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Oxygen Atom Transfer as Key To Reverse Regioselectivity in the Gold(I)-Catalyzed Generation of Aminooxazoles from Ynamides

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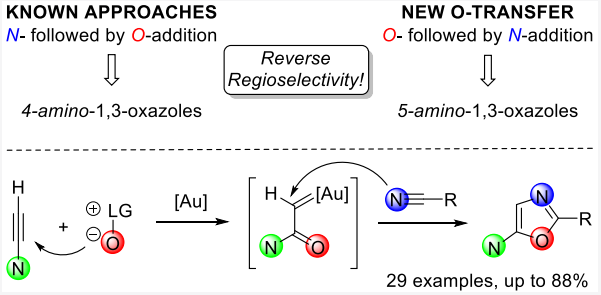
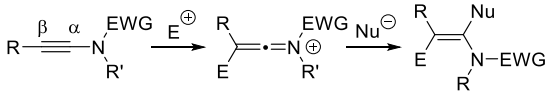
ABSTRACT: We report on gold(I)-catalyzed oxidative annulation involving ynamides, nitriles, and 2,3-dichloropyridine *N*-oxide. The application of 2,3-dichloropyridine *N*-oxide as an oxygen atom transfer reagent reverses the regioselectivity to give *5-amino*-1,3-oxazoles, in comparison with the previously reported syntheses of aminooxazoles based on gold-catalyzed nitrene transfers to ynamides to furnish *4-amino*-1,3-oxazoles. The developed oxygen atom transfer approach allows the generation of 1,3-oxazoles containing a variety of sulfonyl-protected alkylamino groups in the fifth position of the oxazole ring (29 examples; up to 88% yields). In addition, the use of *N*-substituted nitriles, namely cyanamides, leads to the facile generation of difficult-to-obtain 2,5-diaminooxazoles. The process is feasible for wide ranges of ynamides or nitriles, and it can be conducted in gram scale.



INTRODUCTION

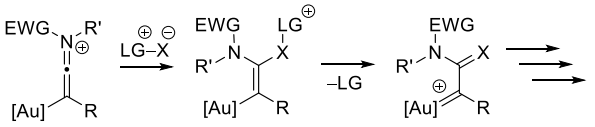
Since the beginning of this century, the chemistry of *N*-substituted alkynes (or ynamides) has transformed from a purely academic curiosity field into a well-developed approach to the construction of molecular architectures.[1,2] The unique balance of stability and predictable reactivity of ynamides determined their popularity as convenient building blocks for the incorporation of nitrogen-based functionalities into target molecules.[3−10] Due to the presence of a nitrogen atom, the ynamide triple bond is significantly polarized, whereas *N*-acyl or *N*-sulfonyl moieties provide the stability of these compounds and can also function as directing groups.[11,12] Moreover, the electrophilic activation by Lewis acids significantly expands the range of synthetic application of ynamides and allows the fine selectivity control of their transformations including, for example, nucleophilic addition (Scheme 1).[13−15]

Scheme 1. Nucleophilic Addition to Electrophilically Activated Ynamides



Today, homogeneous gold-based catalysis is among the most effective methods for the electrophilic activation of alkynes.[16−25] Its importance was proved by the discovery of varieties of new synthetic methodologies.[26−32] It is therefore not surprising that the gold-catalyzed reactions of ynamides exhibit impressive synergy: ynamides combine reactivity and diverse substitution patterns, while Au-based catalysts provide mild reaction conditions with excellent functional group compatibility and tolerance. Of particular interest are gold-catalyzed oxygen atom[33−38] and nitrene[39−42] transfer reactions of ynamides, which grant libraries of *N*-containing products (Scheme 2). Usually these reactions proceed through the initial

Scheme 2. Oxo and Imino Gold Carbenes from Ynamides



attack of the oxygen or nitrogen atom from the corresponding nucleophiles on the gold-activated ynamides (Scheme 1; E = Au). The resulting α-oxo- or α-imino carbenes can be further involved in numerous intra- and intermolecular reactions such as CH-insertions,[43−45] cyclopropanations,[46] carbene transfers,[47] hydride[48,49] and acyl[50] shifts, etc.

In the context of the studies focused on the transformations of gold carbenes, a great deal of progress has been achieved in the molecular design of amino-1,3-oxazoles, privileged heterocyclic compounds contained in a variety of natural

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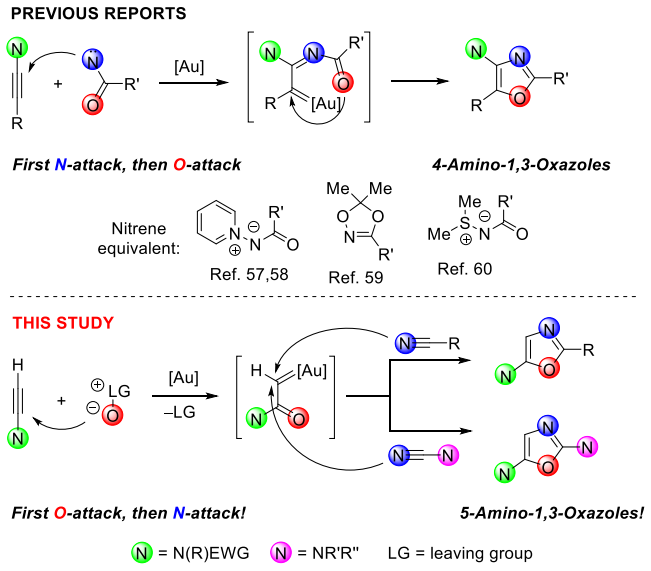
products and valuable synthetic molecules.[51−56] Recently, the first Au-catalyzed synthesis of 4-amino-substituted oxazoles that utilizes the formal [3 + 2] cycloaddition of *N*-ylides (as nitrene transfer reagents) to ynamides was reported (Scheme 3, top panel).[57,58] Next, some other effective nitrene

Scheme 3. Au-Catalyzed Syntheses of Aminooxazoles from Ynamides



equivalents were proposed for this reaction.[59,60] In all these cases,[57−60] nitrene equivalents attack exclusively the *sp*-carbon in the *α*-position of ynamides and, accordingly, the only products of these transformations are oxazoles bearing amino groups in the fourth position.

1,3-Oxazoles featuring a 5-amino group are also of significant importance from viewpoints of medicinal chemistry and drug discovery, functioning as antagonists of histamine[61] or adenosine[62] receptors, antibacterial agents,[63] and remedies for the treatment of prion diseases.[64] 2,5-Diamino-1,3-oxazole (CP-810,123) has been identified as a potential treatment for schizophrenia and Alzheimer's disease.[65] Despite all these, the synthetic approaches toward these heterocyclic systems are rather limited, and the known methods are based either on the amination[66,67] of preprepared oxazoles or on the assembly of the 5-amino-1,3-oxazole[68−73] or 2,5-diamino-1,3-oxazole[74,75] framework. The main disadvantage of both routes is the usage of complex and/or prefunctionalized substrates.

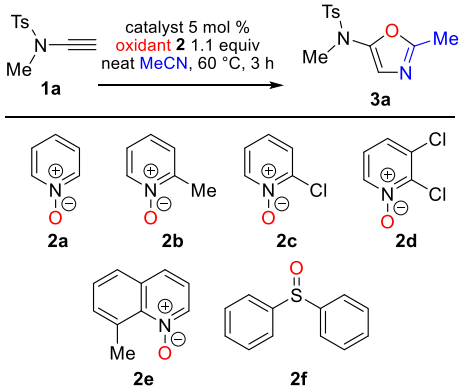
The most appealing method for the construction of 1,3-oxazole entities is based on intermolecular trapping of *α*-oxo gold carbenes (generated from conventional terminal alkynes) by nitriles proposed by Zhang.[76] Recently, we successfully extended this formal [2 + 2 + 1] Au-catalyzed oxidative annulation to the synthesis of oxazoles from internal electron-deficient alkynes, such as propiolate derivatives.[77] Notably, the generation of gold oxo-carbenes from electron-rich ynamides (Scheme 2, X = O) occurs with a reverse regiochemistry as compared with similar reactions of propiolates.[78−84]

In the framework of the Zhang chemistry,[36,76] we assumed that the intramolecular trapping by nitriles of *α*-oxo gold carbenes generated from ynamides can be key to the generation of oxazoles with a 5-amino-substitution pattern (Scheme 3, bottom panel). Moreover, the use of amino-functionalized nitriles, namely cyanamides, could potentially provide a facile access to 2,5-diamino-1,3-oxazoles. All our results relevant to this novel synthetic method are consequently disclosed in sections that follow.

RESULTS AND DISCUSSION

To evaluate our idea (Scheme 3, bottom panel), we attempted the reaction between terminal ynamide **1a** and pyridine *N*-oxide (**2a**) in neat acetonitrile in the presence of the gold NHC-based complex IPrAuNTf$_2$,[85] and target aminooxazole **3a** was obtained in 49% yield (Table 1, entry 1). Inspired by

Table 1. Optimization of the Gold(I)-Catalyzed Synthesis of 5-Aminooxazoles[a]



entry	*N*-oxide	catalyst	yield,%[b]
1	**2a**	IPrAuNTf$_2$	49
2	**2b**	IPrAuNTf$_2$	37
3	**2c**	IPrAuNTf$_2$	71
4	**2d**	IPrAuNTf$_2$	83
5	**2e**	IPrAuNTf$_2$	27
6	**2f**	IPrAuNTf$_2$	12
7	**2d**	Ph$_3$PAuNTf$_2$	53
8	**2d**	L1AuCl/AgNTf$_2$[c]	59
9	**2d**	L2AuCl/AgNTf$_2$[c]	61
10	**2d**	PicAuCl$_2$	46
11	**2d**	IPrAuCl/AgOTf	56
12	**2d**	IPrAuCl/AgNTf$_2$	65
13	**2d**	IPrAuCl/AgSbF$_6$	45
14	**2d**	TfOH	–
15	**2d**	IPrAuNTf$_2$	16[d]

[a]All reactions were carried out on a 0.1 mmol scale (0.2 M). [b]Estimated by ^{1}H NMR spectroscopy using durene as an internal standard. [c]L1 = JohnPhos, L2 = *t*BuXPhos. [d]10 equiv of MeCN in PhCF$_3$ were used.

this success, we tested a number of the oxygen sources (**2b−f**) under the same reaction conditions, because it is known that the choice of an oxidizing agent is a crucial factor in the gold-based catalysis.[86−89] The application of 2,3-dichloropyridine *N*-oxide (**2d**, entry 4), previously proposed by us as an effective oxidizing agent,[90] led to the best results.

Next, we studied the effect of various catalysts, including the phosphine gold complexes (entries 7−9), the gold(III) complex PicAuCl$_2$ (entry 10), and systems containing silver salts (entries 11−13), but their application was not as efficient as the initially used IPrAuNTf$_2$. Triflic acid was completely inactive with respect to the studied reaction (entry 14). When PhCF$_3$ was used as a solvent with 10 equiv of MeCN, the yield of **3a** dropped dramatically (entry 15). Finally, experiments to

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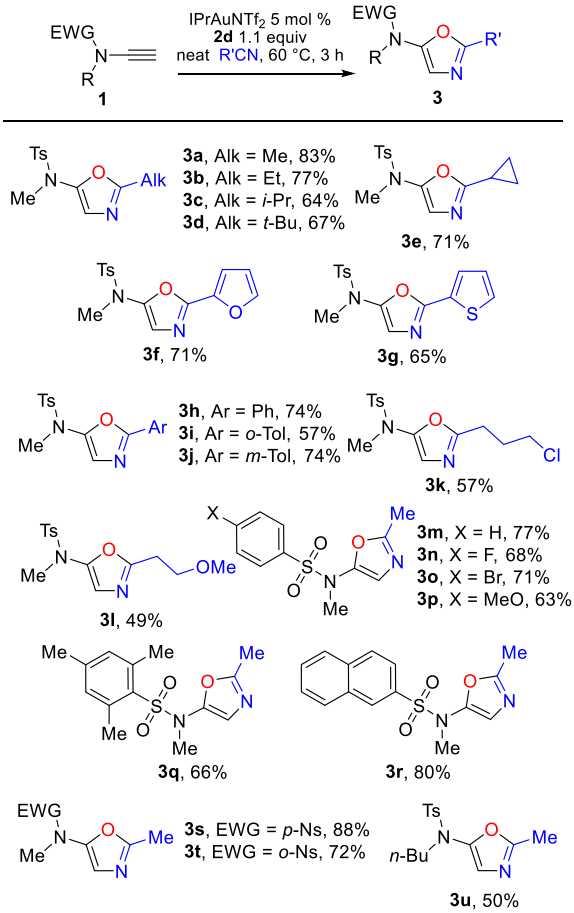
optimize the reaction temperature and time indicated that the best yield of **3a** was achieved at 60 °C for 3 h (entry 4).

With optimal conditions in hand, the oxidative annulation scope was then examined. We explored different nitriles with ynamide **1a** taken as the alkyne component (Table 2). Various

Table 2. Scope for the Synthesis of 5-Aminooxazoles[a]

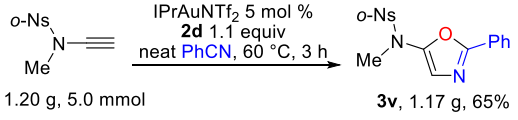


[a]All reactions were carried out on a 0.2 mmol scale (0.2 M). Isolated yields are reported.

aliphatic (primary, secondary, tertiary, and cyclic) heteroaromatic (α-furyl, α-thienyl) and aromatic nitriles reacted to grant corresponding oxazoles **3a−j** in 57−83% yields. Saturated nitriles with functional substituents (MeO, Cl) gave, however, moderate yields of target products **3k,l**. A range of terminal ynamides was then tested using acetonitrile as the reaction partner. The reaction proceeded smoothly with various functionalities at the *N*-sulfonyl substituent including electron-donating, electron-withdrawing, and bulky substituents in various positions of the aromatic ring (**3m−r**). Oxazoles **3s,t**, bearing an easily cleavable *o*- or *p*-nosyl protective group, were obtained in 72−88% yields. The ynamide featuring a primary butyl group also delivered the corresponding oxazole **3u**.

When ynamides with other NR-substituents (R = Ph, Bn, allyl) were employed, we observed the generation of complex product mixtures. In these cases, intramolecular reactions of gold oxo-carbenes (e.g., CH-insertions[91,92] and cyclopropanations[93]) with the involvement of NR-substituents are prevailing. The developed oxidative annulation can be readily performed in gram scale (Scheme 4). We tried to remove the

Scheme 4. Gram-Scale Synthesis of 3v



o-nosyl group from **3v**, but the isolation of the corresponding deprotected oxazole or its derivatives failed. This is probably because of the instability of oxazoles containing NH in the fifth position.

The 5-amino substitution pattern of oxazoles **3** was unambiguously confirmed by X-ray diffraction of oxazole **3o** (Figure 1).[94]

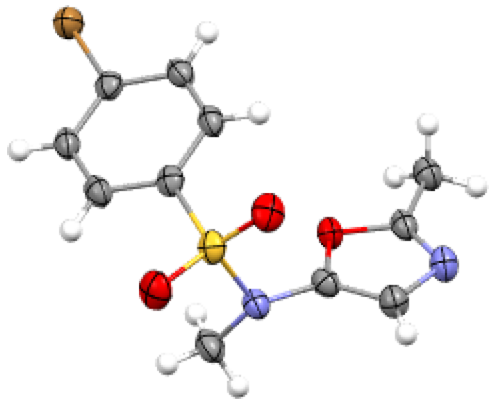
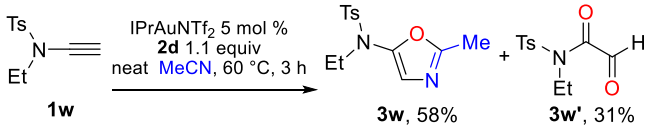


Figure 1. Molecular structure of **3o** (50% probability amplitude displacement ellipsoids).

We tested internal ynamides in our heterocyclization; however, they are not suitable substrates for the reported transformation, as the only products formed are α-ketoamides that result from gold-catalyzed overoxidation of the C≡C triple bonds.[90,95] Notably, terminal ynamides also undergo competitive overoxidation. A mixture of oxazole **3w** and glyoxamide **3w′** was isolated when ynamide **1w** was used as starting material (Scheme 5, NMR yield, the products exhibit

Scheme 5. Annulation and Overoxidation of 1w



the same polarity). A plausible related mechanism for the formation of oxazoles and the dicarbonyl byproducts from propiolates has been discussed in our recent works.[77,88]

After the successful synthesis of 2-amino-1,3-oxazoles, our idea was to demonstrate the utility of our synthetic approach to construct the 2,5-diamino-substituted heterocycles (Table 3) starting from cyanamides **4** as amino-functionalized building blocks. According to our expectations, application of both *N,N*-dimethyl- and *N,N*-diethylcyanamides led to good yields of corresponding oxazoles **5a,b**. The reaction conditions were satisfactory for introducing a diversity of amino functionalities (such as pyrrolidine, piperidine, morpholine, and isoquinoline heterocyclic fragments **5c−f**) into the fifth position of the oxazole core. Unfortunately, when the unsubstituted cyanamide NH_2CN was employed as a reactant, complex mixtures of

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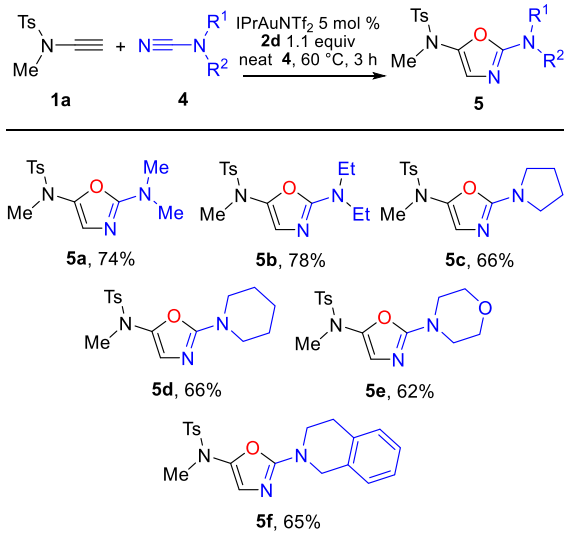
Table 3. Scope for the Synthesis of 2,5-Diaminooxazoles[a]



[a]All reactions were carried out on a 0.2 mmol scale (0.2 M). Isolated yields are reported.

products were detected, probably because of competing gold-catalyzed hydroamination of the starting ynamides.[96]

CONCLUSIONS

Summarizing, we developed a facile gold-catalyzed method, based on the integration of ynamides and nitriles, for the construction of 1,3-oxazoles featuring an amino group in the fifth position. The proposed approach involves oxygen atom transfer, as the key step, to give gold α-oxocarbenes followed by their trapping by nitriles. In contrast to the previously described methods for the synthesis of 4-amino-1,3-oxazoles through the reactions of gold α-iminocarbenes, our annulation demonstrates completely reverse regioselectivity. Probably, the reason for the observed regioselectivity is the higher rate of nucleophilic addition of *N*-oxides to gold-activated ynamides in comparison with nitriles, as well as the reversibility of the addition of the nitriles. The main advantage of the proposed methodology over other routes to 5-amino-oxazoles is the ability to use simple and easily accessible building blocks. The optimized reaction conditions are easily scalable and demonstrate a high functional group tolerance. In addition, the use of cyanamides, as a nitrile component, grant valuable 2,5-diamino-substituted heterocycles.

EXPERIMENTAL SECTION

General Information. NMR spectra were recorded at ambient temperature with a Bruker Avance III 400 instrument at 400.13 MHz (^{1}H NMR) and 100.61 MHz (^{13}C NMR) in $CDCl_3$ or DMSO-d_6. Chemical shifts (δ) are given in ppm relative to resonances of the solvents (^{1}H: δ = 7.26 for residual $CHCl_3$ peak, δ = 2.50 for residual DMSO peak; ^{13}C: δ = 77.2 for $CDCl_3$, δ = 39.5 for DMSO-d_6). Mass spectra were recorded on Bruker MicroTOF (ESI) and Bruker maXis HRMS-ESI-QTOF instruments. Chromatographic separation was carried out on Macherey–Nagel silica gel 60 M (0.04–0.063 mm). Analytical TLC was performed on unmodified Merck ready-to-use plates (TLC silica gel 60 F254); detection was achieved with a UV lamp. Melting points were measured with Stuart smp30 apparatus. Gold complexes ($IPrAuNTf_2$,[85] $Ph_3PAuNTf_2$,[97] $PicAuCl_2$[98]) were synthesized according to the published protocols. Known ynamides **1**[12,99] and *N*-oxides **2**[90] were prepared by the literature procedures. The solvents were purified using standard techniques and stored over activated 4 Å molecular sieves before use. Other reagents were purchased from commercial vendors and were used as received.

General Procedure for the Gold(I)-Catalyzed Synthesis of Aminooxazoles 3 and 5. $IPrAuNTf_2$ (8.7 mg, 10.0 μmol, 5 mol %) was added to a solution of ynamide (**1**, 0.2 mmol) and 2,3-dichloropyridine *N*-oxide **2d** (36.1 mg, 0.22 mmol, 1.1 equiv) in nitriles **3** (0.5 mL). The resulting solution was stirred at 60 °C in an oil bath for 3 h. After completion, all volatile components were removed in vacuo, and the residue was purified by silica gel chromatography, eluting with hexane/EtOAc to afford oxazoles **3** and **5**.

*N,4-Dimethyl-N-(2-methyloxazol-5-yl)benzenesulfonamide (**3a**).* Colorless solid (44.2 mg, 83%); mp 108.0–109.0 °C (hexane/EtOAc); R_f 0.45 (hexane/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 6.66 (s, 1H), 3.12 (s, 3H), 2.43 (s, 3H), 2.34 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.5, 146.1, 144.6, 134.2, 129.8, 127.9, 121.0, 37.7, 21.7, 14.4; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{12}H_{15}N_2O_3S^+$: 267.0798; found: 267.0799.

*N-(2-Ethyloxazol-5-yl)-N,4-dimethylbenzenesulfonamide (**3b**).* Colorless solid (43.2 mg, 77%); mp 106.0–107.0 °C (hexane/EtOAc); R_f 0.40 (hexane/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 7.6 Hz, 2H), 6.70 (s, 1H), 3.14 (s, 3H), 2.67 (q, J = 7.6 Hz, 2H), 2.44 (s, 3H), 1.25 (t, J = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.9, 145.9, 144.6, 134.2, 129.9, 127.9, 121.0, 37.7, 22.1, 21.7, 11.0; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{13}H_{17}N_2O_3S^+$: 281.0954; found: 281.0955.

*N-(2-Isopropyloxazol-5-yl)-N,4-dimethylbenzenesulfonamide (**3c**).* Colorless oil (37.7 mg, 64%); R_f 0.40 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 6.72 (s, 1H), 3.14 (s, 3H), 2.94 (hept, J = 7.0 Hz, 1H), 2.43 (s, 3H), 1.25 (d, J = 6.9 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.0, 145.7, 144.5, 134.3, 129.8, 127.9, 121.0, 37.6, 28.8, 21.7, 20.2; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{14}H_{19}N_2O_3S^+$: 295.1111; found: 295.1109.

*N-(2-(tert-Butyl)oxazol-5-yl)-N,4-dimethylbenzenesulfonamide (**3d**).* Colorless oil (41.3 mg, 67%); R_f 0.45 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 6.73 (s, 1H), 3.14 (s, 3H), 2.43 (s, 3H), 1.26 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.1, 145.6, 144.5, 134.3, 129.8, 127.9, 121.0, 37.5, 34.0, 28.3, 21.7; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{15}H_{21}N_2O_3S^+$: 309.1267; found: 309.1270.

*N-(2-Cyclopropyloxazol-5-yl)-N,4-dimethylbenzenesulfonamide (**3e**).* Colorless solid (41.5 mg, 71%); mp 69.0–71.0 °C (hexane/EtOAc); R_f 0.50 (hexane/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 7.8 Hz, 2H), 6.65 (s, 1H), 3.12 (s, 3H), 2.45 (s, 3H), 1.97–1.90 (m, 1H), 1.00–0.90 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.2, 145.1, 144.5, 134.3, 129.8, 128.0, 121.4, 37.8, 21.7, 9.3, 8.3; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{14}H_{17}N_2O_3S^+$: 293.0954; found: 293.0958.

*N-(2-(Furan-2-yl)oxazol-5-yl)-N,4-dimethylbenzenesulfonamide (**3f**).* Colorless oil (45.2 mg, 71%); R_f 0.30 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 8.0 Hz, 2H), 7.53 (s, 1H), 7.32 (d, J = 7.9 Hz, 2H), 6.95–6.94 (m, 2H), 6.52–6.51 (m, 1H), 3.21 (s, 3H), 2.44 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.1, 146.0, 144.9, 144.8, 142.4, 134.1, 130.0, 128.0, 121.7, 112.2, 112.1, 37.6, 21.8; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{15}H_{15}N_2O_4S^+$: 319.0747; found: 319.0751.

*N,4-Dimethyl-N-(2-(thiophen-2-yl)oxazol-5-yl)-benzenesulfonamide (**3g**).* Colorless oil (43.4 mg, 65%); R_f 0.35 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.4 Hz, 2H), 7.55–7.54 (m, 1H), 7.43–7.41 (m, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.10–7.07 (m, 1H), 6.90 (s, 1H), 3.21 (s, 3H), 2.45 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 155.7, 145.9, 144.8, 134.2, 130.0, 129.8, 128.9, 128.1, 128.1, 128.0, 122.2, 37.8, 21.8; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{15}H_{15}N_2O_3S_2^+$: 335.0519; found: 335.0527.

*N,4-Dimethyl-N-(2-phenyloxazol-5-yl)benzenesulfonamide (**3h**).* Yellowish oil (48.6 mg, 74%); R_f 0.50 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89–7.87 (m, 2H), 7.68 (d, J = 8.3 Hz, 2H),

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7.45−7.40 (m, 3H), 7.32 (d, J = 8.0 Hz, 2H), 6.95 (s, 1H), 3.24 (s, 3H), 2.45 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.3, 146.3, 144.7, 134.2, 130.7, 130.0, 128.9, 128.0, 127.3, 126.3, 122.2, 37.7, 21.8; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{17}H_{17}N_2O_3S^+$: 329.0954; found: 329.0966.

*N,4-Dimethyl-N-(2-(o-tolyl)oxazol-5-yl)benzenesulfonamide (**3i**).* Colorless oil (39.0 mg, 57%); R_f 0.35 (hexane/EtOAc 4:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 7.3 Hz, 1H), 7.67 (d, J = 8.3 Hz, 2H), 7.34−7.31 (m, 3H), 7.26−7.22 (m, 2H), 7.01 (s, 1H), 3.24 (s, 3H), 2.53 (s, 3H), 2.44 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.8 (br.), 146.1 (br.), 144.8, 137.6, 134.1, 131.8, 130.5, 130.0, 128.9, 127.9, 126.2, 125.9, 121.3, 37.5, 21.9, 21.7; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{18}H_{19}N_2O_3S^+$: 343.1111; found: 343.1108.

*N,4-Dimethyl-N-(2-(m-tolyl)oxazol-5-yl)benzenesulfonamide (**3g**).* Colorless solid (52.7 mg, 74%); mp 59.0−60.0 °C (hexane/EtOAc); R_f 0.30 (hexane/EtOAc 4:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.77−7.66 (m, 4H), 7.36−7.24 (m, 4H), 6.94 (s, 1H), 3.23 (s, 3H), 2.44 (s, 3H), 2.39 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.5, 146.3, 144.7, 138.7, 134.2, 131.6, 129.9, 128.8, 128.0, 127.0, 126.9, 123.4, 121.9, 37.7, 21.7, 21.4; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{18}H_{19}N_2O_3S^+$: 343.1111; found: 343.1104.

*N-(2-(3-Chloropropyl)oxazol-5-yl)-N,4-dimethylbenzenesulfonamide (**3k**).* Colorless oil (37.5 mg, 57%); R_f 0.50 (hexane/EtOAc 1:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 6.73 (s, 1H), 3.57 (t, J = 6.4 Hz, 2H), 3.14 (s, 3H), 2.83 (t, J = 7.3 Hz, 2H), 2.44 (s, 3H), 2.15 (p, J = 6.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.4, 146.2, 144.7, 134.2, 129.9, 127.9, 121.0, 43.7, 37.6, 29.4, 25.7, 21.7; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{18}ClN_2O_3S^+$: 329.0721; found: 329.0718.

*N-(2-(2-Methoxyethyl)oxazol-5-yl)-N,4-dimethylbenzenesulfonamide (**3l**).* Yellowish oil (30.4 mg, 49%); R_f 0.30 (hexane/EtOAc 1:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 7.6 Hz, 2H), 6.73 (s, 1H), 3.69 (t, J = 6.6 Hz, 2H), 3.34 (s, 3H), 3.13 (s, 3H), 2.92 (t, J = 6.6 Hz, 2H), 2.44 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.3, 146.2, 144.6, 134.2, 129.9, 128.0, 121.1, 69.1, 58.9, 37.6, 29.3, 21.7; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{19}N_2O_4S^+$: 311.1060; found: 311.1067.

*N-Methyl-N-(2-methyloxazol-5-yl)benzenesulfonamide (**3m**).* Colorless oil (38.9 mg, 77%); R_f 0.30 (hexane/EtOAc 1:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.77−7.75 (m, 2H), 7.64 (t, J = 7.5 Hz, 1H), 7.53 (t, J = 7.7 Hz, 2H), 6.69 (s, 1H), 3.16 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 145.9, 137.3, 133.6, 129.3, 127.9, 121.2, 37.8, 14.4; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{11}H_{13}N_2O_3S^+$: 253.0641; found: 253.0645.

*4-Fluoro-N-methyl-N-(2-methyloxazol-5-yl)benzenesulfonamide (**3n**).* Colorless solid (36.8 mg, 68%); mp 95.0−97.0 °C (hexane/EtOAc); R_f 0.35 (hexane/EtOAc 1:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.74−7.79 (m, 2H), 7.17−7.23 (m, 2H), 6.70 (s, 1H), 3.15 (s, 3H), 2.35 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.7 (d, J_F = 256.2 Hz), 159.7, 145.7, 133.3 (d, J_F = 3.4 Hz), 130.6 (d, J_F = 9.4 Hz), 121.4, 116.6 (d, J_F = 22.7 Hz), 37.8, 14.4; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{11}H_{12}FN_2O_3S^+$: 271.0547; found: 271.0545.

*4-Bromo-N-methyl-N-(2-methyloxazol-5-yl)benzenesulfonamide (**3o**).* Yellow solid (47.0 mg, 71%); mp 96.0−98.0 °C (hexane/EtOAc); R_f 0.40 (hexane/EtOAc 1:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.70−7.66 (m, 2H), 7.63−7.60 (m, 2H), 6.72 (s, 1H), 3.16 (s, 3H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.9, 145.6, 136.2, 132.6, 129.3, 128.9, 121.2, 37.8, 14.4; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{11}H_{11}BrN_2NaO_3S^+$: 352.9566; found: 352.9561.

*4-Methoxy-N-methyl-N-(2-methyloxazol-5-yl)benzenesulfonamide (**3p**).* Colorless oil (35.6 mg, 63%, 91% purity form NMR assay); R_f 0.40 (hexane/EtOAc 1:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.9 Hz, 2H), 6.98 (d, J = 8.9 Hz, 2H), 6.67 (s, 1H,), 3.88 (s, 3H), 3.13 (s, 3H), 2.36 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.7, 159.5, 146.3, 130.1, 128.7, 121.0, 114.4, 55.8, 37.7, 14.5; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{12}H_{15}N_2O_4S^+$: 283.0747; found: 283.0753.

*N,2,4,6-Tetramethyl-N-(2-methyloxazol-5-yl)benzenesulfonamide (**3q**).* Colorless solid (38.9 mg, 66%); mp 85.0−87.0 °C (hexane/EtOAc); R_f 0.30 (hexane/EtOAc 2:1); ^1H NMR (400 MHz, $CDCl_3$) δ 6.95 (s, 2H), 6.53 (s, 1H), 3.21 (s, 3H), 2.53 (s, 6H), 2.42 (s, 3H), 2.30 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.1, 146.1, 143.7, 140.8, 132.2, 131.4, 120.0, 36.5, 22.9, 21.1, 14.3; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{19}N_2O_3S^+$: 295.1111; found: 295.1106.

*N-Methyl-N-(2-methyloxazol-5-yl)naphthalene-2-sulfonamide (**3r**).* Brownish oil (48.4 mg, 80%); R_f 0.30 (hexane/EtOAc 1:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.97 (d, J = 8.5 Hz, 2H), 7.94 (d, J = 8.2 Hz, 1H), 7.71−7.62 (m, 3H), 6.73 (s, 1H), 3.20 (s, 3H), 2.34 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.7, 146.0, 135.3, 134.2, 132.2, 129.6, 129.58, 129.5, 129.4, 128.1, 127.9, 122.8, 121.3, 37.9, 14.5; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{15}H_{14}N_2NaO_3S^+$: 325.0617; found: 325.0609.

*N-Methyl-N-(2-methyloxazol-5-yl)-4-nitrobenzenesulfonamide (**3s**).* Yellow solid (52.3 mg, 88%); mp 113.0−115.0 °C (hexane/EtOAc); R_f 0.30 (hexane/EtOAc 1:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 8.8 Hz, 2H), 7.95 (d, J = 8.8 Hz, 2H), 6.78 (s, 1H), 3.21 (s, 3H), 2.36 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.1, 150.7, 144.9, 143.1, 129.1, 124.6, 121.9, 38.0, 14.5; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{11}H_{12}N_3O_5S^+$: 298.0492; found: 298.0488.

*N-Methyl-N-(2-methyloxazol-5-yl)-2-nitrobenzenesulfonamide (**3t**).* Yellow solid (42.8 mg, 72%); mp 44.5−46.0 °C (hexane/EtOAc); R_f 0.40 (hexane/EtOAc 1:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.1 Hz, 1H), 7.78−7.75 (m, 1H), 7.70−7.66 (m, 2H), 6.77 (s, 1H), 3.36 (s, 3H), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.5, 148.3, 144.7, 134.7, 131.9, 131.7, 131.2, 124.6, 121.6, 38.5, 14.4.; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{11}H_{12}N_3O_5S^+$: 298.0492; found: 298.0481.

*N-Butyl-4-methyl-N-(2-methyloxazol-5-yl)benzenesulfonamide (**3u**).* Colorless oil (30.8 mg, 50%); R_f 0.40 (hexane/EtOAc 2:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 6.68 (s, 1H), 3.43 (t, J = 7.2 Hz, 2H), 2.44 (s, 3H), 2.37 (s, 3H), 1.49−1.42 (m, 2H), 1.36−1.29 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.3, 144.5, 144.3, 135.7, 129.8, 127.8, 123.4, 50.4, 30.5, 21.7, 19.6, 14.6, 13.7; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{21}N_2O_3S^+$: 309.1267; found: 309.1273.

*N-Ethyl-4-methyl-N-(2-methyloxazol-5-yl)benzenesulfonamide (**3w**) and N-Ethyl-2-oxo-N-tosylacetamide (**3w′**).* Brownish oil (49.0 mg, 58% (**3w**), 31% (**3w′**)); R_f 0.60 (hexane/ethyl acetate 1:1); ^1H NMR for **3w** (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 6.74 (s, 1H), 3.52 (q, J = 7.2 Hz, 2H), 2.44 (s, 3H), 2.43 (s, 3H), 1.12 (t, J = 7.2 Hz, 3H); ^1H NMR for **3w′** (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 3.63 (q, J = 7.1 Hz, 2H), 2.46 (s, 3H), 1.17−1.14 (m, 3H); $^{13}C\{^1H\}$ NMR for **3w** and **3w′** (100 MHz, $CDCl_3$) δ 184.3, 166.1, 160.7, 151.0, 146.2, 144.5, 135.6, 134.4, 130.4, 129.9, 128.2, 127.8, 122.6, 45.8, 40.9, 21.8, 21.7, 14.5, 14.1, 13.6; HRMS (ESI) for 3w: m/z $[M + H]^+$ calcd for $C_{13}H_{17}N_2O_3S^+$: 281.0954; found: 281.0944; HRMS (ESI) for 3w′: m/z $[M + Na]^+$ calcd for $C_{10}H_{11}NNaO_4S^+$: 264.0301; found: 264.0305.

*N-(2-(Dimethylamino)oxazol-5-yl)-N,4-dimethylbenzenesulfonamide (**5a**).* Brown oil (43.7 mg, 74%); R_f 0.30 (hexane/EtOAc 1:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 6.46 (s, 1H), 3.11 (s, 3H), 2.95 (s, 6H), 2.44 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.1, 144.2, 139.9, 134.7, 129.7, 128.1, 123.1, 38.6, 37.4, 21.7; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{13}H_{18}N_3O_3S^+$: 296.1063; found: 296.1071.

*N-(2-(Diethylamino)oxazol-5-yl)-N,4-dimethylbenzenesulfonamide (**5b**).* Browm oil (50.5 mg, 78%); R_f 0.50 (hexane/EtOAc 1:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 6.49 (s, 1H), 3.34 (q, J = 7.1 Hz, 4H), 3.13 (s, 3H), 2.43 (s, 3H), 1.13 (t, J = 7.1 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.1, 144.1, 139.3, 134.9, 129.7, 128.0, 123.0, 42.5, 38.5, 21.7, 13.4; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{22}N_3O_3S^+$: 324.1376; found: 324.1387.

*N,4-Dimethyl-N-(2-(pyrrolidin-1-yl)oxazol-5-yl)benzenesulfonamide (**5c**).* Yellowish oil (42.4 mg, 66%); R_f 0.50 (hexane/EtOAc 1:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 7.6 Hz, 2H), 6.45 (s, 1H), 3.40−3.37 (m, 4H), 3.10 (s, 3H), 2.43 (s, 3H), 1.97−1.91 (m, 4H); $^{13}C\{^1H\}$ NMR (100

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MHz, $CDCl_3$) δ 158.3, 144.2, 139.7, 134.7, 129.7, 128.1, 123.0, 47.1, 38.6, 25.6, 21.7; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{20}N_3O_3S^+$: 322.1220; found: 322.1224.

*N,4-Dimethyl-N-(2-(piperidin-1-yl)oxazol-5-yl)-benzenesulfonamide (**5d**).* Brown oil (44.3 mg, 66%); R_f 0.50 (hexane/EtOAc 1:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.3 Hz, 2H, Ar), 7.31 (d, J = 7.9 Hz, 2H, Ar), 6.47 (s, 1H, Ar), 3.36−3.34 (m, 4H, $2CH_2$), 3.11 (s, 3H, NMe), 2.44 (s, 3H, Me), 1.60−1.58 (m, 6H, $3CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 144.2, 139.7, 134.8, 129.7, 128.1, 122.8, 46.2, 38.6, 25.1, 24.1, 21.7; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{16}H_{22}N_3O_3S^+$: 336.1376; found: 336.1380.

*N,4-Dimethyl-N-(2-morpholinooxazol-5-yl)benzenesulfonamide (**5e**).* Brown oil (41.8 mg, 62%); R_f 0.30 (hexane/EtOAc 1:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 6.48 (s, 1H), 3.75−3.72 (m, 4H), 3.39−3.37 (m, 4H), 3.12 (s, 3H), 2.45 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.2, 144.4, 140.6, 134.7, 129.8, 128.1, 122.6, 66.2, 45.5, 38.6, 21.7; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{20}N_3O_4S^+$: 338.1169; found: 338.1171.

*N-(2-(3,4-Dihydroisoquinolin-2(1H)-yl)oxazol-5-yl)-N,4-dimethylbenzenesulfonamide (**5f**).* Brown oil (49.9 mg, 65%); R_f 0.30 (hexane/EtOAc 2:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.21−7.09 (m, 4H), 6.51 (s, 1H), 4.56 (s, 2H), 3.67 (t, J = 5.9 Hz, 2H), 3.14 (s, 3H), 2.91 (t, J = 5.9 Hz, 2H), 2.44 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.1, 144.3, 140.1, 134.7, 134.1, 132.5, 129.7, 128.9, 128.0, 126.8, 126.5, 126.4, 122.8, 46.8, 42.7, 38.6, 28.4, 21.7; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{20}H_{22}N_3O_3S^+$: 384.1376; found: 384.1373.

Gram-Scale Synthesis of 3v. $IPrAuNTf_2$ (218 mg, 0.25 mmol, 5 mol %) was added to a solution of *N*-ethynyl-*N*-methyl-2-nitrobenzenesulfonamide (**1t**, 5.0 mmol, 1.20 g) and 2,3-dichloropyridine *N*-oxide **2d** (0.90 g, 5.50 mmol, 1.1 equiv) in benzonitrile (5.0 mL). The resulting solution was stirred at 60 °C in an oil bath for 3 h. After completion, all volatile components were removed in vacuo and the residue was purified by silica gel chromatography, eluting with hexane/EtOAc to afford oxazole **3v**.

*N-Methyl-2-nitro-N-(2-phenyloxazol-5-yl)benzenesulfonamide (**3v**).* Yellow oil (1.17 g, 65%); R_f 0.50 (hexane/EtOAc 1:1); ^1H NMR (400 MHz, $CDCl_3$) 7.95−7.89 (m, 3H), 7.77−7.72 (m, 1H), 7.69−7.64 (m, 2H), 7.45−7.39 (m, 3H), 7.00 (s, 1H), 3.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 148.4, 144.8, 134.7, 131.9, 131.8, 131.3, 131.1, 129.0, 126.9, 126.4, 124.6, 123.0, 38.6; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{16}H_{14}N_3O_5S^+$: 360.0649; found: 360.0635.

Synthesis of Starting Ynamides. General Procedure for the Preparation of 1,2-Dichloroenamides 1q′,r′,w′. Trichloroethylene (1.31 g, 10.0 mmol, 2.0 equiv) was added dropwise to a stirred suspension of amide (5.0 mmol) and K_2CO_3 (2.07 g, 15.0 mmol, 3.0 equiv) in DMF (5.0 mL) at 70 °C in an oil bath under argon atmosphere. The reaction mixture was stirred overnight, cooled to rt, diluted with water (50 mL), and extracted with DCM (3 × 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4. After filtration, the solvent was removed in vacuo and the residue was purified by silica gel chromatography, eluting with hexane/EtOAc to afford 1,2-dichloroenamides **1q′**,**r′**,**w′**.

*(E)-N-(1,2-Dichlorovinyl)-N,2,4,6-tetramethylbenzenesulfonamide (**1q′**).* Colorless solid (1.33 mg, 84%); mp 145.0−147.0 °C (hexane/EtOAc); R_f 0.45 (hexane/EtOAc 8:1); ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 2H), 6.22 (s, 1H), 3.06 (s, 3H), 2.64 (s, 6H), 2.28 (s, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 135.3, 134.5, 132.1, 131.5, 130.3, 129.5, 129.44, 129.38, 128.1, 127.8, 123.3, 120.0, 35.5; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{12}H_{15}Cl_2NNaO_2S^+$: 330.0093; found: 330.0099.

*(E)-N-(1,2-Dichlorovinyl)-N-methylnaphthalene-2-sulfonamide (**1r′**).* Colorless solid (1.33 mg, 84%); mp 114.0−115.0 °C (hexane/EtOAc); R_f 0.45 (hexane/EtOAc 4:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H,), 7.98 (d, J = 8.5 Hz, 2H), 7.93−7.90 (m, 2H), 7.69−7.60 (m, 2H), 6.42 (s, 1H), 3.00 (s, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 135.3, 134.5, 132.1, 131.5, 130.3, 129.5, 129.44, 129.38, 128.1, 127.8, 123.3, 120.0, 35.5; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{13}H_{11}Cl_2NNaO_2S^+$: 337.9780; found: 337.9779.

*(E)-N-(1,2-Dichlorovinyl)-N-ethyl-4-methylbenzenesulfonamide (**1w′**).* Colorless solid (1.35 g, 92%); mp 56.0−58.0 °C (hexane/EtOAc); R_f 0.50 (hexane/EtOAc 4:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 6.51 (s, 1H), 3.30 (br. s, 2H), 2.41 (s, 3H), 1.15 (t, J = 7.2 Hz, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 144.5, 135.2, 129.6, 129.4, 128.2, 121.5, 43.0, 21.5, 12.8; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{11}H_{13}Cl_2NNaO_2S^+$: 315.9936; found: 315.9937.

General Procedure for the Synthesis of Ynamides 1q,r,w Using *n*-Butyllithium. A solution of 1,2-dichloroenamide (**1q′**, **1r′**, or **1w′**, 1.0 mmol) in anhydrous THF (5 mL) was stirred under argon atmosphere and cooled to −78 °C in an acetone/dry ice bath. A solution of *n*-butyllithium (2.5 M in hexane, 1.4 mL, 3.5 equiv) was then added dropwise over 10 min, such that the reaction did not exceed −70 °C, and the resulting mixture was then stirred at −78 °C for 30 min. Next, water (1 mL) was added at −78 °C and the stirred mixture was allowed to warm to room temperature, diluted with water (30 mL), and extracted with DCM (3 × 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4. After filtration, the solvent was removed in vacuo to afford pure terminal ynamides **1q**, **1r**, or **1w**.

*N-Ethynyl-N,2,4,6-tetramethylbenzenesulfonamide (**1q**).* Brown solid (225 mg, 95%); mp 65.0−67.0 °C (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 6.99 (s, 2H), 3.13 (s, 3H), 2.71 (s, 1H), 2.65 (s, 6H), 2.32 (s, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 143.5, 141.1, 132.4, 132.1, 131.9, 118.7, 35.3, 23.4, 21.1.; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{12}H_{15}NNO_2S^+$: 260.0716; found: 260.0718.

*N-Ethynyl-N-methylnaphthalene-2-sulfonamide (**1r**).* Brown solid (233 mg, 95%); mp 58.5−60.0 °C (DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.03−8.01 (m, 2H), 7.96−7.90 (m, 2H), 7.71−7.63 (m, 2H), 3.13 (s, 3H), 2.71 (s, 1H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 135.5, 133.4, 132.2, 129.71, 129.68, 129.63, 129.5, 128.1, 127.9, 122.7, 77.6, 57.8, 39.1; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{13}H_{11}NNaO_2S^+$: 268.0403; found: 268.0405.

*N-Ethyl-N-ethynyl-4-methylbenzenesulfonamide (**1w**).* Yellowish oil (226 mg, 97%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 3.37 (q, J = 7.2 Hz, 2H), 2.72 (s, 1H), 2.43 (s, 3H), 1.19 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 133.4, 132.2, 129.71, 129.68, 129.63, 129.5, 128.1, 127.9, 122.7, 77.6, 57.8, 39.1; HRMS (ESI): m/z $[M + Na + H_2O]^+$ calcd for $C_{11}H_{15}NNaO_3S^+$: 264.0665; found: 264.0673.

Synthesis of Ynamide 1t. A mixture of *N*-methyl-2-nitrobenzenesulfonamide (10 mmol, 2.16 g), K_2CO_3 (2.76 g, 20 mmol, 2 equiv), $CuSO_4·5H_2O$ (250 mg, 1.0 mmol, 10 mol %), 1,10-phenanthroline (360 mg, 2.0 mmol, 20 mol %), 1-bromo-2-triisopropylsilylacetylene (2.86 mg, 11 mmol, 1.1 equiv), and toluene (50 mL) was stirred at 70 °C under argon atmosphere in an oil bath overnight After completion, the reaction mixture was cooled to rt, diluted with DCM (150 mL), filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography, eluting with hexane/EtOAc to afford the TIPS-protected ynamide, as a yellow solid (1.82 g, R_f 0.40 (hexane/EtOAc 4:1)) that was used further without additional purification. Next, a solution of TBAF (1 M in THF, 0.12 mmol, 12 mL) was added dropwise to a stirred solution of the TIPS-protected ynamide (1.82 g) in anhydrous THF (30 mL) at 0 °C in an ice bath. The resulting dark solution was stirred at 0 °C in an ice bath for 1 h, allowed to warm to rt, diluted with water (70 mL), and extracted with DCM (3 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4. After filtration, the solvent was removed in vacuo and the residue was purified by silica gel chromatography, eluting with hexane/EtOAc to afford **1t**.

*N-Ethynyl-N-methyl-2-nitrobenzenesulfonamide (**1t**).* Yellow solid (1.88 g, 83% relative to starting sulfonamide); mp 100.0−101.0 °C (hexane/EtOAc); R_f 0.35 (hexane/EtOAc 2:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.17−8.15 (m, 2H), 7.82−7.72 (m, 2H), 3.32 (s, 3H), 2.76 (s, 1H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 148.1, 135.0, 132.1, 132.0, 130.1, 124.5, 77.2, 76.1, 59.0, 39.5; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_9H_8N_2NaO_4S^+$: 263.0097; found: 263.0099.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02584.

Copies of ^{1}H and $^{13}C\{1H\}$ NMR spectra and XRD data (PDF)

FAIR data, including the primary NMR FID files, for all compounds **1q**, **1q′**, **1r**, **1r′**, **1t**, **1w**, **1w′**, **3a**−**w**, and **5a**−**f** (ZIP)

Accession Codes

CCDC 2035080 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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