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Cu-Catalyzed Aerobic Oxidative Three-Component Coupling Route to *N*-Sulfonyl Amidines via an Ynamine Intermediate

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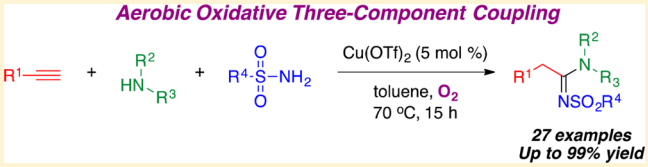
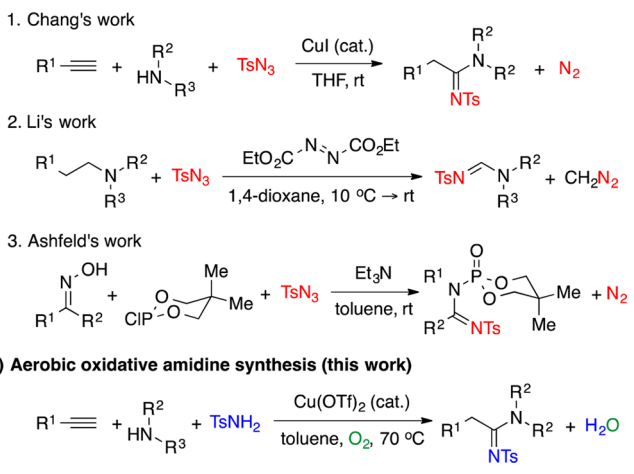
Supporting Information

ABSTRACT: Cu-catalyzed aerobic oxidative three-component coupling of a terminal alkyne, secondary amine, and sulfonamide enables efficient synthesis of amidines. The use of $Cu(OTf)_2$ (5 mol %) produces amidines selectively without Glaser−Hay alkyne homocoupling products. Preliminary studies suggest that the reaction pathway involves initial oxidative coupling of the terminal alkyne with the secondary amine, followed by hydroamidation of the ynamine intermediate with the sulfonamide.



Amidines are important functional groups in organic chemistry.[1] They represent unique structural components of bioactive pharmacophores and natural products,[2] and they also serve as a useful building block for the synthesis of heterocyclic compounds[3] and as ligands for transition metals.[4] Numerous methods are available for the synthesis of amidines,[1] and several recent reports that employ organic azides are conceptually related to the catalytic strategy described herein (Scheme 1). Chang and co-workers revealed that Cu-catalyzed three-component coupling of a terminal alkyne, sulfonyl azide, and amine produces *N*-sulfonyl amidines[5] through nucelophilic addition of an amine onto an in situ generated ketenimine intermediate.[6] Li[7] and others[8] reported oxidative dehydrogenation of a tertiary amine and followed by 1,3-dipolar cycloaddition of sulfonyl azide with the resulting vinyl amine to access *N*-sulfonyl amidine. And, Ashfeld and co-workers developed a phosphite-mediated Beckmann-type rearrangement for the construction of amidines from oximes and sulfonyl azide.[9] Here, we describe a complementary Cu-catalyzed aerobic three-component (terminal alkyne, amine, and sulfonamide) oxidative coupling strategy for the preparation of *N*-sulfonyl amidines that does not rely on the use of tosylazides.[10]

Scheme 1. (a) Synthesis of *N*-Toluene Sulfonyl Amidine with TsN_3; (b) Aerobic Oxidative *N*-Toluene Sulfonyl Amidine Synthesis (Azide-Free)



In 2008, we reported a Cu-catalyzed method for the preparation of ynamides via aerobic oxidative coupling terminal alkynes and diverse nitrogen nucleophiles.[11,12] In the presence of $CuCl_2$ (20 mol %), Na_2CO_3 (2 equiv), and pyridine (2 equiv), various terminal alkynes undergo reaction with secondary amides, secondary sulfonamides, or electron deficient indoles to produce the corresponding cross-coupled products under aerobic conditions. Subsequently, a number of additional Cu-catalyzed methods were developed for the oxidative cross-coupling of terminal alkynes and electron-deficient amides and related nucleophiles.[13] Ynamides are rather stable and are amenable to isolation and storage. In contrast, ynamines are quite reactive and, if they can be prepared, are susceptible to hydration or other decomposition pathways.[14] We envisioned that the inclusion of primary sulfonamides in Cu-catalyzed aerobic oxidative coupling reactions terminal alkynes and secondary amines could produce stable amidines via addition of the sulfonamide to an intermediate ynamine.[15] We speculated that the acidity of the sulfonamide might minimize the concentration of acetylide anion and/or steady-state Cu-acetylides and thereby suppress the undesired alkyne homocoupling side reaction.

To probe the effect of using a primary sulfonamide in Cu-catalyzed ynamide synthesis, we investigated the reaction of phenylacetylene (**1a**), diisopropyl amine (**2a**) and sulfonamide (**3a**) under aerobic conditions (Table 1). Under our previously

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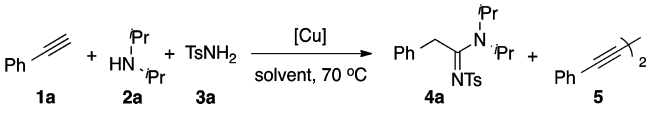
Table 1. Optimization of Cu-Catalyzed Aerobic Oxidative Three-Component Coupling for Amidine[a]



entry	Cu (mol %)	additive (equiv)	solvent	yield (%)[b] 4a	5
1	$CuCl_2$ (20)	pyridine (2), Na_2CO_3 (2)	toluene	42	46
2	$CuCl_2$ (20)	–	toluene	49	15
3	CuCl (20)	–	toluene	53	20
4	$Cu(CH_3CN)_4OTf$ (20)	–	toluene	88	–
5	$CuBr_2$ (20)	–	toluene	54	10
6	$Cu(OAc)_2$ (20)	–	toluene	46	48
7	$Cu(OTf)_2$ (20)	–	toluene	93	–
8	**$Cu(OTf)_2$ (5)**	–	**toluene**	**96**	–
9[c]	$Cu(OTf)_2$ (5)	–	toluene	93	–
10	$Cu(OTf)_2$ (5)	–	DMSO	20	80

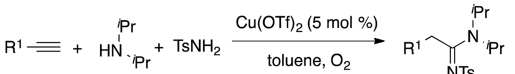
[a]Conditions: **1a** (0.3 mmol), **2a** (2.0 equiv), **3a** (2.0 equiv) and Cu in solvent (3.0 mL) under O_2 balloon at 70 °C for 15 h. [b]Yield determined by ^1H NMR (internal standard: 1,1,2,2-tetrachloroethane). [c]Carried out under air.

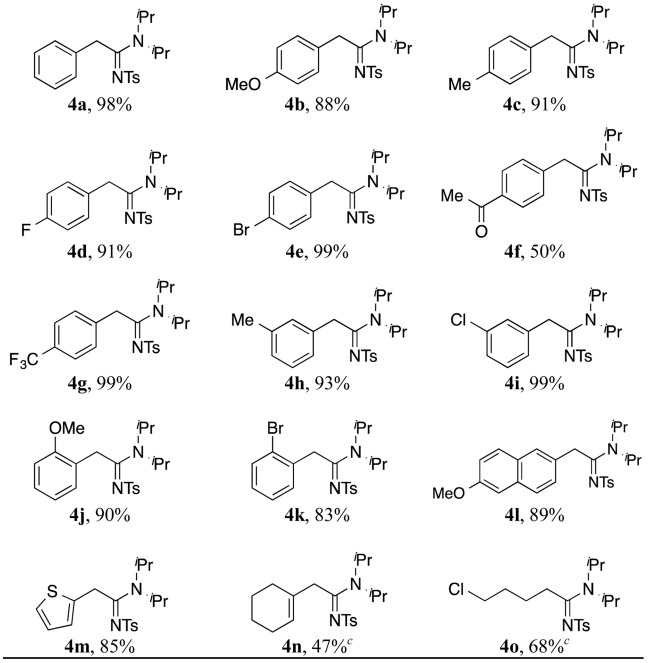
reported oxidative coupling conditions, we obtained a 42% yield of amidine (**4a**), together with a 46% yield of the alkyne homocoupling product (**5**) (entry 1). Both the yield and selectivity of the amidine product increased in the absence of pyridine and Na_2CO_3 (entry 2). Among copper sources tested, Cu^I and Cu^{II} salts with noncoordinating anions, such as $[Cu(CH_3CN)_4]OTf$ and $Cu(OTf)_2$, gave the best results and completely avoided formation of the diyne homocoupling product (entries 4, 7–9). The catalyst loading could be reduced to 5 mol % and the reaction performed under air without significant effect on yield or selectivity (entries 8 and 9). Slow addition of the terminal alkyne, which has been used previously to minimize alkyne homocoupling,[11,13b,c] was not necessary under the optimized reaction conditions. Use of the polar solvent DMSO instead of toluene led to a reversal of selectivity, forming diyne as the major product (entry 10).

The optimized reaction conditions (Table 1, entry 8) were then tested with a number of other substrate partners (Table 2). Substituted phenyl acetylenes (**1a–1k**) underwent three-component coupling to amidines in yields ranging from 50–99%. These reactions were largely unaffected by electronic effects, although 4-acetyl phenyl acetylene proceeded in only moderate yield (**4f**). Polycyclic or heteroaromatic alkynes, such as 2-ethynyl-6-methoxynaphthalene (**1l**) and 2-ethynylthiophene (**1m**), were effectively converted into the corresponding amidines. Coupling reactions of allylic or aliphatic alkynes (**1n** or **1o**) were less reactive, although reasonable yields could be obtained by using 10 mol % of catalyst. The present aerobic oxidative three-component coupling was effective on a larger scale. Terminal alkyne **1a** underwent three-component coupling on a 10 mmol scale, resulting in a 76% yield of the amidine, even with decreased catalyst loading (3 mol %) under ambient air. By using X-ray crystallographic analysis of compound **4c**, we observed that the C–N double bond of the amidine product has a *E* conformation.

A number of different secondary amines were effective substrate partners in the Cu-catalyzed aerobic oxidative three-component coupling (Table 3). In addition to the symmetrical

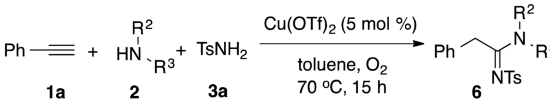
Table 2. Substrate Scope of Terminal Alkynes in the $Cu(OTf)_2$-Catalyzed Aerobic Oxidative Three-Component Coupling[a,b]

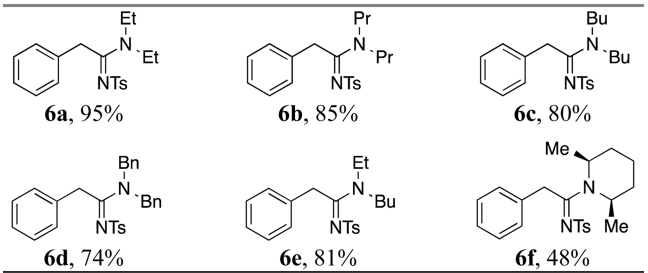




[a]Conditions: **1** (0.3 mmol), **2a** (0.6 mmol), **3a** (0.6 mmol), and $Cu(OTf)_2$ (5 mol %) in toluene (3.0 mL) under O_2 balloon at 70 °C for 15 h. [b]Isolated yield. [c]10 mol % of $Cu(OTf)_2$ was employed.

Table 3. Substrate Scope of Secondary Amines in the $Cu(OTf)_2$-Catalyzed Aerobic Oxidative Three-Component Coupling[a,b]





[a]Conditions: **1a** (0.3 mmol), **2** (0.6 mmol), **3a** (0.6 mmol), and $Cu(OTf)_2$ (5 mol %) in toluene (3.0 mL) under O_2 balloon at 70 °C for 15 h. [b]Isolated yield.

amines used in the formation of **6a–6d**, the unsymmetrical secondary amine, ethyl butyl amine **2e**, produced the corresponding amidines in good yields (**6a–6e**). However, use of the cyclic amine *cis*-2,6-dimethylpiperidine resulted in a diminished yield (**6f**). In addition, primary amines (benzyl amine, cyclohexyl amine, and hexyl amine) provided no amidine product when they were used as coupling partners. The lack of primary amine reactivity suggests that the present

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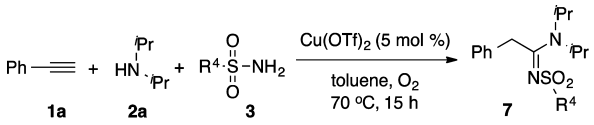
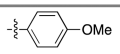
transformation does not follow ketenimine pathway (vide infra).[6]

We also investigated additional sulfonamide substrates (Table 4). A number of substituted benzenesulfonamide

Table 4. Sulfonamide Substrate Scope in the $Cu(OTf)_2$-Catalyzed Aerobic Oxidative Three-Component Coupling[a]



entry	R^4 =		yield (%)[b]	entry	R^4 =		yield (%)[b]
1		**7a**	85	2		**7b**	98
3		**7c**	99	4		**7d**	61
5		**7e**	37	6		**7f**	80

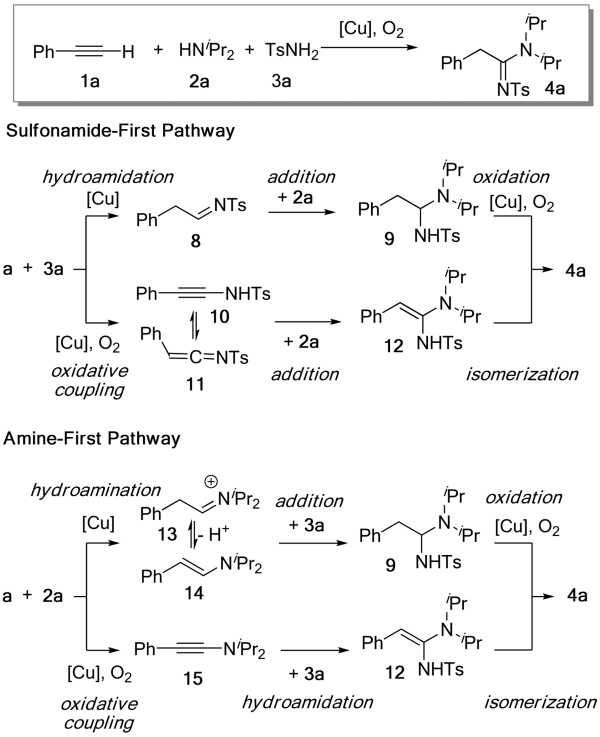
[a]Conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), **3** (0.6 mmol), and $Cu(OTf)_2$ (5 mol %) in toluene (3.0 mL) under O_2 balloon at 70 °C for 15 h. [b]Isolated yield.

derivatives exhibited good yields (**7a**–**7c**), while naphthalene sulfonamide and thiophene sulfonamide were less effective (**7d** and **7e**). The aliphatic sulfonamide, butane sulfonamide, showed good reactivity (**7f**). Carboxamides, such as benzamide, and carbamates, such as benzyl carbamate were not effective in the reaction (not shown).

Several reaction sequences are plausible for these three-component coupling reactions, based on literature precedents for related reactions (Scheme 2).[15,16] The first pair of pathways involves initial reaction of the sulfonamide and the alkyne (Scheme 2A). Cu-mediated coupling of the alkyne and sulfonamide could proceed via a redox-neutral (i.e., hydroamidation)[17] or an oxidative pathway.[11,13] In the former route, hydroamidation of **1a** with **3a**, followed by tautomerization, generates the imine **8**. Nucleophilic addition of diisopropyl amine **2a** and subsequent Cu-catalyzed oxidation of the aminal produces amidine **4a**. Cu-mediated oxidative amidation of the alkyne with $TsNH_2$ generates the ynamide **10**. When such a reaction occurs with secondary amides,[11,13] the ynamide is stable and may be isolated; however, the ynamide derived from $TsNH_2$ can undergo tautomerization to generate the ketenimine **11**, which is susceptible to facile addition of the amine, resulting in formation of the amidine **4a**. The intermediacy of the ketenimine in this pathway resembles the proposed pathway for amidine formation from alkynes and tosyl azides.[5]

The second pair of pathways involves initial reaction of the secondary amine and the alkyne (Scheme 2B). Once again this reaction could proceed via a redox-neutral or oxidative pathway. In the former case, hydroamination of the alkyne affords an iminium intermediate **13** that could undergo addition of the sulfonamide, followed by oxidation of the aminal, to afford the amidine **4a**.[18] The second pathway involves oxidative coupling of phenyl acetylene and the secondary amine to form the ynamine. Subsequent hydroamidation of $TsNH_2$ and following tautomerization produces **4a**.

Scheme 2. Possible Reaction Sequences for Amidine Formation



To probe the sulfonamide-first pathways in Scheme 1A, we tested reactions with primary amines, alcohols, and water instead of the secondary amine as a coupling partner. None of the targeted amidine (or related) product was observed with these alternate nucleophiles. A competition experiment was performed, in which both a primary amine (benzylamine, hexylamine, and cyclohexylmethyl amine were tested) and a secondary amine ($^i Pr_2NH$) were included together in the three-component coupling reaction. Only amidine product derived from $^i Pr_2NH$ was observed (8–10% yield) under these conditions.[19] Together, these observations disfavor the sulfonamide-first pathways.

In the amine-first pathways, hydroamination of phenylacetylene generates an iminium species **13** (which will be in equilibrium with enamine **14**). This pathway was simulated by combining phenyl acetaldehyde and $^i Pr_2NH$ under the three-component coupling conditions. That no amidine product **4a** was generated from this reaction suggests the hydroamination initiated sequence in Scheme 1B is unlikely. Ynamines derived from secondary amines, such as **15**, are known to be very reactive and not easy to isolate. Although no catalytic method for ynamine synthesis has been known, the coupling of phenylacetylene and Et_2NH with stoichiometric Cu has been reported previously to afford the corresponding ynamine in moderate yield.[14] Efforts to reproduce this protocol were only moderately successful, but they provided a basis for testing the ynamine reaction pathway (Scheme 3). Treatment of in situ generated ynamine **16** with an aqueous solution of NH_4Cl gave amide product **17** in 10% yield (via addition of water to the ynamine) together with a 90% yield of alkyne homocoupling product. If the intermediate ynamine was treated with $TsNH_2$ **3a** instead, the amidine product **6a** was obtained in 11% yield. On the basis of these collective observations, the amine-first pathway involving oxidative coupling to ynamine **15** appears to

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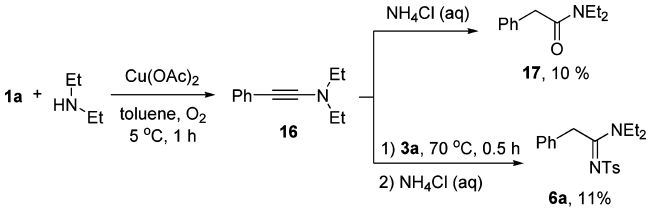
Scheme 3. Reaction of Water or $TsNH_2$ with In Situ Generated Ynamine



be most plausible pathway for formation of the amidine product.

In conclusion, we have identified aerobic oxidative three-component-coupling conditions that provide a compelling alternative to azide-based methods for amidine formation. The reactions proceed effectively without requiring slow addition of the alkyne to avoid unwanted formation of the diyne byproduct. The most likely pathway involves oxidative coupling of the secondary amine and the alkyne, followed by addition of the sulfonamide reaction partner.

EXPERIMENTAL SECTION

General Considerations. All commercially available compounds and solvents were purchased and used as received, unless otherwise noted. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F254 plates. Visualization on TLC was achieved by the use of UV light (254 nm) and treatment with phosphomolybdic acid stain followed by heating. Flash chromatography was performed using silica gel (particle size 40−63 μm, 230−400 mesh). ^{1}H and ^{13}C NMR spectra were recorded at 25 °C on 400 MHz (400 MHz for ^{1}H, 101 MHz for ^{13}C) or 500 MHz (500 MHz for ^{1}H, 126 MHz for ^{13}C) spectrometer. Chemical shift values are given in parts per million relative to internal TMS (0.00 ppm for ^{1}H) or $CDCl_3$ (77.06 ppm for ^{13}C). The following abbreviations were used to describe peak splitting patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, dd = double of doublet, dt = double of triplet, td = triple of doublet. Coupling constants, J, were reported in hertz unit (Hz). Melting points were determined with a micromelting point apparatus without corrections. IR spectral data were obtained using the ATR (attenuated total reflectance) technique. High-resolution mass spectra were obtained on TOF system for the electron spray ionization (ESI) experiment.

General Procedure for Optimization of Cu-Catalyzed Aerobic Three-Component Oxidative Coupling (Table 1). A 16 mm culture tube, which was equipped with a magnetic stir bar and charged with copper salt and *p*-toluene sulfonamide, was evacuated and backfilled with oxygen (this process was repeated 3 times). After 2 mL of solvent was added, phenyl acetylene, diisopropyl amine, and solvent (1 mL) were added in sequence. The solution was stirred for 15 h at 70 °C under O_2 balloon, after which the reaction was diluted by adding EtOAc and filtered through silica plugs. The silica was washed with EtOAc several times, and the solvent was evaporated. A ^{1}H NMR yield of the desired product was determined by integration using an internal standard (1,1,2,2-tetrachloroethane). See Table S1 in the Supporting Information for the detail optimization.

General Procedure for Cu-Catalyzed Three-Component Oxidative Coupling Procedure (Table 2). A 16 mm culture tube, which was equipped with a magnetic stir bar and charged with $Cu(OTf)_2$ (0.015 mmol, 5 mol % or 0.03 mmol, 10 mol %) and sulfonamide (0.6 mmol), was evacuated and backfilled with oxygen (this process was repeated 3 times). After 2 mL of toluene was added, terminal alkyne (0.3 mmol), secondary amine (0.6 mmol), and toluene (1 mL) were added in sequence. The solution was stirred for 15 h at 70 °C under an O_2 balloon, then the reaction was diluted by adding EtOAc and filtered through silica plugs. The plugs were washed with EtOAc several times, and the solvent was removed under a vacuum. The residue was purified by column chromatography with Hx:EtOAc (1:1−3:1) to give the amidine product. Spectral properties of known products are consistent with literature values.

***N*^{1},*N*^{1}-Diisopropyl-*N*^{2}-(4-methylbenzenesulfonyl)-2-phenylacetamidine (4a).**[5] White solid: 110 mg, 98% of yield; mp 137−138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.2 Hz, 2H), 7.35−7.03 (m, 9H), 4.40 (s, 3H), 4.00 (p, J = 6.6 Hz, 1H), 3.53−3.36 (m, 1H), 2.38 (s, 4H), 1.39 (d, J = 6.8 Hz, 8H), 0.87 (d, J = 6.6 Hz, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4, 141.6, 141.5, 134.9, 129.0, 128.8, 128.0, 126.7, 126.2, 50.4, 48.0, 38.7, 21.4, 19.8; IR (neat) ν 1540, 1458, 1375, 1261, 1136, 1083, 1051, 940, 803, 754, 716, 697, 684, 658 cm^{-1}; EMM (ESI, TOF) calc. for $C_{21}H_{29}N_2O_2S$ [M + H]$^+$ 373.1945, found 373.1941.

***N*^{1},*N*^{1}-Diisopropyl-*N*^{2}-(4-methylbenzenesulfonyl)-2-(4-methoxyphenyl)acetamidine (4b).**[20] White solid: 106 mg, 88% of yield; mp 130−131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 8.0 Hz, 3H), 7.12 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 4.32 (s, 2H), 4.02 (p, J = 6.6 Hz, 1H), 3.76 (s, 4H), 3.54−3.36 (m, 1H), 2.38 (s, 3H), 1.37 (d, J = 6.8 Hz, 8H), 0.87 (d, J = 6.6 Hz, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8, 158.4, 141.6, 141.5, 129.1, 129.0, 126.9, 126.2, 114.2, 55.2, 50.4, 48.0, 37.9, 21.4, 19.9, 19.8; IR (neat) ν 1541, 1511, 1444, 1374, 1260, 1134, 1079, 811, 795 cm^{-1}; EMM (ESI, TOF) calc. for $C_{22}H_{31}N_2O_3S$ [M + H]$^+$ 403.2050, found 403.2056.

***N*^{1},*N*^{1}-Diisopropyl-*N*^{2}-(4-methylbenzenesulfonyl)-2-(4-methyphenyl)acetamidine (4c).**[5] White solid: 105 mg, 91% of yield; mp 188−189 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 1.1 Hz, 4H), 4.35 (s, 2H), 4.01 (p, J = 6.6 Hz, 1H), 3.53−3.37 (m, 1H), 2.39 (s, 3H), 2.30 (s, 3H), 1.38 (d, J = 6.8 Hz, 6H), 0.88 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7, 141.6, 141.5, 136.3, 131.8, 129.5, 129.0, 127.8, 126.2, 50.4, 48.0, 38.4, 21.5, 21.1, 19.9, 19.8; IR (neat) ν 1544, 1444, 1371, 1267, 1206, 1137, 1079, 1055, 961, 900, 811, 795, 738, 681 cm^{-1}; EMM (ESI, TOF) calc. for $C_{22}H_{31}N_2O_2S$ [M + H]$^+$ 387.2101, found 387.2096.

***N*^{1},*N*^{1}-Diisopropyl-*N*^{2}-(4-methylbenzenesulfonyl)-2-(4-fluorophenyl)acetamidine (4d).**[20] White solid: 107 mg, 91% of yield; mp 154−155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.20 (dd, J = 8.5, 5.4 Hz, 2H), 6.98 (t, J = 8.6 Hz, 2H), 4.37 (s, 2H), 3.97 (p, J = 6.6 Hz, 1H), 3.53−3.38 (m, 1H), 2.39 (s, 3H), 1.37 (d, J = 6.8 Hz, 6H), 0.89 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 161.7 (d, J = 245.4 Hz), 141.7, 141.4, 130.7 (d, J = 3.3 Hz), 129.6 (d, J = 8.0 Hz), 129.1, 126.2, 115.7 (d, J = 21.5 Hz), 50.4, 48.1, 37.9, 21.4, 19.9, 19.8; IR (neat) ν 1542, 1449, 1375, 1258, 1135, 1081, 811, 777 cm^{-1}; EMM (ESI, TOF) calc. for $C_{21}H_{28}FN_2O_2S$ [M + H]$^+$ 391.1851, found 391.1862.

***N*^{1},*N*^{1}-Diisopropyl-*N*^{2}-(4-methylbenzenesulfonyl)-2-(4-bromophenyl)acetamidine (4e).**[20] White solid: 135 mg, 99% of yield; mp 158−159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.3 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.3 Hz, 2H), 4.35 (s, 2H), 3.93 (p, J = 6.6 Hz, 1H), 3.45 (q, J = 7.0 Hz, 1H), 2.39 (s, 3H), 1.38 (d, J = 6.8 Hz, 6H), 0.91 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 141.8, 141.3, 134.0, 131.9, 129.7, 129.1, 126.2, 120.7, 50.5, 48.1, 38.0, 21.48, 19.9, 19.8; IR (neat) ν 1540, 1441, 1372, 1263, 1137, 1080, 810, 662 cm^{-1}; EMM (ESI, TOF) calc. for $C_{21}H_{28}BrN_2O_2S$ [M + H]$^+$ 451.1050, found 451.1043.

***N*^{1},*N*^{1}-Diisopropyl-*N*^{2}-(4-methylbenzenesulfonyl)-2-(4-acetylphenyl)acetamidine (4f).** White solid: 62 mg, 50% of yield; mp 126−127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.3 Hz, 2H), 7.82 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 7.9 Hz, 2H), 4.48 (s, 2H), 3.92 (p, J = 6.6 Hz, 1H), 3.55−3.38 (m, 1H), 2.59 (s, 3H), 2.39 (s, 3H), 1.39 (d, J = 6.8 Hz, 6H), 0.90 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.6, 162.4, 141.8, 141.3, 140.5, 135.8, 129.1, 128.9, 128.2, 126.2, 50.5, 48.2, 38.6, 26.6, 21.5, 19.9, 19.8; IR (neat) ν 1678, 1606, 1533, 1449, 1360, 1272, 1139, 1082, 1062, 962, 897, 805, 743, 666 cm^{-1}; EMM (ESI, TOF) calc. for $C_{23}H_{31}N_2O_3S$ [M + H]$^+$ 415.2050, found 415.2063.

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N^1,N^1-Diisopropyl-N^2-(4-methylbenzenesulfonyl)-2-(4-trifluoromethylphenyl)acetamidine (4g).[5] White solid: 132 mg, 99% of yield; mp 106−107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 4.48 (s, 2H), 3.91 (p, J = 6.6 Hz, 1H), 3.60−3.36 (m, 1H), 2.38 (s, 3H), 1.40 (d, J = 6.7 Hz, 6H), 0.91 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 141.9, 141.1, 139.1, 129.1 (q, J_2 = 32.6 Hz), 129.1, 128.3, 126.2, 125.8 (q, J_3 = 3.8 Hz), 124.1 (q, J_1 = 272.9 Hz), 50.5, 48.2, 38.2, 21.4, 19.9, 19.8; IR (neat) ν 1543, 1323, 1254, 1077, 1051, 810, 744, 665 cm^{-1}; EMM (ESI, TOF) calc. for $C_{22}H_{28}F_3N_2O_2S$ $[M + H]^+$ 441.1819, found 441.1833.

N^1,N^1-Diisopropyl-N^2-(4-methylbenzenesulfonyl)-2-(3-methylphenyl)acetamidine (4h). White solid: 108 mg, 93% of yield; mp 114−115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.3 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 7.15 (t, J = 7.6 Hz, 1H), 6.99 (d, J = 7.5 Hz, 1H), 6.95 (d, J = 7.7 Hz, 1H), 6.90 (s, 1H), 4.36 (s, 2H), 3.98 (p, J = 6.6 Hz, 1H), 3.52−3.35 (m, 1H), 2.37 (s, 3H), 2.27 (s, 3H), 1.40 (d, J = 6.8 Hz, 6H), 0.88 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 141.5, 141.5, 138.3, 134.7, 129.0, 128.7, 128.6, 127.4, 126.3, 124.9, 50.4, 48.0, 38.3, 21.4, 21.4, 19.9, 19.8; IR (neat) ν 1538, 1451, 1372, 1261, 1137, 1084, 1048, 952, 909, 825, 782, 731, 696, 660 cm^{-1}; EMM (ESI, TOF) calc. for $C_{22}H_{31}N_2O_2S$ $[M + H]^+$ 387.2101, found 387.2094.

N^1,N^1-Diisopropyl-N^2-(4-methylbenzenesulfonyl)-2-(3-acetylphenyl)acetamidine (4i). White solid: 122 mg, 99% of yield; mp 122−123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.2 Hz, 2H), 7.25−7.15 (m, 5H), 7.11−7.08 (m, 2H), 4.39 (s, 2H), 3.91 (p, J = 6.6 Hz, 1H), 3.51−3.44 (m, 1H), 2.38 (s, 3H), 1.40 (d, J = 6.8 Hz, 6H), 0.91 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6, 141.8, 141.2, 136.9, 134.5, 130.1, 129.1, 128.0, 127.0, 126.2, 126.1, 50.5, 48.2, 37.9, 21.5, 19.9, 19.8; IR (neat) ν 1541, 1451, 1373, 1260, 1136, 1083, 1050, 900, 808, 785, 715, 659 cm^{-1}; EMM (ESI, TOF) calc. for $C_{21}H_{28}ClN_2O_2S$ $[M + H]^+$ 407.1555, found 407.1547.

N^1,N^1-Diisopropyl-N^2-(4-methylbenzenesulfonyl)-2-(2-methoxyphenyl)acetamidine (4j). White solid: 109 mg, 90% of yield; mp 178−179 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.2 Hz, 2H), 7.22−7.15 (m, 3H), 7.08 (dd, J = 7.4, 1.2 Hz, 1H), 6.86−6.82 (m, 2H), 4.32 (s, 2H), 3.89−3.77 (m, 4H), 3.49−3.43 (m, 1H), 2.37 (s, 3H), 1.41 (d, J = 6.8 Hz, 6H), 0.88 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 156.0, 141.6, 141.4, 129.0, 128.5, 128.0, 126.2, 123.3, 120.9, 110.3, 55.5, 50.2, 47.9, 31.9, 21.4, 19.9; IR (neat) ν 1544, 1493, 1444, 1373, 1261, 1245, 1130, 1107, 1077, 1052, 959, 816, 743, 688, 657 cm^{-1}; EMM (ESI, TOF) calc. for $C_{22}H_{31}N_2O_3S$ $[M + H]^+$ 403.2050, found 403.2050.

N^1,N^1-Diisopropyl-N^2-(4-methylbenzenesulfonyl)-2-(2-bromophenyl)acetamidine (4k). White solid: 112 mg, 83% of yield; mp 191−192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 7.5 Hz, 1H), 7.25−7.19 (m, 4H), 7.13−7.06 (m, 1H), 4.47 (s, 2H), 3.72 (p, J = 6.6 Hz, 1H), 3.55−3.40 (m, 1H), 2.38 (s, 3H), 1.41 (d, J = 6.8 Hz, 6H), 0.91 (d, J = 6.6 Hz, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 141.7, 141.3, 134.5, 132.8, 129.2, 129.1, 128.5, 127.9, 126.2, 123.9, 50.6, 48.1, 38.5, 21.5, 19.8, 19.8; IR (neat) ν 1546, 1438, 1372, 1267, 1208, 1132, 1078, 1053, 1025, 955, 813, 754, 704, 669 cm^{-1}; EMM (ESI, TOF) calc. for $C_{21}H_{28}BrN_2O_2S$ $[M + H]^+$ 451.1050, found 451.1041.

N^1,N^1-Diisopropyl-N^2-(4-methylbenzenesulfonyl)-2-(6-methoxynaphtalen-2-yl)acetamidine (4l). White solid: 121 mg, 89% of yield; mp 160−161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 77.82 (d, J = 8.0 Hz, 2H), 7.66 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.39 (d, J = 2.0 Hz, 1H), 7.29 (dd, J = 8.4, 1.8 Hz, 1H), 7.20−7.06 (m, 4H), 4.51 (s, 2H), 4.07 (p, J = 6.6 Hz, 1H), 3.89 (s, 3H), 3.50−3.43 (m, 1H), 2.30 (s, 3H), 1.44 (d, J = 6.8 Hz, 6H), 0.84 (d, J = 6.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7, 157.8, 141.6, 141.5, 133.3, 129.9, 129.1, 129.0, 128.9, 127.4, 126.7, 126.3, 126.2, 119.0, 105.6, 55.3, 50.5, 48.1, 38.3, 21.4, 19.9; IR (neat) ν 1538, 1444, 1374, 1262, 1228, 1132, 1047, 843, 791, 730, 674 cm^{-1}; EMM (ESI, TOF) calc. for $C_{26}H_{33}N_2O_3S$ $[M + H]^+$ 453.2207, found 453.2216.

N^1,N^1-Diisopropyl-N^2-(4-methylbenzenesulfonyl)-2-(thiophen-2-yl)phenylacetamidine (4m). White solid: 96 mg, 85% of yield; mp 136−137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.2 Hz, 2H), 7.29−7.20 (m, 4H), 7.04−6.98 (m, 2H), 4.36 (s, 2H), 4.06 (p, J = 6.6 Hz, 1H), 3.55−3.36 (m, 1H), 2.39 (s, 3H), 1.37 (d, J = 6.8 Hz, 6H), 0.93 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 141.6, 141.5, 134.4, 129.0, 127.8, 126.2, 126.1, 121.9, 50.5, 48.1, 33.8, 21.5, 19.9, 19.8; IR (neat) ν 1543, 1263, 1082, 1051, 807, 778, 669 cm^{-1}; EMM (ESI, TOF) calc. for $C_{19}H_{27}N_2O_2S_2$ $[M + H]^+$ 379.1509, found 379.1501.

N^1,N^1-Diisopropyl-N^2-(4-methylbenzenesulfonyl)-2-(cyclohexenyl)acetamidine (4n).[5] White solid: 53 mg, 47% of yield; mp 80−81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 5.22 (dt, J = 3.8, 1.9 Hz, 1H), 3.94 (p, J = 6.6 Hz, 1H), 3.57 (d, J = 2.6 Hz, 2H), 3.54−3.43 (m, 1H), 2.38 (s, 3H), 2.02−1.83 (m, 4H), 1.64−1.55 (m, 2H), 1.53−1.44 (m, 2H), 1.40 (d, J = 6.8 Hz, 6H), 1.14 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8, 141.7, 141.3, 131.2, 128.9, 126.3, 123.3, 50.2, 48.0, 39.8, 28.5, 25.2, 22.7, 22.0, 21.4, 20.3, 20.1; IR (neat) ν 1541, 1446, 1371, 1266, 1133, 1083, 1052, 811, 793, 666 cm^{-1}; EMM (ESI, TOF) calc. for $C_{21}H_{33}N_2O_2S$ $[M + H]^+$ 377.2258, found 377.2265.

N^1,N^1-Diisopropyl-N^2-(4-methylbenzenesulfonyl)-(5-chloro)-pentanamidine (4o).[5] White solid: 76 mg, 68% of yield; mp 91−92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 4.07 (p, J = 6.6 Hz, 1H), 3.62−3.52 (m, 3H), 3.02−2.83 (m, 2H), 2.39 (s, 3H), 2.02−1.68 (m, 4H), 1.32 (d, J = 6.7 Hz, 6H), 1.24 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 141.7, 141.5, 129.1, 126.0, 50.1, 48.0, 44.4, 32.0, 31.8, 24.2, 21.5, 20.7, 20.0; IR (neat) ν 1538, 1445, 1372, 1255, 1128, 1080, 1050, 821, 807, 792, 688 cm^{-1}; EMM (ESI, TOF) calc. for $C_{18}H_{30}ClN_2O_2S$ $[M + H]^+$ 373.1712, found 373.1711.

N^1,N^1-Diethyl-N^2-(4-methylbenzenesulfonyl)-2-phenylacetamidine (6a).[21] White solid: 98 mg, 95% of yield; mp 116−117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.2 Hz, 2H), 7.28−7.15 (m, 5H), 7.11 (dd, J = 7.1, 1.8 Hz, 2H), 4.38 (s, 2H), 3.50 (q, J = 7.1 Hz, 2H), 3.20 (q, J = 7.1 Hz, 2H), 2.36 (s, 3H), 1.15 (t, J = 7.1 Hz, 3H), 0.94 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5, 141.7, 141.3, 134.4, 129.0, 128.8, 127.8, 126.7, 126.2, 43.4, 43.3, 36.6, 21.4, 13.4, 11.9; IR (neat) ν 1549, 1471, 1274, 1140, 1076, 827, 762, 724, 658 cm^{-1}; EMM (ESI, TOF) calc. for $C_{19}H_{25}N_2O_2S$ $[M + H]^+$ 345.1632, found 345.1636.

N^1,N^1-Dipropyl-N^2-(4-methylbenzenesulfonyl)-2-phenylacetamidine (6b). Yellow solid: 95 mg, 85% of yield; mp 84−85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.0 Hz, 2H), 7.29−7.10 (m, 7H), 4.38 (s, 2H), 3.48−3.28 (m, 2H), 3.17−2.99 (m, 2H), 2.36 (s, 3H), 1.60 (q, J = 7.6 Hz, 2H), 1.42−1.25 (m, 2H), 0.84 (td, J = 7.5, 1.1 Hz, 3H), 0.74 (td, J = 7.5, 1.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8, 141.6, 141.4, 134.5, 129.0, 128.8, 128.0, 126.8, 126.2, 50.8, 50.6, 36.8, 21.7, 21.4, 20.1, 11.5, 11.1; IR (neat) ν 1545, 1473, 1272, 1141, 1087, 953, 839, 726, 690 cm^{-1}; EMM (ESI, TOF) calc. for $C_{21}H_{29}N_2O_2S$ $[M + H]^+$ 373.1945, found 373.1947.

N^1,N^1-Dibutyl-N^2-(4-methylbenzenesulfonyl)-2-phenylacetamidine (6c). Yellow solid: 96 mg, 80% of yield; mp 66−67 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.2 Hz, 2H), 7.31−7.09 (m, 7H), 4.39 (s, 2H), 3.51−3.31 (m, 2H), 3.21−3.01 (m, 2H), 2.37 (s, 3H), 1.61−1.45 (m, 2H), 1.36−1.19 (m, 4H), 1.19−1.10 (m, 2H), 0.86 (t, J = 7.3 Hz, 3H), 0.81 (t, J = 7.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 141.6, 141.5, 134.6, 128.9, 128.9, 128.9, 128.0, 126.8, 126.2, 49.0, 48.8, 36.9, 30.5, 28.7, 21.4, 20.2, 20.0, 13.8, 13.7; IR (neat) ν 1552, 1474, 1258, 1135, 1084, 952, 858, 815, 728, 691, 675 cm^{-1}; EMM (ESI, TOF) calc. for $C_{23}H_{33}N_2O_2S$ $[M + H]^+$ 401.2258, found 401.2271.

N^1,N^1-Dibenzyl-N^2-(4-methylbenzenesulfonyl)-2-phenylacetamidine (6d). Clear oil: 104 mg, 74% of yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.3 Hz, 2H), 7.37−7.11 (m, 15H), 7.05−6.91 (m, 2H), 4.71 (s, 2H), 4.49 (s, 2H), 4.37 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 142.0, 140.9, 136.0, 134.9, 134.1, 129.2, 129.1, 129.0, 128.7, 128.3, 128.1, 128.1, 127.8, 127.0, 126.4, 51.2, 51.0, 37.0, 21.5; IR (neat) ν 1537, 1453, 1277, 1141, 1088, 853, 729, 691 cm^{-1}; EMM (ESI, TOF) calc. for $C_{29}H_{29}N_2O_2S$ $[M + H]^+$ 469.1945, found 469.1945.

N^1-Butyl-N^1-ethyl-N^2-(4-methylbenzenesulfonyl)-2-phenylacetamidine (6e). Yellow solid: 91 mg, 81% of yield; mp 64−65 °C;

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^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 6.3 Hz, 2H), 7.38−7.00 (m, 7H), 4.38 (d, J = 5.9 Hz, 2H), 3.50 (q, J = 7.1 Hz, 1H), 3.44−3.37 (m, 1H), 3.20 (q, J = 7.1 Hz, 1H), 3.13−3.06 (m, 1H), 2.37 (s, 3H), 1.57−1.51 (m, 1H), 1.32−1.23 (m, 2H), 1.16−0.93 (m, 4H), 0.83 (dt, J = 23.5, 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 164.5, 141.6, 141.6, 141.4, 141.4, 134.5, 134.4, 129.0, 128.9, 128.8, 127.9, 127.9, 126.8, 126.7, 126.2, 126.2, 48.7, 48.2, 43.9, 43.7, 36.8, 36.7, 30.5, 28.8, 21.4, 20.2, 20.0, 13.8, 13.7, 13.4, 11.9; IR (neat) ν 1547, 1451, 1254, 1131, 1075, 941, 715, 676 cm^{-1}; EMM (ESI, TOF) calc. for $C_{21}H_{29}N_2O_2S$ $[M + H]^+$ 373.1945, found 373.1945.

N^1-2,6-Dimethylpiperidinyl-N^2-(4-methylbenzenesulfonyl)-2-phenylacetamidine (6f).[22] White solid: 55 mg, 48% of yield; mp 118−119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.2 Hz, 2H), 7.33−7.02 (m, 7H), 5.03 (dt, J = 8.1, 4.1 Hz, 1H), 4.83 (d, J = 16.2 Hz, 1H), 4.14−3.93 (m, 2H), 2.36 (s, 3H), 1.82−1.68 (m, 1H), 1.61−1.56 (m, 2H), 1.45−1.38 (m, 2H), 1.35−1.27 (m, 1H), 1.24 (d, J = 7.1 Hz, 3H), 1.10 (d, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 141.6, 141.6, 134.7, 129.0, 128.8, 127.7, 126.7, 126.2, 48.7, 47.4, 37.1, 30.2, 29.8, 21.4, 21.2, 19.6, 13.7; IR (neat) ν 1527, 1450, 1269, 1143, 1106, 1084, 962, 845, 792, 745, 693 cm^{-1}; EMM (ESI, TOF) calc. for $C_{22}H_{29}N_2O_2S$ $[M + H]^+$ 385.1945, found 385.1945.

N^1,N^1-Diisopropyl-N^2-(benzenesulfonyl)-2-phenylacetamidine (7a).[22] White solid: 91 mg, 85% of yield; mp 113−114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, J = 7.9, 1.8 Hz, 2H), 7.50−7.40 (m, 3H), 7.32−7.26 (m, 2H), 7.24−7.17 (m, 3H), 4.41 (s, 2H), 4.00 (p, J = 6.6 Hz, 1H), 3.48−3.41 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 0.87 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5, 144.3, 134.8, 131.2, 128.9, 128.4, 128.0, 126.8, 126.2, 50.5, 48.1, 38.8, 19.8; IR (neat) ν 1544, 1445, 1270, 1134, 1081, 805, 750, 622, 612 cm^{-1}; EMM (ESI, TOF) calc. for $C_{20}H_{27}N_2O_2S$ $[M + H]^+$ 359.1783, found 359.1776.

N^1,N^1-Diisopropyl-N^2-(4-methoxylbenzenesulfonyl)-2-phenylacetamidine (7b). White solid: 114 mg, 98% of yield; mp 143−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.9 Hz, 2H), 7.39−7.09 (m, 5H), 6.90 (d, J = 8.9 Hz, 2H), 4.40 (s, 2H), 3.99 (p, J = 6.6 Hz, 1H), 3.84 (s, 3H), 3.48−3.41 (m, 1H), 1.39 (d, J = 6.7 Hz, 6H), 0.87 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3, 161.7, 136.6, 134.9, 128.8, 128.2, 128.0, 126.7, 113.6, 55.5, 50.4, 48.0, 38.6, 19.8, 19.8; IR (neat) ν 1540, 1374, 1257, 1136, 1083, 949, 795, 716, 702 cm^{-1}; EMM (ESI, TOF) calc. for $C_{21}H_{29}N_2O_3S$ $[M + H]^+$ 389.1894, found 389.1893.

N^1,N^1-Diisopropyl-N^2-(4-bromobenzenesulfonyl)-2-phenylacetamidine (7c).[5] White solid: 130 mg, 99% of yield; mp 146−147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.6 Hz, 2H), 7.56 (d, J = 8.6 Hz, 2H), 7.33−7.15 (m, 5H), 4.40 (s, 2H), 4.01 (p, J = 6.6 Hz, 1H), 3.50−3.43 (m, 1H), 1.37 (d, J = 6.8 Hz, 6H), 0.89 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 143.3, 134.6, 131.7, 128.9, 127.9, 127.9, 126.9, 125.9, 50.7, 48.2, 38.9, 19.8; IR (neat) ν 1542, 1442, 1373, 1264, 1137, 1068, 763, 740, 629 cm^{-1}; EMM (ESI, TOF) calc. for $C_{20}H_{26}BrN_2O_2S$ $[M + H]^+$ 437.0893, found 437.0891.

N^1,N^1-Diisopropyl-N^2-(naphtalene sulfonyl)-2-phenylacetamidine (7d). White solid: 75 mg, 61% of yield; mp 215−216 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99−8.91 (m, 1H), 8.26−8.20 (m, 1H), 7.92−7.83 (m, 2H), 7.62 (ddd, J = 8.5, 6.9, 1.4 Hz, 1H), 7.54 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 7.37 (dd, J = 8.2, 7.3 Hz, 1H), 7.13 (dd, J = 5.1, 1.9 Hz, 3H), 7.02−6.96 (m, 2H), 4.41 (s, 2H), 3.95 (p, J = 6.6 Hz, 1H), 3.53−3.29 (m, 1H), 1.33 (d, J = 6.8 Hz, 6H), 0.86 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 139.3, 134.6, 134.1, 132.7, 128.7, 128.6, 128.4, 127.6, 127.1, 126.7, 126.7, 126.6, 126.4, 124.1, 50.6, 48.2, 38.4, 20.0, 19.8; IR (neat) ν 1547, 1447, 1275, 1257, 1107, 809, 795, 775, 688, 612 cm^{-1}; EMM (ESI, TOF) calc. for $C_{24}H_{29}N_2O_2S$ $[M + H]^+$ 409.1945, found 409.1957.

N^1,N^1-Diisopropyl-N^2-(2-thiophene sulfonyl)-2-phenylacetamidine (7e). White solid: 41 mg, 37% of yield; mp 110−111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, J = 3.7, 1.4 Hz, 1H), 7.45 (dd, J = 5.0, 1.4 Hz, 1H), 7.33−7.13 (m, 5H), 6.97 (dd, J = 5.0, 3.7 Hz, 1H), 4.40 (s, 2H), 4.02 (p, J = 6.6 Hz, 1H), 3.52−4.38 (m, 1H), 1.48 (d, J = 6.8 Hz, 6H), 0.89 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7, 146.1, 134.7, 129.8, 129.6, 128.9, 127.9, 126.9, 126.5, 50.7, 48.4, 38.9, 19.8, 19.8; IR (neat) ν 1542, 1445, 1373, 1280, 1126, 1088, 1014, 796, 754, 714, 607 cm^{-1}; EMM (ESI, TOF) calc. for $C_{18}H_{25}N_2O_2S_2$ $[M + H]^+$ 365.1274, found 365.1272.

N^1,N^1-Diisopropyl-N^2-(butane sulfonyl)-2-phenylacetamidine (7f). White solid: 81 mg, 80% of yield; mp 71−72 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.12 (m, 5H), 4.35 (s, 2H), 4.00 (p, J = 6.6 Hz, 1H), 3.50−3.42 (m, 1H), 3.18−3.03 (m, 2H), 1.95−1.90 (m, 2H), 1.50−1.48 (m, 8H), 0.97 (t, J = 7.4 Hz, 3H), 0.87 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 135.0, 128.9, 128.1, 126.8, 55.4, 50.3, 47.8, 39.6, 25.6, 21.8, 20.0, 19.8, 13.8; IR (neat) ν 1543, 1461, 1376, 1261, 1112, 1051, 948, 916, 837, 819, 743, 710 cm^{-1}; EMM (ESI, TOF) calc. for $C_{18}H_{31}N_2O_2S$ $[M + H]^+$ 339.2101, found 339.2092.

Synthesis of Starting Materials. Terminal alkyne **1f** was prepared by Sonogashira-coupling and TMS deprotection following a literature procedure.[23] Sulfonamides **3b**, **3c**, **3d**, **3e**, and **3f** were prepared by the reaction of sulfonyl chloride with aqueous ammonia.[24]

4-Acetylphenylacetylene (1f). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, J = 8.3 Hz, 2H), 7.57 (d, J = 8.2 Hz, 2H), 3.26 (s, 1H), 2.60 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.3, 136.7, 132.3, 128.2, 126.9, 82.7, 80.4, 26.7.

Experimental Procedure for 10 mmol Scale Reaction. A 250 mL round-bottom flask was equipped with a magnetic stir bar and charged with $Cu(OTf)_2$ (0.3 mmol, 3 mol %) and sulfonamide **3a** (20 mmol). After 50 mL of toluene was added, terminal alkyne **1a** (10 mmol, 1 g), secondary amine **2a** (20 mmol), and toluene (50 mL) were added in sequence. The solution was stirred for 21 h at 70 °C under air, and the solvent was removed under a vacuum. The reaction was diluted by adding EtOAc and aqueous NH_4Cl solution. The two layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and the solvent was removed under a vacuum. The residue was purified by recrystallization with ethyl acetate and hexane to give an amidine product (2.83g, 76%).

Experiment to Probe the Involvement of Pathway A vs B in Scheme 2 (Competition Experiment with Primary Amine and Secondary Amine). A 16 mm culture tube, which was equipped with a magnetic stir bar and charged with copper salt and *p*-toluene sulfonamide (0.6 mmol), was evacuated and backfilled with oxygen (this process was repeated 3 times). After 2 mL of toluene was added, phenyl acetylene (0.3 mmol), primary amine such as benzylamine, hexylamine, and cyclohexylamine (0.18 mmol) and diisopropyl amine (0.18 mmol), and toluene (1 mL) were added in sequence. The solution was stirred for 15 h at 70 °C under O_2 balloon, then the reaction was diluted by adding EtOAc and filtered through silica plugs. The plugs were washed with EtOAc several times, and the solvent was removed under a vacuum. The ^{1}H NMR yield of desired product was determined by integration using an internal standard (1,1,2,2-tetrachloroethane).

Experiment for Pathway C. A 16 mm culture tube, which was equipped with a magnetic stir bar and charged with copper salt and *p*-toluene sulfonamide (0.6 mmol), was evacuated and backfilled with oxygen (this process was repeated 3 times). After 2 mL of toluene was added, phenyl acetaldehyde (0.3 mmol) and diisopropyl amine (0.6 mmol), and toluene (1 mL) were added in sequence. The solution was stirred for 15 h at 70 °C under O_2 balloon, then the reaction was diluted by adding EtOAc and filtered through silica plugs. The plugs were washed with EtOAc several times, and the solvent was removed under a vacuum.

Experiment for Pathway D. The ynamine was synthesized by following a previously reported procedure.[14a] After the reaction, the addition of NH_4Cl solution in water produced amide (10%) with homocouplied alkyne (90%), while the addition of $TsNH_2$ at 70 °C produced amidine product (11%) with homocoupled alkyne (89%).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full screening data for optimization, ^{1}H and ^{13}C NMR spectra, and X-ray crystallographic analysis data are included. This

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Notes

The authors declare no competing financial interest.

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