 °C until for 5 h. The reaction was quenched with 50 mL of cold water and then extracted three times with 50 mL of TBME. The organic phases were collected, dried with sodium sulfate, and evaporated to dryness. The crude product was dissolved in 20 mL of DCM, and 20 mL of water was added. The aqueous phase was extracted three times with 30 mL of DCM. The organic phases were collected and dried with sodium sulfate, and the solvent was then evaporated. After purification by column chromatography (eluent: DCM/heptane 80:20), the product was obtained as a yellow solid in 73% yield (1.18 g). mp 44−47 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.95 (d, *J* = 3.2 Hz, 1 H), 7.24−7.21 (m, 1 H), 7.17 (s broad, 2 H), 6.85 (dd, *J* = 9.0, 4.2 Hz, 1 H), 3.05 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 159.8, 156.0, 154.0 (d, J_{FC} = 243.9 Hz), 131.8 (d, J_{FC} = 27.1 Hz), 125.1 (d, J_{FC} = 19.8 Hz), 120.7, 36.7; HRMS (ESI-QTOF) *m*/*z*: $[M + H]^+$ Calcd for $C_8H_{12}FN_4$: 183.1040, found 183.1046; HPLC (method A): t_R = 2.9−3.1 min.

3-(5-Bromopyridin-2-yl)-1,1-dimethyl-guanidine (**3i**). The general procedure A was followed on 1.5 g (8.67 mmol) of 5-bromopyridin-2-amine. After purification by column chromatography (eluent: DCM/MeOH 90:10), the product was obtained as a yellow powder in 91% yield (1.93 g). mp 67−70 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.12 (dd, *J* = 2.7, 0.6 Hz, 1 H), 7.50 (dd, *J* = 8.7, 2.5 Hz, 1 H), 7.25 (s broad, 2 H), 6.76 (dd, *J* = 8.7, 0.6 Hz, 1 H), 3.06 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 161.6, 156.4, 146.0, 139.4, 121.7, 109.0, 36.7; HRMS (ESI-QTOF) *m*/*z*: $[M + H]^+$ Calcd for $C_8H_{12}BrN_4$: 243.0241, found 243.0255; HPLC (method A): t_R = 6.3−6.4 min.

3-(5-Iodopyridin-2-yl)-1,1-dimethyl-guanidine (**3j**). The general procedure A was followed on 1.5 g (6.82 mmol) of 5-iodopyridin-2-amine. After purification by column chromatography (eluent: DCM/heptane 80:20), the product was obtained as a white solid in 89% yield (1.76 g). mp 95−99 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.25 (d, *J* = 2.4 Hz, 1 H), 7.64 (dd, *J* = 8.7, 2.4 Hz, 1 H), 7.27 (s broad, 2 H), 6.68 (d, *J* = 8.7 Hz, 1 H), 3.06 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 161.8, 156.5, 151.2, 144.6, 122.5, 79.2, 36.8; HRMS (ESI-QTOF) *m*/*z*: $[M + H]^+$ Calcd for $C_8H_{12}IN_4$: 291.0101, found 291.0114; HPLC (method A): t_R = 7.1−7.4 min.

1,1-Dimethyl-3-(5-methyl-2-pyridyl)guanidine (**3k**). Under a stream of argon, sodium hydride (1.39 g, 34.7 mmol, 1.5 equiv) was added to a well stirred solution of 5-methylpyridin-2-amine (2.5 g, 23.1 mmol, 1.00 equiv) in DMSO (15 mL). The reaction mixture was stirred at RT for 20 min. Then, a solution of *N*,*N*-dimethylcyanamide (2.11 g, 30.1 mmol, 1.3 equiv) in DMSO (10 mL) was added dropwise. The solution was stirred at 50 °C for 3 h. The reaction was quenched with 80 mL of cold water and extracted with DCM (3 × 80 mL). The organic phases were collected, washed with water (100 mL), dried with sodium sulfate, and evaporated to dryness. The crude product was purified by column chromatography (eluent: DCM/heptane 80:20) to obtain the title compound as a yellow solid in 79% yield (3.31 g). mp 107−108 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.94 (d, *J* = 2.4 Hz, 1 H), 7.30 (dd, *J* = 2.7, 8.3 Hz, 1 H), 7.29 (br s, exch., 2 H), 6.81 (d, *J* = 8.3 Hz, 1 H), 3.05 (s, 6 H), 2.20 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 161.0, 156.2, 145.2, 138.2, 123.4, 119.6, 36.8, 17.7; HRMS (ESI-QTOF) *m*/*z*: $[M + H]^+$ Calcd for $C_9H_{15}N_4$: 179.1291, found 179.130; HPLC (method B): t_R = 2.6 min.

1,1-Dimethyl-3-(5-phenylpyridin-2-yl)guanidine (**3l**). Under a stream of argon, NaH (282 mg, 7.05 mmol, 1.2 equiv) was added to a well stirred solution of 5-phenylpyridin-2-amine (1 g, 5.88 mmol, 1.00 equiv) in DMSO (10 mL). The reaction mixture was stirred at RT for 20 min. Then, the *N*,*N*-dimethylcyanamide (562 μL, 7.05 mmol, 1.2 equiv) was added dropwise. The solution was stirred 30 min at RT, and then it was heated at 50 °C for 4 h. The reaction was quenched with 50 mL of cold water and extracted three times with 50 mL of DCM. The organic phases were collected, dried with sodium sulfate, and evaporated to dryness. The crude product was triturated in water, filtered, and washed with cold water and cold heptane, and then dried under vacuum. It was obtained as a yellow solid in 87% yield (1.23 g). mp 134−137 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.38 (dd, *J* = 3.3, 0.7 Hz, 1 H), 7.72 (dd, *J* = 8.5, 2.7 Hz, 1 H), 7.55−7.53 (m, 2 H), 7.42 (s broad, 2 H), 7.42−7.40 (m, 2 H), 7.31−7.28 (m, 1 H), 6.94 (dd, *J* = 8.5, 0.6 Hz, 1 H), 3.08 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 162.2, 156.5, 143.7, 138.6, 135.6, 128.8, 127.2, 126.6, 126.1, 119.9, 36.8; HRMS (ESI-QTOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{14}H_{17}N_4$: 241.1449, found 241.1461; HPLC (method A): t_R = 9.2 min.

3-(6-Chloropyridin-2-yl)-1,1-dimethyl-guanidine (**3m**). The general procedure A was followed on 1 g (7.78 mmol) of 6-chloropyridin-2-amine. After purification by column chromatography (eluent: DCM/MeOH 98:2), the product was obtained as a yellow powder in 87% yield (1.35 g). mp 119−121 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.38 (dd, *J* = 8.1, 7.5 Hz, 1 H), 7.12 (s broad, 2 H), 6.74 (dd, *J* = 8.1, 0.7 Hz, 1 H), 6.65 (dd, *J* = 7.4, 0.7 Hz, 1 H), 3.06 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 162.6, 156.3, 146.5, 138.9, 117.8, 113.3, 36.7; LCMS: *m*/*z*: $[M]^+$ Calcd for $C_8H_{11}ClN_4$ *m*/*z* $[M^+]$: 198.0666, found 198; HPLC (method A): t_R = 6.2 min.

3-(Isoquinolin-1-yl)-1,1-dimethyl-guanidine (**3n**). Under a stream of argon, NaH (467 mg, 11.7 mmol, 1.4 equiv) was added to a well stirred solution of isoquinolin-1-amine (1.2 g, 8.32 mmol, 1.00 equiv) in DMSO (12 mL). The mixture was stirred for 30 min at RT. Then, *N*,*N*-dimethylcyanamide (800 μL, 10.0 mmol, 1.21 equiv) was added dropwise and the solution was heated at 50 °C for 2 h. After this time, 660 μL (1 equiv) of *N*,*N*-dimethylcyanamide were added. After 20 h, the reaction was quenched with 50 mL of cold water and then extracted three times with 50 mL of DCM. The organic phases were collected, dried with sodium sulfate, and evaporated to dryness. After purification by column chromatography, the product was obtained as a pink solid in 83% yield (1.48 g). mp 99−102 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.74 (d, *J* = 8.4 Hz, 1 H), 7.98 (d, *J* = 5.8 Hz, 1 H), 7.88 (s broad, 2 H), 7.61 (d, *J* = 8.0 Hz, 1 H), 7.56 (t, *J* = 6.7 Hz, 1 H), 7.46 (t, *J* = 6.7 Hz, 1 H), 7.01 (d, *J* = 4.7 Hz, 1 H), 3.20 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 160.9, 157.0, 139.4, 137.3, 129.5, 126.5, 126.1, 125.7, 125.4, 112.1, 36.8; HRMS (ESI-QTOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{12}H_{15}N_4$: 215.1291, found 215.1299; HPLC (method A): t_R = 9.3−9.5 min.

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*1,1-Diethyl-3-(2-pyridyl)guanidine (**3o**).* Under a stream of argon, sodium hydride (1.59 g, 39.8 mmol, 1.5 equiv) was added to a well stirred solution of pyridin-2-amine (2.5 g, 26.6 mmol, 1.00 equiv) in DMSO (15 mL). The reaction mixture was stirred at RT for 20 min. Then, a solution of *N*,*N*-diethylcyanamide (3.13 g, 31.9 mmol, 1.2 equiv) in DMSO (10 mL) was added dropwise. The solution was stirred at 50 °C for 3 h. The reaction was quenched with 80 mL of cold water and extracted with DCM (4 × 80 mL). The organic phases were collected, washed with water (100 mL), dried with sodium sulfate, and evaporated to dryness. The crude product was purified by column chromatography (eluent: DCM/heptane 80:20) to afford the title compound as a yellow oil in 67% yield (3.44 g). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.09 (ddd, J = 0.8, 2.1, 5.1 Hz, 1 H), 7.43 (ddd, J = 2.1, 7.0, 8.3 Hz, 1 H), 7.35 (br s, exch, 2 H), 6.84 (ddd, J = 0.9, 0.9, 8.3 Hz, 1 H), 6.63 (ddd, J = 1.2, 5.0, 7.1 Hz, 1 H), 3.45 (q, J = 7.1 Hz, 4 H), 1.20 (t, J = 7.1 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 163.4, 155.0, 145.5, 136.9, 120.3, 114.2, 41.4, 13.6; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_{10}H_{17}N_4$: 193.1447, found 193.1457; HPLC (method B): t_R = 3.3 min.

*1,1-Diisopropyl-2-(2-pyridyl)guanidine (**3p**).* In a 2-neck reaction flask fitted with a reflux condenser closed by a gas bubbler that is filled with a 15% aqueous sodium hypochlorite solution, 2-methyl-3-(2-pyridyl)isothiourea hydroiodide[17] (4 g, 13.6 mmol, 1.00 equiv) was dissolved in diisopropylamine (36.1 g, 50 mL). The reaction mixture was heated at reflux under a steady flow of Ar bubbled through the reaction mixture using a a gas inlet to help remove the formed MeSH. After 28 h at reflux, the mixture was cooled to RT, and dichloromethane (30 mL) and a 10% aqueous sodium hydroxide solution (30 mL) were added. The phases were separated, and the organic phase was dried (potassium carbonate) and concentrated in vacuo to afford 1.32 g of the title compound as a yellow solid (40% yield). mp 64−65 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.09 (ddd, J = 0.8, 2.1, 5.0 Hz, 1 H), 7.43 (ddd, J = 2.1, 7.1, 8.4 Hz, 1 H), 7.35 (br s, exch, 2 H), 6.83 (d, J = 8.3 Hz, 1 H), 6.62 (ddd, J = 1.1, 5.1, 7.0 Hz, 1 H), 4.29 (hept, J = 6.9 Hz, 2 H), 1.32 (t, J = 6.9 Hz, 12 H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 163.4, 155.4, 145.5, 136.9, 120.5, 114.1, 45.2, 21.4; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{21}N_4$: 221.1761, found 221.1763; HPLC (method B): t_R = 6.5 min.

*N-(2-Pyridyl)pyrrolidine-1-carboxamidine (**3q**).* Under a stream of argon, sodium hydride (1.59 g, 39.8 mmol, 1.5 equiv) was added to a well stirred solution of pyridin-2-amine (2.5 g, 26.6 mmol, 1.00 equiv) in DMSO (15 mL). The reaction mixture was stirred at RT for 20 min. Then, a solution of pyrrolidine-1-carbonitrile (3.32 g, 34.5 mmol, 1.3 equiv) in DMSO (10 mL) was added dropwise. The solution was stirred at 50 °C for 3 h. The reaction was quenched with 80 mL of cold water and extracted with DCM (4 × 80 mL). The organic phases were collected, washed with water (100 mL), dried with sodium sulfate, and evaporated to dryness. The crude product was purified by column chromatography (eluent: DCM/heptane 80:20) to obtain the title compound as a light brown solid in 92% yield (4.76 g). mp 90−91 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.10 (ddd, J = 0.8, 2.1, 5.1 Hz, 1 H), 7.44 (ddd, J = 2.1, 7.0, 8.3 Hz, 1 H), 7.25 (br s, exch, 2 H), 6.86 (ddd, J = 0.9, 1.0, 8.3 Hz, 1 H), 6.64 (ddd, J = 1.1, 5.1, 7.1 Hz, 1 H), 3.48 (t, J = 6.6 Hz, 4 H), 1.95 (t, J = 6.7 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 163.4, 154.7, 145.6, 137.0, 119.9, 114.3, 45.9, 25.4; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_{10}H_{15}N_4$: 191.1291, found 191.1302; HPLC (method B): t_R = 2.4 min.

*3-Hydroxy-N′-(2-pyridyl)pyrrolidine-1-carboxamidine (**3r**).* In a 2-neck reaction flask fitted with a reflux condenser closed by a gas bubbler that is filled with a 15% aqueous sodium hypochlorite solution, 2-methyl-3-(2-pyridyl)isothiourea hydroiodide[17] (9 g, 30.5 mmol, 1.00 equiv) was dissolved in *tert*-butanol (20 mL), and pyrrolidin-3-ol (3.98 g, 3.7 mL, 45.7 mmol, 1.5 equiv) was added. The reaction mixture was heated at reflux under a steady flow of Ar bubbled through the reaction mixture using a a gas inlet to help remove the formed MeSH. After 2 h at reflux, the mixture was cooled to RT, and dichloromethane (30 mL) and a 10% aqueous sodium hydroxide solution (30 mL) were added. The formed precipitate was filtered, washed with dichloromethane (20 mL), and dried in vacuo to give 2.13 g of the title compound as white crystals (34% yield). mp 147−148 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.11 (ddd, J = 0.7, 2.1, 5.0 Hz, 1 H), 7.47 (ddd, J = 2.2, 7.1, 8.4 Hz, 1 H), 7.25 (br s, exch, 2 H), 6.91 (ddd, J = 0.9, 0.9, 8.3 Hz, 1 H), 6.68 (ddd, J = 1.0, 5.1, 7.1 Hz, 1 H), 4.51−4.54 (m, 1 H), 3.56−3.66 (m, 4 H), 2.00−2.11 (m, 2 H), 1.93 (br s, exch, 1 H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 162.8, 154.7, 145.7, 137.2, 119.8, 114.9, 70.6, 54.7, 43.8, 33.9; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_{10}H_{15}N_4O$: 207.1240, found 207.1253; HPLC (method B): t_R = 1.5 min.

*N-(Pyridine-2-yl)morpholine-4-carboxamidine (**3s**).* Under a stream of argon, NaH (595 mg, 14.9 mmol, 1.4 equiv) was added to a well stirred solution of pyridin-2-amine (1 g, 10.6 mmol, 1.00 equiv) in DMSO (10 mL). The mixture was stirred for 45 min at RT. Then, morpholine-4-carbonitrile (1.29 mL, 12.8 mmol, 1.2 equiv) was added dropwise and the solution was heated at 50 °C for 2 h. The reaction was quenched with 50 mL of cold water and then extracted three times with 50 mL of DCM. The organic phases were collected, dried with sodium sulfate, and evaporated to dryness. After purification by column chromatography (eluent: DCM), the product was obtained as a white solid in 77% yield (1.7 g). mp 117−120 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.14 (ddd, J = 5.0, 1.9, 0.6 Hz, 1 H), 7.50−7.47 (m, 1 H), 7.46 (s broad, 2 H), 6.89 (dt, J = 8.2, 0.9 Hz, 1 H), 6.72 (ddd, J = 7.1, 5.1 Hz, 1.0 Hz, 1 H), 3.76−3.74 (m, 4 H), 3.54−3.52 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 162.6, 155.8, 145.5, 137.2, 120.4, 115.3, 66.5, 44.5; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_{10}H_{15}N_4O$: 207.1240, found 207.1253; HPLC (method A): t_R = 3.6 min.

*N-(5-Fluoropyridin-2-yl)morpholine-4-carboxamidine (**3t**).* The general procedure A was followed on 5-fluoropyridin-2-amine (0.9 g, 8.03 mmol, 1.00 equiv) and morpholine-4-carbonitrile (974 μL, 9.63 mmol, 1.2 equiv). After purification by column chromatography (eluent: DCM/heptane 75:25), the product was obtained as a light brown solid in 85% yield (1.54 g). mp 101−104 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.99 (dt, J = 3.1, 0.6 Hz, 1 H), 7.27−7.24 (m, 1 H), 7.23 (s broad, 2 H), 6.88−6.86 (m, 1 H), 3.76−3.74 (m, 4 H), 3.52−3.51 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 159.2, 155.3, 154.4 (d, J_{FC} = 245.7 Hz), 132.1 (d, J_{FC} = 25.2 Hz), 125.1 (d, J_{FC} = 20.1 Hz), 121.2 (d, J_{FC} = 4.0 Hz), 66.5, 44.6; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_{10}H_{14}FN_4O$: 225.1146, found 225.1148; HPLC (method A): t_R = 4.7 min.

*1,1-Dimethyl-3-pyrimidin-2-yl-guanidine (**3u**).* The general procedure A was followed on pyrimidin-2-amine (2.5 g, 26.3 mmol, 1.00 equiv), sodium *tert*-butoxide (3.79 g, 39.4 mmol, 1.5 equiv), and *N*,*N*-dimethylcyanamide (1.84 g, 2.98 mL, 26.3 mmol, 1.00 equiv). The crude was crystallized from a solution in DCM/heptane (60 mL, 2:1 v/v), which was slowly concentrated in vacuo at 30 °C to ca. 40% of the volume and stirred in an ice bath for 0.5 h. The crystallized product was filtered, washed with heptane, and dried in vacuo (40 °C, 15 mbar) to afford the title compound as off-white crystalline material (2.39 g, 55% yield). mp 187−188 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.42 (d, J = 4.7 Hz, 2 H), 7.41 (br s, exch., 2 H), 6.61 (t, J = 4.8 Hz, 1 H), 3.13 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 166.1, 157.9, 157.2, 111.5, 37.1; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_7H_{12}N_5$: 166.1087, found 166.1099; HPLC (method B): t_R = 0.9 min.

*1,1-Dimethyl-3-pyrazin-2-yl-guanidine (**3v**).* The general procedure A was followed on pyrazin-2-amine (2.5 g, 26.3 mmol, 1.00 equiv), sodium *tert*-butoxide (4.55 g, 47.4 mmol, 1.8 equiv), and *N*,*N*-dimethylcyanamide (3.13 g, 44.68 mmol, 1.7 equiv). The crude was crystallized from a solution in DCM/heptane (40 mL, 1:1 v/v), which was slowly concentrated in vacuo at 40 °C to ca. 60% of the volume. The product crystallized as yellow needles, which were filtered, washed with heptane, and dried in vacuo (40 °C, 15 mbar) to yield the title compound as an off-white crystalline material (needles, 3.23 g, 75% yield). mp 127−129 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.21 (d, J = 1.4 Hz, 1 H), 7.94 (dd, J = 1.4, 2.9 Hz, 1 H), 7.82 (d, J = 2.9 Hz, 1 H), 7.32 (br s, 2 H), 3.10 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 159.0, 157.4, 144.3, 139.1, 133.3, 36.8; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_7H_{12}N_5$: 166.1087, found 166.1100; HPLC (method B): t_R = 1.7 min.

*1,1-Dimethyl-3-pyrimidin-4-yl-guanidine (**3w**).* The general procedure A was followed on pyrimidin-4-amine (2.5 g, 26.3 mmol, 1.00

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equiv), sodium *tert*-butoxide (4.55 g, 47.3 mmol, 1.8 equiv), and *N,N*-dimethylcyanamide (3.13 g, 44.7 mmol, 1.7 equiv). The crude was crystallized from a solution in DCM/heptane (40 mL, 1:1 v/v), which was slowly concentrated in vacuo at 40 °C to ca. 60% of the volume and stirred in an ice bath for 0.5 h. The crystallized product was filtered, washed with heptane, and dried in vacuo (40 °C, 15 mbar) to afford the title compound as an off-white crystalline material (2.90 g, 67% yield). mp 120−121 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.61 (s, 1 H), 8.20 (dd, J = 0.6, 5.8 Hz, 1 H), 7.63 (br s, 2 H), 6.69 (dd, J = 1.3, 5.8 Hz, 1 H), 3.10 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 167.0, 158.0, 156.5, 155.1, 116.5, 36.8; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_7H_{12}N_5$: 166.1087, found 166.1090; HPLC (method B): t_R = 1.3 min.

*1,1-Dimethyl-3-pyridazin-3-yl-guanidine (**3x**).* The general procedure A was followed on pyridazin-3-amine (2.5 g, 26.3 mmol, 1.00 equiv), sodium *tert*-butoxide (3.79 g, 39.4 mmol, 1.5 equiv), and *N,N*-dimethylcyanamide (1.84 g, 26.3 mmol, 1.00 equiv). The crude was crystallized from a solution in DCM/heptane (60 mL, 2:1 v/v), which was slowly concentrated in vacuo at 30 °C to ca. 40% of the volume and stirred in an ice bath for 0.5 h. The crystallized product was filtered, washed with heptane, and dried in vacuo (40 °C, 15 mbar) to afford the title compound as a yellow crystalline material (1.54 g, 36% yield). mp 92−93 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.53 (dd, J = 1.6, 4.4 Hz 1 H), 7.67 (br s, exch., 2 H), 7.19 (ddd, J = 0.6, 4.4, 8.9 Hz, 1 H), 7.00 (dd, J = 1.6, 8.9 Hz, 1 H), 3.10 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 37.0, 125.4, 127.2, 144.1, 156.7, 164.7; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_7H_{12}N_5$: 166.1087, found 166.1100; HPLC (method B): t_R = 1.1 min.

*3-(3-Bromopyridin-2-yl)-1,1-dimethyl-guanidine (**3y**).* The general procedure A was followed on 1.5 g (8.67 mmol) of 3-bromopyridin-2-amine. After purification by column chromatography (eluent: DCM), the product was obtained as a yellow oil in 65% yield (1.37 g). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.02 (dd, J = 4.9, 1.8 Hz, 1 H), 7.77 (dd, J = 7.6, 1.8 Hz, 1 H), 7.35 (s broad, 2 H), 6.51 (dd, J = 7.6, 4.9 Hz, 1 H), 3.12 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 159.0, 156.3, 144.3, 140.2, 116.1, 114.6, 36.6; LCMS: m/z calcd for $C_8H_{11}BrN_4$: 242.0161, found 242; HPLC (method A): t_R = 7.6 min.

*3-(6-Bromopyridin-2-yl)-1,1-dimethyl-guanidine (**3z**).* The general procedure A was followed on 1.5 g (8.67 mmol) of 6-bromopyridin-2-amine. After purification by column chromatography (eluent: DCM/MeOH 90:10), the product was obtained as hygroscopic solid in 90% yield (1.90 g). mp 107−121 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.29−7.27 (m, 1 H), 7.11 (s broad, 2 H), 6.80 (dd, J = 7.4, 0.7 Hz, 1 H), 6.76 (dd, J = 8.1, 0.8 Hz, 1 H), 3.06 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 162.8, 156.2, 138.8, 137.0, 118.2, 117.1, 36.7; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_8H_{12}BrN_4$: 243.0239, found 243.0246; HPLC (method A): t_R = 7.0 min.

General Procedure B: Oxidative Cyclization. A 2-neck reaction flask fitted with a reflux condenser closed by a gas bubbler was charged with the substrate (1.00 equiv), copper(I) bromide (0.04 equiv), 1,10-phenanthroline (0.04 equiv), and DMSO (C = 0.1 g/mL). The flask was fitted with a gas inlet connected to the air pipe. The mixture was heated with a steady stream of air bubbling through the solution until full conversion (for reaction time and temperature, please refer to Table 2). The mixture was quenched with HCl 2 M at 0 °C. Then, NaOH (32% aqueous solution) was added until pH 10 was reached, and the mixture was stirred at 0 °C for 30 min. The suspension was filtered over dicalite, and the filtrate was extracted three times with AcOEt. The organic phases were collected, dried with sodium sulfate, and evaporated to dryness. The crude was purified by column chromatography on silica gel. The column chromatography was performed using prepacked silica columns that were neutralized with the respective eluent enriched with 1−10% of triethylamine.

*N,N-Dimethyl[1,2,4]triazolo[1,5-a]pyridin-2-amine (**4a**).* Following the general procedure B on 300 mg of **3a**, the product was obtained as a yellow powder in 87% yield (259 mg). mp 110−118 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.32 (dt, J = 6.6, 1.0 Hz, 1 H), 7.39 (dt, J = 8.7, 1.1 Hz, 1 H), 7.34−7.32 (m, 1 H), 6.76 (td, J = 6.8, 1.3 Hz, 1 H), 3.14 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 167.8, 151.4, 128.7, 127.1, 113.3, 111.1, 38.1; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_8H_{11}N_4$: 163.0978, found 163.1003; HPLC (method A): t_R = 3.8 min.

*8-Chloro-N,N-dimethyl[1,2,4]triazolo[1,5-a]pyridin-2-amine (**4b**).* The general procedure B was followed on 300 mg of **3b** employing 0.08 equiv of copper(I) bromide and 0.08 equiv of 1,10-phenanthroline. After column chromatography (eluent: DCM/heptane 50:50), the product was obtained in 79% yield (235 mg). mp 108−112 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.24 (dd, J = 6.6, 1.0 Hz, 1 H), 7.38 (dd, J = 7.7, 1.0 Hz, 1 H), 6.70 (dd, J = 7.7, 6.6 Hz, 1 H), 3.16 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 167.7, 149.6, 127.9, 125.8, 118.8, 110.5, 38.1; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_8H_{10}ClN_4$: 197.0588, found 197.0608; HPLC (method A): t_R = 5.9 min.

*N,N,8-Trimethyl[1,2,4]triazolo[1,5-a]pyridin-2-amine (**4c**).* The general procedure B was followed on 300 mg of **3c**. After column chromatography (eluent: DCM/heptane 75:25), the product was obtained in 86% yield (255 mg). mp 81−84 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.19−8.17 (m, 1 H), 7.10 (dt, J = 7.0, 1.0 Hz, 1 H), 6.66 (t, J = 6.9 Hz, 1 H), 3.14 (s, 6 H), 2.53 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 167.6, 151.7, 127.6, 124.8, 123.6, 110.9, 38.2, 16.8; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_9H_{13}N_4$: 177.1134, found 177.1154; HPLC (method A): t_R = 5.6 min.

*7-Chloro-N,N-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine (**4d**).* The general procedure B was followed on 315 mg of **3d** employing 0.06 equiv of copper(I) bromide and 0.06 equiv of 1,10-phenanthroline. After column chromatography (eluent: DCM/heptane 80:20), the product was obtained as an off-white solid in 78% yield (230 mg). mp 156−157 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.21 (dd, J = 7.1, 0.7 Hz, 1 H), 7.36 (dd, J = 2.2, 0.6 Hz, 1 H), 6.74 (dd, J = 7.1, 2.2 Hz, 1 H), 3.13 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 168.4, 151.6, 135.2, 127.2, 112.3, 38.0; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_8H_{10}ClN_4$: 197.0588, found 197.0600; HPLC (method B): t_R = 6.2 min.

*N,N,7-Trimethyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine (**4e**).* The general procedure B was followed on 375 mg of **3e** employing 0.08 equiv of copper(I) bromide and 0.08 equiv of 1,10-phenanthroline. After column chromatography (eluent: DCM/heptane 50:50), the product was obtained as a white solid in 55% yield (163 mg). mp 128−129 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.18 (d, J = 6.8 Hz, 1 H), 7.15−7.17 (m, 1 H), 6.58 (dd, J = 1.7, 6.8 Hz, 1 H), 3.12 (s, 6 H), 2.39 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 167.9, 151.6, 140.1, 126.2, 113.3, 112.3, 38.2, 21.5; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_9H_{13}N_4$: 177.1135, found 177.1140; HPLC (method B): t_R = 4.9 min.

*7-Methoxy-N,N-dimethyl[1,2,4]triazolo[1,5-a]pyridin-2-amine (**4f**).* A 2-neck reaction flask fitted with a reflux condenser closed by a gas bubbler was charged with **3f** (300 mg, 1.54 mmol, 1.00 equiv), copper(I) bromide (17.7 mg, 0.124 mmol, 0.08 equiv), 1,10-phenanthroline (22.3 mg, 0.124 mmol, 0.08 equiv), and DMSO (10 mL). The flask was fitted with a gas inlet connected to the air pipe. The mixture was heated at 110 °C with a steady stream of air bubbling through the solution for 23 h. The solvent was evaporated, and the residue was purified by column chromatography (eluent: DCM/heptane 80:20). The product was obtained in 80% yield (239 mg). mp 124−127 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.11 (d, J = 7.3 Hz, 1 H), 6.73 (d, J = 2.5 Hz, 1 H), 6.42 (dd, J = 7.3, 2.7 Hz, 1 H), 3.84 (s, 3 H), 3.11 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 168.2, 160.8, 152.8, 127.4, 104.2, 92.4, 55.6, 38.1; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_9H_{13}N_4O$: 193.1083, found 193.1096; HPLC (method A): t_R = 4.9 min.

*6-Chloro-N,N-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine (**4g**).* The general procedure B was followed on 313 mg of **3g** employing 0.08 equiv of copper(I) bromide and 0.08 equiv of 1,10-phenanthroline. After column chromatography (eluent: DCM/heptane 80:20), the product was obtained as a light brown solid in 82% yield (252 mg). mp 123−124 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.36 (dd, J = 1.2, 1.2 Hz, 1 H), 7.30−7.32 (m, 2 H), 3.13 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 168.2, 150.1, 129.8, 125.6, 118.5, 113.1, 38.1; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_8H_{10}ClN_4$: 197.0588, found 197.0602; HPLC (method B): t_R = 6.6 min.

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*6-Fluoro-N,N-dimethyl[1,2,4]triazolo[1,5-a]pyridin-2-amine (**4h**).* The general procedure B was followed on 300 mg of **3h**. After column chromatography (eluent: DCM/heptane 50:50), the product was obtained in 74% yield (220 mg). mp 153−163 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.29−8.28 (m, 1 H), 7.34−7.32 (m, 1 H), 7.26−7.23 (m, 1 H), 3.13 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 168.5, 151.9 (d, J_{FC} = 235.4 Hz), 149.1, 119.4 (d, J_{FC} = 23.8 Hz), 115.2 (d, J_{FC} = 34.5 Hz), 112.6, 38.0; HRMS (ESI-QTOF) *m*/*z*: [M + H]$^+$ Calcd for $C_8H_{10}FN_4$: 181.0884, found 181.0907; HPLC (method A): t_R = 5.0 min.

*6-Bromo-N,N-dimethyl[1,2,4]triazolo[1,5-a]pyridin-2-amine (**4i**).*[18] The general procedure B was followed on 300 mg of **3i**. After column chromatography (eluent: DCM/heptane 75:25), the product was obtained in 67% yield (200 mg). mp 93−96 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.45 (dd, *J* = 1.9, 0.7 Hz, 1 H), 7.40 (dd, *J* = 9.3, 1.9 Hz, 1 H), 7.27 (dd, *J* = 9.4, 0.8 Hz, 1 H), 3.13 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 168.0, 150.2, 131.9, 127.6, 113.4, 104.3, 38.0; HRMS (ESI-QTOF) *m*/*z*: [M + H]$^+$ Calcd for $C_8H_{10}BrN_4$: 241.0083, found 241.0090; HPLC (method A): t_R = 7.3 min.

*6-Iodo-N,N-dimethyl[1,2,4]triazolo[1,5-a]pyridin-2-amine (**4j**).* The general procedure B was followed on 300 mg of **3j** employing 0.08 equiv of copper iodide and 0.08 equiv of 1,10-phenanthroline. After column chromatography (eluent: DCM/heptane 50:50), the product was obtained in 83% yield (247 mg). mp 110−113 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.55 (dd, *J* = 1.7, 0.7 Hz, 1 H), 7.51 (dd, *J* = 9.1, 1.6 Hz, 1 H), 7.18 (dd, *J* = 9.1, 0.7 Hz, 1 H), 3.13 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 167.7, 150.4, 136.6, 132.2, 114.1, 71.5, 38.1; HRMS (ESI-QTOF) *m*/*z*: [M + H]$^+$ Calcd for $C_8H_{10}IN_4$: 288.9944, found 288.9961; HPLC (method A): t_R = 7.9 min.

*N,N,6-Trimethyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine (**4k**).* The general procedure B was followed on 305 mg of **3k** employing 0.04 equiv of copper(I) bromide and 0.04 equiv of 1,10-phenanthroline. After column chromatography (eluent: DCM/heptane 50:50), the product was obtained as a white crystalline solid in 79% yield (233 mg). mp 110−111 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.12−8.14 (m, 1 H), 7.30 (dd, *J* = 0.5, 9.0 Hz, 1 H), 7.18 (ddd, *J* = 0.4, 1.3, 8.9 Hz, 1 H), 3.12 (s, 6 H), 2.32 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 167.7, 150.0, 131.3, 125.6, 121.0, 112.6, 38.2, 17.9; HRMS (ESI-QTOF) *m*/*z*: [M + H]$^+$ Calcd for $C_9H_{13}N_4$: 177.1135, found 177.1143; HPLC (method B): t_R = 5.1 min.

*N,N-Dimethyl-6-phenyl[1,2,4]triazolo[1,5-a]pyridin-2-amine (**4l**).* The general procedure B was followed on 300 mg of **3l**. After column chromatography (eluent: AcOEt/heptane 50:50), the product was obtained in 77% yield (297 mg). mp 122−124 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.55 (dd, *J* = 1.8, 0.8 Hz, 1 H), 7.60 (dd, *J* = 9.0, 1.9 Hz, 1 H), 7.54−7.53 (m, 2 H), 7.47−7.44 (m, 3 H), 7.39−7.37 (m, 1 H), 3.16 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 168.1, 150.7, 136.8, 129.2, 128.9, 127.8, 126.6, 125.8, 124.7, 124.6, 112.9, 38.2; HRMS (ESI-QTOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{14}H_{15}N_4$: 239.1291, found 239.1310; HPLC (method A): t_R = 10.1 min.

*5-Chloro-N,N-dimethyl[1,2,4]triazolo[1,5-a]pyridin-2-amine (**4m**).* The general procedure B was followed on 300 mg of **3m**. After column chromatography (eluent: DCM/heptane 50:50 to 90:10), the product was obtained in 77% yield (231 mg). mp 49−51 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.33−7.27 (m, 2 H), 6.85 (dd, *J* = 7.2, 1.4 Hz, 1 H), 3.18 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 167.4, 152.6, 128.8, 128.2, 111.1, 110.9, 38.0; HRMS (ESI-QTOF) *m*/*z*: [M + H]$^+$ Calcd for $C_8H_{10}ClN_4$: 197.0588, found 197.0601; HPLC (method A): t_R = 6.5 min.

*N,N-Dimethyl[1,2,4]triazolo[5,1-a]isoquinolin-2-amine (**4n**).* The general procedure B was followed on 300 mg of **3n** employing 0.08 equiv of copper(I) bromide and 0.08 equiv of 1,10-phenanthroline. After column chromatography (eluent: AcOEt/heptane 50:50), the product was obtained in 83% yield (248 mg). mp 148−152 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.51−8.49 (m, 1 H), 8.14 (d, *J* = 7.3 Hz, 1 H), 7.76−7.74 (m, 1 H), 7.63−7.61 (m, 2 H), 7.05 (d, *J* = 7.2 Hz, 1 H), 3.19 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 167.5, 149.5, 131.4, 129.2, 127.5, 126.9, 124.13, 124.09, 121.0, 111.1, 38.4; HRMS (ESI-QTOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{12}H_{13}N_4$: 213.1134, found 213.1156; HPLC (method A): t_R = 8.6 min.

*N,N-Diethyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine (**4o**).* The general procedure B was followed on 315 mg of **3o** employing 0.08 equiv of copper(I) bromide and 0.08 equiv of 1,10-phenanthroline. After column chromatography (eluent: DCM/heptane 50:50), the product was obtained as a light yellow solid in 45% yield (127 mg). mp 71−72 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.31 (ddd, *J* = 1.0, 1.2, 6.7 Hz, 1 H), 7.38 (ddd, *J* = 1.0, 1.3, 8.9 Hz, 1 H), 7.31 (ddd, *J* = 1.3, 7.0, 8.9 Hz, 1 H), 6.73 (ddd, *J* = 1.3, 6.8, 6.8 Hz, 1 H), 3.57 (q, *J* = 7.1 Hz, 4 H), 1.24 (t, *J* = 7.1 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 166.4, 151.4, 128.4, 127.0, 112.9, 110.8, 42.4, 13.2; HRMS (ESI-QTOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{10}H_{15}N_4$: 191.1291, found 191.1289; HPLC (method B): t_R = 7.1 min.

*2-Pyrrolidin-1-yl-[1,2,4]triazolo[1,5-a]pyridine (**4q**).* The general procedure B was followed on 300 mg of **3q** employing 0.08 equiv of copper(I) bromide and 0.08 equiv of 1,10-phenanthroline. After column chromatography (eluent: DCM/heptane 80:20), the product was obtained as a white crystalline solid in 93% yield (277 mg). mp 134−136 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.34 (ddd, *J* = 1.0, 1.3, 6.8 Hz, 1 H), 7.41 (ddd, *J* = 1.0, 1.3, 8.8 Hz, 1 H), 7.33 (ddd, *J* = 1.3, 7.0, 8.8 Hz, 1 H), 6.76 (ddd, *J* = 1.3, 6.8, 6.8 Hz, 1 H), 3.55−3.60 (m, 4 H), 2.00−2.05 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 165.4, 151.4, 128.7, 127.1, 113.1, 111.0, 47.4, 25.7; HRMS (ESI-QTOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{10}H_{13}N_4$: 189.1135, found 189.1150; HPLC (method B): t_R = 5.0 min.

*1-([1,2,4]Triazolo[1,5-a]pyridin-2-yl)pyrrolidin-3-ol (**4r**).* A 2-neck reaction flask fitted with a reflux condenser closed by a gas bubbler was charged with the with (*E*)-3-hydroxy-*N*′-(pyridin-2-yl)pyrrolidine-1-carboxamidine (**3r**) (300 mg, 1.45 mmol, 1.00 equiv), copper(I) bromide (12.5 mg, 87.3 μmol, 0.06 equiv), 1,10-phenanthroline (15.7 mg, 87.3 μmol, 0.06 equiv), and DMSO (3 mL). The flask was fitted with a gas inlet connected to the air pipe. The mixture was heated at 130 °C for 22 h with a steady stream of air bubbling through the solution. After full conversion has been obtained, water (10 mL) was added at RT and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic phase was washed with brine (20 mL), dried (sodium sulfate), and concentrated in vacuo. The crude was purified by column chromatography on silica gel. The column chromatography was performed using prepacked silica columns and a mixture of dichloromethane/methanol (gradient 98:2 to 95:5) as eluent to afford 170 mg of the title compound as a light yellow solid (57%). mp 154−156 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.34 (ddd, *J* = 1.1, 1.1, 6.7 Hz, 1 H), 7.41 (ddd, *J* = 1.1, 1.1, 8.9 Hz, 1 H), 7.35 (ddd, *J* = 1.3, 7.2, 8.8 Hz, 1 H), 6.78 (ddd, *J* = 1.3, 6.9, 6.9 Hz, 1 H), 4.61−4.64 (m, 1 H), 3.68−3.78 (m, 3 H), 3.64 (ddd, *J* = 1.6, 1.6, 11.0 Hz, 1 H), 2.14−2.22 (m, 2 H), 2.06−2.12 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 165.3, 151.3, 128.9, 127.2, 113.2, 111.3, 71.3, 56.1, 45.4, 34.4; HRMS (ESI-QTOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{10}H_{13}N_4O$: 205.1084, found 205.1094; HPLC (method B): t_R = 1.9 min.

*2-(Morpholin-4-yl)[1,2,4]triazolo[1,5-a]pyridine (**4s**).* The general procedure B was followed on 300 mg of **3s**. After column chromatography (eluent: DCM/heptane 60:40), the product was obtained in 70% yield (209 mg). mp 123−127 °C ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.33 (br d, *J* = 6.8 Hz, 1 H), 7.43−7.37 (m, 2 H), 6.82 (br t, *J* = 6.8 Hz, 1 H), 3.84−3.82 (m, 4 H), 3.61−3.60 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 167.2, 151.1, 129.0, 127.3, 113.6, 111.6, 66.4, 46.2; HRMS (ESI-QTOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{10}H_{11}N_4O$: 205.1083, found 205.1101; HPLC (method A): t_R = 4.1 min.

*6-Fluoro-2-(morpholin-4-yl)[1,2,4]triazolo[1,5-a]pyridine (**4t**).* The general procedure B was followed on 300 mg of **3t**. Crystallization of the crude material from AcOEt (hot/cold) afforded the product in 70% yield (209 mg). mp 197−199 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.30−8.29 (m,1 H), 7.37 (dd, *J* = 10.2, 5.0 Hz, 1 H), 7.31−7.28 (m, 1 H), 3.84−3.82 (m, 4 H), 3.59−3.58 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 167.9, 152.2 (d, J_{FC} = 236.5 Hz), 148.8, 119.9 (d, J_{FC} = 23.8 Hz), 115.4 (d, J_{FC} = 39.9 Hz), 113.2 (d, J_{FC} = 9.1 Hz), 66.4, 46.2; HRMS (ESI-QTOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{10}H_{12}FN_4O$: 223.0989, found 223.1003; HPLC (method A): t_R = 5.1 min.

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*N,N-Dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine (**4u**).* The general procedure B was followed on 315 mg of **3u** employing 0.08 equiv of copper(I) bromide and 0.08 equiv of 1,10-phenanthroline. After column chromatography (eluent: DCM/heptane 80:20), the product was obtained as white crystals in 77% yield (227 mg). mp 169−170 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.53 (dd, J = 2.0, 6.5 Hz, 1 H), 8.49 (dd, J = 1.9, 4.5 Hz, 1 H), 6.82 (dd, J = 4.5, 6.5 Hz, 1 H), 3.17 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 168.7, 155.9, 151.8, 133.3, 107.5, 37.6; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_7H_{10}N_5$: 164.0931, found 164.0946; HPLC (method B): t_R = 1.5 min.

*N,N-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-amine (**4v**).* The general procedure B was followed on 305 mg of **3v** employing 0.08 equiv of copper(I) bromide and 0.08 equiv of 1,10-phenanthroline. After column chromatography (eluent: DCM/heptane 80:20), the product was obtained as a light brown solid in 78% yield (235 mg). mp 157−158 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.87 (d, J = 1.4 Hz, 1 H), 8.28 (dd, J = 1.4, 4.3 Hz, 1 H), 7.97 (d, J = 4.2 Hz, 1 H), 3.18 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 167.9, 147.2, 138.3, 130.0, 120.4, 38.0; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_7H_{10}N_5$: 164.0931, found 164.0944; HPLC (method B): t_R = 2.4 min.

*N,N-Dimethyl-[1,2,4]triazolo[1,5-c]pyrimidin-2-amine (**4w**).* A 2-neck reaction flask fitted with a reflux condenser closed by a gas bubbler was charged with 1,1-dimethyl-3-(pyrimidin-4-yl)guanidine (**3w**, 315 mg, 1.81 mmol, 1.00 equiv), copper(I) bromide (20.8 mg, 145 μmol, 0.08 equiv), 1,10-phenanthroline (26.1 mg, 145 μmol, 0.08 equiv), and DMSO (3.15 mL). The flask was fitted with a gas inlet connected to the air pipe. The mixture was stirred 130 °C for 46 h with a steady stream of air bubbling through the solution. The mixture was quenched with water (10 mL) at 0 °C. Then, the mixture was stirred at 0 °C for 5 min, and the suspension was extracted with AcOEt (3 × 10 mL) and DCM (2 × 10 mL). The organic phases were combined, dried with sodium sulfate, and evaporated to dryness. After column chromatography (eluent: DCM/heptane 80:20), the product was obtained as a light yellow solid in 67% yield (198 mg). mp 106−107 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.08 (d, J = 1.3 Hz, 1 H), 8.07 (d, J = 6.2 Hz, 1 H), 7.29 (dd, J = 1.3, 6.2 Hz, 1 H), 3.17 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 168.5, 152.7, 144.3, 139.2, 108.4, 37.9; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_7H_{10}N_5$: 164.0931, found 164.0941; HPLC (method B): t_R = 2.4 min.

*N,N-Dimethyl-[1,2,4]triazolo[1,5-b]pyridazin-2-amine (**4x**).* The general procedure B was followed on 315 mg of **3x** employing 0.08 equiv of copper(I) bromide and 0.08 equiv of 1,10-phenanthroline. After column chromatography (eluent: DCM/heptane 80:20), the product was obtained as a yellow solid in 40% yield (126 mg). mp 109−111 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.20 (dd, J = 1.7, 4.6 Hz, 1 H), 7.72 (dd, J = 1.8, 9.0 Hz, 1 H), 7.21 (dd, J = 4.6, 9.0 Hz, 1 H), 3.19 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 166.2, 145.8, 139.3, 120.8, 120.6, 37.8; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_7H_{10}N_5$: 164.0931, found 164.0946; HPLC (method B): t_R = 2.3 min.

■ ASSOCIATED CONTENT

Supporting Information

Further optimization data, analytical methods, and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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(9) For details, see the Supporting Information.

(10) Under the present reaction conditions, both the guanidine starting material and the triazole product could act as a ligand for copper.

(11) Product **4a** was obtained in 77% HPLC yield using 4 mol % CuBr and **5a** in DMSO after 44 h at 130 °C. The possibility to carry out the reaction with 5% v/v oxygen is important in industrial settings where, for safety reasons, higher O_2 concentrations are not tolerated.

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