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Rhodium Catalysis

Rhodium(II)-Catalyzed Annulation of Azavinyl Carbenes Through Ring-Expansion of 1,3,5-Trioxane: Rapid Access to Nine-Membered 1,3,5,7-Trioxazonines

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Abstract: The rhodium(II)-catalyzed denitrogenative coupling of *N*-alkylsulfonyl 1,2,3-triazoles with 1,3,5-trioxane led to nine-membered-ringed trioxazonines in moderate-to-good yields. 1,3,5-Trioxane, acting as an oxygen nucleophile, reacted with the α-aza-vinylcarbene intermediate, giving rise to ylide formation, which was probably the key step in the reaction. Triazoles that contained aryl substituents with various electronic and steric features on the C4 carbon atom were well-tolerated. The synthesis of trioxazonine derivatives was achieved through a one-pot, two-step procedure from 1-mesylazide and a terminal alkyne by combining Cu^{I}-catalyzed 1,3-dipolar cycloaddition and rhodium-catalyzed transformations.

Introduction

1,3,5-Trioxane (**1**) is a safe, stable solid that is used in synthetic organic chemistry essentially as a clean and anhydrous source of formaldehyde (Figure 1).[1] It is surprising that, so far, compound **1** has not been used to build-up or decorate molecules of potential pharmaceutical interest, although related structurally motifs are present in molecules that have long been known to be antidepressant and antimalarial agents, such as paraldehyde and artemisinin.[2]

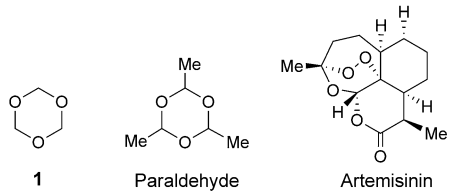

Figure 1. 1,3,5-Trioxane (**1**) and related derivatives of pharmaceutical interest.

The reason for this lack of use of 1,3,5-trioxane may be the lack of synthetic methods that are capable of its efficient use. Only a few examples have been reported in the literature and these examples involve the installation of *s*-trioxane onto sp^3 or sp^2 carbon atoms through radical transformations.[3,4]

The discovery of methods that allow the connection of such readily available building blocks, which are otherwise hardly utilizable, with high chemo-, regio-, and stereoselectivity is of fundamental and practical interest.

Catalytic methods that utilize di-rhodium–carbene species constitute a versatile synthetic tool, in particular for CH-functionalization reactions. In addition, readily generated electrophilic metal–carbenes show high reactivities towards cyclopropanation reactions, X–H (X = O, S, N) bond insertions, 1,2-shifts, dipolar cycloaddition reactions, and ylide formations.[5] Hence, in recent years, the number of applications of these methods has increased parallel to the development of improved synthetic procedures for the preparation of the corresponding diazo-based precursors.[6] For instance, specific donor/acceptor diazo-compounds, such as diazo imines **2′**, have recently drawn considerable attention (Scheme 1).[7] These compounds are formed by ring-chain tautomerization of *N*-sulfonyl 1,2,3-triazoles (**2**), which are easily accessible through the copper(I)-catalyzed 1,3-dipolar cycloaddition of sulfonyl azides to terminal alkynes.[8] In the presence of a di-rhodium tetracarboxylate catalyst, compounds **2′** give rise to the corresponding metal-bound α-imino carbenes (**3**), which react with weak unsaturated or protic nucleophiles.

Clearly, compound **1** is a challenging coupling partner for compound **3**: the lone pairs of electrons on the oxygen atoms impart nucleophilic character onto compound **1**, whilst the same oxygen atoms might also facilitate C–H cleavage through an inductive effect, thus favoring C–H insertion.[9]

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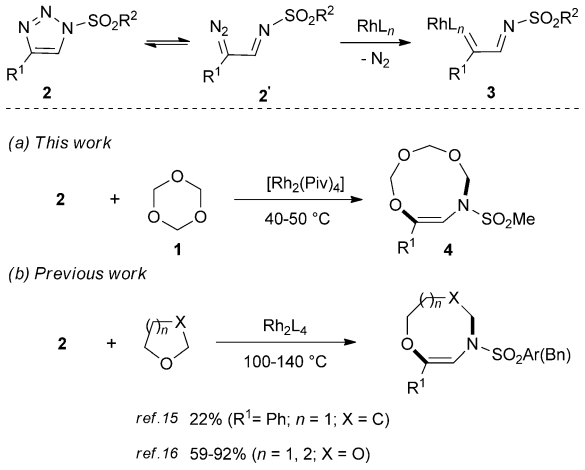


Scheme 1. a) Aim of this work; b) developments by the groups of Fokin and Lacour.

Herein, we report the first application of compound **1** as a coupling partner for the rhodium(II)-catalyzed decomposition of *N*-mesyl 1,2,3-triazoles (**2**), thereby affording 1,3,5,7-trioxazonine derivatives **4**, which are a new class of N,O-heterocycles (Scheme 1 a).

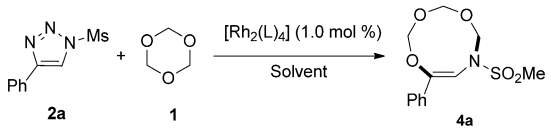
The synthesis of medium-sized ring systems continues to attract significant attention because of the broad abundance of this scaffold in natural and synthetic products, as well as the therapeutic success of these compounds, such as taxol[10] and a number of polycyclic ethers.[11] Clearly, the formation of seven-to-11-membered rings constitutes a significant synthetic challenge, because it is often hampered by adverse entropic or unfavorable transannular interactions.[12] Until now, these compounds have typically been obtained through macrocyclization,[13] fragmentation, ring expansion, and ring-closing metathesis reactions.[14]

The catalytic decomposition of *N*-sulfonyl triazoles in the presence of cyclic ethers was first observed by the groups of Fokin and Gevorgyan (Scheme 1 b).[15] While this work was in progress, Lacour and co-workers reported related reactions with cyclic acetals, such as 1,3-dioxolane and 1,3-dioxane, to give eight- and nine-membered dioxazocines and dioxazonines, respectively (Scheme 1 b).[16]

Results and Discussion

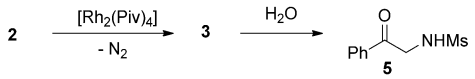
First, we investigated the reaction of compound **1** with compound **2a** (R^1 = Ph, R^2 = Ms) in detail in the presence of a series of di-rhodium catalysts (Table 1, entries 1–6). A preliminary screening found that the most-promising results were obtained by using $[Rh_2(Piv)_4]$ (1 mol%) as a catalyst, which promoted the complete consumption of compound **2a** and the formation of nine-membered N,O-heterocycle **4a** in fair yield (Table 1, entry 3). The use of more-sterically hindered $[Rh_2(Ad)_4]$ and $[Rh_2(esp)_2]$ only afforded the product in slightly lower yields (Table 1, entries 5 and 6, respectively), whilst the presence of $[Rh_2(OAc)_4]$, $[Rh_2(Oct)_4]$, and $[Rh_2(TPA)_4]$ afforded modest conversions (Table 1, entries 1, 2, and 4, respectively).

Table 1. Optimization of the reaction conditions for the model system.[a]



	Rh^{II} catalyst	Solvent[b]	GC yield[c]
1	$[Rh_2(OAc)_4]$	1,2-DCE	10
2	$[Rh_2(Oct)_4]$	1,2-DCE	<5
3	$[Rh_2(Piv)_4]$	1,2-DCE	60
4	$[Rh_2(TPA)_4]$	1,2-DCE	<5
5	$[Rh_2(Ad)_4]$	1,2-DCE	55
6	$[Rh_2(esp)_2]$	1,2-DCE	45
7	$[Rh_2(Piv)_4]$	CH_2Cl_2	10
8	$[Rh_2(Piv)_4]$	$CHCl_3$	72
9	$[Rh_2(Piv)_4]$	*n*-heptane	<5
10	$[Rh_2(Piv)_4]$	cyclohexane	15
11	$[Rh_2(Piv)_4]$	toluene	54

[a] Reaction conditions: compound **2a** (0.5 mmol), compound **1** (2.5 mmol), Rh^{II} catalyst (1 mol%), dry solvent (2.0 mL), 40 °C, 16 h; [**2a**] = 0.5 M. [b] 1,2-DCE = 1,2-dichloroethane; Ms = methanesulfonyl; Ac = acetyl; Oct = octanoate; Piv = pivalate; TPA = triphenylacetate; Ad = 1-adamantanecarboxylate; esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropanoate. [c] Determined through GC analysis of the crude reaction mixture.



Scheme 2. Formation of compound **5**.

A brief solvent screening revealed that halogenated solvents, such as 1,2-DCE and $CHCl_3$, were superior to toluene and other aliphatic solvents that were tested (Table 1, entries 7–11): in $CHCl_3$, the yield of compound **4a** increased to 72% (Table 1, entry 8). Higher reaction temperatures (up to 80 °C) did not improve the selectivity. Notably, the complete exclusion of water was necessary for a selective transformation. Water, as a nucleophile, competes with compound **1** in the reaction with compound **3**, thereby leading to α-aminoketone **5**[17] along with compound **4a** (**5**/**4a** = 25:75, by ^{1}H NMR analysis; Scheme 2).

Electronic and steric variation of the sulfonyl derivatives played a role in determining the reactivity of compound **2**. Under the optimized conditions (Table 1, entry 8), both benzylsulfonyl and isopropylsulfonyl triazoles **2b** and **2c** reacted smoothly with compound **1**, thereby giving the corresponding nine-membered-ringed derivatives (**4b** and **4c**, respectively), the latter in moderate yield, probably owing to the increased steric encumbrance of the resulting di-rhodium–carbene intermediate (**3**; Table 2, entries 2–3). Surprisingly, on switching to 1-tosyltriazole (**2d**), no transformation occurred (Table 2, entry 4). Apparently, the use of 1-alkylsulfonyl-triazoles as carbene precursors was crucial in the reaction with compound **1**. In contrast, 1-arylsulfonyl triazoles have been reported to give the best results with 1,3-dioxolane or 1,2-dioxane in the pres-

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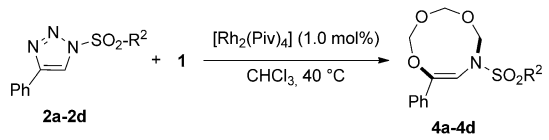
Table 2. Catalytic reactions using different 1-sulfonyl-4-phenyl-1,2,3-triazoles.[a]



2a-2d 4a-4d

	R^2	Conversion [%][b]	Yield [%][c]
1	Me	**2a** (100)	**4a** (72)
2	Bn	**2b** (100)	**4b** (61)
3	*i*Pr	**2c** (100)	**4c** (40)
4	Tol	**2d** (100)	**4d** (–)

[a] Reaction conditions: compound **2a** (0.2 mmol), compound **1** (1.0 mmol), Rh^{II} catalyst (1 mol%), dry $CHCl_3$ (0.4 mL), 40 °C, 16 h; [**2a**] = 0.5 M. [b] Determined through ^1H NMR analysis of the crude reaction mixture. Bn = benzyl, Tol = tolyl. [c] Yield of the isolated product.

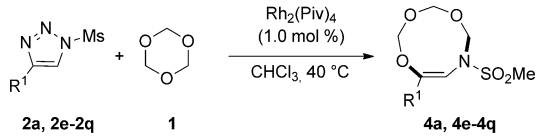
ence of $[Rh_2(OAc)_4]$ as a catalyst in toluene at 100 °C.[15,16] It is important to note that this reaction is orthogonal to the previously reported procedures.

Next, the general scope of the reaction with 1-mesyl triazoles that contained various substituents at the C4 carbon atom was examined. Triazoles that contained mono- and disubstituted 4-aryl substituents with different electronic features were well-tolerated (Table 3). Substrates that contained electron-donating groups, such as Me, *t*Bu, and MeO groups, at the *meta* or *para* positions of the benzene ring afforded the corresponding products (**4e**, **4f**, **4h**, and **4i**) in fair-to-good yields. Triazoles that contained bulkier substituents, such as 2,5-dimethylphenyl or 6-methoxynaphtyl groups, led to the corresponding products (**4g** and **4l**) in moderate yields. Electron-withdrawing halide functional groups, which are commonly used in cross-coupling reactions, were also well-tolerated and substrates that contained C4 aryl groups that contained chloro, bromo, and fluoro groups at the *meta* and/or *para* positions allowed us to obtain the corresponding products (**4m**–**4q**) in fair-to-good yields.

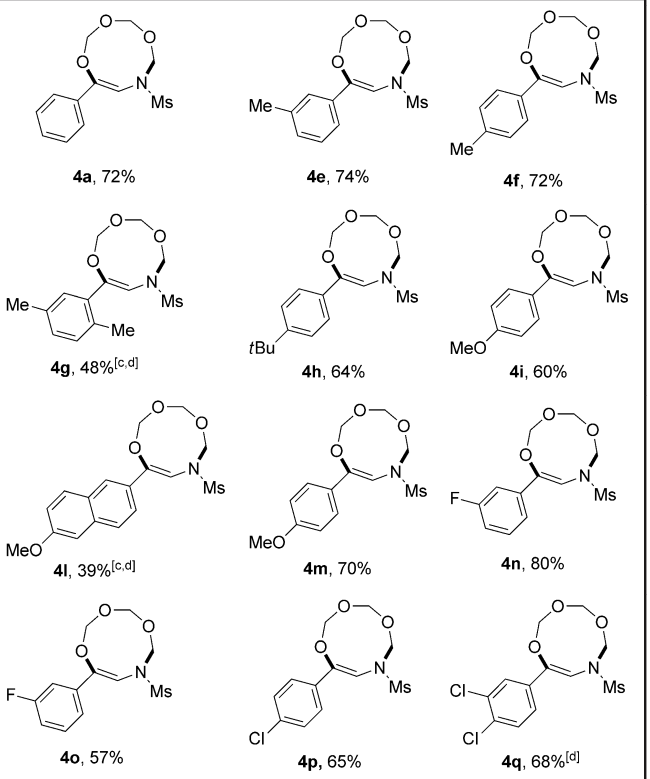
Disappointingly, attempts to extend the scope of the reaction to include 4-heteroaryl- (R^1 = 3-thiophenyl) and 4-alkyl-substituted triazoles (R^1 = hexyl and 1-cyclohexenyl) failed. In each case, the reaction led to a complex mixture that only contained trace amounts of the desired products. ^1H and ^{13}C NMR analysis was consistent with the structures assigned to compounds **4**, as further confirmed by X-ray diffraction studies (Figure 2).

According to the mechanism reported by Lacour and coworkers, the reaction likely proceeds through the formation of [1,2]-dipolar rhodium-associated oxonium ylide **6**, which results from the coupling of O-nucleophile **1** to the transient Rh–carbene species **3** (Scheme 3).[19] Subsequent trioxanyl ring opening occurs through C–O bond cleavage, assisted by one of the unshared electronic pair of the non-bonded oxygen atom. The resulting unsaturated oxo-carbenium ion (**7**)[19] is then trapped by the nitrogen atom of the tethered sulfonylimino group through a 9-*endo-trig* cyclization to form compound **4**.

Table 3. Catalytic reactions using different 1-mesyl-4-aryl-triazoles.[a,b]



2a, 2e-2q 1 4a, 4e-4q



[a] Reaction conditions: compound **2** (0.2 mmol), compound **1** (5 equiv), $[Rh_2(Piv)_4]$ (1 mol%), dry $CHCl_3$ (0.4 mL), 40 °C,16 h; [**2**] = 0.5 M. In all of the examples, complete conversion of compound **2** was observed by ^1H NMR analysis of the crude reaction mixture.is not Lacour [b] Yield of the isolated product. [c] Compound **1** (10 equiv). [d] The reaction was performed at 50 °C.

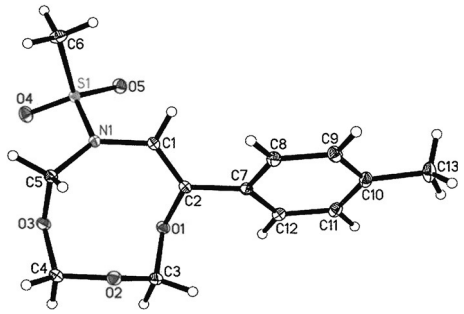


Figure 2. X-ray data and structure of compound **4f**.

In principle, compounds **4** can be synthesized in a one-pot, two-step procedure directly from mesylazide and a terminal alkyne, thereby avoiding the necessary isolation of compound **2** (Scheme 4). For instance, a 0.25 M solution of compound **2a**

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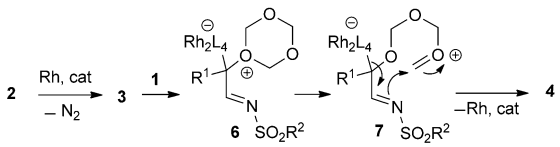
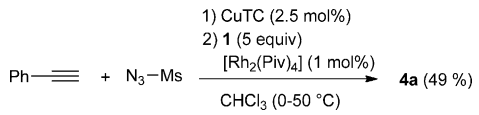


Scheme 3. Proposed mechanism.



Scheme 4. Synthesis of compound **4a** through a one-pot, two-step procedure.

in $CHCl_3$, which was formed from a copper(I)–thiophene-2-carboxylate (CuTC)-catalyzed cycloaddition reaction, was sequentially treated with compound **1** and $[Rh_2(Piv)_4]$. The resulting reaction mixture was heated at 50 °C to give compound **4a** in 49% yield (see the Experimental Section). Apparently, the metal catalysts did not interfere with each other. Temperature control at the stage of triazole synthesis turned out to be necessary to obtaining a reproducible transformation.

Conclusion

In conclusion, readily available 1,3,5-trioxane is an effective coupling partner in the Rh^{II}-catalyzed decomposition of 1-mesyl 1,2,3-triazoles (**2**). Reaction with the corresponding aza-vinylcarbene intermediate (**3**) triggers the ring opening of compound **1**, which then takes part in the construction of a new class of nine-membered heterocycles (**4**) that contain the unusual O–C–O–C–O–C atom sequence, which is otherwise hardly accessible. Interestingly, the use of *N*-alkylsulfonyl 1,2,3-triazoles instead of *N*-arylsulfonyl 1,2,3-triazoles as metal–carbene precursors is decisive for the success of the reaction. A variety of electron-rich and electron-poor substituents at the C4 position of compound **2** are well-tolerated. The combination of copper(I)-catalyzed 1,3-dipolar cycloaddition and rhodium(II)-catalyzed denitrogenative coupling led to compound **4a** in 49% yield through a one-pot, two-step procedure from 1-mesylazide and phenylacetylene, thus confirming the practical and synthetic utility of this new reaction.

Experimental Section

General Information

The reactions that were catalyzed by di-rhodium catalysts were performed under an argon atmosphere. Anhydrous solvents ($CHCl_3$, 1,2-DCE, and toluene) were purchased from Sigma–Aldrich and used without further purification. All of the chemicals were purchased from Acros, TCI, or Sigma–Aldrich and used as received unless otherwise stated. 1,3,5-Trioxane was purified by sublimation and stored under an argon atmosphere. $[Rh_2(Piv)_4]$,[7e] $[Rh_2(Oct)_4]$,[20] and $[Rh_2(Ad)_4]$[20] were synthesized according to reported procedures. Methansulfonylazide, benzylsulfonylazide, and toluensulfonylazide are known compounds and were prepared as described in the literature.[21]

Caution: Azides are potentially hazardous compounds and adequate safety measures should be taken. Melting points (m.p.) were recorded on a Stuart melting point apparatus by using open glass capillaries and are uncorrected. IR spectra were recorded on a BRUKER ALPHA-P spectrometer. Absorption is given in wavenumbers (cm^{-1}). The spectra were recorded within the range 4000–400 cm^{-1} and the following abbreviations are used for characterization: s (strong), m (medium), w (weak). NMR spectra were recorded on Bruker Avance 300 (300 MHz) and 400 (400 MHz) spectrometers. Chemical shifts are reported relative to the solvent peaks: $CDCl_3$, $\delta = 7.26$ ppm (^1H) and 77.00 ppm (^{13}C); CD_2Cl_2, $\delta = 5.36$ ppm (^1H) and 53.9 ppm (^{13}C). All of the measurements were performed at RT. GCMS analysis was performed on an Agilent 5973 chromatography mass-selective detector system. HRMS was performed on MAT 95XP (EI) and Agilent 6210 Time-of-Flight LC/MS (ESI) systems. Crystallographic data were collected on a BRUKER KAPPA APEX II DUO diffractometer. The structures was solved by using direct methods and refined by full-matrix least-squares procedures on *F*2 with the SHELXTL software package.[22] XP (BRUKERAXS) was used for graphical representation. Displacement ellipsoids are set at the 30% probability level.

Synthesis of 4

General procedure: 1,3,5-Trioxane (**1**; 90 mg, 1.0 mmol) was added to a solution of triazole **2** (0.2 mmol) in dry $CHCl_3$ (0.4 mL). The mixture was stirred for 2 min at RT and $[Rh_2(Piv)_4]$ (1.2 mg, 1 mol%) was added. The resulting reaction mixture was stirred for 16 h at 40 °C, before being concentrated under reduced pressure. The crude residue was purified by chromatography through a short pad of neutral aluminum oxide (EtOAc/pentane).

(Z)-7-(Methylsulfonyl)-9-(phenyl)-6,7-dihydro-1,3,5,7-trioxazonine (4a)

Yield 72% (41 mg); m.p. 101–102 °C; ^1H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.47–7.41 (m, 2H), 7.41–7.31 (m, 3H), 6.51 (s, 1H), 5.54 (s, 2H), 5.00 (s, 2H), 4.93 (s, 2H), 3.13 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 142.5 (Cq), 133.4 (Cq), 128.9 (CH), 128.9 (CH), 125.9 (CH), 113.8 (CH), 96.7 (CH_2), 93.9 (CH_2), 77.9 (CH_2), 41.9 ppm (CH_3); IR (ATR, neat): $\tilde{\nu} = 2964$ (w), 2936 (w), 2895 (w), 1343 (s), 1147 (s), 1100 (m), 1056 (s), 929 (s), 773 (s), 697 (m), 509 cm^{-1} (s); MS (GCMS): *m/z* (%): 285 (13) $[M]^+$, 255 (8), 225 (6), 146 (100), 105 (78), 91 (83), 77 (37); HRMS (ESI-TOF): *m/z* calcd for $C_{12}H_{15}NSO_5$: 308.0563 $[M+Na]^+$; found: 308.0566.

(Z)-7-(Benzylsulfonyl)-9-phenyl-6,7-dihydro-1,3,5,7-trioxazonine (4b)

Yield 61% (44 mg); m.p. 101–102 °C; ^1H NMR (300 MHz, CD_2Cl_2): $\delta = 7.60$ (m, 2H), 7.46 (m, 3H), 7.36 (m, 3H), 7.20 (m, 2H), 6.25 (s, 1H), 5.66 (s, 2H), 5.09 (s, 2H), 4.93 (s, 2H), 4.54 ppm (s, 2H); ^{13}C NMR (75 MHz, CD_2Cl_2): $\delta = 138.3$ (Cq), 134.1 (Cq), 131.8 (CH), 129.2 (CH), 129.1 (CH), 128.8 (Cq), 128.6 (CH), 126.0 (CH), 114.4 (CH), 97.6 (CH_2), 94.1 (CH_2), 78.2 (CH_2), 61.0 ppm (CH_2); IR (ATR, neat): $\tilde{\nu} = 3067$ (w), 2989 (w), 2926 (w), 1665 (m), 1446 (m), 1342 (s), 1227 (m), 1139 (s), 1074 (s), 1048 (s), 996 (m), 913 (s), 877 (s), 847 (m), 788 (s), 769 (s), 696 cm^{-1} (s); MS (GCMS): *m/z* (%): 361 (1) $[M]^+$, 146 (33), 105 (27), 91 (100), 77 (25); HRMS (ESI-TOF): *m/z* calcd for $C_{18}H_{19}NO_5S$: 384.08761 $[M+Na]^+$; found: 384.08812.

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(Z)-7-(Isopropylsulfonyl)-9-phenyl-6,7-dihydro-1,3,5,7-trioxazonine (4c)

Yield 40% (25 mg); m.p. 89–90 °C; ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.34–7.19 (m, 5H), 6.50 (s, 1H), 5.51 (s, 2H), 4.92 (s, 2H), 4.81 (s, 2H), 3.34 (sep, J = 9 Hz, 1H), 1.35 ppm (d, J = 9 Hz, 6H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 137.8 (Cq), 134.4 (Cq), 129.1 (CH), 128.5 (CH), 125.9 (CH), 115.0 (CH), 97.3 (CH_2), 94.2 (CH_2), 77.9 (CH_2), 56.4 (CH), 16.6 ppm (CH_3); IR (ATR, neat): $\tilde{\nu}$ = 2983 (w), 2919 (w), 1665 (m), 1444 (m), 1329 (s), 1225 (s), 1145 (s), 1051 (s), 995 (m), 951 (m), 901 (s), 823 (m), 761 (s), 690 (s), 646 cm^{-1} (m); MS (GCMS): *m/z* (%): 313 (3), 146 (65), 105 (52), 91 (100), 77 (52), 43 (49); HRMS (ESI-TOF): *m/z* calcd for $C_{14}H_{19}NO_5S$: 336.08761 $[M+Na]^+$; found: 336.08805.

(Z)-7-(Methylsulfonyl)-9-(m-tolyl)-6,7-dihydro-1,3,5,7-trioxazonine (4e)

Yield 74% (45 mg); m.p. 91–92 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22 (m, 4H), 6.42 (s, 1H), 5.46 (s, 2H), 4.94 (s, 2H), 4.87 (s, 2H), 3.07 (s, 3H), 2.30 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.7 (Cq), 138.5 (Cq), 133.2 (Cq),129.6 (CH), 128.7 (CH), 126. 5 (CH), 123 (CH), 113.5 (CH), 96.6 (CH_2), 93.8 (CH_2), 77.8 (CH_2), 41.7 (CH_3), 21.4 ppm (CH_3); IR (ATR, neat): $\tilde{\nu}$ = 3101 (w), 2983 (w), 2911 (w), 1663 (m), 1476 (w), 1330 (s), 1218 (m), 1198 (m), 1146 (s), 1077 (s), 1053 (s), 906 (s), 827 (s), 792 (s), 770 (s), 722 (w), 708 (w), 685 (s), 646 cm^{-1} (m); MS (GCMS): *m/z* (%): 299 (4) $[M]^+$, 160 (55%), 119 (53%), 105 (100%), 91 (50%), 79 (27%); HRMS (ESI-TOF): *m/z* calcd for $C_{13}H_{17}NO_5S$: 322.07196 $[M+Na]^+$; found: 322.07228.

(Z)-7-(Methylsulfonyl)-9-(p-tolyl)-6,7-dihydro-1,3,5,7-trioxazonine (4f)

Yield 72% (43 mg); m.p. 122–123 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 (d, J = 8.2 Hz, 2H), 7.17 (d, J = 7.8 Hz, 2H), 6.45 (s, 1H), 5.50 (s, 2H), 5.00 (s, 2H), 4.94 (s, 2H), 3.13 (s, 3H), 2.36 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.5 (Cq), 139.1 (Cq), 130.4 (Cq), 129.6 (CH), 126.0 (CH), 113.2 (CH), 96.6 (CH_2), 93.9 (CH_2), 77.8 (CH_2), 41.8 (CH_3), 21.4 ppm (CH_3); IR (ATR, neat): $\tilde{\nu}$ = 2956 (w), 2901 (w), 1332 (m), 1323 (m), 1145 (m), 1145 (s), 1109 (s), 1072 (s), 927 (s), 814 (s), 767 (m), 516 cm^{-1} (s); MS (GCMS): *m/z* (%): 299 (6) $[M]^+$, 269 (3), 160 (71), 119 (59), 105 (100), 91 (38); HRMS (ESI-TOF): *m/z* calcd for $C_{13}H_{17}NO_5S$: 299.0822 $[M]^+$; found: 299.0823.

(Z)-9-(2,5-Dimethylphenyl)-7-(methylsulfonyl)-6,7-dihydro-1,3,5,7-trioxazonine (4g)

Yield 48% (30 mg); m.p. 87–88 °C; ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.06 (br s, 1H), 7.015 (br d, 2H), 6.03 (s, 1H), 5.46 (s, 2H), 4.91 (s, 2H), 4.68 (s, 2H), 3.07 (s, 3H), 2.26 (s, 3H), 2.25 ppm (s, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 143.8 (Cq), 135.7 (Cq), 134.9 (Cq), 132.6 (Cq), 131.6 (CH), 130.9 (CH), 130.3 (CH), 115.5 (CH), 97.2 (CH_2), 93.1 (CH_2), 78.7 (CH_2), 41.7 (CH_3), 20.9 (CH_3), 20.0 ppm (CH_3); IR (ATR, neat): $\tilde{\nu}$ = 2964 (w), 2924 (w), 2902 (w), 1686 (m), 1352 (m), 1325 (s), 1223 (m), 1143 (s), 1077 (s), 1051 (s), 973 (s), 920 (s), 895 (s), 817 (s), 772 cm^{-1} (s); MS (GCMS): *m/z* (%): 313 (4) $[M]^+$, 174 (51), 133 (41), 119 (100), 105 (18); HRMS (ESI-TOF): *m/z* calcd for $C_{14}H_{19}NO_5S$: 336.08761 $[M+Na]^+$; found: 336.08768.

(Z)-9-(4-(tert-Butyl)phenyl)-7-(methylsulfonyl)-6,7-dihydro-1,3,5,7-trioxazonine (4h)

Yield 64% (44 mg); m.p. 112–113 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19 (m, 4H), 6.39 (s, 1H), 5.43 (s, 2H), 4.92 (s, 2H), 4.88 (s, 2H), 3.04 (s, 3H), 1.25 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.2 (Cq), 143.4 (Cq), 130.3 (Cq), 125.8 (CH), 125.7 (CH), 113.21 (CH), 96.5 (CH_2), 93.9 (CH_2), 77.9 (CH_2), 41.7 (CH_3), 34.7 (Cq), 31.3 ppm (CH_3); IR (ATR, neat): $\tilde{\nu}$ = 2956 (s), 1606 (w), 1408 (w), 1327 (s), 1062 (m), 833 (m), 620 (w), 510 (s), 442 cm^{-1} (w); MS (GCMS): *m/z* (%): 341 (5) $[M]^+$, 202 (68), 161 (40), 147 (100), 132 (10), 118 (23), 91 (15); HRMS (ESI-TOF): *m/z* calcd for $C_{16}H_{23}NO_5S$: 364.11891 $[M+Na]^+$; found: 364.11923.

(Z)-7-(Methylsulfonyl)-9-(p-anisyl)-6,7-dihydro-1,3,5,7-trioxazonine (4i)

Yield: 60% (38 mg); ^{1}H NMR (300 MHz,): δ = 7.29 (d, J = 9.0 Hz, 2H), 6.84 (d, J = 9.0 Hz, 2H), 6.28 (s, 1H), 5.38 (s, 2H), 4.92 (d, J = 12.7 Hz, 4H), 3.76 (s, 3H), 3.05 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.4 (Cq), 144.5 (Cq), 127.6 (CH), 125.3 (Cq), 114.2 (CH), 112.5 (Cq), 96.4 (CH_2), 93.7 (CH_2), 78.1 (CH_2), 55.4 (CH_3), 41.7 ppm (CH_3); IR (ATR, neat): $\tilde{\nu}$ = 2962 (w), 2840 (w), 1683 (m), 1599 (s), 1511 (s), 1147 (s), 830 (w), 506 cm^{-1} (m); MS (GCMS): *m/z* (%): 315 (10) $[M]^+$, 252 (19), 250 (13), 235 (11), 207 (21), 177 (19), 176 (100), 175 (69); HRMS (EI): *m/z* calcd for $C_{13}H_{17}NO_6S$: 316.08548 $[M+H]^+$; found: 316.08549.

(Z)-9-(6-Methoxynaphthalen-2-yl)-7-(methylsulfonyl)-6,7-dihydro-1,3,5,7-trioxazonine (4l)

Yield 39% (28.5 mg); m.p. 162–163 °C; ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.75 (br d, 1H), 7.67–7.64 (m, 2H), 7.42 (dd, J = 9.0, 3.0 Hz, 1H), 7.08–7.04 (m, 2H), 6.49 (s, 1H), 5.45 (s, 2H), 4.92 (s, 2H), 4.89 (s, 2H), 3.81 (s, 3H), 3.05 ppm (s, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 158.7 (Cq), 142.8 (Cq), 135.1 (Cq), 130.0 (CH), 129. 127.7 (CH), 125.2 (CH), 124.3 (CH), 119.8 (CH), 113.7 (CH), 106.1 (CH), 97.1 (CH_2), 94.4 (CH_2), 78.3 (CH_2), 55.7 (CH_3), 42.0 ppm (CH_3); IR (ATR, neat): $\tilde{\nu}$ = 3016 (w), 2966 (w), 2926 (w), 1602 (m), 1845 (m), 1342 (s), 1206 (s), 1161 (s), 1150 (s), 1107 (s), 1055 (s), 1023 (s), 969 (s), 905 (s), 821 (s), 767 cm^{-1} (s); MS (GCMS): *m/z* (%): 365 (11) $[M]^+$, 226 (50), 185 (54), 171 (100), 142 (21); HRMS (ESI-TOF): *m/z* calcd for $C_{17}H_{19}NO_6S$: 388.08253 $[M+Na]^+$; found: 388.08282.

(Z)-7-(Methylsulfonyl)-9-(4-bromophenyl)-6,7-dihydro-1,3,5,7-trioxazonine (4m)

Yield 70% (50.5 mg); m.p. 141–142 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49 (d, J = 8.7 Hz, 2H), 7.30 (d, J = 8.7 Hz, 2H), 6.53 (s, 1H), 5.56 (s, 2H), 5.01 (s, 2H), 4.90 (s, 2H), 3.13 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.4 (Cq), 132.6 (Cq), 132.1 (Cq), 127.3 (CH), 122.8 (CH), 114.2 (CH), 96.9 (CH_2), 94.0 (CH_2), 77.8 (CH_2), 42.0 ppm (CH_3); IR (ATR, neat): $\tilde{\nu}$ = 2961 (w), 2895 (w), 1670 (w), 1478 (w), 1341 (s), 1219 (m), 1145 (s), 1049 (s), 998 (s), 969 (s), 904 (s), 832 (s), 812 (s), 512 (s), 475 cm^{-1} (m); MS (GCMS): *m/z* (%): 363 (6) $[M]^+$, 333 (5), 303 (2), 224 (100), 183 (57), 169 (99), 155 (33); HRMS (ESI-TOF): *m/z* calcd for $C_{12}H_{14}BrNO_5S$: 303.0571 $[M]^+$; found: 303.0568.

(Z)-9-(3-Fluorophenyl)-7-(methylsulfonyl)-6,7-dihydro-1,3,5,7-trioxazonine (4n)

Yield: 80% (48.5 mg); m.p. 118–119 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 (td, J = 8.0, 5.8 Hz, 1H), 7.22 (ddd, J = 7.8, 1.7, 1.1 Hz, 1H), 7.15–7.09 (m, 1H), 7.01 (tdd, J = 8.3, 2.6, 1.1 Hz, 1H), 6.59 (s, 1H), 5.59 (d, J = 2.1 Hz, 2H), 5.02 (s, 2H), 4.92 (s, 2H), 3.13 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.2 (d, $^1J_{(C,F)}$ = 246.3 Hz; Cq), 139.8 (d, $^4J_{(C,F)}$ = 2.7 Hz; Cq), 136.2 (d, $^3J_{(C,F)}$ = 7.6 Hz; Cq), 130.5 (d, $^3J_{(C,F)}$ = 8.4 Hz; CH), 121.4 (d, $^4J_{(C,F)}$ = 2.9 Hz; CH), 115.6 (d, $^2J_{(C,F)}$ = 21.4 Hz; CH), 114.7 (CH), 112.6 (d, $^2J_{(C,F)}$ = 23.1 Hz; CH), 97.0 (CH_2), 94.1 (CH_2), 77.8 (CH_2), 42.0 ppm (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$): δ =

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−111.9 ppm; IR (ATR, neat): $\tilde{\nu}$ = 3015 (w), 2925 (w), 1361 (m), 1347 (m), 1146 (s), 1052 (m), 968 (m), 906 8 (s), 795 8 (m), 768 (s); 508 cm^{-1} (s); MS (GCMS): *m/z* (%): 303 (3) $[M]^+$, 273 (4), 164 (89), 123 (53), 109 (100), 95 (42); HRMS (ESI-TOF): *m/z* calcd for $C_{12}H_{14}NFO_5S$: 303.0571 $[M]^+$; found: 303.0568.

(Z)-9-(4-Fluorophenyl)-7-(methylsulfonyl)-6,7-dihydro-1,3,5,7-trioxazonine (4o)

Yield: 57% (34.5 mg); m.p. 113–114 °C; ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.36 (m, 2H), 7.0 (m, 2H), 6.34 (s, 1H), 5.42 (s, 2H), 4.91 (s, 2H), 4.83 (s, 2H), 3.02 ppm (s, 3H); ^{13}C (75 MHz, CD_2Cl_2): δ = 163.4 (d, $^1J_{(C,F)}$ = 246 Hz; Cq), 141.8 (Cq), 130.0 (d, $^4J_{(C,F)}$ = 3.0 Hz; Cq), 128.1 (d, $^3J_{(C,F)}$ = 7.5 Hz; CH), 116.1 (d, $^2J_{(C,F)}$ = 22.5 Hz; CH), 113.9 (CH), 97.1 (CH_2), 94.1 (CH_2), 78.2 (CH_2), 42 ppm (CH_3); ^{19}F NMR (282 MHz, CD_2Cl_2): δ = −113.0 ppm; IR (ATR, neat): $\tilde{\nu}$ = 2903 (w), 1600 (w), 1506 (w), 1327 (s), 1217 (m), 1150 (s), 1063 (s), 1050 (s), 932 (s), 900 (m), 833 (m), 772 (s), 717 cm^{-1} (m); MS (GCMS): *m/z* (%): 303 (5) $[M]^+$, 164 (100), 123 (56), 109 (90), 95 (25); HRMS (ESI-TOF): *m/z* calcd for $C_{12}H_{14}FNO_5S$: 326.04689 $[M+Na]^+$; found: 326. 04717.

(Z)-7-(Methylsulfonyl)-9-(4-chlorophenyl)-6,7-dihydro-1,3,5,7-trioxazonine (4p)

Yield 65% (42 mg); m.p. 110–111 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29 (m, 4H), 6.45 (s, 1H), 5.49 (s, 2H), 4.94 (s, 2H), 4.84 (s, 2H), 3.06 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.5 (Cq), 134.6 (Cq), 132.0 (Cq), 129.0 (CH), 127.0 (CH), 114.1 (CH), 96.8 (CH_2), 93.9 (CH_2), 77.8 (CH_2), 41.9 (CH_3); IR (ATR, neat): $\tilde{\nu}$ = 2975 (w), 2795 (w), 1636 (w), 1488 (m), 1325 (s), 1151 (s), 833 (m), 688 (w), 511 cm^{-1} (m); MS (GCMS): *m/z* (%): 319 (5) $[M]^+$, 180 (82), 139 (61), 125 (100), 111 ppm (36); HRMS (EI): *m/z* calcd for $C_{12}H_{14}NO_5S$: 319.0281 $[M]^+$; found: 319.0274.

(Z)-9-(3,4-Dichlorophenyl)-7-(methylsulfonyl)-6,7-dihydro-1,3,5,7-trioxazonine (4q)

Yield 68% (48 mg); m.p. 130--131 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44 (d, J = 2.4 Hz, 1H), 7.365 (d, J = 8.4 Hz, 1H), 7.21–7.18 (m, 1H), 6.52 (s, 1H), 5.54 (s, 2H), 4.96 (s, 2H), 4.83 (s, 2H), 3.07 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.9 (Cq), 134.0 (Cq), 133.1 (Cq), 132.4 (Cq), 130.8 (CH), 127.3 (CH), 124.7 (CH), 114.9 (CH), 97.0 (CH_2), 94.0 (CH_2), 77.6 (CH_2), 42.0 ppm (CH_3); IR (ATR, neat): $\tilde{\nu}$ = 3088 (w), 2996 (w), 2962 (w), 2889 (w), 1664 (m), 1470 (m), 1328 (s), 1218 (m), 1145 (s), 1050 (s), 1012 (s), 955 (s), 903 (s), 826 (s), 763 (s), 682 cm^{-1} (m); MS (GCMS): *m/z* (%): 353 (5) $[M+H]^+$, 214 (100), 173 (39), 159 (87), 145 (22), 109 (9); HRMS (ESI-TOF, *m/z*) calculated for $C_{12}H_{13}Cl_2NO_5S$: 375.97837 $[M+Na]^+$; found: 375.7777.

Procedure for the One-Pot Synthesis of Compound 4a

Copper(I) thiophene-2-carboxylate (CuTC; 1.1 mg, 0.0057 mmol, 2.5 mol%) was added to a stirring solution of the alkyne (23.5 mg, 0.23 mmol) and methanesulfonyl azide (28 mg, 0.23 mmol) in dry $CHCl_3$ (0.9 mL) at 0 °C under an argon atmosphere. The resulting suspension was stirred at 0 °C for about 3 h and then was allowed to warm to RT and stirred overnight. Compound **1** (104 mg, 1.15 mmol) and $[Rh_2(Piv)_4]$ (1.4 mg, 1 mol%) were added and the reaction mixture was stirred at 50 °C for 9 h, before being concentrated at reduced pressure. The crude residue was purified by column chromatography on neutral aluminum oxide (EtOAc/pentane, 1:3) to give compound **4a** (32 mg).

Synthesis of 2

N-Sulfonyl 1,2,3-triazoles (**2**) were prepared according to the previously reported CuTC-catalyzed azide-alkyne cycloaddition (CuAAC) procedure.[23] Copper(I) thiophene-2-carboxylate (CuTC; 0.019 g, 0.01 mmol, 5 mol%) was added to a stirring solution of the alkyne (2.0 mmol) in toluene (5 mL) at RT. After stirring for 5 min, a solution of the sulfonyl azide (2.0 mmol) in toluene (3 mL) was added dropwise to the resulting suspension. The reaction mixture was concentrated under reduced pressure and filtered through a short plug of silica gel to remove the copper catalyst (EtOAc/pentane, 3:10). Removal of the solvent under vacuum gave a solid residue that was crystallized from EtOAc/pentane to afford the desired product. Data for compounds **2a**,[25] **2b**, [22] **2c**, [23] **2d**, [22] **2f**, [25] **2i**, [23] **2l**, [23] **2m**, [26] **2n**, [27] **2o**, [25] and **2p**[24] have been reported previously.

1-(Methylsulfonyl)-4-(m-tolyl)-1H-1,2,3-triazole (2e)

Yield: 85% (402 mg); m.p. 82–83 °C; ^{1}H NMR (CD_2Cl_2, 400 MHz): δ = 8.37 (s, 1H), 7.76 (br s, 1H), 7.69 (br d, J = 8.0 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.28 (br d, J = 8.0 Hz, 1H), 3.59 (s, 3H), 2.46 ppm (s, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 147.4 (Cq), 139.1 (Cq), 130.0 (CH), 128.9 (CH), 128.6 (CH), 126.6 (CH), 123.1 (CH), 119.3 (CH), 42.8 (CH_3), 21.1 ppm (CH_3); IR (ATR, neat): $\tilde{\nu}$ = 3140, 3013, 2972, 1626, 1590, 1489, 1478, 1385, 1373, 1352, 1231, 1176, 1090, 1041, 1008, 981, 955, 837, 789, 775, 715, 700, 645 cm^{-1}; HRMS (ESI-TOF): *m/z* calcd for $C_{10}H_{11}N_3O_2S$: 238.06447 $[M+H]^+$; found: 238.06458.

4-(2,5-Dimethylphenyl)-1-(methylsulfonyl)-1H-1,2,3-triazole (2g)

Yield: 77% (386 mg); m.p. 88–89 °C; ^{1}H NMR (CD_2Cl_2, 300 MHz): δ = 8.25 (s, 1H), 7.67 (br s, 1H), 7.24 (dd, J = 9.0 Hz, 1H), 7.19 (br d, J = 9.0 Hz, 1H), 3.61 (s, 3H), 2.47 (s, 3H), 2.41 ppm (s, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 147.1 (Cq), 136.3 (Cq), 133.3 (Cq), 131.4(CH), 130.2 (CH), 129.9 (CH), 128.2 (Cq), 121.5 (CH), 43.2 (CH_3), 21.0 ppm (CH_3); IR (ATR, neat): $\tilde{\nu}$ = 3163, 3013, 2929, 2870, 1504, 1379, 1242, 1180, 1149, 1090, 1029, 1004, 991, 975, 956, 900, 861, 834, 809, 764, 684, 638 cm^{-1}; MS (GCMS): *m/z* (%): 173 (100) $[M-SO_2Me]^+$, 158 (29), 144 (47), 130 (72), 115 (75), 102 (35), 77 (51).

1-(Methylsulfonyl)-4-(tert-butylphenyl)-1H-1,2,3-triazole (2h)

Yield: 62% (345 mg); m.p. 119–120 °C; ^{1}H NMR (CD_2Cl_2, 300 MHz): δ = 8.35 (s, 1H), 7.83 (br dt, J = 9.0, 1.5 Hz, 2H), 7.54 (dt, J = 9.0, 1.5 Hz), 3.58 (s, 3H), 1.38 ppm (s, 9H); ^{13}C NMR (CD_2Cl_2, 75 MHz): δ = 152.6 (Cq), 147.3 (Cq), 126.0 (CH), 125.9 (Cq), 125.8 (CH), 119.0 (CH), 42.8 (CH3), 34.7 (Cq), 31.0 ppm (CH_3); IR (ATR, neat): $\tilde{\nu}$ = 3139 (w), 3039 (w), 2963 (m), 1495 (m), 1376 (s), 1321 (m), 1233 (w), 1180 (s), 1119 (m), 997 (s), 947 (s), 840 (m), 815 (m), 768 cm^{-1} (s); HRMS (ESI-TOF): *m/z* calcd for $C_{13}H_{17}N_3O_2S$: 280.11142 $[M+H]^+$; found: 280.11102.

Synthesis of 4-(3,4-Dichlorophenyl)-1-(methylsulfonyl)-1H-1,2,3-triazole (2q)

A solution of 1,2-dichloro-ethynylbenzene (342 mg, 2.0 mmol) in toluene (8 mL), copper(I) thiophene-2-carboxylate (CuTC; 0.019 g, 0.01 mmol, 5 mol%), and methanesulfonyl azide (0.243 g, 2.0 mmol), prepared as described above, was stirred at RT for 15 h. A second addition of the catalyst (0.01 mmol) and methanesulfonyl azide (2.0 mmol) was required to promote complete conversion of the alkyne. The reaction mixture was stirred at RT for an additional

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24 h and worked-up as reported above to give the product. Yield: 73% (423 mg); m.p. 157–158 °C; ^{1}H NMR (CD_2Cl_2, 400 MHz): $\delta =$ 8.41 (s, 1H), 8.06 (d, $J = 2.0$ Hz, 1H), 7.76 (d, $J = 8.0$, 2.0 Hz, 1H), 7.61 (d, $J = 8.0$ Hz, 1H), 3.61 ppm (s, 3H); ^{13}C NMR (CD_2Cl_2, 75 MHz): $\delta =$ 145.6 (Cq), 133.6 (Cq), 133.5 (Cq), 131.5 (CH), 129.3 (Cq), 128.2 (CH), 125.7 (CH), 120.3 (CH), 43.2 ppm (CH_3); IR (ATR, neat): $\tilde{\nu} =$ 3122, 3070, 3011, 2929, 1563, 1478, 1460, 1415, 1400, 1378, 1340, 1326, 1275, 1257, 1235, 1179, 1137, 1103, 1030, 995, 976, 942, 907, 818, 794, 771, 675, 636 cm^{-1}; HRMS (ESI-TOF): *m/z* calcd for $C_9H_7Cl_2N_3O_2S$: 291.97088 $[M+H]^+$; found: 291.97096.

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