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Copper-Catalyzed Reaction of Ketenimine and in Situ Generated Immonium Ion: Access to α,β-Unsaturated Amidines

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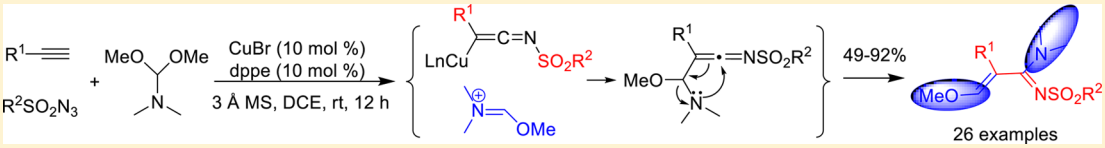
Supporting Information



ABSTRACT: A Cu-catalyzed three-component reaction of alkyne, azides (sulfonyl or phosphoryl azides), and *N*,*N*-dialkyloxyformamide dialkyl acetal via electrophilic addition of immonium ion to copper ketenimine is reported. This new protocol for the preparation of α,β-unsaturated amidine derivatives appears to offer high yield, mild conditions, and wide substrate scope. The reaction might involve the processes of copper ketenimine intermediate formation, electrophilic addition, and isomerization.

INTRODUCTION

Click chemistry[1] involving the copper-catalyzed azide−alkyne cycloaddition (CuAAC) reaction to produce regioselectively 1,4-disubstituted 1,2,3-triazoles[2] has aroused considerable interest because of its countless applications in organic synthesis,[3] material sciences,[4] bioconjugation,[5] and medical chemistry.[6] Among the azides utilized in the CuAAC reaction, the employment of sulfonyl azides resulted in apparently different outcomes and smoothly generated in situ a reactive ketenimine intermediate by ring-opening rearrangement of *N*-sulfonyl copper trizole species.[7] This facile and versatile route to a ketenimine has dramatically broadened the scope and utility of the CuAAC reaction. Elegant examples of multicomponent reactions[8−10] have been developed by trapping in situ generated ketenimine via this CuAAC process.[11] However, these transformations mainly focused on the addition to the central carbon of ketenimine, which was reactive toward various nucleophiles. As could be concluded from the resonance structures of ketenimine intermediates, they could be captured by both nucleophiles and electrophiles, while the reaction of electrophiles with ketenimine generated through the CuAAC mechanism has not yet been investigated to date (Scheme 1).

Recently we have developed an efficient synthesis of 3-amino-1,4-diynes via copper-catalyzed coupling reactions of terminal alkynes with C−OMe bonds adjacent to a nitrogen atom, which involves an immonium ion intermediate generated in situ through elimination of MeOH from terminal alkynes and *N*,*N*-dimethylformamide dialkyl acetals.[12] Encouraged by these results, we decided to expand the scope of this reaction by using sulfonyl azides. Herein, we report a unique Cu-catalyzed three-component reaction of alkyne, azide, and *N*,*N*-dialkyloxyformamide dialkyl acetal, which might involve an electrophilic addition of immonium ion to an in situ generated copper ketenimine intermediate. This transformation results in the efficient formation of synthetically important and pharmacologically useful amidine derivatives.[13]

RESULTS AND DISCUSSION

Under the protocol used for the synthesis of 3-amino-1,4-diynes in our previous work, phenylacetylene (**1a**; 0.6 mmol), tolylsulfonyl azide (**2a**; 0.6 mmol), and *N*,*N*-dimethylformamide dimethyl acetal (**3a**; 0.5 mmol) were reacted in toluene at 80 °C in the presence of CuBr (10 mol %), dppp (10 mol %), and 3 Å MS (molecular sieves). Surprisingly, unsaturated amidine **4a** was obtained in 74% isolated yield (Scheme 2), and its structure was further confirmed by X-ray structural analysis, which disclosed that the C═N double bond had an *E* configuration (Figure 1).

After this seminal experiment, we decided to optimize reaction conditions. As shown in Table 1, commonly used solvents, such as acetonitrile (MeCN), dioxane, and THF were also suitable for this transformation; in comparison, dichloroethane (DCE) gave better yields (Table 1, entries 1−5). The reaction could run smoothly and efficiently even at room temperature (Table 1, entries 5−7). The use of phosphine ligands was crucial to this reaction; both monodentate and bidentate phosphine ligands showed effects on the transformation, while dppe displayed the best reactivity and afforded a 91% yield of **4a** (Table 1, entries 7−11). Other copper

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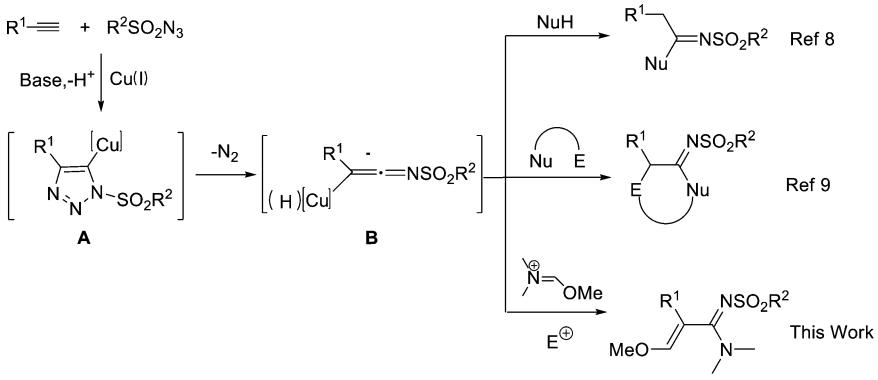
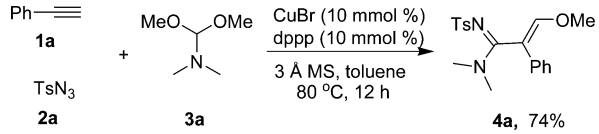
Scheme 1. Divergent Transformation of Ketenimine Intermediate B



Scheme 2. Formatiom of Unsaturated Amidine 4a



species, such as CuCl and CuI, were also reactive but provided a slightly lower yield (Table 1, entries 12 and 13). The addition of 3 Å MS facilitated the three-component reaction, and the yield of **4a** decreased without the use of 3 Å MS (Table 1, entries 10 and 14). Thus, the reaction efficiently proceeded when 10 mol % of CuBr and 10 mol % of dppe were used in combination with 3 Å MS in DCE at room temperature.

With the optimal reaction conditions in hand, we next studied the scope and generality of this reaction (Table 2). A variety of terminal alkynes could be used in the reaction to produce unsaturated amidines in good to excellent yields. The use of arylacetylenes provided the desired products in similar yields with little influence of the steric and electronic variation on the aromatic moiety (Table 2, entries 1–7). Heteroaromatic acetylene was also tolerated, and conjugated enynes turned out to be another viable substrate type for the transformation (Table 2, entries 8 and 9). Aliphatic alkynes bearing certain functional groups (cyclopropanyl or phenoxyl) and a sterically bulky group around the triple bond of alkynes were also compatible under this reaction conditions (Table 2, entries 10–13). Functionalized alkynes such as silylacetylene and but-3-yn-2-one could participate smoothly under the same conditions to afford the corresponding unsaturated amidines in excellent yields (Table 2, entries 14 and 15). The scope of the reaction with respect to the azide component was also investigated. As can be seen from Table 2, both methyl and aryl substituents of sulfonyl azides could be involved in the reaction. The nature of the substituents on the phenylsulfonyl azides affected the efficiency of the reaction: electron-rich azides led to yields of amidines higher than those with electron-withdrawing groups on the phenyl rings (Table 2, entries 16–20).

We subsequently explored the application of various *N,N*-dialkyloxyformamide dialkyl acetals (Table 3). Both acyclic and cyclic formamide dimethyl acetals were accommodated with good efficiency (Table 3, entries 1–4). *N,N*-dimethylformamide diethyl acetal could afford its corresponding α-phenyl-β-ethoxyl-α,β-unsaturated amidine **6e** in 75% yield (Table 3, entry 5).

Diphenylphosphoryl azide (DPPA)[14] also could be successfully employed as a reaction partner in our reaction system to afford the unsaturated phosphoryl amidine **8** in 49% yield (Scheme 3), which provided an alternative route for the synthesis of bioactive phosphoryl amidines.[15]

On the basis of our previous studies[12] and the mechanistic studies of copper-catalyzed multicomponent reactions involving

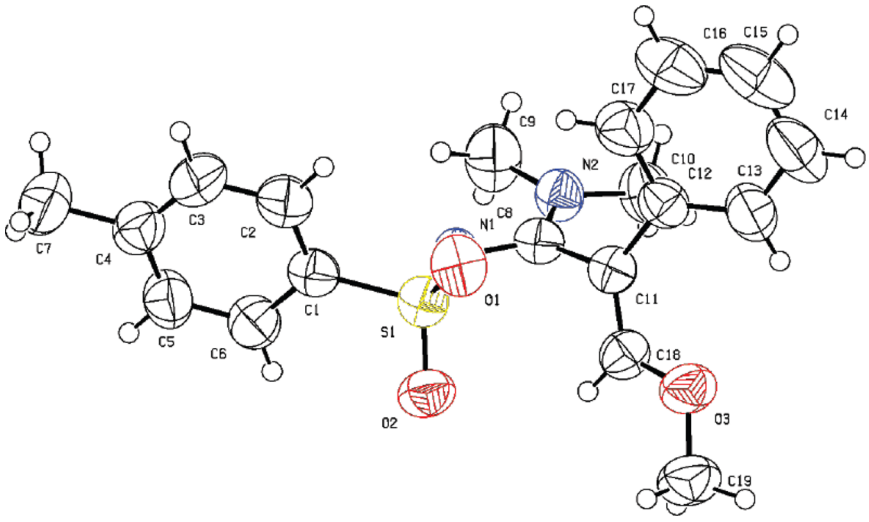


Figure 1. ORTEP drawing of compound **4a**.

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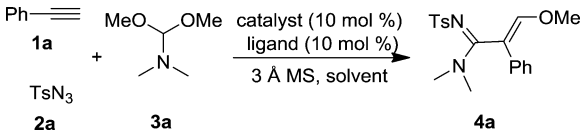
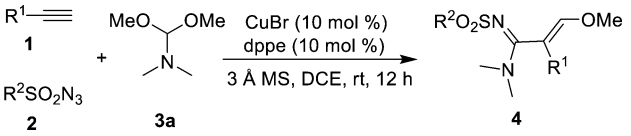
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	ligand[b]	solvent	temp (°C)	yield (%)[c]
1	CuBr	dppp	toluene	80	74
2	CuBr	dppp	MeCN	80	69
3	CuBr	dppp	dioxane	80	81
4	CuBr	dppp	THF	68	79
5	CuBr	dppp	DCE	80	91
6	CuBr	dppp	DCE	60	90
7	CuBr	dppp	DCE	room temp	89
8	CuBr		DCE	room temp	75
9	CuBr	PPh_3	DCE	room temp	85
10	CuBr	dppe	DCE	room temp	91
11	CuBr	dppb	DCE	room temp	87
12	CuCl	dppe	DCE	room temp	87
13	CuI	dppe	DCE	room temp	89
14	CuBr	dppe	DCE	room temp	69[d]
15	CuBr		DCE	room temp	35[d]

[a]Reaction conditions: **1a** (0.6 mmol), **2a** (0.6 mmol), **3a** (0.5 mmol), catalyst (0.05 mmol), ligand (0.05 mmol), and solvent (4 mL), under N_2, for 12 h. [b]Abbreviations: dppe, 1,2-bis(diphenylphosphino)ethane; dppp, 1,2-bis(diphenylphosphino)propane; dppb, 1,2-bis-(diphenylphosphino)butane. [c]Yields refer to **3a**. [d]No 3 Å MS added.

Table 2. Multicomponent Reaction with Variation of Terminal Alkynes and Sulfonyl Azides[a]

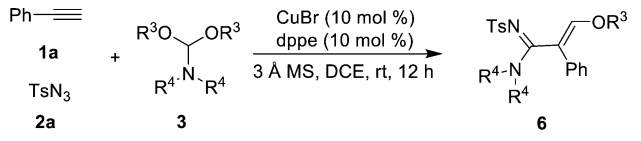


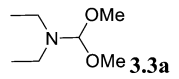
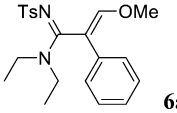
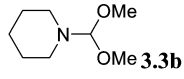
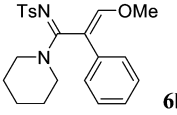
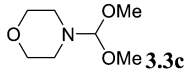
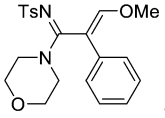
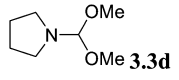
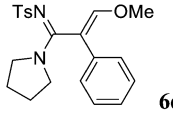
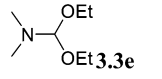
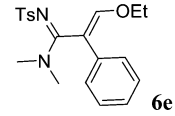
entry	R^1 of **1**	R^2 of **2**	**4**	yield (%)[b]
1	Ph (**1a**)	4-MeC_6H_4 (**2a**)	**4a**	91
2	4-MeC_6H_4 (**1b**)	4-MeC_6H_4 (**2a**)	**4b**	92
3	3-MeC_6H_4 (**1c**)	4-MeC_6H_4 (**2a**)	**4c**	90
4	2-MeC_6H_4 (**1d**)	4-MeC_6H_4 (**2a**)	**4d**	86[c]
5	4-$MeOC_6H_4$ (**1e**)	4-MeC_6H_4 (**2a**)	**4e**	88
6	4-ClC_6H_4 (**1f**)	4-MeC_6H_4 (**2a**)	**4f**	90
7	4-FC_6H_4 (**1f**)	4-MeC_6H_4 (**2a**)	**4g**	89
8	3-thienyl (**1h**)	4-MeC_6H_4 (**2a**)	**4h**	87
9	1-cyclohexenyl (**1i**)	4-MeC_6H_4 (**2a**)	**4i**	91
10	$CH_3(CH_2)_5$ (**1j**)	4-MeC_6H_4 (**2a**)	**4j**	87
11	cyclopropanyl (**1k**)	4-MeC_6H_4 (**2a**)	**4k**	84
12	$(CH_3)_3C$ (**1l**)	4-MeC_6H_4 (**2a**)	**4l**	86
13	$PhOCH_2$ (**1m**)	4-MeC_6H_4 (**2a**)	**4m**	88
14	$(CH_3)_3Si$ (**1n**)	4-MeC_6H_4 (**2a**)	**4n**	90
15	$COCH_3$ (**1o**)	4-MeC_6H_4 (**2a**)	**4o**	87
16	Ph (**1a**)	Ph (**2b**)	**4p**	81
17	Ph (**1a**)	4-$MeOC_6H_4$ (**2c**)	**4q**	91
18	Ph (**1a**)	4-ClC_6H_4 (**2d**)	**4r**	68
19	Ph (**1a**)	4-$O_2NC_6H_4$ (**2e**)	**4s**	56
20	Ph (**1a**)	CH_3 (**2f**)	**4t**	90

[a]Reaction conditions: **1** (0.6 mmol), **2** (0.6 mmol), **3a** (0.5 mmol), CuBr (0.05 mmol), dppe (0.05 mmol), and DCE (4 mL), N_2, 12 h. [b]Yields refer to **3a**. [c]In toluene at 80 °C.

ketenimine,[7b,16] we assumed that unsaturated amidine **4a** might be produced from the reaction of an in situ generated

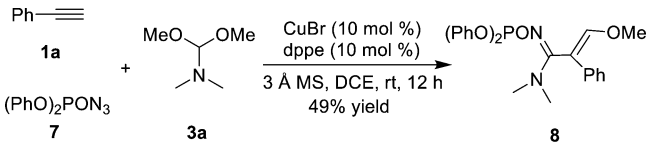
Table 3. Multicomponent Reactions with Variation of *N,N*-Dialkylformamide Acetal 3[a]



entry	**3**	**6**	yield/%[a]
1	 **3.3a**	 **6a**	77
2	 **3.3b**	 **6b**	80
3	 **3.3c**	 **6c**	90
4	 **3.3d**	 **6d**	78
5	 **3.3e**	 **6e**	75

[a]Reaction conditions: **1a** (0.6 mmol), **2a** (0.6 mmol), **3** (0.5 mmol), CuBr (0.05 mmol), dppe (0.05 mmol), and DCE (4 mL), N_2, 12 h. [b]Yields refer to **3**.

Scheme 3. Synthesis of Phosphoryl Amidines



ketenimine intermediate with immonium ion. Several experiments were carried out to test this hypothesis (Scheme 4). First, ketenimine **10** prepared by the known procedure[17] was treated with *N,N*-dimethylformamide dimethyl acetal **3a** or iminium salt **11**. Though protonated ketenimine **10** could be trapped with a nucleophilic reagent, none of the desired **4a** was detected whether in the presence or in the absence of CuBr (Scheme 4, eqs 1 and 2). This result implicated that the product was not generated via the common nucleophilic attack process and an unprotonated copper ketenimine intermediate might be involved. On the other hand, iminium salt **11** participated in the reaction under the standard reaction conditions to give **4a** in 42% yield, demonstrating a possible electrophilic process (Scheme 4, eq 3).

We assumed that **4a** might be the result of a cascade reaction of an in situ generated copper ketenimine intermediate with immonium ion. To verify this hypothesis, we investigated the intermolecular reaction of metalated ketenimine species[10b,18]

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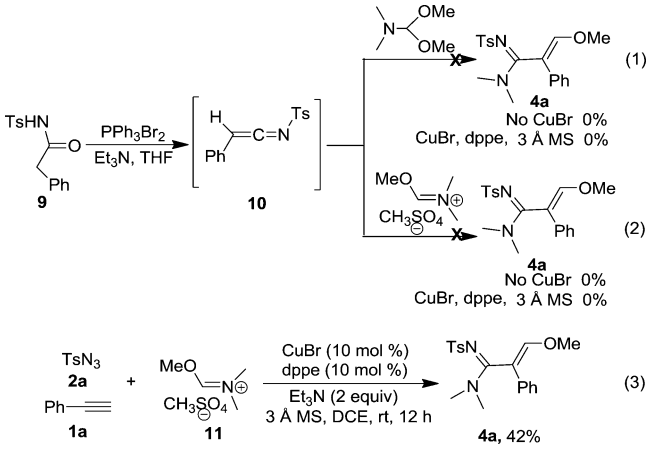
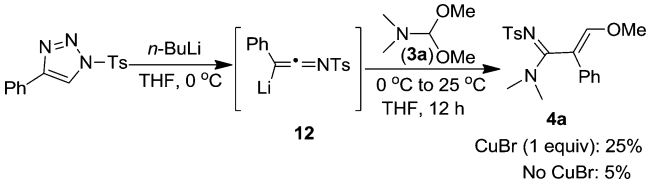
Scheme 4. Control Experiments Carried Out To Investigate the Reaction Mechanism



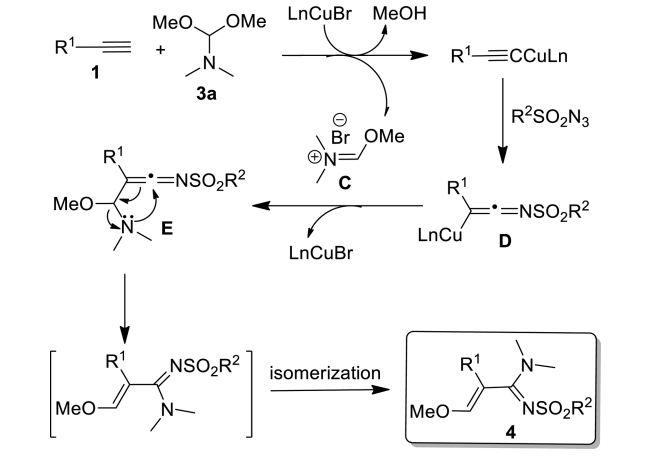
with **3a**. Gratifyingly, amidine **4a** could be obtained in 25% yield with the assistance of CuBr (Scheme 5).

Scheme 5. Reaction of Metalated Ketenimine Species with 3a



On the basis of the above experimental observations, a plausible mechanism is proposed as shown in Scheme 6. The

Scheme 6. Plausible Mechanism for the Formation of Unsaturated Amidine 4



reaction of terminal alkynes and *N,N*-dimethylformamide dimethyl acetal affords immonium ion intermediate **C**[12] and copper acetylide. The in situ formation of copper ketenimine intermediate **D** from copper acetylide and sulfonyl azide[7] reacts with the immonium ion **C** to give the intermediate **E**, which undergoes intramolecular nucleophilic addition of nitrogen to the central carbon of **E** and affords the desired product **4** by isomerization via C–N bond cleavage. The stability of copper ketenimine intermediate **D** is one of the crucial factors for this reaction. Phosphine ligands help to stabilize copper ketenimine intermediate **D**, and 3 Å MS helps to absorb the in situ generated methanol.

CONCLUSION

In summary, we have developed a new copper-catalyzed three-component reaction of alkyne, azide, and *N,N*-dialkyloxyformamide dialkyl acetal, which might involve an electrophilic addition of immonium ion to copper ketenimine. The procedure provided a general and efficient method for the synthesis of pharmacologically useful unsaturated amidines. Both sulfonyl and phosphoryl azides underwent the reaction smoothly; in addition, this new protocol was characterized with wide substrate scope, mild conditions, and high yield. The determination of further mechanistic details and applications is currently underway.

EXPERIMENTAL SECTION

General Considerations. Infrared spectra were recorded with a FTIR spectrometer. NMR spectra were recorded for ^{1}H NMR at 400 or 500 MHz and ^{13}C NMR at 100 or 125 MHz using TMS as an internal standard. The following abbreviations were used to describe peak patterns where appropriate: singlet (s), doublet (d), doublet of doublets (dd), triplet (t), quartet (q), multiplet (m), broad resonances (br). Mass spectroscopy data of the products were collected on an HRMS-EI-TOF instrument or a low-resolution MS instrument using EI or ESI ionization.

General Procedure for Preparation of *α,β*-Unsaturated Amidine Derivatives. To a solution of CuBr (0.05 mmol), dppe (0.05 mmol), and 3 Å MS (100 mg) in DCE (1.5 mL) protected by argon was added a solution of alkyne (0.6 mmol), *N,N*-dialkyloxyformamide dialkyl acetal (0.5 mmol), and azide (0.6 mmol) in DCE (2.5 mL) via syringe, and the mixture was reacted at room temperature for 12 h. Then the mixture was filtered, the filtrate was concentrated, and the resulting residue was purified by flash column chromatography with ethyl acetate/petroleum ether (1/1, v/v) as eluent to obtain the desired products.

Characterization Data of the Products. *(2E)-3-Methoxy-N,N-dimethyl-2-phenyl-N′-tosylacrylamidine (**4a**):* new compound; white solid (163 mg, 91% yield); mp 118–120 °C (uncorrected); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.68–7.69 (d, J = 6.8 Hz, 2 H), 7.23–7.25 (d, J = 6.0 Hz, 2 H), 7.16–7.19 (t, J = 6.0 Hz, 2 H), 7.09–7.12 (t, J = 5.8 Hz, 1 H), 7.06–7.07 (d, J = 6.4 Hz, 2 H), 6.51 (s, 1 H), 3.84 (s, 3 H), 3.14 (s, 3 H), 2.81 (s, 3 H), 2.28 (s, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 165.8, 151.9, 141.6, 141.2, 133.1, 128.9, 128.3, 127.6, 127.1, 126.7, 110.6, 61.9, 39.6, 35.6, 21.5 ppm; IR (neat) ν 2919, 2851, 1641, 1598, 1544, 1473, 1397, 1276, 1258, 1140, 1084, 851, 684 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{22}N_2O_3S$ (M^+) 358.1351, found 358.1359.

*(2E)-3-Methoxy-N,N-dimethyl-2-p-tolyl-N′-tosylacrylamidine (**4b**):* new compound; yellowish solid (171 mg, 92% yield); mp 141–143 °C (uncorrected); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.68–7.70 (d, J = 7.6 Hz, 2 H), 7.13–7.15 (d, J = 8.0 Hz, 2 H), 7.06–7.09 (d, J = 8.0 Hz, 2 H), 6.98–7.00 (d, J = 8.0 Hz, 1 H), 6.47 (s, 1 H), 3.83 (s, 3 H), 3.14 (s, 3 H), 2.81 (s, 3 H), 2.30 (s, 3 H), 2.28 (s, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 165.7, 151.0, 141.3, 141.0, 136.2, 130.0, 128.8, 128.7, 127.2, 126.9, 110.4, 61.6, 39.4, 38.3, 21.3, 21.1 ppm; IR (neat) ν 2921, 1638, 1546, 1475, 1399, 1265, 1139, 1109, 1087, 880, 685 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{24}N_2O_3S$ (M^+) 372.1508, found 372.1515.

*(2E)-3-Methoxy-N,N-dimethyl-2-m-tolyl-N′-tosylacrylamidine (**4c**):* new compound; white solid (167 mg, 90% yield); mp 153–155 °C (uncorrected); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.67–7.69 (d, J = 7.6 Hz, 2 H), 7.05–7.06 (m, 3 H), 6.93 (s, 2 H), 6.51 (s, 1 H), 3.85 (s, 3 H), 3.16 (s, 3 H), 2.85 (s, 3 H), 2.28 (s, 3 H), 2.23 (s, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 165.7, 151.6, 141.3, 140.9, 137.4, 132.7, 128.6, 128.0, 127.8, 127.3, 127.0, 124.5, 111.2, 61.7, 39.4, 38.37, 21.5, 21.2 ppm; IR (neat) ν 2929, 1649, 1545, 1482,

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1403, 1264, 1137, 1082, 885, 857, 681 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{24}N_2O_3S$ (M^+) 372.1508, found 372.1509.

*(2Z)-3-Methoxy-N,N-dimethyl-2-o-tolyl-N′-tosylacrylamidine (**4d**):* new compound; white solid (160 mg, 86% yield); mp 173−175 °C (uncorrected); ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.87−7.89 (d, J = 7.2 Hz, 2 H), 7.24−7.26 (d, J = 8.0 Hz, 2 H), 7.10−7.20 (m, 5 H), 3.88 (s, 3 H), 2.97 (s, 3 H), 2.60 (s, 3 H), 2.40 (s, 3 H), 2.27 (s, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 168.4, 156.0, 142.5, 141.3, 136.7, 132.8, 130.5, 130.2, 129.0, 127.4, 126.1, 125.7, 111.0, 61.5, 39.4, 39.0, 21.4, 20.4 ppm; IR (neat) ν 2924, 1634, 1535, 1476, 1399, 1255, 1140, 1087, 867, 673 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{24}N_2O_3S$ (M^+) 372.1508, found 372.1512.

*(2E)-3-Methoxy-2-(4-methoxyphenyl)-N,N-dimethyl-N′-tosylacrylamidine (**4e**):* new compound; yellowish solid (171 mg, 88% yield); mp 148−150 °C (uncorrected); ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.69−7.71 (d, J = 8.0 Hz, 2 H), 7.19−7.21 (d, J = 8.4 Hz, 2 H), 7.08−7.10 (d, J = 8.0 Hz, 2 H), 6.73−6.75 (d, J = 8.4 Hz, 1 H), 6.42 (s, 1 H), 3.81 (s, 3 H), 3.77 (s, 3 H), 3.14 (s, 3 H), 2.83 (s, 3 H), 2.31 (s, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 165.8, 158.0, 150.2, 141.4, 141.1, 128.7, 128.69, 126.9, 125.6, 61.5, 55.1, 39.4, 38.3, 21.3 ppm; IR (neat) ν 2920, 1636, 1544, 1509, 1489, 1248, 1138, 1106, 1085, 875, 670 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{24}N_2O_4S$ (M^+) 388.1457, found 388.1451.

*(2E)-2-(4-Chlorophenyl)-3-methoxy-N,N-dimethyl-N′-tosylacrylamidine (**4f**):* new compound; white solid (177 mg, 90% yield); mp 136−138 °C (uncorrected); ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.66−7.68 (d, J = 7.6 Hz, 2 H), 7.18−7.20 (d, J = 8.8 Hz, 2 H), 7.16−7.18 (d, J = 9.2 Hz, 2 H), 7.07−7.09 (d, J = 8.0 Hz, 2 H), 6.53 (s, 1 H), 3.86 (s, 3 H), 3.15 (s, 3 H), 2.83 (s, 3 H), 2.31 (s, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 165.1, 151.9, 141.7, 140.8, 132.0, 131.3, 128.8, 128.6, 128.3, 126.9, 109.2, 61.9, 39.3, 38.4, 21.7 ppm; IR (neat) ν 2924, 1638, 1541, 1488, 1401, 1268, 1139, 1086, 861, 821, 682 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{21}N_2O_3SCl$ (M^+) 392.0961, found 392.0966.

*(2E)-2-(4-Fluorophenyl)-3-methoxy-N,N-dimethyl-N′-tosylacrylamidine (**4g**):* new compound; white solid (167 mg, 89% yield); mp 135−137 °C (uncorrected); ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.69−7.71 (d, J = 7.2 Hz, 2 H), 7.24−7.26 (m, 2 H), 7.09−7.11 (d, J = 8.0 Hz, 2 H), 6.87−6.91 (t, J = 8.6 Hz, 2 H), 6.51 (s, 1 H), 3.85 (s, 3 H), 3.14 (s, 3 H), 2.82 (s, 3 H), 2.32 (s, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz, TMS) δ 165.59, 161.38 (d, $^1J_{C-F}$ = 244.6 Hz), 151.5, 141.8, 141.2, 129.4 (d, $^3J_{C-F}$ = 8.0 Hz), 129.3 (d, $^4J_{C-F}$ = 2.8 Hz), 129.0, 127.1, 115.3 (d, $^2J_{C-F}$ = 21.6 Hz), 109.8, 61.9, 39.6, 38.6, 21.5 ppm; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −114.9 ppm; IR (neat) ν 2926, 1642, 1544, 1510, 1478, 1278, 1258, 1142, 1086, 843, 687 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{21}N_2O_3SF$ (M^+) 376.1257, found 376.1267.

*(2E)-3-Methoxy-N,N-dimethyl-2-(thiophen-3-yl)-N′-tosylacrylamidine (**4h**):* new compound; yellowish solid (158 mg, 87% yield); mp 135−137 °C (uncorrected); ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.61−7.63 (d, J = 7.2 Hz, 2 H), 7.09 (s, 2 H), 7.02−7.04 (d, J = 8.0 Hz, 2 H), 6.85−6.86 (t, J = 1.8 Hz, 1 H), 6.39−6.40 (d, J = 4.0 Hz, 1 H), 3.87 (s, 3 H), 3.18 (s, 3 H), 2.87 (s, 3 H), 2.29 (s, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 164.9, 150.0, 141.4, 140.5, 132.8, 128.6, 127.0, 126.7, 124.3, 121.9, 106.4, 61.5, 39.4, 38.2, 21.3 ppm; IR (neat) ν 2922, 1640, 1544, 1480, 1399, 1272, 1230, 1141, 1086, 878, 852, 686 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{20}N_2O_3S_2$ (M^+) 364.0915, found 364.0923.

*(2E)-2-Cyclohexenyl-3-methoxy-N,N-dimethyl-N′-tosylacrylamidine (**4i**):* new compound; yellow liquid (165 mg, 91% yield); ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.30−7.50 (d, J = 7.6 Hz, 2 H), 7.18−7.20 (d, J = 8.0 Hz, 2 H), 6.12 (s, 1 H), 5.26 (s, 1 H), 3.70 (s, 3 H), 3.10 (s, 3 H), 2.95 (s, 3 H), 2.37 (s, 3 H), 2.15 (b, 2 H), 1.90 (b, 2 H), 1.44−1.51 (m, 4 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 166.0, 149.3, 141.2, 141.2, 130.9, 128.6, 127.1, 125.8, 112.8, 61.1, 39.2, 38.1, 27.4, 25.5, 22.7, 21.7, 21.3 ppm; IR (neat) ν 2922, 2853, 1638, 1541, 1476, 1397, 1275, 1246, 1142, 1113, 1086, 878, 683 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{26}N_2O_3S$ (M^+) 362.1664, found 362.1661.

*(2E)-2-(Methoxymethylene)-N,N-dimethyl-N′-tosyloctanamidine (**4j**):* new compound; white solid (159 mg, 87% yield); mp 73−75 °C (uncorrected); ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.77−7.79 (d, J = 8.4 Hz, 2 H), 7.21−7.23 (d, J = 8.0 Hz, 2 H), 6.14 (s, 1 H), 3.66 (s, 3 H), 3.03 (s, 6 H), 2.38 (s, 3 H), 2.21−2.25 (t, J = 8.0 Hz, 2 H), 1.25−1.37 (m, 8 H), 0.85−0.88 (t, J = 6.6 Hz, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz, TMS) δ 166.9, 150.3, 142.2, 141.5, 129.0, 126.6, 111.4, 60.6, 39.9, 38.3, 31.7, 29.9, 28.1, 27.2, 22.8, 21.5, 14.2 ppm; IR (neat) ν 2923, 2855, 1649, 1533, 1483, 1394, 1266, 1136, 1083, 859, 680 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{30}N_2O_3S$ (M^+) 366.1977, found 366.1987.

*(2E)-2-Cyclopropyl-3-methoxy-N,N-dimethyl-N′-tosylacrylamidine (**4k**):* new compound; white solid (135 mg, 84% yield); mp 117−118 °C (uncorrected); ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.76−7.78 (d, J = 7.6 Hz, 2 H), 7.21−7.23 (d, J = 8.0 Hz, 2 H), 6.46 (s, 1 H), 3.72 (s, 3 H), 3.09 (s, 3 H), 3.03 (s, 3 H), 2.38 (s, 3 H), 1.44−1.48 (m, 1 H), 0.67−0.69 (m, 4 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 165.9, 153.5, 142.2, 141.3, 128.9, 126.3, 111.7, 60.8, 39.5, 38.2, 21.3, 9.1, 5.7 ppm; IR (neat) ν 2924, 1649, 1540, 1475, 1398, 1274, 1240, 1141, 1121, 1086, 879, 679 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{22}N_2O_3S$ (M^+) 322.1351, found 322.1346.

*(2E)-2-(Methoxymethylene)-N,N,3,3-tetramethyl-N′-tosylbutanimidamide (**4l**):* new compound; yellow solid (145 mg, 86% yield); mp 118−120 °C (uncorrected); ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.80−7.82 (d, J = 7.2 Hz, 2 H), 7.22−7.24 (d, J = 8.0 Hz, 2 H), 5.80 (s, 1 H), 3.59 (s, 3 H), 3.10 (s, 3 H), 3.06 (s, 3 H), 2.39 (s, 3 H), 1.29 (s, 9 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 166.2, 148.4, 142.4, 141.2, 128.9, 126.3, 118.0, 60.4, 40.2, 38.2, 34.1, 28.8, 21.4 ppm; IR (neat) ν 2923, 1646, 1533, 1482, 1270, 1123, 1084, 988, 878, 850, 684 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{26}N_2O_3S$ (M^+) 338.1664, found 338.1663.

*(2Z)-3-Methoxy-N,N-dimethyl-2-(phenoxymethyl)-N′-tosylacrylamidine (**4m**):* new compound; white solid (171 mg, 88% yield); mp 120−122 °C (uncorrected); ^1H NMR (d_6-DMSO, 500 MHz, TMS) δ 7.61−7.63 (d, J = 8.0 Hz, 2 H), 7.26−7.31 (m, 4 H), 6.92−6.95 (t, J = 7.3 Hz, 1 H), 6.85−6.87 (d, J = 8.0 Hz, 2 H), 6.19 (s, 1 H), 4.66 (s, 2 H), 3.64 (s, 3 H), 3.05 (s, 3 H), 3.01 (s, 3 H), 2.35 (s, 3 H) ppm; ^{13}C NMR (d_6-DMSO, 125 MHz, TMS) δ 164.6, 158.6, 153.0, 142.2, 141.9, 130.0, 129.6, 126.6, 121.3, 114.9, 106.2, 63.2, 61.3, 40.7, 39.4, 21.4 ppm; IR (neat) ν 2921, 1667, 1554, 1483, 1397, 1273, 1241, 1217, 1143, 1085, 1007, 918, 818, 684 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{24}N_2O_4S$ (M^+) 388.1457, found 388.1455.

*(2Z)-3-Methoxy-N,N-dimethyl-N′-tosyl-2-(trimethylsilyl)-acrylimidamide (**4n**):* new compound; white solid (159 mg, 90% yield); mp 126−128 °C (uncorrected); ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.77−7.79 (d, J = 8.4 Hz, 2 H), 7.21−7.23 (d, J = 8.0 Hz, 2 H), 6.19 (s, 1 H), 3.54 (s, 3 H), 3.09 (s, 3 H), 3.03 (s, 3 H), 2.38 (s, 3 H), 0.22 (s, 9 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 168.2, 157.9, 142.5, 141.2, 128.8, 126.5, 110.5, 60.1, 39.6, 38.0, 21.3, −1.1 ppm; IR (neat) ν 2924, 1614, 1531, 1461, 1392, 1267, 1229, 1131, 1085, 843, 680 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{26}N_2O_3SSi$ (M^+) 354.1433, found 354.1426.

*(2Z)-2-(Methoxymethylene)-N,N-dimethyl-3-oxo-N′-tosylbutanimidamide (**4o**):* new compound; brown solid (141 mg, 87% yield); mp 182−184 °C (uncorrected); ^1H NMR (d_6-DMSO, 500 MHz, TMS) δ 7.54−7.55 (d, J = 8.0 Hz, 2 H), 7.31 (s, 1 H), 7.28−7.29 (d, J = 8.0 Hz, 2 H), 3.58 (s, 3 H), 3.03 (s, 3 H), 2.85 (s, 3 H), 2.35 (s, 3H), 2.16 (s, 3 H) ppm; ^{13}C NMR (d_6-DMSO, 125 MHz, TMS) δ 192.8, 162.2, 161.8, 141.7, 141.4, 129.3, 126.8, 115.2, 62.6, 38.7, 37.8, 26.4, 21.4 ppm; IR (neat) ν 2922, 1654, 1630, 1555, 1477, 1394, 1300, 1258, 1139, 1084, 967, 850, 694 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{20}N_2O_4S$ (M^+) 324.1144, found 324.1152.

*(2E)-3-Methoxy-N,N-dimethyl-2-phenyl-N′-benzenesulfonylacrylamidine (**4p**):* new compound; yellow solid (139 mg, 81% yield); mp 73−75 °C (uncorrected); ^1H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.82−7.84 (d, J = 8.0 Hz, 2 H), 7.26−7.35 (m, 5 H), 7.18−7.22 (t, J = 7.4 Hz, 2 H), 7.10−7.12 (t, J = 7.2 Hz, 1 H), 6.51 (s, 1 H), 3.83 (s, 3 H), 3.14 (s, 3 H), 2.82 (s, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 165.8, 151.7, 144.0, 132.9, 131.0, 128.2, 128.2, 127.4, 126.8, 126.6, 110.6, 61.7, 39.4, 38.4 ppm; IR (neat) ν 2922, 1642, 1553, 1478, 1403, 1262, 1134, 1087, 857, 764, 691 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{20}N_2O_3S$ (M^+) 344.1195, found 344.1190.

*(2E)-3-Methoxy-N,N-dimethyl-2-phenyl-N′-(4-methoxybenzene)-1-sulfonylacrylamidine (**4q**):* new compound; white solid (170 mg,

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91% yield); mp 92−94 °C (uncorrected); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.71−7.73 (d, J = 8.0 Hz, 2 H), 7.13−7.24 (m, 4 H), 7.09−7.12 (t, J = 7.0 Hz, 1 H), 6.72−6.74 (d, J = 8.8 Hz, 2 H), 6.54 (s, 1 H), 3.87 (s, 3 H), 3.75 (s, 3 H), 3.16 (s, 3 H), 2.82 (s, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 165.4, 161.6, 151.7, 135.8, 132.8, 128.8, 128.1, 127.2, 126.4, 113.2, 110.1, 61.6, 55.3, 39.4, 38.3 ppm; IR (neat) ν 2922, 1646, 1543, 1491, 1404, 1309, 1268, 1183, 1137, 1117, 1084, 893, 684 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{22}N_2O_4S$ (M^+) 374.1300, found 374.1300.

*(2E)-3-Methoxy-N,N-dimethyl-2-phenyl-N′-(4-chlorobenzene)-1-sulfonylacrylamidine (**4r**):* new compound; white solid (129 mg, 68% yield); mp 126−128 °C (uncorrected); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.71−7.73 (d, J = 8.0 Hz, 2 H), 7.14−7.23 (m, 7 H), 6.57 (s, 1 H), 3.88 (s, 3 H), 3.16 (s, 3 H), 2.85 (s, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 165.7, 151.8, 142.2, 137.3, 132.5, 128.4, 128.3, 128.27, 127.2, 126.7, 110.2, 61.8, 39.5, 38.4 ppm; IR (neat) ν 2922, 1643, 1546, 1473, 1396, 1290, 1259, 1142, 1083, 884, 753, 670 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{19}N_2O_3SCl$ (M^+) 378.0805, found 378.0806.

*(2E)-3-Methoxy-N,N-dimethyl-2-phenyl-N′-(4-nitrobenzene)-1-sulfonylacrylamidine (**4s**):* new compound; yellow solid (109 mg, 56% yield); mp 174−176 °C (uncorrected); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 8.05−8.07 (d, J = 8.4 Hz, 2 H), 7.92−7.94 (d, J = 8.4 Hz, 2 H), 7.10−7.18 (m, 5 H), 6.65 (s, 1 H), 3.94 (s, 3 H), 3.18 (s, 3 H), 2.90 (s, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 165.8, 152.1, 149.1, 148.9, 132.2, 128.3, 128.1, 127.0, 126.9, 123.3, 110.1, 62.0, 39.7, 38.5 ppm; IR (neat) ν 2924, 1645, 1521, 1472, 1395, 1345, 1258, 1137, 1119, 1085, 903, 739 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{19}N_3O_5S$ (M^+) 389.1045, found 389.1044.

*(2E)-3-Methoxy-N,N-dimethyl-2-phenyl-N′-methanesulfonylacrylamidine (**4t**):* new compound; yellow solid (127 mg, 90% yield); mp 151−153 °C (uncorrected); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.44−7.46 (d, J = 8.4 Hz, 2 H), 7.30−7.34 (t, J = 7.6 Hz, 2 H), 7.17−7.21 (t, J = 7.2 Hz, 1 H), 6.73 (s, 1 H), 3.88 (s, 3 H), 3.12 (s, 3 H), 2.95 (s, 3 H), 2.83 (s, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 165.5, 152.0, 133.1, 128.4, 127.7, 126.8, 110.9, 61.7, 43.3, 39.2, 38.1 ppm; IR (neat) ν 2927, 1642, 1545, 1496, 1402, 1269, 1213, 1118, 982, 854, 766 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{18}N_2O_3S$ (M^+) 282.1038, found 282.1035.

*(2E)-N,N-Diethyl-3-methoxy-2-phenyl-N′-tosylacrylamidine (**6a**):* new compound; white solid (148 mg, 77% yield); mp 114−116 °C (uncorrected); ^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.69−7.70 (d, J = 6.5 Hz, 2 H), 7.29−7.31 (d, J = 8.5 Hz, 2 H), 7.17−7.20 (m, 2 H), 7.11−7.13 (d, J = 7.5 Hz, 1 H), 7.07−7.09 (d, J = 7.5 Hz, 2 H), 6.48 (s, 1 H), 3.84 (s, 3 H), 3.55 (b, 2 H), 3.19−3.20 (m, 2 H), 2.30 (s, 3 H), 1.19−1.22 (t, J = 7.3 Hz, 3 H), 0.84−0.87 (t, J = 7.0 Hz, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 164.2, 150.9, 141.3, 141.1, 133.1, 128.7, 128.0, 127.5, 126.7, 126.5, 110.3, 61.6, 44.1, 42.3, 21.3, 13.3, 11.8 ppm; IR (neat) ν 2940, 1641, 1528, 1443, 1274, 1256, 1139, 1120, 1078, 974, 853, 768, 680 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{26}N_2O_3S$ (M^+) 386.1664, found 386.1667.

*N-((E)-3-methoxy-2-phenyl-1-(piperidin-1-yl)allylidene)-4-methylbenzenesulfonamide (**6b**):* new compound; yellow solid (159 mg, 80% yield); mp 135−137 °C (uncorrected); ^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.67−7.69 (d, J = 7.6 Hz, 2 H), 7.27−7.29 (d, J = 9.2 Hz, 2 H), 7.17−7.20 (t, J = 7.4 Hz, 2 H), 7.11−7.13 (d, J = 6.8 Hz, 1 H), 7.06−7.08 (d, J = 7.2 Hz, 2 H), 6.51 (s, 1 H), 3.84 (s, 3 H), 3.78−3.81 (t, J = 5.0 Hz, 2 H), 3.22−3.25 (t, J = 5.2 Hz, 2 H), 2.29 (s, 3 H), 1.56−1.61 (m, 4 H), 1.24−1.26 (m, 2 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 163.9, 151.3, 141.3, 141.1, 133.1, 128.7, 128.0, 127.6, 126.9, 126.4, 110.2, 61.6, 48.7, 46.0, 25.9, 25.3, 24.0, 21.3 ppm; IR (neat) ν 2935, 1642, 1524, 1445, 1357, 1271, 1126, 1086, 1024, 853, 813, 677 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{26}N_2O_3S$ (M^+) 398.1664, found 398.1660.

*N-((E)-3-Methoxy-1-morpholino-2-phenylallylidene)-4-methylbenzenesulfonamide (**6c**):* new compound; white solid (180 mg, 90% yield); mp 130−132 °C (uncorrected); ^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.67−7.69 (d, J = 8.0 Hz, 2 H), 7.26−7.28 (d, J = 8.4 Hz, 2 H), 7.17−7.21 (t, J = 7.8 Hz, 2 H), 7.11−7.13 (d, J = 7.6 Hz, 1 H), 7.07−7.09 (d, J = 8.0 Hz, 2 H), 6.58 (s, 1 H), 3.85 (s, 3 H), 3.81−3.83 (t, J = 4.2 Hz, 2 H), 3.64−3.66 (t, J = 4.6 Hz, 2 H), 3.33 (b, 2 H), 3.25 (b, 2 H), 2.28 (s, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 164.6, 152.2, 141.7, 140.7, 132.8, 128.8, 128.2, 127.5, 126.9, 126.7, 109.6, 66.3, 66.1, 61.8, 47.7, 45.2, 21.3 ppm; IR (neat) ν 2935, 1640, 1517, 1440, 1360, 1260, 1151, 1131, 1113, 1085, 1029, 825, 675 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{24}N_2O_4S$ (M^+) 400.1457, found 400.1454.

*N-((E)-3-Methoxy-2-phenyl-1-(pyrrolidin-1-yl)allylidene)-4-methylbenzenesulfonamide (**6d**):* new compound; yellow solid (150 mg, 78% yield); mp 135−137 °C (uncorrected); ^{1}H NMR ($CDCl_3$, 500 MHz, TMS) δ 7.71−7.73 (d, J = 7.2 Hz, 2 H), 7.24−7.26 (d, J = 8.0 Hz, 2 H), 7.16−7.20 (t, J = 7.4 Hz, 2 H), 7.11−7.13 (d, J = 7.2 Hz, 1 H), 7.07−7.09 (d, J = 8.0 Hz, 2 H), 6.59 (s, 1 H), 3.84 (s, 3 H), 3.61−3.65 (t, J = 6.8 Hz, 2 H), 3.08−3.12 (t, J = 7.0 Hz, 2 H), 2.30 (s, 3 H), 1.84−1.88 (m, 2 H), 1.74−1.77 (m, 2 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 163.1, 151.6, 141.3, 141.3, 132.5, 128.7, 128.1, 127.5, 126.9, 126.4, 111.7, 61.6, 48.6, 48.5, 25.5, 24.3, 21.3 ppm; IR (neat) ν 2922, 1640, 1517, 1462, 1271, 1138, 1087, 846, 718, 694 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{24}N_2O_3S$ (M^+) 384.1508, found 384.1516.

*(2E)-3-Ethoxy-N,N-dimethyl-2-phenyl-N′-tosylacrylamidine (**6e**):* new compound; white solid (140 mg, 75% yield); mp 110−112 °C (uncorrected); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.68−7.70 (d, J = 8.0 Hz, 2 H), 7.24−7.26 (d, J = 8.0 Hz, 2 H), 7.16−7.20 (t, J = 7.6 Hz, 2 H), 7.10−7.12 (d, J = 7.2 Hz, 1 H), 7.05−7.07 (d, J = 7.6 Hz, 2 H), 6.65 (s, 1 H), 4.05−4.11 (q, J = 5.7 Hz, 3 H), 3.14 (s, 3 H), 2.82 (s, 3 H), 2.28 (s, 3 H), 1.40−1,44 (t, J = 7.4 Hz, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 165.8, 150.6, 141.4, 141.0, 133.0, 128.7, 128.1, 127.2, 126.9, 126.3, 110.1, 70.5, 39.4, 38.3, 21.3, 15.4 ppm; IR (neat) ν 2919, 1636, 1544, 1476, 1399, 1275, 1245, 1138, 1085, 884, 683 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{24}N_2O_3S$ (M^+) 372.1508, found 372.1503.

*(Z)-Diphenyl ((E)-1-(dimethylamino)-3-methoxy-2-phenylallylidene)phosphoramidate (**8**):* new compound; brown liquid (107 mg, 49% yield); ^{1}H NMR (d_6-DMSO, 500 MHz, TMS) δ 7.29−7.37 (m, 8 H), 7.18−7.21 (m, 1 H), 7.07−7.12 (m, 6 H), 6.60 (s, 1 H), 3.70 (s, 3 H), 3.00 (s, 3 H), 2.81 (s, 3 H) ppm; ^{13}C NMR (d_6-DMSO, 125 MHz, TMS) δ 166.8 (d, J_{C-P} = 13.9 Hz), 152.4 (d, J_{C-P} = 8.0 Hz), 151.4, 134.0, 130.1, 129.0, 127.9, 127.1, 124.6, 120.8 (d, J_{C-P} = 4.1 Hz), 113.1, 62.0, 38.9, 38.1 ppm; ^{31}P NMR ($CDCl_3$, 162 MHz) δ −25.7 ppm; IR (neat) ν 2935, 1641, 1562, 1488, 1249, 1200, 1117, 1058, 1026, 1000, 917, 762, 691 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{25}N_2O_4P$ (M^+) 436.1552, found 436.1549.

■ ASSOCIATED CONTENT

Supporting Information

Figures and CIF files giving ^{1}H and ^{13}C NMR spectra for all new compounds and crystallographic data for compounds **4a,d**. 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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