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.

A midines 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 compounds³ 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

Scheme 1. (a) Synthesis of N-Toluene Sulfonyl Amidine with TsN₃; (b) Aerobic Oxidative N-Toluene Sulfonyl Amidine Synthesis (Azide-Free)



three-component coupling of a terminal alkyne, sulfonyl azide, and amine produces *N*-sulfonyl amidines⁵ through nucelophilic addition of an amine onto an in situ generated ketenimine intermediate.⁶ Li^7 and others⁸ 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

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 CuCl₂ (20 mol %), Na₂CO₃ (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 electrondeficient 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 Cucatalyzed 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

Ph //	[/] Pr + ⊢ + TsNH₂ + HN _{`Pr} 2a 3a	[Cu] solvent, 70 ºC	h	Ph	2 5
				yield	$(\%)^b$
entry	Cu (mol %)	additive (equiv	r) solvent	4a	5
1	$CuCl_2$ (20)	pyridine (2), Na ₂ CO ₃ (2)	toluene	42	46
2	$CuCl_2$ (20)	-	toluene	49	15
3	CuCl (20)	_	toluene	53	20
4	$\begin{array}{c} Cu(CH_3CN)_4OTf\ (20) \end{array}$	-	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 Na₂CO₃ (entry 2). Among copper sources tested, Cu^I and Cu^{II} salts with noncoordinating anions, such as [Cu(CH₃CN)₄]OTf and Cu(OTf)₂, gave the best results and completely avoided formation of the divne 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 threecomponent 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 (11) and 2-ethynylthiophene (1m), were effectively converted into the corresponding amidines. Coupling reactions of allylic or aliphatic alkynes (1n or 10) 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 threecomponent 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

^aConditions: 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. ^bIsolated yield. ^c10 mol % of $Cu(OTf)_2$ was employed.

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



^aConditions: 1a (0.3 mmol), 2 (0.6 mmol), 3a (0.6 mmol), and Cu(OTf)₂ (5 mol %) in toluene (3.0 mL) under O₂ balloon at 70 °C for 15 h. ^bIsolated 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	inv	estigated	ad	lditional	sul	fonamide	substrat	tes
(Table	4).	Α	number	of	substitut	ed	benzenesu	ılfonami	de

Table 4. Sulfonamide Substrate Scope in the $Cu(OTf)_2$ -Catalyzed Aerobic Oxidative Three-Component Coupling^{*a*}



^{*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 threecomponent 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 TsNH₂ 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 TsNH₂ 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 TsNH₂ 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 (${}^{i}Pr_{2}NH$) were included together in the three-component coupling reaction. Only amidine product derived from ${}^{i}Pr_{2}NH$ 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 'Pr₂NH under the threecomponent 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 Et₂NH 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 NH₄Cl 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 TsNH₂ 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

Scheme 3. Reaction of Water or TsNH₂ with In Situ Generated Ynamine



be most plausible pathway for formation of the amidine product.

In conclusion, we have identified aerobic oxidative threecomponent-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 μ m, 230–400 mesh). ¹H and ¹³C NMR spectra were recorded at 25 °C on 400 MHz (400 MHz for ¹H, 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 ¹H) or CDCl₃ (77.06 ppm for ¹³C). 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, $d\tilde{d}$ = 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 O₂ 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 ¹H 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 O₂ 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.

¹ *N*¹,*N*¹-Diisopropyl-*N*²-(4-methylbenzenesulfonyl)-2-phenylacetamidine (4a).⁵ White solid: 110 mg, 98% of yield; mp 137–138 °C; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₂₁H₂₉N₂O₂S [M + H]⁺ 373.1945, found 373.1941.

 N^1 , N^1 -Diiso propyl- N^2 -(4-methylbenzenesulfonyl)-2-(4-methoxyphenyl)acetamidine (4b).²⁰ White solid: 106 mg, 88% of yield; mp 130–131 °C; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₂₂H₃₁N₂O₃S [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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₂₂H₃₁N₂O₂S [M + H]⁺ 387.2101, found 387.2096.

N¹, N¹-Diisopropyl-N²-(4-methylbenzenesulfonyl)-2-(4fluorophenyl)acetamidine (4d).²⁰ White solid: 107 mg, 91% of yield; mp 154–155 °C; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₂₁H₂₈FN₂O₂S [M + H]⁺ 391.1851, found 391.1862.

 N^1 , N^1 -Diisopropyl- N^2 -(4-methylbenzenesulfonyl)-2-(4bromophenyl)acetamidine (4e).²⁰ White solid: 135 mg, 99% of yield; mp 158–159 °C; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₂₁H₂₈BrN₂O₂S [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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₂₃H₃₁N₂O₃S [M + H]⁺ 415.2050, found 415.2063.

*N*¹,*N*¹-Diisopropyl-*N*²-(4-methylbenzenesulfonyl)-2-(4trifluoromethylphenyl)acetamidine (4g).⁵ White solid: 132 mg, 99% of yield; mp 106–107 °C; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₂₂H₂₈F₃N₂O₂S [M + H]⁺ 441.1819, found 441.1833.

*N*¹,*N*¹-Diisopropyl-*N*²-(4-methylbenzenesulfonyl)-2-(3methylphenyl)acetamidine (4h). White solid: 108 mg, 93% of yield; mp 114–115 °C; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₂₂H₃₁N₂O₂S [M + H]⁺ 387.2101, found 387.2094.

 N^1 , N^1 -Diisopropyl- N^2 -(4-methylbenzenesulfonyl)-2-(3acetylphenyl)acetamidine (4i). White solid: 122 mg, 99% of yield; mp 122–123 °C; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₂₁H₂₈ClN₂O₂S [M + H]⁺ 407.1555, found 407.1547.

 N^1 , N^1 -Diisopropyl- N^2 -(4-methylbenzenesulfonyl)-2-(2methoxyphenyl)acetamidine (4j). White solid: 109 mg, 90% of yield; mp 178–179 °C; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₂₂H₃₁N₂O₃S [M + H]⁺ 403.2050, found 403.2050.

*N*¹,*N*¹-Diisopropyl-*N*²-(4-methylbenzenesulfonyl)-2-(2bromophenyl)acetamidine (4k). White solid: 112 mg, 83% of yield; mp 191–192 °C; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₂₁H₂₈BrN₂O₂S [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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₂₆H₃₃N₂O₃S [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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₁₉H₂₇N₂O₂S₂ [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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₂₁H₃₃N₂O₂S [M + H]⁺ 377.2258, found 377.2265.

*N*¹,*N*¹-Diisopropyi-*N*²-(4-methylbenzenesulfonyl)-(5-chloro)pentanamidine (40).⁵ White solid: 76 mg, 68% of yield; mp 91−92 °C; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₁₈H₃₀ClN₂O₂S [M + H]⁺ 373.1712, found 373.1711.

N¹,**N**¹-Diethyl-*N*²-(4-methylbenzenesulfonyl)-2-phenylacetamidine (6a).²¹ White solid: 98 mg, 95% of yield; mp 116–117 °C; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₁₉H₂₅N₂O₂S [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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₂₁H₂₉N₂O₂S [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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) δ 164.6, 141.6, 141.5, 134.6, 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 C₂₃H₃₃N₂O₂S [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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₂₉H₂₉N₂O₂S [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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) δ 164.6, 164.5, 141.6, 141.6, 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 C₂₁H₂₉N₂O₂S [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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₂₂H₂₉N₂O₂S [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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₂₀H₂₇N₂O₂S [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; ¹H NMR (400 MHz, CDCl₃) δ 7.87 (d, J = 8.9 Hz, 2H), 7.39–7.09 (m, SH), 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₂₁H₂₉N₂O₃S [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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₂₀H₂₆BrN₂O₂S [M + H]⁺ 437.0893, found 437.0891.

N¹,**N**¹-**DiisopropyI-N**²-(naphtalene sulfonyI)-2-phenylacetamidine (7d). White solid: 75 mg, 61% of yield; mp 215–216 °C; ¹H NMR (400 MHz, CDCl₃) 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 = 6.6Hz, 1H), 3.53–3.29 (m, 1H), 1.33 (d, J = 6.8 Hz, 6H), 0.86 (d, J = 6.6Hz, 6H); ¹³C NMR (101 MHz, CDCl₃) 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 C₂₄H₂₀N₂O₂S [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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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 C₁₈H₃₁N₂O₂S [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). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) 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 NH₄Cl solution. The two layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO₄, 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 O₂ 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 ¹H NMR yield of desired product was determined by integration using an internal standard (1,1,2,2tetrachloroethane).

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 O₂ 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 NH₄Cl solution in water produced amide (10%) with homocouplied alkyne (90%), while the addition of TsNH₂ at 70 °C produced amidine product (11%) with homocoupled alkyne (89%).

ASSOCIATED CONTENT

S Supporting Information

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

material is available free of charge via the Internet at http:// pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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