JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

Tf_2NH-Catalyzed Formal [3 + 2] Cycloaddition of Ynamides with Dioxazoles: A Metal-Free Approach to Polysubstituted 4-Aminooxazoles

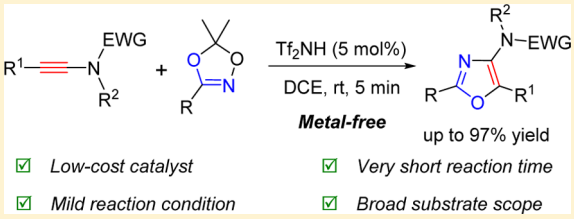
Yingying Zhao,[†,‡,§] Yancheng Hu,[†,§] Chunxiang Wang,[†] Xincheng Li,[*,†] and Boshun Wan[*,†]

[†]Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian 116023, China

[‡]University of Chinese Academy of Sciences, Beijing 10049, China

Supporting Information

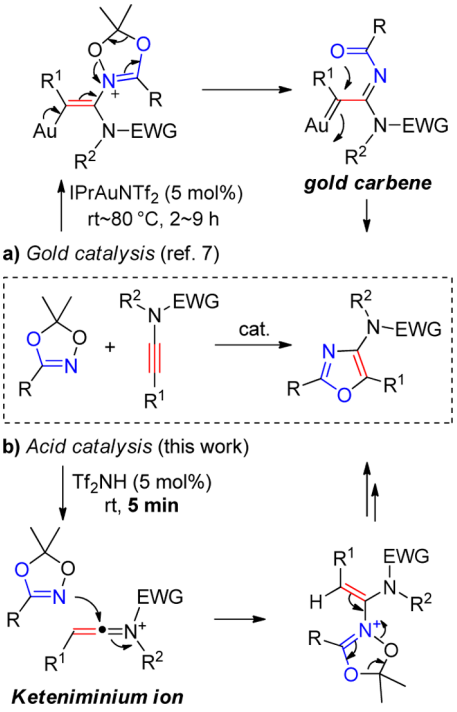
ABSTRACT: An unprecedented Tf_2NH-catalyzed formal [3 + 2] cycloaddition of ynamides with dioxazoles was developed to construct various polysubstituted 4-aminooxazoles. This approach features a metal-free catalytic bimolecular assembly of oxazole motifs, a low-cost catalyst, exceptionally mild reaction conditions, a very short reaction time, a broad substrate scope, and high efficiency. This metal-free protocol may find applications in pharmaceutical-oriented synthesis.



Oxazoles are important structural motifs in a broad range of natural products, bioactive molecules, and pharmaceutical ingredients.[1] Consequently, their synthesis has attracted considerable attention over the past decade. Among those synthetic routes,[2,3] the bimolecular cycloaddition approach, due to its formation of multiple new bonds in one step, is arguably the simplest and most straightforward.[3,7] However, most of them rely on transition-metal catalysis. By contrast, the metal-free catalytic cycloadditions are extremely rare.[9] The metal-free protocol avoids the utilization of transition metal catalysts, thus resulting in no metal residues in the system, which is highly advantageous in the pharmaceutical-oriented synthesis.[4] In this context, the exploration of metal-free catalytic bimolecular assembly of oxazoles is in high demand.

In recent years, ynamides have emerged as versatile building blocks to elaborate complex heterocyclic scaffolds due to their specific reactivity.[5] For example, gold-catalyzed cycloadditions of ynamides with various unsaturated precursors have been extensively investigated.[6,7] In these reactions, α-imino gold carbene was suggested to be the key intermediate. Following the same principle, very recently, Liu et al. presented a gold-catalyzed cycloaddition of ynamides with dioxazoles for the synthesis of functionalized oxazoles (Scheme 1a).[7] Besides gold catalysis, ynamides could also be activated by acid catalysts to form keteniminium ion intermediates, which then easily underwent the reactions with nucleophiles.[8] This strategy has been employed to construct pyridines, pyrimidines, and isoquinolines.[9] Inspired by these elegant works and our long-standing interests in exploring new methodologies toward oxazoles,[10] we envisioned that if ynamides would be first activated by Brønsted acids such as Tf_2NH and TfOH,[8,9] then the in situ generated keteniminium ion intermediates undergo the cycloadditions with dioxazoles to give 4-aminooxazoles (Scheme 1b). Indeed, the reaction proceeded efficiently in the presence of Tf_2NH at room temperature within a very short reaction time (5 min). Remarkably, the $IPrAuNTf_2$ catalyst used in Liu's work is nearly 44 times more expensive than Tf_2NH and 1390 times more expensive than TfOH,[11] making

Scheme 1. Gold- versus Acid-Catalyzed Cycloadditions of Ynamides with Dioxazoles



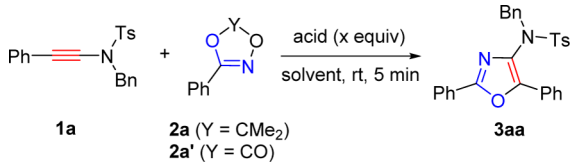
Received: January 11, 2017

DOI: 10.1021/acs.joc.7b00076
J. Org. Chem. XXXX, XXX, XXX−XXX

the metal-free approach a highly economical alternative to a noble metal catalyst. Thus, our approach features the first metal-free acid-catalyzed [3 + 2] cycloaddition toward oxazoles, a low-cost catalyst, exceptionally mild reaction conditions, and a very short reaction time. These amazing advantages will certainly enable this metal-free catalytic protocol to find applications in organic synthesis, especially in the synthesis of pharmaceuticals. Herein, we report the results of our studies.

We initiated our investigation by reacting ynamide **1a** and dioxazole **2a** in the presence of Tf_2NH (1.2 equiv). As expected, the cycloaddition proceeded efficiently under this condition, providing the desired product **3aa** in 82% yield (Table 1, entry 1). Notably, the reaction can be finished within

Table 1. Optimization of the Reaction Conditions[a]



1a **2a** (Y = CMe_2) **2a'** (Y = CO) **3aa**

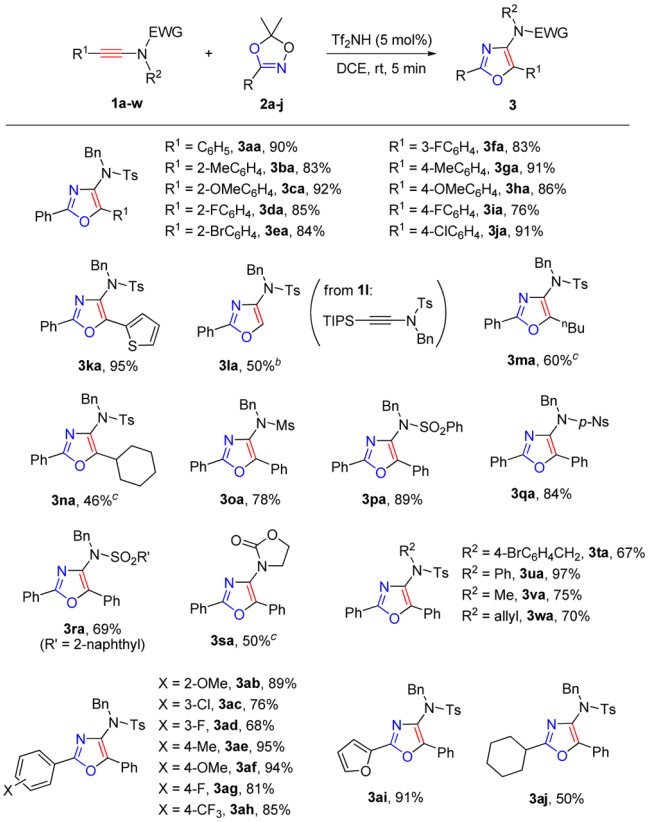
entry	acid	x	dioxazole	solvent	yield (%)[b]
1	Tf_2NH	1.2	**2a**	DCE	82
2	Tf_2NH	1.2	**2a'**	DCE	28
3	Tf_2NH	0.1	**2a**	DCE	81
4	Tf_2NH	0.05	**2a**	DCE	82
5	Tf_2NH	0.025	**2a**	DCE	77
6[c]	Tf_2NH	0.05	**2a**	DCE	86
7[c]	TfOH	0.05	**2a**	DCE	83
8[c]	CF_3CO_2H	0.05	**2a**	DCE	0
9[c]	TsOH	0.05	**2a**	DCE	0
10[c]	Tf_2NH	0.05	**2a**	DCM	70
11[c]	Tf_2NH	0.05	**2a**	THF	0
12[c,d]	Tf_2NH	0.05	**2a**	DCE	77

[a]Reaction conditions: Acid was added to a mixture of **1a** (0.1 mmol) and **2a** (0.2 mmol) in DCE (1.0 mL) and then stirred at room temperature for 5 min. [b]Yields were determined by HPLC using naphthalene as the internal standard. [c]0.12 mmol of **2a** was used. [d]The reaction was conducted under open-air conditions.

5 min. However, the utilization of dioxazole **2a'** as the cycloaddition partner only afforded **3aa** in 28% yield (entry 2). The catalyst loading was then investigated, and a catalytic amount of Tf_2NH was used to promote the reaction. We were delighted to find that 10 mol % of Tf_2NH could efficiently catalyze the cycloaddition, producing **3aa** in a comparable yield (entry 3). A lower catalyst loading (5 mol %) also gave a good result, while 77% yield of **3aa** was achieved in the presence of 2.5 mol % of catalyst (entries 4 and 5). Pleasingly, when the amount of dioxazole **2a** was decreased to 1.2 equiv, the yield of **3aa** increased to 86% (entry 6). It is noteworthy that the use of TfOH as catalyst also delivered the desired oxazole **3aa** in a comparable yield (entry 7).[12] The other Brønsted acids such as CF_3CO_2H and TsOH cannot promote the reaction (entries 8 and 9). When the solvent was changed to DCM, the reaction also occurred but gave an inferior result (entry 10). By contrast, no desired product was obtained when the reaction was performed in THF (entry 11). Disappointedly, when the reaction was conducted under open-air conditions, a moderate yield was obtained (entry 12). It is because the side product amide was easily formed by the acid-catalyzed addition of water with ynamide.[8a]

With the optimal reaction conditions in hand, we first explored the scope of ynamides and the results are summarized in Scheme 2. The variations of R^1 group at the terminal alkyne

Scheme 2. Scope of Substrates[a]



[a]Reaction conditions: Tf_2NH (5 mol %) was added to a mixture of ynamide **1** (0.2 mmol) and dioxazole **2** (0.24 mmol) in DCE (2.0 mL) and then stirred at room temperature for 5 min. [b]1.0 equiv of Tf_2NH was employed. [c]12 h. Ts = *p*-toluenesulfonyl, Ms = methanesulfonyl, *p*-Ns = *p*-nitrobenzenesulfonyl.

were first examined. A series of substituents at the *ortho*-, *meta*-, and *para*-positions of the phenyl ring were all well tolerated, providing the corresponding 4-aminooxazoles **3ba**–**3ja** in good to excellent yields. The electronic properties and positions of the substituents have a neglectable effect on the reactivity. Notably, treatment of 2-thienyl derived ynamide **1k** with a catalytic amount of Tf_2NH afforded the desired product **3ka** in 95% yield. Surprisingly, desilylated oxazole **3la** was found to be the main product when using TIPS-substituted ynamide **1l** as the substrate. Consequently, in this case, 1 equiv of Tf_2NH was required to achieve a moderate yield. Furthermore, other alkyl groups such as *n*-butyl and cyclohexyl in R^1 were also compatible with the process, producing 4-aminooxazoles **3ma** and **3na** in acceptable yields albeit with a longer reaction time. The effects of the electron-withdrawing groups on the nitrogen atom were next investigated. The reactions of ynamides bearing *N*-Ms, *N*-SO_2Ph, and *N*-Ns with **2a** furnished the corresponding products **3oa**–**3qa** in 78–89% yields. However, when the sterically hindered 2-naphthyl substituent was employed in the sulfonyl group, 4-aminooxazole **3ra** was only afforded in 69% yield. The more electron-rich ynamide **1s** possessing an oxazolidine group can also participate in the reaction, giving **3sa** in a moderate yield after prolonging the reaction time to 12

DOI: 10.1021/acs.joc.7b00076
J. Org. Chem. XXXX, XXX, XXX–XXX

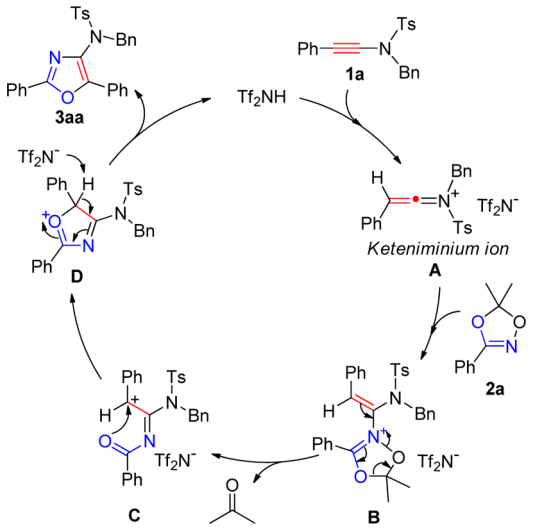
h. The substituted benzyl group such as 4-$BrC_6H_4CH_2$ on the nitrogen atom was compatible with this process (**3ta**). Notably, when R^2 was changed to the phenyl group, the cycloaddition also proceeded with high efficiency (**3ua**, 97%). In the cases of *N*-methyl and *N*-allyl ynamides **1v** and **1w**, the reactions afforded the corresponding oxazoles in 75% and 70% yield, respectively.

Subsequently, a wide range of substituted dioxazoles were surveyed. Dioxazole **2b** with an electron-donating group 2-OMe on the phenyl ring underwent the reaction efficiently, generating product **3ab** in 89% yield. A variety of *meta*- and *para*-substituted groups, such as Cl, F, Me, OMe, and CF_3, were all suitable for this process, leading to the formation of highly functionalized 4-aminooxazoles **3ac**−**3ah** in good to excellent yields. These results reveal that the steric and electronic factors had little influence on the reaction course. The cycloaddition of 2-furyl substituted dioxazole **2i** with ynamide **1a** produced the desired oxazole **3ai** in 91% yield. Besides, when an alkyl substituent such as cyclohexyl was employed in R (**2j**), the reaction also occurred under the standard conditions albeit with a slightly decreased yield.

To illustrate the practical application of this method, a gram-scale experiment was conducted. Ynamide **1a** (2.7 mmol) and dioxazole **2a** (3.2 mmol) were dissolved in 30 mL of DCE. Then a catalytic amount of Tf_2NH (5 mol %) was added, and the mixture was stirred at room temperature for 5 min. The reaction was quenched by Et_3N, and removal of the solvent and direct crystallization in DCM/petroleum ether afforded **3aa** in 84% yield (1.09 g). Alternatively, a comparable yield could also be obtained by using a much cheaper TfOH catalyst albeit with a slightly longer reaction time (20 min). To further demonstrate the advantage of our protocol, we also conducted the reaction using a gold catalyst (5 mol % of $IPrAuNTf_2$, Liu's work). It is noted that a much longer reaction time (6 h versus 5 min) was required to achieve a comparable yield (1.06 g, 81%). Thus, our metal-free catalytic reaction provides an economical alternative for the synthesis of aminooxazoles.

According to the precedents on the chemistry of the keteniminium ion,[8,9] a plausible mechanism was proposed in Scheme 3. Initially, in the presence of Tf_2NH, ynamide **1a** proceeds through a protonation step to form keteniminium ion intermediate **A**. Then, **A** is attacked by the nitrogen atom of dioxazole **2a** to afford the intermediate **B**. A subsequent ring fragmentation of **B** occurs, leading to the formation of benzylic carbocation **C** with the elimination of acetone. The nucleophilic attack of the carbonyl oxygen atom onto the carbocation produces intermediate **D**. Finally, deprotonation of **D** delivers the desired product **3aa** and regenerates the acid catalyst.

Scheme 3. Proposed Mechanism



In summary, we describe herein an unprecedented Tf_2NH-catalyzed formal [3 + 2] cycloaddition of ynamides with dioxazoles for the construction of various polysubstituted 4-aminooxazoles. This approach features a metal-free catalytic bimolecular assembly of oxazole motifs, a low-cost catalyst, exceptionally mild reaction conditions, a very short reaction time, a broad substrate scope, and high efficiency. We believe that this work will pave a new way for the exploration of acid-catalyzed cycloadditions of ynamides with other unsaturated precursors.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all manipulations and reactions were conducted under an inert atmosphere using standard Schlenk techniques or in an argon-filled glovebox. All chemicals were purchased from commercial sources and were used without further purification. Solvents were treated prior to use according to the standard methods. Column chromatography was carried out on silica gel (300−400 mesh) using a forced flow of eluent at 0.3−0.5 bar pressure. NMR spectra were recorded at room temperature in $CDCl_3$ on 400 MHz spectrometers. The chemical shifts for ^1H NMR were recorded in ppm downfield from tetramethylsilane (TMS) with $CDCl_3$ (7.26 ppm) as the internal standard. The chemical shifts for ^{13}C NMR were recorded in ppm downfield using the central peak of $CDCl_3$ (77.16 ppm) as the internal standard. Coupling constants (*J*) are reported in hertz and refer to apparent peak multiplications. The abbreviations *s*, *d*, *t*, *q*, and *m* stand for singlet, doublet, triplet, quartet, and multiplet in that order. HRMS data were obtained with a Micromass HPLC-Q-TOF mass spectrometer (ESI).

General Procedure for the Synthesis of Ynamides. *N*-Alkyl substituted ynamides **1a**−**1t**, **1v**, and **1w** were synthesized by copper-catalyzed cross-couplings of amides with the corresponding alkynyl bromides.[7,13] *N*-Phenyl substituted ynamide **1u** was synthesized by iron-catalyzed cross-coupling of phenylbenzenesulfonamide with (bromoethynyl)benzene.[7]

General Procedure 1 (GP 1). In a 50 mL flame-dried Schlenk tube, *N*-alkyl substituted amides (5.0 mmol), $CuSO_4·5H_2O$ (10 mol %, 125.0 mg), 1,10-phenanthroline (20 mol %, 180.0 mg), K_2CO_3 (2.0 equiv, 1.38 g), and toluene (20 mL) were added in sequence under an argon atmosphere. Then alkynyl bromides (6.0 mmol) were introduced, and the resulting mixture was stirred at 80 °C for 12 h. Afterward, the crude mixture was filtered through a short pad of Celite and washed with ethyl acetate. Removal of the solvent and purification by silica gel column chromatography yielded the *N*-alkyl substituted ynamides (eluent: petroleum ether/ethyl acetate 10/1).

General Procedure 2 (GP 2). In a 50 mL flame-dried Schlenk tube, 4-methyl-*N*-phenylbenzenesulfonamide (5.0 mmol, 1.24 g), $FeCl_3·6H_2O$ (10 mol %, 135.2 mg), K_2CO_3 (2.0 equiv, 1.38 g), and toluene (20 mL) were added in sequence under an argon atmosphere. Then *N*,*N*′-dimethyl-1,2-ethanediamine (DMEDA, 20 mol %, 108 μL) and (bromoethynyl)benzene (6.0 mmol, 1.09 g) were introduced. The resulting mixture was stirred at 90 °C for 12 h. Afterward, the crude mixture was filtered through a short pad of Celite and washed with ethyl acetate. Removal of the solvent and purification by silica gel column chromatography yielded the *N*-phenyl ynamide **1u** (eluent: petroleum ether/ethyl acetate 10/1).

*N-Benzyl-4-methyl-N-(phenylethynyl)benzenesulfonamide (**1a**).* Known compound;[13] 7.8 g (in 25 mmol scale); 96% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.2 Hz, 2H), 7.36−7.28 (m, 7H), 7.26−7.19 (m, 5H), 4.58 (s, 2H), 2.44 (s, 3H).

*N-Benzyl-4-methyl-N-(o-tolylethynyl)benzenesulfonamide (**1b**).* Known compound;[8a] 790.0 mg (in 3.0 mmol scale); 70% yield; ^1H

DOI: 10.1021/acs.joc.7b00076
J. Org. Chem. XXXX, XXX, XXX−XXX

NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.1 Hz, 2H), 7.38−7.26 (m, 7H), 7.18 (d, J = 7.5 Hz, 1H), 7.14−7.02 (m, 3H), 4.59 (s, 2H), 2.42 (s, 3H), 2.16 (s, 3H).

*N-Benzyl-N-((2-methoxyphenyl)ethynyl)-4-methylbenzenesulfonamide (**1c**).* Known compound;[13] 843.5 mg (in 3.0 mmol scale); 72% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.0 Hz, 2H), 7.40−7.34 (m, 2H), 7.33−7.24 (m, 5H), 7.23−7.16 (m, 2H), 6.88−6.73 (m, 2H), 4.59 (s, 2H), 3.81 (s, 3H), 2.42 (s, 3H).

*N-Benzyl-N-((2-fluorophenyl)ethynyl)-4-methylbenzenesulfonamide (**1d**).* White solid; 1.12 g (in 3.4 mmol scale); 87% yield; mp 72−73 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.2 Hz, 2H), 7.37−7.27 (m, 7H), 7.26−7.17 (m, 2H), 7.05−6.96 (m, 2H), 4.59 (s, 2H), 2.43 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.4 (d, J = 250.6 Hz), 144.8, 134.7, 134.4, 133.0 (d, J = 1.4 Hz), 129.8, 1129.3 (d, J = 7.8 Hz), 129.1, 128.6, 128.5, 127.9, 123.9 (d, J = 3.7 Hz), 115.4 (d, J = 20.7 Hz), 111.6 (d, J = 15.7 Hz), 87.5, 65.3, 55.9, 21.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ −110.27. HRMS (ESI) calcd for $C_{22}H_{19}FNO_2S$ $[M + H]^+$ 380.1115, found 380.1121.

*N-Benzyl-N-((2-bromophenyl)ethynyl)-4-methylbenzenesulfonamide (**1e**).* Known compound;[18] 0.9 g (in 2.5 mmol scale); 82% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.1 Hz, 2H), 7.49 (d, J = 7.8 Hz, 1H), 7.40−7.34 (m, 2H), 7.34−7.27 (m, 5H), 7.24−7.14 (m, 2H), 7.10−7.03 (m, 1H), 4.62 (s, 2H), 2.43 (s, 3H).

*N-Benzyl-N-((3-fluorophenyl)ethynyl)-4-methylbenzenesulfonamide (**1f**).* Yellow solid; 0.98 g (in 3.0 mmol scale); 86% yield; mp 69−70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.3 Hz, 2H), 7.37−7.29 (m, 7H), 7.23−7.16 (m, 1H), 7.01−6.86 (m, 3H), 4.58 (s, 2H), 2.45 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.4 (d, J = 246.2 Hz), 145.0, 134.7, 134.3, 129.93, 129.9 (d, J = 9.2 Hz), 129.0, 128.7 128.6, 127.8, 126.9 (d, J = 3.1 Hz), 124.8 (d, J = 9.6 Hz), 117.8 (d, J = 22.8 Hz), 115.0 (d, J = 21.2 Hz), 83.7, 70.7 (d, J = 3.5 Hz), 55.7, 21.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.16. HRMS (ESI) calcd for $C_{22}H_{19}FNO_2S$ $[M + H]^+$ 380.1115, found 380.1119.

*N-Benzyl-4-methyl-N-(p-tolylethynyl)benzenesulfonamide (**1g**).* Known compound;[16] 680 mg (in 2.5 mmol scale); 73% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.1 Hz, 2H), 7.39−7.25 (m, 7H), 7.13 (d, J = 7.9 Hz, 2H), 7.04 (d, J = 7.9 Hz, 2H), 4.56 (s, 2H), 2.43 (s, 3H), 2.30 (s, 3H).

*N-Benzyl-N-((4-methoxyphenyl)ethynyl)-4-methylbenzenesulfonamide (**1h**).* Known compound;[16] 341.0 mg (in 3.0 mmol scale); 29% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.3 Hz, 2H), 7.36−7.26 (m, 7H), 7.19 (d, J = 8.8 Hz, 2H), 6.77 (d, J = 8.8 Hz, 2H), 4.56 (s, 2H), 3.77 (s, 3H), 2.44 (s, 3H).

*N-Benzyl-N-((4-fluorophenyl)ethynyl)-4-methylbenzenesulfonamide (**1i**).* Known compound;[18] 510.0 mg (in 2.5 mmol scale); 54% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.2 Hz, 2H), 7.37−7.27 (m, 7H), 7.19 (dd, J = 8.5, 5.4 Hz, 2H), 6.92 (t, J = 8.6 Hz, 2H), 4.56 (s, 2H), 2.43 (s, 3H).

*N-Benzyl-N-((4-chlorophenyl)ethynyl)-4-methylbenzenesulfonamide (**1j**).* Known compound;[19] 1.38 g (in 4.0 mmol scale); 88% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.3 Hz, 2H), 7.35−7.27 (m, 7H), 7.20 (d, J = 8.5 Hz, 2H), 7.13 (d, J = 8.6 Hz, 2H), 4.57 (s, 2H), 2.43 (s, 3H).

*N-Benzyl-4-methyl-N-(thiophen-2-ylethynyl)benzenesulfonamide (**1k**).* Known compound;[19] 1.47 g (in 5.0 mmol scale); 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.3 Hz, 2H), 7.34−7.28 (m, 7H), 7.22 (d, J = 5.2 Hz, 1H), 7.08 (d, J = 3.6 Hz, 1H), 6.92 (dd, J = 5.2, 3.6 Hz, 1H), 4.58 (s, 2H), 2.45 (s, 3H).

*N-Benzyl-4-methyl-N-((triisopropylsilyl)ethynyl)-benzenesulfonamide (**1l**).* Known compound;[13] 1.0 g (in 5.0 mmol scale); 45% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.3 Hz, 2H), 7.32−7.23 (m, 7H), 4.49 (s, 2H), 2.43 (s, 3H), 0.97−0.91 (m, 21H).

*N-Benzyl-N-(hex-1-ynyl)-4-methylbenzenesulfonamide (**1m**).* Known compound;[18] 5.0 g (in 20 mmol scale); 73% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.3 Hz, 2H), 7.33−7.22 (m, 7H), 4.43 (s, 2H), 2.43 (s, 3H), 2.15 (t, J = 6.9 Hz, 2H), 1.39−1.30 (m, 2H), 1.28−1.17 (m, 2H), 0.82 (t, J = 7.3 Hz, 3H).

*N-Benzyl-N-(cyclohexylethynyl)-4-methylbenzenesulfonamide (**1n**).* Known compound;[20] 1.2 g (in 5.0 mmol scale); 70% yield; ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.79 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.36−7.24 (m, 5H), 4.43 (s, 2H), 2.46−2.30 (m, 4H), 1.63−1.46 (m, 4H), 1.42−1.32 (m, 1H), 1.31−1.17 (m, 5H).

*N-Benzyl-N-(phenylethynyl)methanesulfonamide (**1o**).* Known compound;[7] 785.6 mg (in 4.0 mmol scale); 69% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51−7.46 (m, 2H), 7.43−7.32 (m, 5H), 7.31−7.25 (m, 3H), 4.71 (s, 2H), 2.93 (s, 3H).

*N-Benzyl-N-(phenylethynyl)benzenesulfonamide (**1p**).* Known compound;[13] 500.0 mg (in 5.0 mmol scale); 29% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 7.7 Hz, 2H), 7.63 (t, J = 7.4 Hz, 1H), 7.52 (t, J = 7.7 Hz, 2H), 7.35−7.28 (m, 5H), 7.27−7.20 (m, 5H), 4.61 (s, 2H).

*N-Benzyl-4-nitro-N-(phenylethynyl)benzenesulfonamide (**1q**).* Known compound;[13] 574.0 mg (in 2.5 mmol scale); 58% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 8.6 Hz, 2H), 7.98 (d, J = 8.5 Hz, 2H), 7.39−7.22 (m, 10H), 4.68 (s, 2H).

*N-Benzyl-N-(phenylethynyl)naphthalene-2-sulfonamide (**1r**).* Yellow solid; 570.0 mg (in 2.5 mmol scale); 80% yield; mp 109−110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.97−7.86 (m, 4H), 7.68−7.57 (m, 2H), 7.36−7.30 (m, 2H), 7.28−7.19 (m, 8H), 4.64 (s, 2H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 135.3, 134.6, 134.4, 132.1, 131.3, 129.5, 129.4, 129.0, 128.6, 128.5, 128.3, 128.1, 127.9, 127.78, 122.77, 122.7, 82.7, 71.5, 56.0. HRMS (ESI) calcd for $C_{25}H_{20}NO_2S$ $[M + H]^+$ 398.1209, found 398.1215.

*3-(Phenylethynyl)oxazolidin-2-one (**1s**).* Known compound;[7] 200.0 mg (in 2.5 mmol scale); 43% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.40 (m, 2H), 7.35−7.27 (m, 3H), 4.53−4.43 (m, 2H), 4.04−3.95 (m, 2H).

*N-(4-Bromobenzyl)-4-methyl-N-(phenylethynyl)benzenesulfonamide (**1t**).* Yellow solid; 790.0 mg (in 2.5 mmol scale); 72% yield; mp 65−66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.27−7.16 (m, 6H), 4.52 (s, 2H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 134.7, 133.7, 131.8, 131.3, 130.6, 129.9, 128.4, 128.0, 127.8, 122.7, 122.6, 82.5, 71.6, 55.2, 21.8. HRMS (ESI) calcd for $C_{22}H_{19}BrNO_2S$ $[M + H]^+$ 440.0314, found 440.0313.

*4-Mehyl-N-phenyl-N-(phenylethynyl)benzenesulfonamide (**1u**).* Known compound;[13] 500.0 mg (in 5 mmol scale); 29% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.3 Hz, 2H), 7.43−7.25 (m, 12H), 2.44 (s, 3H).

*N,4-Dimethyl-N-(phenylethynyl)benzenesulfonamide (**1v**).* Known compound;[7] 1.3 g (in 5.0 mmol scale); 91% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.3 Hz, 2H), 7.40−7.33 (m, 4H), 7.31−7.23 (m, 3H), 3.14 (s, 3H), 2.45 (s, 3H).

*N-Allyl-4-methyl-N-(phenylethynyl)benzenesulfonamide (**1w**).* Known compound;[13] 1.2 g (in 5.0 mmol scale); 77% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.3 Hz, 2H), 7.40−7.31 (m, 4H), 7.30−7.24 (m, 3H), 5.86−5.71 (m, 1H), 5.36−5.20 (m, 2H), 4.05 (d, J = 6.4 Hz, 2H), 2.44 (s, 3H).

General Procedure for the Synthesis of Dioxazoles. 5,5-Dimethyl-1,4,2-dioxazoles **2a**−**2j** were prepared by camphorsulfonic acid catalyzed reactions of 2,2-dimethoxypropane and the corresponding hydoxamic acids.[14] 1,4,2-Dioxazol-5-one **2a′** was synthesized by the reaction of benzohydroxamic acid with 1,1′-carbonyldiimidazole (CDI).[14,15]

*General Procedure for **2a**−**2j**.* In a 100 mL flask, $NH_2OH{\cdot}HCl$ (10.0 mmol, 0.70 g), K_2CO_3 (2.0 equiv, 2.76 g), ethyl acetate (40 mL), and H_2O (20 mL) were added in sequence. After cooling to 0 °C, acyl chloride (5.0 mmol) was added dropwise. The resulting mixture was then stirred at room temperature for 16 h. The solution was diluted with water, extracted with ethyl acetate, and dried over anhydrous $MgSO_4$. Upon removal of the solvent, the crude product was used directly for the next step without further purification.

In a 100 mL flask, the crude hydoxamic acid was dissolved in DCM (30 mL). Subsequently, 2,2-dimethoxypropane (15 mmol, 1.8 mL) and camphorsulfonic acid (5.5 mmol, 1.28 g) were added. The resulting solution was stirred at room temperature for 3 h. The reaction was quenched with saturated $NaHCO_3$ solution, extracted with dichloromethane, and dried over anhydrous $MgSO_4$. Removal of the solvent and purification by silica gel column chromatography

DOI: 10.1021/acs.joc.7b00076
J. Org. Chem. XXXX, XXX, XXX−XXX

afforded the dioxazoles **2a**–**2j** (eluent: petroleum ether/ethyl acetate 50/1).

*General Procedure for **2a′***. In a 250 mL flask, *N*-hydroxybenzamide (15 mmol, 2.06 g) and 1,1′-carbonyldiimidazole (CDI, 15 mmol, 2.43 g) were dissolved in DCM (150 mL). The resulting mixture was stirred at room temperature for 2 h. The reaction was quenched with 1 M HCl, extracted with dichloromethane, washed with water, and dried over anhydrous $MgSO_4$. Removal of the solvent and direct crystallization produced **2a′** as a white solid.

*5,5-Dimethyl-3-phenyl-1,4,2-dioxazole (**2a**).* Known compound;[7] 2.5 g (in 20.0 mmol scale); 71% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.76 (m, 2H), 7.48–7.39 (m, 3H), 1.68 (s, 6H).

*3-Phenyl-1,4,2-dioxazol-5-one (**2a′**).* Known compound;[7] 1.7 g (in 15.0 mmol scale); 70% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 7.2 Hz, 2H), 7.66 (t, J = 7.5 Hz, 1H), 7.55 (t, J = 7.7 Hz, 2H).

*3-(2-Methoxyphenyl)-5,5-dimethyl-1,4,2-dioxazole (**2b**).* Pale yellow oil; 200 mg (in 5.0 mmol scale); 20% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.62 (m, 1H), 7.48–7.39 (m, 1H), 7.03–6.96 (m, 2H), 3.94 (s, 3H), 1.67 (s, 6H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.1, 156.8, 132.5, 129.8, 120.3, 113.8, 112.4, 111.5, 55.9, 24.8. HRMS (ESI) calcd for $C_{11}H_{14}NO_3$ $[M + H]^+$ 208.0968, found 208.0969.

*3-(3-Chlorophenyl)-5,5-dimethyl-1,4,2-dioxazole (**2c**).* Pale yellow oil; 430 mg (in 5.0 mmol scale); 41% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.74 (m, 1H), 7.69–7.65 (m, 1H), 7.46–7.41 (m, 1H), 7.35 (t, J = 7.9 Hz, 1H), 1.68 (s, 6H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.3, 134.7, 131.3, 130.0, 126.7, 125.5, 124.8, 116.2, 25.0. HRMS (ESI) calcd for $C_{10}H_{11}ClNO_2$ $[M + H]^+$ 212.0473, found 212.0479.

*3-(3-Fluorophenyl)-5,5-dimethyl-1,4,2-dioxazole (**2d**).* Pale yellow oil; 230 mg (in 5.0 mmol scale); 24% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.54 (m, 1H), 7.50–7.44 (m, 1H), 7.43–7.36 (m, 1H), 7.20–7.13 (m, 1H), 1.69 (s, 6H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.6 (d, J = 246.9 Hz), 157.5 (d, J = 3.3 Hz), 130.5 (d, J = 8.1 Hz), 125.7 (d, J = 8.7 Hz), 122.5 (d, J = 3.3 Hz), 118.3 (d, J = 21.2 Hz), 116.2, 113.8 (d, J = 24.2 Hz), 25.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ −111.83. HRMS (ESI) calcd for $C_{11}H_{11}FNO_2$ $[M + H]^+$ 196.0768, found 196.0771.

*5,5-Dimethyl-3-p-tolyl-1,4,2-dioxazole (**2e**).* Pale yellow oil; 500 mg (in 5.0 mmol scale); 52% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 2.39 (s, 3H), 1.67 (s, 6H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.5, 141.8, 129.4, 126.7, 120.9, 115.4, 25.0, 21.7. HRMS (ESI) calcd for $C_{11}H_{14}NO_2$ $[M + H]^+$ 192.1019, found 192.1023.

*3-(4-Methoxyphenyl)-5,5-dimethyl-1,4,2-dioxazole (**2f**).* Known compound;[7] 350 mg (in 5.0 mmol scale); 34% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H), 1.67 (s, 6H).

*3-(4-Fluorophenyl)-5,5-dimethyl-1,4,2-dioxazole (**2g**).* Known compound;[7] 550 mg (in 5.0 mmol scale); 56% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89–7.60 (m, 2H), 7.21–7.04 (m, 2H), 1.68 (s, 6H).

*5,5-Dimethyl-3-(4-(trifluoromethyl)phenyl)-1,4,2-dioxazole (**2h**).* Known compound;[7] 1.65 g (in 10.0 mmol scale); 67% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.1 Hz, 2H), 7.68 (d, J = 8.1 Hz, 2H), 1.70 (s, 6H).

*3-(Furan-2-yl)-5,5-dimethyl-1,4,2-dioxazole (**2i**).* Known compound;[7] 500 mg (in 5.0 mmol scale); 60% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.49 (m, 1H), 6.90–6.81 (m, 1H), 6.54–6.44 (m, 1H), 1.62 (s, 6H).

*3-Cyclohexyl-5,5-dimethyl-1,4,2-dioxazole (**2j**).* Known compound;[7] 300 mg (in 5.0 mmol scale); 33% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42–2.30 (m, 1H), 1.96–1.86 (m, 2H), 1.82–1.74 (m, 2H), 1.71–1.63 (m, 1H), 1.55 (s, 6H), 1.50–1.39 (m, 2H), 1.33–1.25 (m, 3H).

Representative Procedure for the Tf_2NH-Catalyzed Cycloaddition. In a 10 mL Schlenk flask, **1a** (0.2 mmol, 72.2 mg), **2a** (0.24 mmol, 1.2 equiv, 42.5 mg), and DCE (1.5 mL) were added in sequence. Then a solution of Tf_2NH (5 mol %, 2.8 mg) in DCE (0.5 mL) was added dropwise to the system. The resulting mixture was stirred at room temperature for 5 min. The reaction was quenched by Et_3N solution (10 vol % in pentane) and extracted with DCM (3 × 5 mL). The combined organic phase was washed by water and dried with anhydrous sodium sulfate. Upon removal of the solvent, the crude product was purified by silica gel column chromatography to give the desired product **3aa** (eluent: petroleum ether/ethyl acetate 10/1).

*N-Benzyl-N-(2,5-diphenyloxazol-4-yl)-4-methylbenzenesulfonamide (**3aa**).* White solid; 86.2 mg; 90% yield; mp 131–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99–7.90 (m, 2H), 7.86–7.77 (m, 4H), 7.49–7.41 (m, 3H), 7.39–7.26 (m, 5H), 7.22–7.16 (m, 2H), 7.10–6.99 (m, 3H), 4.62 (s, 2H), 2.48 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.0, 147.8, 144.1, 135.6, 134.9, 132.9, 130.7, 129.6, 129.38, 128.91, 128.85, 128.4, 128.3, 128.0, 127.3, 126.9, 126.4, 125.7, 54.2, 21.8. HRMS (ESI) calcd for $C_{29}H_{25}N_2O_3S$ $[M + H]^+$ 481.1580, found 481.1600.

*N-Benzyl-4-methyl-N-(2-phenyl-5-o-tolyloxazol-4-yl)benzenesulfonamide (**3ba**).* White solid; 81.8 mg; 83% yield; mp 146–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96–7.85 (m, 4H), 7.48–7.39 (m, 4H), 7.35 (d, J = 8.0 Hz, 2H), 7.30–7.22 (m, 1H), 7.17 (t, J = 7.5 Hz, 1H), 7.14–7.06 (m, 2H), 7.06–6.96 (m, 4H), 4.52 (s, 2H), 2.49 (s, 3H), 1.93 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.6, 149.0, 144.0, 137.8, 135.9, 134.9, 133.8, 130.61, 130.56, 130.3, 129.7, 129.5, 129.3, 128.9, 128.2, 127.8, 127.5, 126.2, 125.7, 54.0, 21.8, 20.3. HRMS (ESI) calcd for $C_{30}H_{27}N_2O_3S$ $[M + H]^+$ 495.1737, found 495.1741.

*N-Benzyl-N-(5-(2-methoxyphenyl)-2-phenyloxazol-4-yl)-4-methylbenzenesulfonamide (**3ca**).* White solid; 94.0 mg; 92% yield; mp 176–177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98–7.93 (m, 2H), 7.92–7.86 (m, 2H), 7.48–7.41 (m, 4H), 7.36–7.29 (m, 3H), 7.10–6.98 (m, 5H), 6.97–6.90 (m, 1H), 6.80 (d, J = 8.3 Hz, 1H), 4.53 (s, 2H), 3.63 (s, 3H), 2.47 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.7, 157.5, 146.2, 143.7, 136.4, 135.2, 134.3, 131.1, 131.0, 130.4, 129.5, 129.2, 128.8, 128.0, 127.7, 127.5, 126.4, 120.4, 116.3, 111.0, 55.5, 54.0, 21.8. HRMS (ESI) calcd for $C_{30}H_{27}N_2O_4S$ $[M + H]^+$ 511.1686, found 511.1683.

*N-Benzyl-N-(5-(2-fluorophenyl)-2-phenyloxazol-4-yl)-4-methylbenzenesulfonamide (**3da**).* White solid; 84.8 mg; 85% yield; mp 101–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99–7.92 (m, 2H), 7.85 (d, J = 8.0 Hz, 2H), 7.74–7.66 (m, 1H), 7.49–7.41 (m, 3H), 7.38–7.27 (m, 3H), 7.15–6.96 (m, 7H), 4.58 (s, 2H), 2.48 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.4 (d, J = 253.9 Hz), 159.1, 144.0, 135.8, 134.8, 134.7, 131.0 (d, J = 8.2 Hz), 130.8, 130.09, 130.07, 129.6, 129.4, 128.9, 128.8, 128.2, 127.9, 127.3 126.5, 124.0 (d, J = 3.6 Hz), 116.0 (d, J = 21.3 Hz), 115.2 (d, J = 13.0 Hz), 54.1, 21.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ −111.90. HRMS (ESI) calcd for $C_{29}H_{24}FN_2O_3S$ $[M + H]^+$ 499.1486, found 499.1502.

*N-Benzyl-N-(5-(2-bromophenyl)-2-phenyloxazol-4-yl)-4-methylbenzenesulfonamide (**3ea**).* White solid; 93.5 mg; 84% yield; mp 180–181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00–7.93 (m, 2H), 7.92–7.82 (m, 2H), 7.55–7.49 (m, 2H), 7.49–7.41 (m, 3H), 7.36 (d, J = 7.9 Hz, 2H), 7.33–7.27 (m, 1H), 7.24–7.19 (m, 1H), 7.15–7.10 (m, 1H), 7.09–7.00 (m, 4H), 4.62–4.45 (m, 2H), 2.48 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.1, 146.9, 144.0, 135.9, 134.8, 133.2, 132.5, 130.9, 130.8, 129.6, 129.2, 128.92, 128.85, 128.3, 128.02, 127.97, 127.4, 127.2, 126.5, 123.3, 54.1, 21.8. HRMS (ESI) calcd for $C_{29}H_{24}BrN_2O_3S$ $[M + H]^+$ 559.0686, found 559.0696.

*N-Benzyl-N-(5-(3-fluorophenyl)-2-phenyloxazol-4-yl)-4-methylbenzenesulfonamide (**3fa**).* White solid; 82.7 mg; 83% yield; mp 179–180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98–7.90 (m, 2H), 7.83 (d, J = 8.0 Hz, 2H), 7.89–7.79. (m, 1H), 7.49–7.41 (m, 4H), 7.35 (d, J = 8.0 Hz, 2H), 7.32–7.26 (m, 1H), 7.23–7.16 (m, 2H), 7.12–7.05 (m, 3H), 7.00–6.93 (m, 1H), 4.62 (s, 2H), 2.48 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.7 (d, J = 245.3 Hz), 158.4, 146.6, 144.2, 135.4, 134.7, 133.6, 130.9, 130.1 (d, J = 8.4 Hz), 129.6, 129.4, 129.0, 128.9, 128.8 (d, J = 8.9 Hz), 128.4, 128.1, 127.1, 126.5, 121.4 (d, J = 3.2 Hz), 115.7 (d, J = 21.2 Hz), 112.5 (d, J = 24.2 Hz), 54.2, 21.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ −112.59. HRMS (ESI) calcd for $C_{29}H_{24}FN_2O_3S$ $[M + H]^+$ 499.1486, found 499.1494.

*N-Benzyl-4-methyl-N-(2-phenyl-5-p-tolyloxazol-4-yl)benzenesulfonamide (**3ga**).* White solid; 90.0 mg; 91% yield; mp 197–198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98–7.88 (m, 2H), 7.83 (d, J =

DOI: 10.1021/acs.joc.7b00076
J. Org. Chem. XXXX, XXX, XXX–XXX

8.0 Hz, 2H), 7.70 (d, J = 8.0 Hz, 2H), 7.48−7.40 (m, 3H), 7.34 (d, J = 7.9 Hz, 2H), 7.24−7.17 (m, 2H), 7.14 (d, J = 8.0 Hz, 2H), 7.11−7.04 (m, 3H), 4.63 (s, 2H), 2.47 (s, 3H), 2.35 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.6, 148.0, 144.0, 138.9, 135.6, 135.0, 132.3, 130.5, 129.5, 129.4, 129.2, 128.9, 128.3, 127.9, 127.4, 126.3, 125.65, 124.2, 54.1, 21.8, 21.6. HRMS (ESI) calcd for $C_{30}H_{27}N_2O_3S$ [M + H]$^+$ 495.1737, found 495.1760.

*N-Benzyl-N-(5-(4-methoxyphenyl)-2-phenyloxazol-4-yl)-4-methylbenzenesulfonamide (**3ha**).* White solid; 87.0 mg; 86% yield; mp 181−182 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95−7.89 (m, 2H), 7.84 (dd, J = 8.2, 1.4 Hz, 2H), 7.75 (dd, J = 8.9, 1.7 Hz, 2H), 7.48−7.42 (m, 3H), 7.35 (d, J = 7.9 Hz, 2H), 7.23−7.16 (m, 2H), 7.12−7.03 (m, 3H), 6.91−6.83 (m, 2H), 4.61 (s, 2H), 3.82 (s, 3H), 2.48 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.1, 157.4, 147.9, 144.0, 135.6, 135.0, 131.5, 130.4, 129.5, 129.4, 128.90, 128.87, 128.3, 127.9, 127.5, 127.3, 126.2, 119.8, 113.9, 55.4, 54.1, 21.8. HRMS (ESI) calcd for $C_{30}H_{27}N_2O_4S$ [M + H]$^+$ 511.1686, found 511.1702.

*N-Benzyl-N-(5-(4-fluorophenyl)-2-phenyloxazol-4-yl)-4-methylbenzenesulfonamide (**3ia**).* White solid; 75.0 mg; 76% yield; mp 167−168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97−7.90 (m, 2H), 7.84 (dd, J = 8.3, 1.7 Hz, 2H), 7.81−7.75 (m, 2H), 7.50−7.43 (m, 3H), 7.36 (d, J = 8.0 Hz, 2H), 7.21−7.14 (m, 2H), 7.11−6.98 (m, 5H), 4.61 (s, 2H), 2.48 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.9 (d, J = 249.2 Hz), 158.0, 147.1, 144.2, 135.5, 134.8, 132.5, 130.8, 129.6, 129.4, 128.93, 128.88, 128.3, 128.1, 127.7 (d, J = 8.3 Hz), 127.2, 126.4, 123.2 (d, J = 3.0 Hz), 115.6 (d, J = 22.1 Hz), 54.2, 21.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ −111.56. HRMS (ESI) calcd for $C_{29}H_{24}FN_2O_3S$ [M + H]$^+$ 499.1486, found 499.1492.

*N-Benzyl-N-(5-(4-chlorophenyl)-2-phenyloxazol-4-yl)-4-methylbenzenesulfonamide (**3ja**).* White solid; 93.1 mg; 91% yield; mp 167−168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98−7.89 (m, 2H), 7.82 (d, J = 8.2 Hz, 2H), 7.76−7.70 (m, 2H), 7.49−7.42 (m, 3H), 7.35 (d, J = 8.1 Hz, 2H), 7.32−7.27 (m, 2H), 7.22−7.14 (m, 2H), 7.11−7.04 (m, 3H), 4.61 (s, 2H), 2.47 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.2, 146.8, 144.2, 135.4, 134.8, 134.6, 133.2, 130.8, 129.6, 129.4, 128.93, 128.85, 128.7, 128.4, 128.1, 127.1, 126.9, 126.4, 125.4, 54.1, 21.8. HRMS (ESI) calcd for $C_{29}H_{24}ClN_2O_3S$ [M + H]$^+$ 515.1191, found 515.1199.

*N-Benzyl-4-methyl-N-(2-phenyl-5-(thien-2-yl)oxazol-4-yl)-benzenesulfonamide (**3ka**).* Blue solid; 91.9 mg; 95% yield; mp 138−139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96−7.89 (m, 2H), 7.83 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 3.6 Hz, 1H), 7.49−7.42 (m, 3H), 7.38−7.30 (m, 3H), 7.25−7.19 (m, 2H), 7.14−7.07 (m, 3H), 7.05−7.00 (m, 1H), 4.60 (s, 2H), 2.49 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.6, 144.7, 144.1, 135.5, 134.9, 131.7, 130.7, 129.6, 129.3, 128.9, 128.8, 128.3, 128.0, 127.9, 127.4, 127.1, 126.9, 126.4, 126.4, 54.0, 21.8. HRMS (ESI) calcd for $C_{27}H_{23}N_2O_3S2$ [M + H]$^+$ 487.1145, found 487.1140.

*N-Benzyl-4-methyl-N-(2-phenyloxazol-4-yl)benzenesulfonamide (**3la**).* Oil; 45.3 mg; 50% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94−7.85 (m, 2H), 7.71−7.63 (m, 3H), 7.45−7.36 (m, 5H), 7.31−7.20 (m, 5H), 4.87 (s, 2H), 2.41 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.6, 144.0, 138.7, 136.4, 136.0, 132.6, 130.7, 129.8, 128.9, 128.8, 128.5, 127.8, 127.7, 127.3, 126.4, 52.1, 21.7. HRMS (ESI) calcd for $C_{23}H_{21}N_2O_3S$ [M + H]$^+$ 405.1267, found 405.1275.

*N-Benzyl-N-(5-butyl-2-phenyloxazol-4-yl)-4-methylbenzenesulfonamide (**3ma**).* Yellow oil; 55.0 mg; 60% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90−7.82 (m, 2H), 7.77 (d, J = 8.3 Hz, 2H), 7.44−7.38 (m, 3H), 7.32 (d, J = 8.2 Hz, 2H), 7.29−7.19 (m, 5H), 4.56 (s, 2H), 2.55−2.43 (m, 5H), 1.28−1.21 (m, 2H), 1.17−1.10 (m, 2H), 0.80 (t, J = 7.2 Hz, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.9, 151.8, 143.8, 136.0, 135.9, 132.4, 130.2, 129.6, 129.3, 128.8, 128.5, 128.4, 127.9, 127.7, 126.1, 53.4, 29.5, 24.1, 22.4, 21.8, 13.9. HRMS (ESI) calcd for $C_{27}H_{29}N_2O_3S$ [M + H]$^+$ 461.1893, found 461.1893.

*N-Benzyl-N-(5-cyclohexyl-2-phenyloxazol-4-yl)-4-methylbenzenesulfonamide (**3na**).* Yellow oil; 44.8 mg; 46% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90−7.83 (m, 2H), 7.81 (d, J = 8.3 Hz, 2H), 7.45−7.38 (m, 3H), 7.33 (d, J = 8.0 Hz, 2H), 7.30−7.20 (m, 5H), 4.55 (s, 2H), 2.63−2.51 (m, 1H), 2.46 (s, 3H), 1.70−1.64 (m, 2H), 1.37−1.13 (m, 8H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.8, 155.4, 143.7, 136.2, 135.9, 130.9, 130.3, 129.6, 129.3, 128.8, 128.5, 128.4, 127.9, 127.8, 126.0, 53.5, 34.1, 30.7, 26.1, 25.9, 21.8. HRMS (ESI) calcd for $C_{29}H_{31}N_2O_3S$ [M + H]$^+$ 487.2050, found 487.2074.

*N-Benzyl-N-(2,5-diphenyloxazol-4-yl)methanesulfonamide (**3oa**).* Known compound;[7] 63.2 mg; 78% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09−7.99 (m, 2H), 7.81−7.70 (m, 2H), 7.54−7.43 (m, 3H), 7.35−7.21 (m, 5H), 7.15−7.02 (m, 3H), 4.81 (s, 2H), 3.19 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.5, 147.4, 134.7, 132.8, 130.9, 129.5, 129.00, 128.97, 128.5, 128.4, 128.2, 127.1, 126.6, 126.4, 125.7, 55.0, 38.6.

*N-Benzyl-N-(2,5-diphenyloxazol-4-yl)benzenesulfonamide (**3pa**).* White solid; 82.9 mg; 89% yield; mp 145−146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05−7.96 (m, 4H), 7.84−7.77 (m, 2H), 7.67 (t, J = 7.5 Hz, 1H), 7.56 (t, J = 7.8 Hz, 2H), 7.50−7.42 (m, 3H), 7.39−7.27 (m, 3H), 7.23−7.15 (m, 2H), 7.12−7.01 (m, 3H), 4.65 (s, 2H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.0, 147.8, 138.56, 134.8, 133.3, 132.7, 130.7, 129.4, 128.94, 128.88, 128.5, 128.3, 128.0, 127.3, 126.9, 126.4, 125.7, 54.3. HRMS (ESI) calcd for $C_{28}H_{23}N_2O_3S$ [M + H]$^+$ 467.1424, found 467.1432.

*N-Benzyl-N-(2,5-diphenyloxazol-4-yl)-4-nitrobenzenesulfonamide (**3qa**).* Yellow solid; 85.5 mg; 84% yield; mp 162−163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 8.4 Hz, 2H), 8.13 (d, J = 8.5 Hz, 2H), 7.99−7.87 (m, 2H), 7.74 (d, J = 7.3 Hz, 2H), 7.48 (d, J = 5.3 Hz, 3H), 7.39−7.28 (m, 3H), 7.21−7.14 (m, 2H), 7.12−7.02 (m, 3H), 4.67 (s, 2H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.4, 150.5, 148.0, 144.4, 133.9, 132.0, 131.0, 130.1, 129.5, 129.2, 129.1, 128.6, 128.43, 128.37, 126.9, 126.5, 126.3, 125.7, 124.1, 54.8. HRMS (ESI) calcd for $C_{28}H_{22}N_3O_5S$ [M + H]$^+$ 512.1275, found 512.1278.

*N-Benzyl-N-(2,5-diphenyloxazol-4-yl)naphthalene-2-sulfonamide (**3ra**).* White solid; 71.2 mg; 69% yield; mp 160−161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.03−7.92 (m, 4H), 7.93−7.86 (m, 2H), 7.83 (d, J = 7.8 Hz, 2H), 7.68 (t, J = 7.5 Hz, 1H), 7.62 (t, J = 7.4 Hz, 1H), 7.47−7.38 (m, 3H), 7.38−7.25 (m, 3H), 7.22−7.16 (m, 2H), 7.11−6.98 (m, 3H), 4.67 (s, 2H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.0, 147.8, 135.5, 135.3, 134.7, 132.8, 132.3, 130.7, 130.4, 129.6, 129.4, 129.0, 129.0, 128.9, 128.9, 128.5, 128.3, 128.1, 128.0, 127.5, 127.2, 126.9, 126.3, 125.7, 124.2, 54.4. HRMS (ESI) calcd for $C_{32}H_{25}N_2O_3S$ [M + H]$^+$ 517.1580, found 517.1580.

*3-(2,5-Diphenyloxazol-4-yl)oxazolidin-2-one (**3sa**).* Known compound;[7] 30.6 mg; 50% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13−8.04 (m, 2H), 7.74 (d, J = 8.7 Hz, 2H), 7.54−7.44 (m, 5H), 7.37 (t, J = 7.4 Hz, 1H), 4.61 (t, J = 7.9 Hz, 2H), 4.13 (t, J = 7.9 Hz, 2H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.9, 156.4, 143.7, 131.0, 129.0, 128.9, 127.2, 127.0, 126.5, 125.5, 63.1, 46.3.

*N-(4-Bromobenzyl)-N-(2,5-diphenyloxazol-4-yl)-4-methylbenzenesulfonamide (**3ta**).* White solid; 74.7 mg; 67% yield; mp 172−173 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97−7.91 (m, 2H), 7.87−7.78 (m, 4H), 7.49−7.43 (m, 3H), 7.40−7.31 (m, 5H), 7.16 (dd, J = 8.4, 1.9 Hz, 2H), 7.05 (dd, J = 8.4, 2.3 Hz, 2H), 4.56 (s, 2H), 2.49 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.1, 147.8, 144.2, 135.4, 134.0, 132.7, 131.4, 131.0, 130.8, 129.6, 129.1, 129.0, 128.9, 128.6, 127.2, 126.8, 126.4, 125.8, 122.1, 53.6, 21.8. HRMS (ESI) calcd for $C_{29}H_{24}BrN_2O_3S$ [M + H]$^+$ 559.0686, found 559.0695.

*N-(2,5-Diphenyloxazol-4-yl)-4-methyl-N-phenylbenzenesulfonamide (**3ua**).* Known compound;[7] 89.0 mg; 97% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 7.5 Hz, 2H), 8.07−7.99 (m, 2H), 7.71 (d, J = 8.2 Hz, 2H), 7.56−7.43 (m, 7H), 7.37 (t, J = 7.4 Hz, 1H), 7.28−7.18 (m, 5H), 2.45 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.0, 146.6, 144.04, 139.99, 135.5, 134.5, 130.8, 129.3, 129.1, 129.1, 129.0, 127.7, 127.6, 127.4, 127.1, 126.4, 125.6, 21.8.

*N-(2,5-Diphenyloxazol-4-yl)-N,4-dimethylbenzenesulfonamide (**3va**).* White solid; 60.6 mg; 75% yield; mp 182−183 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12−8.02 (m, 2H), 8.01−7.94 (m, 2H), 7.88−7.77 (m, 2H), 7.52−7.43 (m, 5H), 7.40−7.31 (m, 3H), 3.16 (s, 3H), 2.47 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.1, 145.8, 144.1, 135.18, 134.6, 130.8, 129.5, 129.1, 129.0, 128.9, 127.3, 126.4, 125.5, 37.5, 21.8. HRMS (ESI) calcd for $C_{23}H_{21}N_2O_3S$ [M + H]$^+$ 405.1267, found 405.1261.

*N-Allyl-N-(2,5-diphenyloxazol-4-yl)-4-methylbenzenesulfonamide (**3wa**).* White solid; 60.2 mg; 70% yield; mp 120−121 °C; ^{1}H

DOI: 10.1021/acs.joc.7b00076
J. Org. Chem. XXXX, XXX, XXX−XXX

NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 7.2 Hz, 2H), 8.02−7.91 (m, 2H), 7.82 (d, J = 8.2 Hz, 2H), 7.51−7.43 (m, 5H), 7.41−7.30 (m, 3H), 5.83−5.67 (m, 1H), 5.10−4.91 (m, 2H), 4.12 (d, J = 6.7 Hz, 2H), 2.47 (s, 3H). ^{13}C {^1H} NMR (100 MHz, $CDCl_3$) δ 158.0, 147.4, 144.1, 135.5, 133.2, 131.9, 130.7, 129.5, 129.0, 128.9, 128.8, 127.32, 127.25, 126.4, 125.6, 119.9, 53.2, 21.8. HRMS (ESI) calcd for $C_{25}H_{23}N_2O_3S$ $[M + H]^+$ 431.1424, found 431.1420.

*N-Benzyl-N-(2-(2-methoxyphenyl)-5-phenyloxazol-4-yl)-4-methylbenzenesulfonamide (**3ab**).* Oil; 90.9 mg; 89% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J = 8.2, 1.5 Hz, 2H), 7.84−7.76 (m, 3H), 7.42 (t, J = 7.9 Hz, 1H), 7.37−7.29 (m, 4H), 7.29−7.19 (m, 3H), 7.11−7.05 (m, 3H), 7.02 (t, J = 8.2 Hz, 2H), 4.64 (s, 2H), 3.92 (s, 3H), 2.46 (s, 3H). ^{13}C {^1H} NMR (100 MHz, $CDCl_3$) δ 157.8, 156.9, 147.3, 143.9, 135.6, 135.0, 132.3, 132.0, 130.3, 129.5, 129.3, 128.9, 128.6, 128.3, 128.2, 127.9, 127.1, 125.6, 120.7, 116.5, 112.3, 56.1, 54.1, 21.7. HRMS (ESI) calcd for $C_{30}H_{27}N_2O_4S$ $[M + H]^+$ 511.1686, found 511.1690.

*N-Benzyl-N-(2-(3-chlorophenyl)-5-phenyloxazol-4-yl)-4-methylbenzenesulfonamide (**3ac**).* White solid; 78.0 mg; 76% yield; mp 152−153 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.85−7.77 (m, 5H), 7.44−7.29 (m, 7H), 7.21−7.15 (m, 2H), 7.09−7.03 (m, 3H), 4.62 (s, 2H), 2.49 (s, 3H). ^{13}C {^1H} NMR (100 MHz, $CDCl_3$) δ 156.6, 148.3, 144.2, 135.4, 135.0, 134.7, 133.0, 130.6, 130.3, 129.6, 129.3, 129.1, 128.87, 128.85, 128.5, 128.3, 128.0, 126.6, 126.4, 125.8, 124.3, 54.2, 21.8. HRMS (ESI) calcd for $C_{29}H_{24}ClN_2O_3S$ $[M + H]^+$ 515.1191, found 515.1191.

*N-Benzyl-N-(2-(3-fluorophenyl)-5-phenyloxazol-4-yl)-4-methylbenzenesulfonamide (**3ad**).* White solid; 67.7 mg; 68% yield; mp 166−167 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86−7.78 (m, 4H), 7.75−7.70 (m, 1H), 7.64−7.59 (m, 1H), 7.46−7.40 (m, 1H), 7.38−7.27 (m, 5H), 7.20−7.13 (m, 3H), 7.10−7.03 (m, 3H), 4.62 (s, 2H), 2.49 (s, 3H). ^{13}C {^1H} NMR (100 MHz, $CDCl_3$) δ 163.0 (d, J = 246.8 Hz), 156.8, 148.2, 144.2, 135.4, 134.8, 133.0, 130.7 (d, J = 8.3 Hz), 129.6, 129.4, 129.2 (d, J = 8.5 Hz), 129.1, 128.9 128.5, 128.3, 128.0, 126.7, 125.8, 122.0 (d, J = 3.0 Hz), 117.7 (d, J = 21.4 Hz), 113.3 (d, J = 24.0 Hz), 54.2, 21.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ −111.93. HRMS (ESI) calcd for $C_{29}H_{24}FN_2O_3S$ $[M + H]^+$ 499.1486, found 499.1495.

*N-Benzyl-4-methyl-N-(5-phenyl-2-p-tolyloxazol-4-yl)benzenesulfonamide (**3ae**).* White solid; 93.6 mg; 95% yield; mp 126−127 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97−7.77 (m, 6H), 7.38−7.24 (m, 7H), 7.24−7.16 (m, 2H), 7.12−7.00 (m, 3H), 4.62 (s, 2H), 2.48 (s, 3H), 2.42 (s, 3H). ^{13}C {^1H} NMR (100 MHz, $CDCl_3$) δ 158.2, 147.4, 144.0, 141.0, 135.6, 134.9, 132.7, 129.62, 129.55, 129.4, 128.9, 128.7, 128.4, 128.3, 128.0, 127.0, 126.3, 125.6, 124.7, 54.1, 21.8, 21.7. HRMS (ESI) calcd for $C_{30}H_{27}N_2O_3S$ $[M + H]^+$ 495.1737, found 495.1739.

*N-Benzyl-N-(2-(4-methoxyphenyl)-5-phenyloxazol-4-yl)-4-methylbenzenesulfonamide (**3af**).* White solid; 96.0 mg; 94% yield; mp 120−121 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89−7.82 (m, 4H), 7.79 (d, J = 7.5 Hz, 2H), 7.34−7.28 (m, 4H), 7.27−7.23 (m, 1H), 7.21−7.17 (m, 2H), 7.07−7.02 (m, 3H), 6.94 (d, J = 8.8 Hz, 2H), 4.62 (s, 2H), 3.82 (s, 3H), 2.45 (s, 3H). ^{13}C {^1H} NMR (100 MHz, $CDCl_3$) δ 161.6, 158.1, 147.1, 144.0, 135.6, 134.9, 132.7, 129.5, 129.3, 128.9, 128.6, 128.3, 128.2, 128.0, 127.9, 127.0, 125.5, 120.0, 114.3, 55.5, 54.1, 21.7. HRMS (ESI) calcd for $C_{30}H_{27}N_2O_4S$ $[M + H]^+$ 511.1686, found 511.1695.

*N-Benzyl-N-(2-(4-fluorophenyl)-5-phenyloxazol-4-yl)-4-methylbenzenesulfonamide (**3ag**).* White solid; 80.9 mg; 81% yield; mp 169−170 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96−7.89 (m, 2H), 7.87−7.74 (m, 4H), 7.38−7.25 (m, 5H), 7.21−7.10 (m, 4H), 7.09−6.99 (m, 3H), 4.61 (s, 2H), 2.48 (s, 3H). ^{13}C {^1H} NMR (100 MHz, $CDCl_3$) δ 164.3 (d, J = 251.5 Hz), 157.2, 147.8, 144.1, 135.5, 134.8, 132.8, 129.6, 129.3, 128.91, 128.88, 128.48 (d, J = 8.6 Hz), 128.45, 128.3, 128.0, 126.8, 125.7, 123.7 (d, J = 3.3 Hz), 116.1 (d, J = 22.2 Hz), 54.1, 21.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ −108.85. HRMS (ESI) calcd for $C_{29}H_{24}FN_2O_3S$ $[M + H]^+$ 499.1486, found 499.1493.

*N-Benzyl-4-methyl-N-(5-phenyl-2-(4-(trifluoromethyl)phenyl)-oxazol-4-yl)benzenesulfonamide (**3ah**).* White solid; 93.1 mg; 85% yield; mp 112−113 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.1 Hz, 2H), 7.82 (d, J = 7.0 Hz, 4H), 7.71 (d, J = 8.2 Hz, 2H), 7.41−7.27 (m, 5H), 7.21−7.14 (m, 2H), 7.11−7.01 (m, 3H), 4.63 (s, 2H), 2.48 (s, 3H). ^{13}C {^1H} NMR (100 MHz, $CDCl_3$) δ 156.5, 148.7, 144.3, 135.4, 134.7, 133.2, 132.2 (q, J = 32.5 Hz), 130.4, 129.6, 129.3, 129.3, 128.9, 128.5, 128.3, 128.1, 126.5, 126.0 (q, J = 3.9 Hz), 125.9, 123.9 (d, J = 272.5 Hz), 54.2, 21.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.84. HRMS (ESI) calcd for $C_{30}H_{24}F_3N_2O_3S$ $[M + H]^+$ 549.1454, found 549.1460.

*N-Benzyl-N-(2-(fur-2-yl)-5-phenyloxazol-4-yl)-4-methylbenzenesulfonamide (**3ai**).* White solid; 85.2 mg; 91% yield; mp 140−141 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85−7.74 (m, 4H), 7.58−7.52 (m, 1H), 7.38−7.27 (m, 5H), 7.23−7.17 (m, 2H), 7.12−7.04 (m, 3H), 7.01−6.94 (m, 1H), 6.58−6.50 (m, 1H), 4.62 (s, 2H), 2.46 (s, 3H). ^{13}C {^1H} NMR (100 MHz, $CDCl_3$) δ 150.9, 147.3, 144.7, 144.3, 142.6, 135.3, 134.8, 132.5, 129.7, 129.3, 129.0, 128.8, 128.4, 128.3, 128.0, 126.5, 125.7, 112.1, 53.9, 21.8. HRMS (ESI) calcd for $C_{27}H_{23}N_2O_4S$ $[M + H]^+$ 471.1373, found 471.1385.

*N-Benzyl-N-(2-cyclohexyl-5-phenyloxazol-4-yl)-4-methylbenzenesulfonamide (**3aj**).* White solid; 47.8 mg; 50% yield; mp 127−128 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.3 Hz, 2H), 7.72 (d, J = 7.1 Hz, 2H), 7.35−7.25 (m, 4H), 7.28−7.20 (m, 1H), 7.20−7.13 (m, 2H), 7.11−7.03 (m, 3H), 4.56 (s, 2H), 2.81−2.64 (m, 1H), 2.44 (s, 3H), 2.00−1.90 (m, 2H), 1.83−1.73 (m, 2H), 1.72−1.63 (m, 1H), 1.61−1.48 (m, 2H), 1.45−1.21 (m, 3H). ^{13}C {^1H} NMR (100 MHz, $CDCl_3$) δ 164.7, 146.7, 144.0, 135.4, 135.0, 131.0, 129.5, 129.3, 128.7, 128.4, 128.3, 128.2, 127.9, 127.2, 125.4, 53.9, 37.5, 30.5, 25.8, 25.4, 21.7. HRMS (ESI) calcd for $C_{29}H_{31}N_2O_3S$ $[M + H]^+$ 487.2050, found 487.2054.

Gram-Scale Experiment. *Acid Catalysis.* In a 50 mL Schlenk flask, **1a** (2.7 mmol, 0.98 g), **2a** (3.2 mmol, 1.2 equiv, 0.57 g), and DCE (30 mL) were added in sequence. Then Tf_2NH (5 mol %, 38 mg) or TfOH (5 mol %, 12 μL) was introduced. The resulting mixture was stirred at room temperature for 5 min (Tf_2NH as catalyst) or 20 min (TfOH as catalyst). The reaction was quenched by Et_3N solution (10 vol % in pentane) and extracted with DCM (3 × 20 mL). The combined organic phase was washed by water (3 × 20 mL) and dried with anhydrous sodium sulfate. Removal of the solvent and direct crystallization in DCM/petroleum ether afforded the desired product **3aa** (1.09 g, 84%, Tf_2NH as catalyst or 1.05 g, 81%, TfOH as catalyst).

Gold Catalysis. In a 50 mL Schlenk flask, **1a** (2.7 mmol, 0.98 g), **2a** (3.2 mmol, 1.2 equiv, 0.57 g), and DCE (30 mL) were added in sequence. Then $IPrAuNTf_2$ (5 mol %, 116.9 mg) was introduced. The resulting mixture was stirred at room temperature for 6 h. Removal of the solvent and purification by silica gel column chromatography (eluent: petroleum ether/ethyl acetate 10/1) afforded the desired product **3aa** in 81% yield (1.06 g).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00076.

Structures of ynamides, structures of dioxazoles, copies of NMR spectroscopy (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: xcli@dicp.ac.cn (X.L.).
*E-mail: bswan@dicp.ac.cn (B.W.).

ORCID

Boshun Wan: 0000-0002-7001-6214

Author Contributions

§Y.Z. and Y.H. contributed equally.

Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.joc.7b00076
J. Org. Chem. XXXX, XXX, XXX−XXX

■ ACKNOWLEDGMENTS

Financial support from the National Natural Science Foundation of China (No. 21572225) is gratefully acknowledged.

■ REFERENCES

(1) (a) Wipf, P. *Chem. Rev.* **1995**, *95*, 2115. (b) Yeh, V. S. C. *Tetrahedron* **2004**, *60*, 11995. (c) Jin, Z. *Nat. Prod. Rep.* **2006**, *23*, 464. (d) Heng, S.; Gryncel, K. R.; Kantrowitz, E. R. *Bioorg. Med. Chem.* **2009**, *17*, 3916. (e) Jin, Z. *Nat. Prod. Rep.* **2009**, *26*, 382.

(2) For some reviews: (a) Hu, Y.; Xin, X.; Wan, B. *Tetrahedron Lett.* **2015**, *56*, 32. (b) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev.* **2013**, *113*, 3084. (c) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180.

(3) For some leading examples: (a) He, W.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* **2011**, *133*, 8482. (b) Cano, I.; Alvarez, E.; Nicasio, M. C.; Perez, P. J. *J. Am. Chem. Soc.* **2011**, *133*, 191. (c) Luo, Y.; Ji, K.; Li, Y.; Zhang, L. *J. Am. Chem. Soc.* **2012**, *134*, 17412. (d) Davies, P. W.; Cremonesi, A.; Dumitrescu, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8931. (e) Zhong, C. L.; Tang, B. Y.; Yin, P.; Chen, Y.; He, L. *J. Org. Chem.* **2012**, *77*, 4271. (f) Gillie, A. D.; Reddy, R. J.; Davies, P. W. *Adv. Synth. Catal.* **2016**, *358*, 226.

(4) (a) Garrett, C. E.; Prasad, K. *Adv. Synth. Catal.* **2004**, *346*, 889. (b) Liu, J.; Zheng, H.-X.; Yao, C.-Z.; Sun, B.-F.; Kang, Y.-B. *J. Am. Chem. Soc.* **2016**, *138*, 3294.

(5) For some leading reviews: (a) Wang, X.-N.; Yeom, H.-S.; Fang, L.-C.; He, S.; Ma, Z.-X.; Kedrowski, B. L.; Hsung, R. P. *Acc. Chem. Res.* **2014**, *47*, 560. (b) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064. (c) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840.

(6) For some recent examples: (a) Dateer, R. B.; Shaibu, B. S.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2012**, *51*, 113. (b) Karad, S. N.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2014**, *53*, 9072. (c) Pawar, S. K.; Sahani, R. L.; Liu, R.-S. *Chem. - Eur. J.* **2015**, *21*, 10843. (d) Wu, Y.; Zhu, L.; Yu, Y.; Luo, X.; Huang, X. *J. Org. Chem.* **2015**, *80*, 11407. (e) Zhu, L.; Yu, Y.; Mao, Z.; Huang, X. *Org. Lett.* **2015**, *17*, 30. (f) Shu, C.; Wang, Y.-H.; Zhou, B.; Li, X.-L.; Ping, Y.-F.; Lu, X.; Ye, L.-W. *J. Am. Chem. Soc.* **2015**, *137*, 9567. (g) Zhou, A.-H.; He, Q.; Shu, C.; Yu, Y.-F.; Liu, S.; Zhao, T.; Zhang, W.; Lu, X.; Ye, L.-W. *Chem. Sci.* **2015**, *6*, 1265. (h) Jin, H.; Huang, L.; Xie, J.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2016**, *55*, 794. (i) Jin, H.; Tian, B.; Song, X.; Xie, J.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2016**, *55*, 12688. (j) Chen, Y.-L.; Sharma, P.; Liu, R.-S. *Chem. Commun.* **2016**, *52*, 3187.

(7) Chen, M.; Sun, N.; Chen, H.; Liu, Y. *Chem. Commun.* **2016**, *52*, 6324.

(8) (a) Theunissen, C.; Metayer, B.; Henry, N.; Compain, G.; Marrot, J.; Martin-Mingot, A.; Thibaudeau, S.; Evano, G. *J. Am. Chem. Soc.* **2014**, *136*, 12528. (b) Lecomte, M.; Evano, G. *Angew. Chem., Int. Ed.* **2016**, *55*, 4547. (c) Tona, V.; Ruider, S. A.; Berger, M.; Shaaban, S.; Padmanaban, M.; Xie, L.-G.; Gonzalez, L.; Maulide, N. *Chem. Sci.* **2016**, *7*, 6032.

(9) (a) Wang, Y.; Song, L.-J.; Zhang, X.; Sun, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 9704. (b) Zhang, J.; Zhang, Q.; Xia, B.; Wu, J.; Wang, X.-N.; Chang, J. *Org. Lett.* **2016**, *18*, 3390. (c) Xie, L.-G.; Shaaban, S.; Chen, X.; Maulide, N. *Angew. Chem., Int. Ed.* **2016**, *55*, 12864. (d) Xie, L.-G.; Niyomchon, S.; Mota, A. J.; González, L.; Maulide, N. *Nat. Commun.* **2016**, *7*, 10914. (e) Chen, P.; Song, C.-X.; Wang, W.-S.; Yu, X.-L.; Tang, Y. *RSC Adv.* **2016**, *6*, 80055.

(10) (a) Hu, Y.; Yi, R.; Wu; Wan, B. *J. Org. Chem.* **2013**, *78*, 7714. (b) Yu, X.; Xin, X.; Wan, B.; Li, X. *J. Org. Chem.* **2013**, *78*, 4895. (c) Hu, Y.; Yi, R.; Wang, C.; Xin, X.; Wu, F.; Wan, B. *J. Org. Chem.* **2014**, *79*, 3052.

(11) The prices of IPrAuNTf$_2$, Tf$_2$NH, and TfOH in Sigma-Aldrich are \$320/mmol, \$7.3/mmol, and \$0.23/mmol, respectively.

(12) In principle, a much cheaper TfOH is preferred to be used as a catalyst to examine the substrate scope in view of its comparable reactivity. However, we would like to note that TfOH is partially soluble in DCE, making it troublesome to weigh the catalyst (0.9 μL) in a 0.2 mmol scale reaction. Thus the catalytic reactivity of TfOH was further demonstrated in a gram-scale reaction.

(13) Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151.

(14) Park, Y.; Park, K. T.; Kim, J. G.; Chang, S. *J. Am. Chem. Soc.* **2015**, *137*, 4534.

(15) Bizet, V.; Buglioni, L.; Bolm, C. *Angew. Chem., Int. Ed.* **2014**, *53*, 5639.

(16) Harkat, H.; Borghese, S.; De Nigris, M.; Kiselev, S.; Beneteau, V.; Pale, P. *Adv. Synth. Catal.* **2014**, *356*, 3842.

(17) Wezeman, T.; Zhong, S.; Nieger, M.; Brase, S. *Angew. Chem., Int. Ed.* **2016**, *55*, 3823.

(18) Yang, Y.; Zhang, X. Y.; Liang, Y. *Tetrahedron Lett.* **2012**, *53*, 6557.

(19) Jouvin, K.; Coste, A.; Bayle, A.; Legrand, F.; Karthikeyan, G.; Tadiparthi, K.; Evano, G. *Organometallics* **2012**, *31*, 7933.

(20) Schotes, C.; Mezzetti, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 3072.

DOI: 10.1021/acs.joc.7b00076
J. Org. Chem. XXXX, XXX, XXX−XXX