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Graphical Abstract

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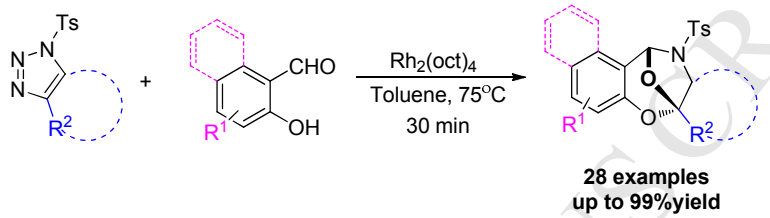

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Synthesis of 2,5-epoxy-1,4-benzoxazepines *via* Rhodium(II)-catalyzed reaction of 1-tosyl-1,2,3-triazoles and salicylaldehydes

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ABSTRACT

The α-imino carbenes generating from 1-tosyl-1,2,3-triazoles have exhibited unique reactivities. A novel and efficient route for the construction of oxa-bridged 2,5-epoxy-1,4-benzoxazepines through a rhodium(II)-catalyzed tandem process of triazoles and salicylaldehydes has been developed. The oxazoles are obtained when 2-methanesulfonamidyl benzaldehyde is used instead of salicylaldehydes.

1. Introduction

Novel synthetic approaches that enable straightforward syntheses of several different heterocyclic cores, especially the nitrogen-containing heterocycles, from a transient intermediate are of great attractiveness. Recently, rapid development has been made in using *N*-sulfonyl-1,2,3-triazoles as precursors for the formation of metal-bound imino carbene intermediates and their transformations to generate nitrogen-containing heterocycles and building blocks.[1] So far, these nitrogen-containing heterocycles have been greatly enriched including pyrroles,[2] indoles,[2h,3] imidazoles,[4] thiazole,[5] azepines,[6] pyrazines[2p,7] and so on.[8] Since the nitrogen-containing heterocycles are of great importance in natural products, potent pharmaceutical drugs and synthons, developing novel methods for the construction of azaheterocycles is still highly demanded.

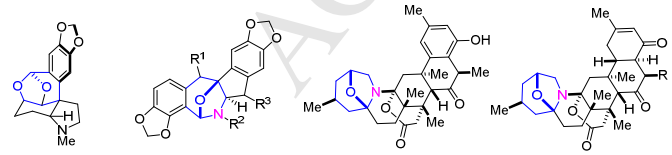

Figure 1. Biologically active natural products

Medium-sized polycyclic ethers containing epoxy-bridged moieties are well-known structural subunits found in a number of biologically important compounds such as brevicomin[9] and frontalin.[10] Among these oxacyclic compounds, biologically active natural products containing a nitrogen atom, such as augastamine,[11] ribasine and its analogues,[12] zoanthamine and its analogues[13] , caused our attention (Figure 1). Generally, 1,3-dipolar cycloaddition of ylides generated from metal-carbenoids with dipolarophiles, such as imines and carbonyl compounds, was used for the construction of these epoxy-bridged bicyclic compounds. However, this method has problems such as low yields and substrates scope limitation.[14]

Fokin and co-workers reported an elegant method to synthesize chiral 4-oxazolines.[4b] Prolonging the reaction time would significantly lower the enantiomeric purity of most products, owing to the lability of the C-O bond (Figure 2a). Then, Murakami and Miura reported an extension of this reaction to α, β-unsaturated aldehydes for diastereoselective synthesis of trans-2,3-disubstituted-2,3-dihydropyrroles (Figure 2b).[2e] With these results and our research interests in natural product-like compounds,[15] we hypothesized that the 4-oxazolines could be a potential 1,3-diploar precursors reacting with various dipolarophiles (Figure 3). Unfortunately, attempts to trap the precursors with electron-rich compounds in an intermolecular manner and electron-deficient compounds in an intramolecular or intermolecular manner were both failed. Surprisingly, 4-oxazolines was observed decomposing in the NMR tube (Figure 3), delivering aldehydes and *a*-amino ketones in quantitative yields credibly through a sequence of ring-opening, hydrolysis process. This finding gained our faith that the zwitterionic

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intermediate was truly formed and could be trapped. Thus, we envisioned that introducing an extra functional group into the aldehyde reagent would be of great possibility to trap the precursor.

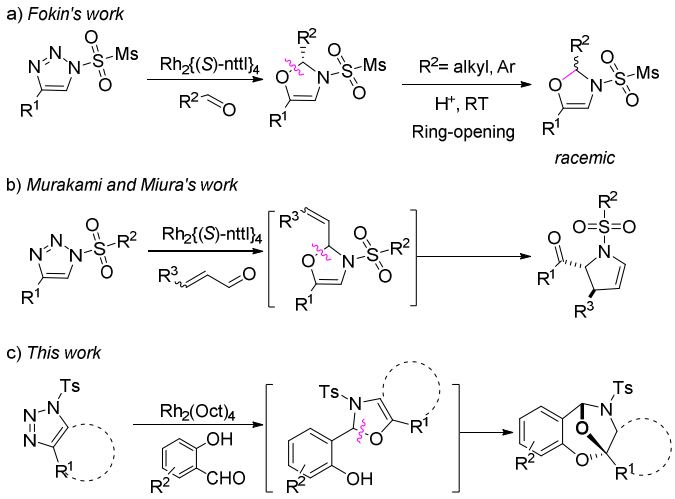


Figure 2. Rh(II)-catalyzed reaction of triazoles with aldehydes

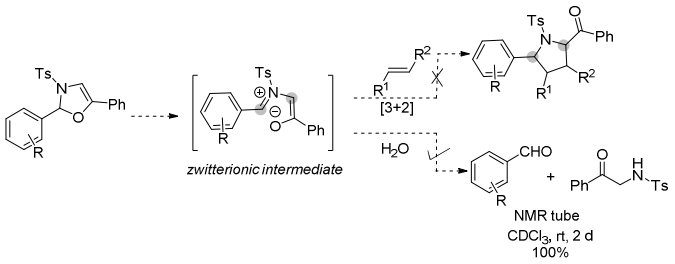


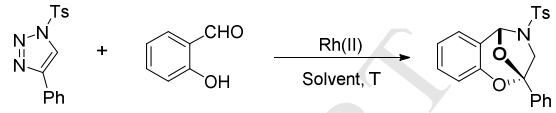
Figure 3. Initial hypothesis and findings.

Salicylaldehydes containing both aldehyde group and hydroxyl group in one molecular are commercially available, and were chosen as the substrates to test our hypothesis. The main challenge is the chemoselectivities between the aldehyde group and the hydroxyl group when salicylaldehydes react with Rh(II)-azavinyl carbines.[4b,16] Herein, we describe a new method to generate 2,5-epoxy-1,4-benzoxazepines via rhodium-catalyzed tandem reaction of salicylaldehydes and readily prepared triazoles (Figure 2c).[17]

2. Results and discussion

We commenced the study by treatment of ready available triazole **1a** and salicylaldehyde **2a** with 2 mol% $Rh_2(oct)_4$ in $CHCl_3$ at 75 °C for 1.5 h. Fortunately, a new compound was isolated in 65% yield (Table 1, entry 1), which was confirmed as 2,5-epoxy-1,4-benzoxazepine **3aa** by NMR spectrum and HRMS analysis. Further experiments proved that the reaction usually completed within 0.5 h (Table 1, entry 2). The examination of Rh(II)-catalysts revealed $Rh_2(oct)_4$ and $Rh_2(piv)_4$ were both effective to catalyze the reaction (Table 1, entries 2 and 3), while $Rh_2(OAc)_4$ did not trigger the reaction even prolonging the reaction time to 5 h (Table 1, entry 4). However, $Rh_2(piv)_4$ was eluted along with the product during the purification. Moreover, taking the cost in consideration, $Rh_2(oct)_4$ was chosen as the optimal catalyst. An attempt to decrease the temperature to 65°C resulted in a lower yield (Table 1, entry 5). Interestingly, additives such as molecular sieve and $MgSO_4$ unexpectedly deteriorate the reaction (Table 1, entries 6 and 7). The previous work showed that solvents usually are critical in Rh-catalyzed ring-opening reactions of triazoles. Thus, solvent effect was then tested with $Rh_2(oct)_4$ as the catalyst. The results revealed that nonpolar solvents Toluene, Chlorobenzene, $PhCF_3$ showed better performance, and Toluene was the best of choice (Table 1, entries 8-11).

Table 1. Optimization of the reaction conditions

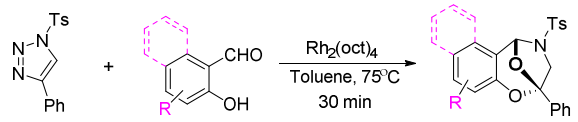


1a 2a 3aa

Entry	Rh (2 mol%)	Solvent	T/°C	t/h	Yield[%][a]
1	$Rh_2(oct)_4$	$CHCl_3$	75	1.5	65
2	$Rh_2(oct)_4$	$CHCl_3$	75	0.5	66
3	$Rh_2(piv)_4$	$CHCl_3$	75	0.5	66
4	$Rh_2(OAc)_4$	$CHCl_3$	75	5	trace
5	$Rh_2(oct)_4$	$CHCl_3$	65	1	51
6	$Rh_2(oct)_4$	$CHCl_3$/4 Å MS	75	0.5	54
7	$Rh_2(oct)_4$	$CHCl_3$/ $MgSO_4$	75	0.5	57
8	$Rh_2(oct)_4$	DCE	75	0.5	53
9	$Rh_2(oct)_4$	Toluene	75	0.5	94
10	$Rh_2(oct)_4$	Chlorobenzene	75	0.5	86
11	$Rh_2(oct)_4$	$PhCF_3$	75	0.5	92

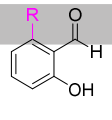
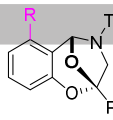
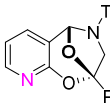
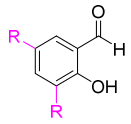
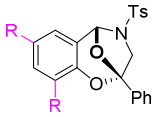
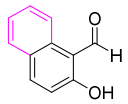
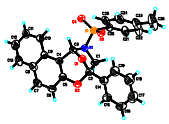
Conditions: Under N_2, **1a** (0.35 mmol), **2a** (0.39 mmol), Rh cat. (2 mol%), and solvent (1.0 mL) were heated until **1a** was consumpted. [a] Isolated yields.

Table 2. Rh(II)-catalyzed reaction of various salicylaldehydes **2b-2o** with triazoles **1a**



1a 2b-2o 3ab-3ao

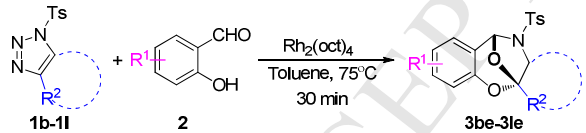
Entry	Substrate/2	Product/3	Yield[%][a]
1	**2b** R = 3-Br	**3ab**	68
2	**2c** R = 3-Me	**3ac**	95
3[b]	**2d** R = 3-OMe	**3ad**	78
4	**2e** R = 4-Me	**3ae**	85
5	**2f** R = 4-Cl	**3af**	81
6	**2g** R = 5-F	**3ag**	64
7	**2h** R = 5-Cl	**3ah**	76
8	**2i** R = 5-Br	**3ai**	94
9	**2j** R = 5-Me	**3aj**	93
10	**2k** R = 5-OMe	**3ak**	61

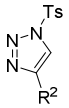
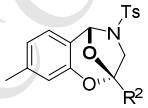
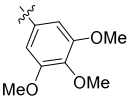
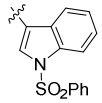
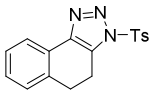
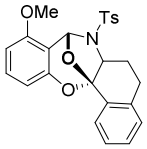
			
11	**2l** R = 6-OMe	**3al**	93
12	**2m** R = 6-F	**3am**	85
			
13[c]	**2n**	**3an**	0
			
14	**2o** R = Cl	**3ao**	64
15	**2p** R = *t*-Bu	**3ap**	76
			
16	**2q**	**3aq**(X-ray)	99

Conditions: Under N_2, **1a** (0.35 mmol), **2** (0.39 mmol), Rh cat. (2 mol%), and solvent (1.0 mL) were heated until **1a** was consumpted. [a] Isolated yields. [b] The reaction was run at 75°C for 30 min, *then* 120°C for 30 min. [c] No product was detected.

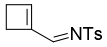
With the optimal reaction conditions in hand, we next turned to examine the substrate scope and generality of this method and found that variously substituted salicylaldehydes reacted smoothly with the triazole **1a** in moderate to excellent yields as shown in Table 2, except for heteroaromatic salicylaldehyde **2l**. Salicylaldehydes with electron-withdrawing substitutents at *ortho*- or *para*- position of the hydroxyl group gave rise to lower yields (Table 2, entries 1, 6, 7 and 14), which was probably due to the decreased nucleophilicity of the hydroxyl group caused by the electron-withdrawing substitutents. As for salicylaldehyde **2n**, the bulky substitutent *t*-Bu did not hamper the reaction, delivering the corresponding product in 76% yield.

Table 3. Rh(II)-catalyzed reaction of various triazoles **1b-1l** with salicylaldehyde **2**



Entry	Substrate/**1**	Product/**3**	Yield[%][a]
			
1	**1b** R^2 = 2-Cl-C_6H_4	**3be**	70
2[b]	**1c** R^2 = 3-CN-C_6H_4	**3ce**	82
3	**1d** R^2 = 3-OMe-C_6H_4	**3de**	81
4	**1e** R^2 = 4-Br-C_6H_4	**3ee**	68
5	**1f** R^2 = 4-Me-C_6H_4	**3fe**	92
6	**1g** R^2 = 4-OMe-C_6H_4	**3ge**	90
	R^2 = 		
7	**1h**	**3he**	94
	R^2 = 		
8	**1i**	**3ie**	78
9	**1j** R^2 = 	**3je**	32
			
10[c]	**1k**	**3kk**	54
11[d]	**1l** R^2 = cyclopropyl	**3le**	0

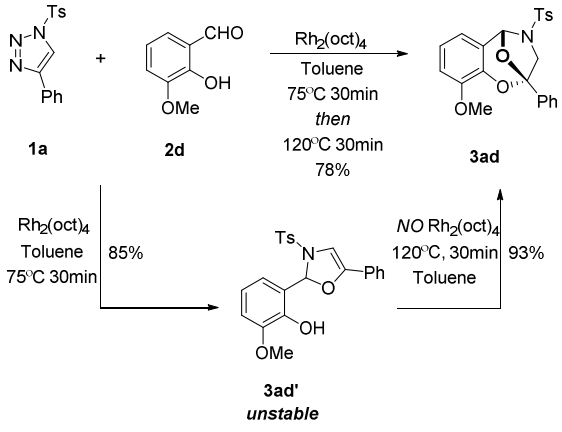
Conditions: Under N_2, **1** (0.35 mmol), **2** (0.39 mmol), Rh cat. (2 mol%), and solvent (1.0 mL) were heated until **1** consumped. [a] Isolated yields. [b] The reaction time was 2 h. [c] Salicylaldehyde **2k** was used, the reaction time was 1 h. [d] Only ring-expansion product **3le'** was obtained in 74% yield.



3le'

After testing the limitation of salicylaldehydes, we moved forward to the study of varying substitution patterns for various triazoles. The results, reported in Table 3, revealed that C4 aryl-substituted triazoles afforded corresponding products in good to excellent yield (Table 3, entry 1-7), which were insignificantly affected by position or electronic properties of the substituents. When C4 heteroaryl-substituted triazole **1i** was used, the reaction still proceeded smoothly affording product **3ie** in 78% yield. C4 Styryl-substituted triazole **1j** was first synthesized from corresponding enyne and tested in this Rh-catalyzed ring-opening reaction of 1-sulfonyl-1,2,3-triazoles. The reaction led to a relatively complex mixture, but the desired product still could be isolated in 32% yield. When tricyclic-triazole **1k** was used in the reaction, the interesting tetracyclic product **3kk** could be isolated in 54% yield. Cyclopropyl-substituted triazole **1l** failed to provide the corresponding product, owing to ring-expansion reaction of the triazole.[18]

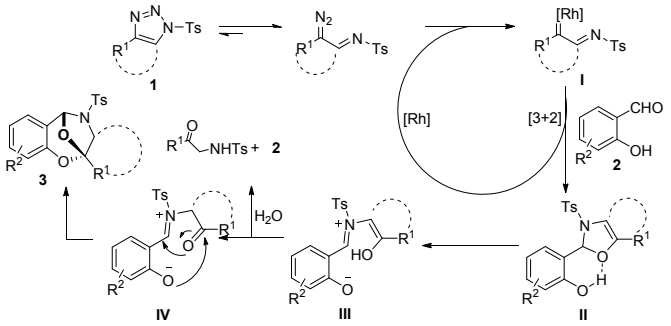
It is important to point out that when the reaction proceeded with triazole **1a** and salicylaldehyde **2d** under the standard conditions, only [3+2] cycloadduct **3ad'** was isolated in 85% yield. We reason that the methoxy group could compete with the oxygen atom in 4-oxazoline forming a hydrogen bond with the hydroxyl group, which stables the [3+2] cycloadduct **3ad'**. According to our hypothesis, the [3+2] cycloadduct would be the key intermediate in the reaction. As expected, barely heating **3ad'** without Rh(II) in toluene at 120°C furnished the desired product **3ad** in 93% yield, which unambiguously supported our hypothesis. And **3ad** was provided in 78% yield in a sequential one-pot two-steps procedure (Scheme 1).



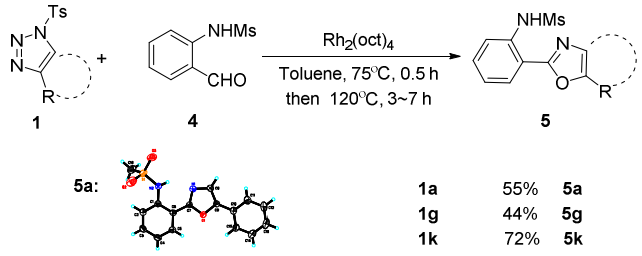
Scheme 1. Rh(II)-catalyzed reaction of **1a** and **2d**

The above outcomes and the previous study on the formation of 4-oxazolines from aldehydes provide informations on the plausible mechanism of the described [3+2] cyclization/ring-opening/closing cascade reaction, as depicted in Scheme 2.

Chemoselectively, the rhodium(II) iminocarbene **I** first reacts with aldehyde to obtain [3+2] intermediate **II**, which then undergoes irreversible ring-opening of 4-oxazoline to form intermediate **III** promoted by the acidic proton of the hydroxyl group through hydrogen bond. Subsequent tautomerization and nucleophilic additions give rise to 2,5-epoxy-1,4-benzoxazepines **3**. Trace amount of water in the reaction system results in hydrolysis of intermediate **III** or **IV**, leads to *α*-amino ketone and salicylaldehyde **2**.

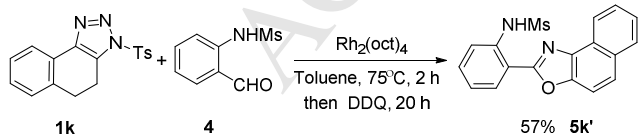


Scheme 2. Proposed mechanism



Scheme 3. Rh(II)-catalyzed reaction of triazoles with 2-methanesulfonamidyl benzaldehyde

With the elaborate study on the Rh(II)-catalyzed reaction of triazoles **1** and salicylaldehydes **2**, we hypothesized if 2-methanesulfonamidyl benzaldehyde **4** could be used instead of salicylaldehydes **2**. Unexpectedly, only the [3+2] cycloadducts were delivered under the standard conditions when reaction of triazole **1a** and 2-methanesulfonamidyl benzaldehyde **4** proceeded. Oxazole products **5** were obtained in 44-72% yields when heating at 120°C for 3-7 h (Scheme 3), which was not reported in previous study by Fokin and co-workers.[4b] Furthermore, benzoxazole type product **5k'** can be obtained through a sequence of Rh(II)-catalyzed [3+2] reaction, elimination of *p*-TsOH, DDQ oxidation steps, as depicted in Scheme 4.



Scheme 4. One-pot synthesis of **5k'**

3. Conclusion

In conclusion, we described a novel and efficient route for the construction of oxa-bridged 2,5-epoxy-1,4-benzoxazepines in good to excellent yields *via* Rh(II)-catalyzed reaction of triazoles and salicylaldehydes under mild conditions. Meantime, Rh(II)-catalyzed reaction of triazoles and 2-methanesulfonamidyl benzaldehyde can afford oxazoles in moderate yields. These findings enriched the reactivities of metal-bound imino carbene intermediates for the formation of azaheterocycles. Further explorations to construct important nitrogen-containing heterocycles are currently underway in our laboratory.

4. Experimental section

4.1 General

All reactions were carried out using standard Schlenk techniques under nitrogen atmosphere unless otherwise stated. $CHCl_3$, 1,2-Dichloroethane(DCE), Chlorobenzene and $PhCF_3$ were dried with CaH_2. Toluene were dried with sodium (Na). Reactions were monitored by thin layer chromatography (TLC) carried out on 0.20-0.3 mm silica gel plates (GF254, Qingdao, China) using UV light as the visualizing agent. Silica gel (200-300 mesh, Qingdao, China) was used for column chromatography. NMR spectra were recorded on Bruker AVANCE III 400M instrument and calibrated using residual undeuterated solvent as an internal reference ($CHCl_3$ @ 7.26 ppm ^{1}H NMR, 77.16 ppm ^{13}C NMR). The following abbreviations (or combinations thereof) were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High-resolution mass spectra (HRMS) were recorded on Agilent 6520 accurate-Mass Q-TOF LC/MS system (1200-6520/Agilent). Melting points were obtained in open capillary tubes using a micro melting point apparatus which were uncorrected.

Rh(II) acetate, Rh(II) octanoate were purchased from Adamas-beta. $Rh_2(piv)_4$ were prepared using literature procedures.[19]

Salicylaldehyde **2a** was fresh distilled before use, other salicylaldehydes **2b-2o** were used directly as received from commercial suppliers, unless specified otherwise. *N*-Sulfonyl-1,2,3-triazoles were prepared according to the literature procedures[20,24]. *N*-sulfonyl-1,2,3-triazoles **1a**[21], **1b**[22], **1e**[21], **1f**[21], **1g**[23], **1k**[24], **1l**[25] were known compounds.

4.2 General procedure for the synthesis of *N*-sulfonyl-1,2,3-triazoles

To a stirred solution of alkyne (12 mmol, 1.2 eq) in 50 ml DCM was added copper(I)-thoiphene-2-carboxylate (CuTc, 95 mg, 0.5 mmol, 0.05 eq). The solution was cooled to 0°C and treated dropwise with a solution of 10 mmol sulfonyl azide in 10 mL DCM. Then, the reaction mixture was stirred a further 12 h, monitored by TLC. After reaction, it was diluted with 30 mL saturated NH_4Cl and extracted with DCM (30 mLx3). The combined organics were washed with brine, dried with Na_2SO_4 and concentrated in vacuo. The crude product was then purified by flash chromatography (Petroleum ether/EtOAc =5:1~1:1). Subsequent recrystallization from EtOAc/Petroleum ether provided the title triazoles substrates.

4.2.1 Compound ***1c***. Yellow solid, MP: 185-187°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.40 (s, 1H), 8.13 (s, 1H), 8.11-8.00 (m, 3H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 2H), 2.46 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 147.9, 145.3, 132.8, 132.5, 130.7, 130.5, 130.3, 130.1, 129.6, 128.9, 119.9, 118.3, 113.5, 22.0. **HRMS** (EI-TOF): calcd for, $C_{16}H_{12}N_4O_2S$ $[M]^+$, 324.0681; found, 324.0680.

4.2.2 *Compound* ***1d***. Yellow solid, MP: 86-88°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.30 (s, 1H), 8.02 (d, *J* = 8.1 Hz, 2H), 7.45-7.29 (m, 5H), 6.91 (d, *J* = 7.8 Hz, 1H), 3.85 (s, 3H), 2.44 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 160.1, 147.5, 147.3,

133.1, 130.6, 130.2, 130.2, 128.8, 119.3, 118.5, 115.2, 111.2, 55.5, 21.9. **HRMS** (EI-TOF): calcd for, $C_{16}H_{15}N_3O_3S$ $[M]^+$, 329.0834; found, 329.0835.

4.2.3 *Compound* ***1h***. Light yellow solid, MP: 156-158°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.28 (s, 1H), 8.03 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.05 (s, 2H), 3.92 (s, 6H), 3.88 (s, 3H), 2.45 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 153.8, 147.5, 147.8, 138.9, 133.1, 130.6, 128.7, 124.4, 118.9, 103.3, 61.1, 56.3, 21.9. **HRMS** (EI-TOF): calcd for, $C_{18}H_{19}N_3O_5S$ $[M]^+$, 389.1045; found, 389.1049.

4.2.4 *Compound* ***1i***. Yellowish brown solid, MP: 98-100°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.37 (s, 1H), 8.08 (s, 1H), 8.05 (dd, *J* = 8.0, 4.5 Hz, 3H), 7.92 (d, *J* = 7.6 Hz, 3H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.48-7.38 (m, 5H), 7.34 (t, *J* = 7.4 Hz, 1H), 2.45 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 147.6, 140.8, 137.9, 135.2, 134.3, 132.9, 130.6, 129.5, 128.8, 127.8, 126.9, 125.6, 124.4, 124.2, 120.9, 119.2, 113.8, 111.9, 21.9. **HRMS** (ESI-TOF): calcd for, $C_{23}H_{18}N_4O_4S_2$ $[M+H]^+$, 479.0842; found, 479.0846.

4.2.5 *Compound* ***1j***. Yellow solid, MP: 145-147°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.10 (s, 1H), 8.01 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 7.3 Hz, 2H), 7.42-7.32 (m, 5H), 7.29 (t, *J* = 7.2 Hz, 1H), 7.00 (d, *J* = 16.4 Hz, 1H), 2.45 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 147.5, 145.9, 136.2, 133.2, 133.1, 130.6, 128.9, 128.7, 128.6, 126.8, 119.6, 114.9, 21.9. **HRMS** (EI-TOF): calcd for, $C_{17}H_{15}N_3O_2S$ $[M]^+$, 325.0885; found, 325.0887.

4.3 General procedure for the Rh(II)-catalyzed reaction of *N*-sulfonyl-1,2,3-triazoles with Salicylaldehyde

To an oven-dried Schlenk tube was added 0.35 mmol (1 eq) *N*-sulfonyl-1,2,3-triazoles, 0.39 mmol (1.1 eq) Salicylaldehyde and 0.007 mmol (2 mol%) Rh(II). The Schlenk tube was sealed with a Rubber plug and the atmosphere was replaced using standard Schlenk techniques under nitrogen atmosphere. The 1 mL dried solvent was added and the reaction mixture was heated at 75°C, with vigorous stirring, for 30 min. Once *N*-sulfonyl-1,2,3-triazoles consumped, the reaction mixture was cooled to ambient temperature and 1 mL DCM was added. The mixture was purified by flash chromatography (petroleum ether/EtOAc= 5:1~3:1) directly to provide the title compound.

4.3.1 *Compound* ***3aa***. White solid, 130 mg, 94% yield, MP: 176-178°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.35-7.29 (m, 3H), 7.29-7.24 (m, 2H), 7.21 (t, *J* = 7.6 Hz, 2H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.95-6.87 (m, 3H), 6.61 (s, 1H), 3.94 (d, *J* = 12.9 Hz, 1H), 3.62 (d, *J* = 12.8 Hz, 1H), 2.49 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 149.9, 144.7, 136.1, 134.5, 130.8, 130.2, 129.3, 128.6, 128.3, 125.4, 124.7, 121.7, 121.2, 116.6, 105.5, 89.7, 59.9, 21.7. **HRMS** (EI-TOF): calcd for, $C_{22}H_{19}NO_4S$ $[M]^+$, 393.1035; found, 393.1039.

4.3.2 *Compound* ***3ab***. White solid, 113 mg, 68% yield, MP: 190-191°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 8.2 Hz, 2H), 7.56-7.48 (m, 1H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.27-7.19 (m, 3H), 6.98 (d, *J* = 7.5 Hz, 2H), 6.91 (t, *J* = 7.8 Hz, 1H), 6.62 (s, 1H), 3.94 (d, *J* = 12.9 Hz, 1H), 3.64 (d, *J* = 12.9 Hz, 1H), 2.53 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 147.0, 144.9, 135.4, 134.4, 134.2, 130.3, 129.5, 128.6, 128.4, 124.9, 124.4, 122.8, 122.6, 110.4, 106.4, 89.3, 60.4, 21.8. **HRMS** (EI-TOF): calcd for, $C_{22}H_{18}BrNO_4S$ $[M]^+$, 471.0140; found, 471.0144.

4.3.3 *Compound* ***3ac***. White solid, 136 mg, 95% yield, MP: 184-186°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 7.6 Hz, 2H), 7.37 (d, *J* = 7.9 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 2H), 7.15 (d, *J* = 7.5 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 6.98-6.87 (m, 3H), 6.61 (s, 1H), 3.91 (d, *J* = 12.8 Hz, 1H), 3.61 (d, *J* = 12.8 Hz, 1H), 2.52 (s, 3H), 2.24 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 147.8, 144.6, 136.4, 134.7, 131.9, 130.2, 129.3, 128.6, 128.3, 125.9, 124.7, 122.8, 121.3, 120.7, 105.4, 89.8, 60.2, 21.7, 15.3. **HRMS** (EI-TOF): calcd for, $C_{23}H_{21}NO_4S$ $[M]^+$, 407.1191; found, 407.1190.

4.3.4 *Compound* ***3ad***. White solid, 116 mg, 78% yield, MP: 160-162°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.31 (dd, *J* = 18.8, 7.7 Hz, 3H), 7.21 (t, *J* = 7.6 Hz, 2H), 7.02-6.94 (m, 3H), 6.93-6.86 (m, 2H), 6.60 (s, 1H), 3.99 (d, *J* = 12.9 Hz, 1H), 3.86 (s, 3H), 3.66 (d, *J* = 12.9 Hz, 1H), 2.50 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 148.1, 144.7, 139.3, 136.0, 134.5, 130.2, 129.3, 128.6, 128.3, 124.8, 121.9, 121.7, 117.2, 113.1, 105.7, 89.5, 59.9, 56.2, 21.7. **HRMS** (EI-TOF): calcd for, $C_{23}H_{21}NO_5S$ $[M]^+$, 423.1140; found, 423.1142.

4.3.5 *Compound* ***3ae***. White solid, 121 mg, 85% yield, MP: 161-164°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 8.1 Hz, 2H), 7.32 (dd, *J* = 16.5, 7.7 Hz, 3H), 7.21 (t, *J* = 7.6 Hz, 2H), 7.14 (d, *J* = 7.7 Hz, 1H), 6.94 (d, *J* = 7.5 Hz, 2H), 6.82 (d, *J* = 7.7 Hz, 1H), 6.74 (s, 1H), 6.59 (s, 1H), 3.93 (d, *J* = 12.8 Hz, 1H), 3.62 (d, *J* = 12.8 Hz, 1H), 2.50 (s, 3H), 2.32 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 149.8, 144.6, 141.1, 136.2, 134.6, 130.1, 129.2, 128.6, 128.2, 125.1, 124.7, 122.5, 118.4, 116.9, 105.4, 89.7, 59.8, 21.7, 21.6. **HRMS** (EI-TOF): calcd for, $C_{23}H_{21}NO_4S$ $[M]^+$, 407.1191; found, 407.1193.

4.3.6 *Compound* ***3af***. White solid, 121 mg, 81% yield, MP: 165-167°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.39-7.28 (m, 3H), 7.27-7.16 (m, 3H), 6.99 (d, *J* = 8.2 Hz, 1H), 6.96-6.89 (m, 3H), 6.60 (s, 1H), 3.94 (d, *J* = 12.9 Hz, 1H), 3.63 (d, *J* = 12.9 Hz, 1H), 2.51 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 150.6, 144.9, 136.0, 135.5, 134.3, 130.2, 129.5, 128.6, 128.4, 126.3, 124.6, 122.0, 119.8, 117.1, 105.7, 89.3, 59.9, 21.8. **HRMS** (EI-TOF): calcd for, $C_{22}H_{18}ClNO_4S$ $[M]^+$, 427.0645; found, 427.0642.

4.3.7 *Compound* ***3ag***. White solid, 87 mg, 64% yield, MP:184-186°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 7.3 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 2H), 7.03-6.97 (m, 2H), 6.95-6.91 (m, 2H), 6.87 (dd, *J* = 9.6, 4.5 Hz, 1H), 6.56 (s, 1H), 3.93 (d, *J* = 12.9 Hz, 1H), 3.63 (d, *J* = 12.9 Hz, 1H), 2.51 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 157.3 (d, *J* = 241.7 Hz), 145.9 (d, *J* = 2.3 Hz), 144.8, 135.8, 134.4, 130.2, 129.4, 128.6, 128.3, 124.6, 121.9 (d, *J* = 7.3 Hz), 117.9 (d, *J* = 7.9 Hz), 117.5 (d, *J* = 23.4 Hz), 112.0 (d, *J* = 24.5 Hz), 105.7, 89.0 (d, *J* = 2.1 Hz), 59.8, 21.7. **HRMS** (EI-TOF): calcd for, $C_{22}H_{18}FNO_4S$ $[M]^+$, 411.0941; found, 411.0942.

4.3.8 *Compound* ***3ah***. White solid, 114 mg, 76% yield, MP: 182-184°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.26 – 7.20 (m, 4H), 6.94 (d, *J* = 7.5 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.56 (s, 1H), 3.93 (d, *J* = 12.9 Hz, 1H), 3.64 (d, *J* = 12.8 Hz, 1H), 2.51 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 148.5, 144.9, 135.6, 134.3, 130.7, 130.2, 129.5, 128.6, 128.4, 126.7, 125.3, 124.6, 122.4, 118.1, 105.8, 89.1, 59.9, 21.8. **HRMS** (EI-TOF): calcd for, $C_{22}H_{18}ClNO_4S$ $[M]^+$, 427.0645; found, 427.0646.

4.3.9 *Compound* ***3ai***. White solid, 156 mg, 94% yield, MP: 201-203°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.42-7.30 (m, 5H), 7.22 (t, *J* = 7.6 Hz, 2H), 6.92 (d, *J* = 7.7 Hz, 2H), 6.81 (d, *J* = 8.4 Hz, 1H), 6.56 (s, 1H), 3.93 (d, *J* = 12.9 Hz, 1H), 3.63 (d, *J* = 12.9 Hz, 1H), 2.51 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 149.0, 144.9, 135.6, 134.2, 133.6, 130.2, 129.5, 128.6, 128.4, 128.2, 124.6, 122.9, 118.5, 113.8, 105.8,

88.9, 59.9, 21.8. **HRMS** (EI-TOF): calcd for, $C_{22}H_{18}BrNO_4S$ $[M]^+$, 471.0140; found, 471.0141.

4.3.10 *Compound **3aj***. White solid, 132 mg, 93% yield, MP: 185-186°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 2H), 7.09 (d, *J* = 6.9 Hz, 2H), 6.93-6.90 (m, 2H), 6.82-6.79 (m, 1H), 6.56 (s, 1H), 3.93 (d, *J* = 12.8 Hz, 1H), 3.60 (d, *J* = 12.8 Hz, 1H), 2.51 (s, 3H), 2.32 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 147.6, 144.6, 136.3, 134.5, 131.3, 131.3, 130.2, 129.2, 128.6, 128.2, 125.7, 124.7, 120.9, 116.3, 105.4, 89.7, 59.8, 21.7, 20.7. **HRMS** (EI-TOF): calcd for, $C_{23}H_{21}NO_4S$ $[M]^+$, 407.1191; found, 407.1194.

4.3.11 *Compound **3ak***. White solid, 90.3 mg, 61% yield, MP: 170-172°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 2H), 6.95-6.89 (m, 2H), 6.851-6.846 (m, 2H), 6.80 (s, 1H), 6.57 (s, 1H), 3.93 (d, *J* = 12.9 Hz, 1H), 3.80 (s, 3H), 3.60 (d, *J* = 12.8 Hz, 1H), 2.51 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 154.3, 144.7, 143.6, 136.2, 134.5, 130.2, 129.2, 128.6, 128.2, 124.6, 121.4, 117.5, 117.1, 109.7, 105.4, 89.5, 59.6, 55.9, 21.7. **HRMS** (EI-TOF): calcd for, $C_{23}H_{21}NO_5S$ $[M]^+$, 423.1140; found, 423.1139.

4.3.12 *Compound **3al***. White solid, 138 mg, 93% yield, MP: 156-158°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 8.1 Hz, 2H), 7.36-7.27 (m, 3H), 7.26-7.16 (m, 3H), 6.98 (d, *J* = 7.5 Hz, 2H), 6.94 (s, 1H), 6.52 (dd, *J* = 8.3, 3.3 Hz, 2H), 3.95 (d, *J* = 13.0 Hz, 1H), 3.88 (s, 3H), 3.71 (d, *J* = 13.0 Hz, 1H), 2.49 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 155.47 , 150.77 , 144.40 , 136.25 , 134.93 , 130.81 , 129.98 , 129.18 , 128.64 , 128.20 , 124.67 , 109.97 , 108.94 , 105.09 , 103.85 , 85.72 , 59.89 , 56.02 , 21.66 . **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 155.5, 150.8, 144.4, 136.3, 134.9, 130.8, 129.9, 129.2, 128.6, 128.2, 124.7, 109.9, 108.9, 105.1, 103.9, 85.7, 59.9, 56.0, 21.7. **HRMS** (EI-TOF): calcd for, $C_{23}H_{21}NO_5S$ $[M]^+$, 423.1140; found, 423.1142.

4.3.13 *Compound **3am***. White solid, 123 mg, 85% yield, M.P. 179-181°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 8.1 Hz, 2H), 7.40-7.30 (m, 3H), 7.29-7.19 (m, 3H), 6.98 (d, *J* = 7.7 Hz, 2H), 6.93 (s, 1H), 6.75-6.70 (m, 2H), 3.96 (d, *J* = 13.0 Hz, 1H), 3.72 (d, *J* = 13.0 Hz, 1H), 2.50 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 157.9 (d, *J* = 249.3 Hz), 151.0 (d, *J* = 6.4 Hz), 144.8, 135.7, 134.6, 131.1 (d, *J* = 9.7 Hz), 130.2, 129.5, 128.6, 128.4, 124.7, 112.3 (d, *J* = 3.4 Hz), 109.9 (d, *J* = 20.9 Hz), 108.5 (d, *J* = 20.1 Hz), 105.7, 84.9 (d, *J* = 4.3 Hz), 59.9, 21.7. **HRMS** (EI-TOF): calcd for, $C_{22}H_{18}FNO_4S$ $[M]^+$, 411.0941; found, 411.0939.

4.3.14 *Compound **3ao***. White solid, 104 mg, 64% yield, MP: 171-173°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.40-7.35 (m, 3H), 7.33 (d, *J* = 7.4 Hz, 1H), 7.28 - 7.20 (m, 2H), 7.19 (d, *J* = 2.3 Hz, 1H), 6.97 (d, *J* = 7.5 Hz, 2H), 6.58 (s, 1H), 3.93 (d, *J* = 12.9 Hz, 1H), 3.65 (d, *J* = 12.9 Hz, 1H), 2.52 (s, 2H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 145.1, 144.8, 134.9, 134.1, 130.8, 130.3, 129.7, 128.6, 128.4, 126.6, 124.8, 123.8, 123.5, 122.5, 106.5, 88.8, 60.3, 21.8. **HRMS** (EI-TOF): calcd for, $C_{22}H_{17}Cl_2NO_4S$ $[M]^+$, 461.0255; found, 461.0256.

4.3.15 *Compound **3ap***. White solid, 134 mg, 76% yield, MP: 253-255°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.34-7.28 (m, 2H), 7.22 (t, *J* = 7.6 Hz, 2H), 7.09 (d, *J* = 2.1 Hz, 1H), 6.94 (d, *J* = 7.5 Hz, 2H), 6.59 (s, 1H), 3.90 (d, *J* = 12.7 Hz, 1H), 3.57 (d, *J* = 12.7 Hz, 1H), 2.52 (s, 3H), 1.40 (s, 9H), 1.32 (s, 9H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 145.8, 144.6, 144.0, 136.9, 136.8, 134.8, 130.2, 129.1, 128.7, 128.3, 125.1, 124.7, 120.4, 120.2, 105.5, 90.4, 60.1, 34.8, 34.6, 31.7, 29.7, 21.8. **HRMS** (EI-TOF): calcd for, $C_{30}H_{35}NO_4S$ $[M]^+$, 505.2287; found, 505.2291.

4.3.16 *Compound **3aq***. White solid, 153mg, 99% yield, MP: 186-187°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.12 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.3 Hz, 2H), 7.85-7.76 (m, 2H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 7.4 Hz, 1H), 7.29 (s, 1H), 7.27-7.20 (m, 2H), 7.11 (d, *J* = 8.9 Hz, 1H), 6.98 (d, *J* = 7.3 Hz, 2H), 4.01 (d, *J* = 13.0 Hz, 1H), 3.70 (d, *J* = 13.0 Hz, 1H), 2.52 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 147.9, 144.8, 136.1, 134.7, 131.2, 130.2, 129.4, 129.4, 129.2, 128.8, 128.7, 128.3, 127.9, 124.7, 124.6, 121.2, 117.5, 113.3, 105.5, 87.2, 60.1, 21.8. **HRMS** (EI-TOF): calcd for, $C_{26}H_{21}NO_4S$ $[M]^+$, 443.1191; found, 443.1192.

4.3.17 *Compound **3be***. Yellow solid, 108 mg, 70% yield, MP: 176-178°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.63 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.29-7.22 (m, 1H), 7.13 (t, *J* = 8.7 Hz, 3H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 7.9 Hz, 1H), 6.81 (d, *J* = 7.7 Hz, 1H), 6.67 (s, 1H), 6.51 (s, 1H), 4.36 (d, *J* = 13.7 Hz, 1H), 3.89 (d, *J* = 13.7 Hz, 1H), 2.36 (s, 3H), 2.29 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 150.1, 144.3, 141.3, 134.4, 134.2, 131.9, 130.5, 130.4, 129.8, 128.2, 126.3, 126.0, 125.4, 122.6, 117.3, 117.0, 104.4, 88.8, 58.3, 21.6, 21.6. **HRMS** (EI-TOF): calcd for $C_{23}H_{20}ClNO_4S$ $[M]^+$ 441.0802, found 441.0800.

4.3.18 *Compound **3ce***. White solid, 124 mg, 82% yield, MP: 87-89°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 7.2 Hz, 1H), 7.45-7.38 (m, 4H), 7.17 (d, *J* = 7.7 Hz, 1H), 6.93 (d, *J* = 1.7 Hz, 1H), 6.85 (d, *J* = 7.7 Hz, 1H), 6.75 (s, 1H), 6.62 (s, 1H), 3.94 (d, *J* = 13.0 Hz, 1H), 3.56 (d, *J* = 13.0 Hz, 1H), 2.57 (s, 3H), 2.33 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 149.2, 145.6, 141.5, 137.9, 134.4, 132.9, 130.4, 129.6, 129.3, 128.6, 128.3, 125.2, 123.0, 118.2, 118.1, 116.9, 112.7, 104.3, 89.9, 59.8, 21.9, 21.6. **HRMS** (EI-TOF): calcd for, $C_{24}H_{20}N_2O_4S$ $[M]^+$, 432.1144; found, 432.1145.

4.3.19 *Compound **3de***. White solid, 124 mg, 81% yield, MP: 171-173°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.76 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.15-7.11 (m, 2H), 6.84-6.80 (m, 2H), 6.73 (s, 1H), 6.57 (s, 1H), 6.56-6.50 (m, 2H), 3.92 (d, *J* = 12.8 Hz, 1H), 3.77 (s, 3H), 3.62 (d, *J* = 12.8 Hz, 1H), 2.48 (s, 3H), 2.32 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 159.6, 149.7, 144.8, 141.1, 137.7, 134.5, 130.1, 129.4, 128.5, 125.0, 122.5, 118.4, 116.96, 116.94, 114.3, 110.8, 105.2, 89.6, 59.8, 55.4, 21.7, 21.6. **HRMS** (EI-TOF): calcd for, $C_{24}H_{23}NO_5S$ $[M]^+$, 437.1297; found, 437.1301.

4.3.20 *Compound **3ee***. White solid, 116 mg, 68% yield, MP: 187-189°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.35 (t, *J* = 7.7 Hz, 4H), 7.14 (d, *J* = 7.7 Hz, 1H), 6.81 (t, *J* = 8.0 Hz, 3H), 6.73 (s, 1H), 6.58 (s, 1H), 3.90 (d, *J* = 12.9 Hz, 1H), 3.57 (d, *J* = 12.9 Hz, 1H), 2.51 (s, 3H), 2.32 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 149.5, 144.7, 141.3, 135.4, 134.6, 131.4, 130.2, 128.6, 126.6, 125.1, 123.5, 122.7, 118.3, 116.9, 104.9, 89.7, 59.7, 21.8, 21.6. **HRMS** (EI-TOF): calcd for, $C_{23}H_{20}BrNO_4S$ $[M]^+$, 485.0296; found, 485.0298.

4.3.21 *Compound **3fe***. White solid, 135 mg, 92% yield, MP: 163-165°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 7.7 Hz, 1H), 7.01 (d, *J* = 7.9 Hz, 2H), 6.86-6.77 (m, 3H), 6.73 (s, 1H), 6.57 (s, 1H), 3.91 (d, *J* = 12.7 Hz, 1H), 3.60 (d, *J* = 12.7 Hz, 1H), 2.51 (s, 3H), 2.33 (s, 3H), 2.32 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 149.8, 144.6, 141.1, 139.1, 134.7, 133.3, 130.1, 128.9, 128.6, 125.0, 124.6, 122.4, 118.5, 116.9, 105.5, 89.6, 59.9, 21.7, 21.6, 21.3. **HRMS** (EI-TOF): calcd for, $C_{24}H_{23}NO_4S$ $[M]^+$, 421.1348; found, 421.1351.

4.3.22 *Compound* ***3ge***. White solid, 138 mg, 90% yield, MP: 190-191°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 7.8 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 7.13 (d, *J* = 7.7 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 7.6 Hz, 1H), 6.73-6.71 (m, 3H), 6.56 (s, 1H), 3.90 (d, *J* = 12.8 Hz, 1H), 3.79 (s, 3H), 3.60 (d, *J* = 12.8 Hz, 1H), 2.49 (s, 3H), 2.32 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 160.2, 149.8, 144.5, 141.1, 134.7, 130.1, 128.6, 128.5, 126.2, 125.1, 122.4, 118.5, 116.9, 113.5, 105.5, 89.6, 59.8, 55.4, 21.7, 21.6. **HRMS** (EI-TOF): calcd for, $C_{24}H_{23}NO_5S$ $[M]^+$, 437.1297; found, 437.1295.

4.3.23 *Compound* ***3he***. White solid, 164 mg, 94% yield, MP: 91-93°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 7.7 Hz, 1H), 6.81 (d, *J* = 7.7 Hz, 1H), 6.74 (s, 1H), 6.57 (s, 1H), 6.48 (s, 2H), 3.94 (d, *J* = 12.6 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 6H), 3.72 (d, *J* = 12.5 Hz, 1H), 2.42 (s, 3H), 2.32 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 153.3, 149.8, 144.5, 141.2, 138.9, 134.9, 131.8, 129.9, 128.4, 124.9, 122.6, 118.5, 116.9, 105.5, 102.3, 89.4, 60.9, 59.8, 56.3, 21.7, 21.6. **HRMS** (EI-TOF): calcd for, $C_{26}H_{27}NO_7S$ $[M]^+$, 497.1508; found, 497.1505.

4.3.24 *Compound* ***3ie***. Yellow solid, 161 mg, 78% yield, MP: 102-104°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.92 (d, *J* = 8.3 Hz, 1H), 7.85 (d, *J* = 7.9 Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.35-7.31 (m, Hz, 4H), 7.20-7.12 (m, 3H), 6.83 (d, *J* = 7.7 Hz, 1H), 6.72 (s, 1H), 6.58 (s, 1H), 4.05 (d, *J* = 12.6 Hz, 1H), 3.83 (d, *J* = 12.6 Hz, 1H), 2.51 (s, 3H), 2.32 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 149.4, 145.3, 141.3, 137.9, 135.1, 134.4, 134.3, 130.2, 129. 6, 128.3, 127.1, 127.0, 125.4, 125.1, 123.8, 123.8, 122.7, 121.0, 118.5, 118.0, 116.8, 113.6, 103.9, 89.3, 58.8, 21.9, 21.6. **HRMS** (ESI-TOF): calcd for, $C_{31}H_{26}N_2O_6S$ $[M+Na]^+$, 609.1124; found, 609.1130.

4.3.25 *Compound* ***3je***. White solid, 49 mg, 32% yield, MP: 162-164°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.83 (d, *J* = 7.9 Hz, 2H), 7.38-7.28 (m, 5H), 7.22 (d, *J* = 7.5 Hz, 2H), 7.12 (d, *J* = 7.7 Hz, 1H), 6.80 (d, *J* = 7.7 Hz, 1H), 6.69 (s, 1H), 6.50 (s, 1H), 6.37 (d, *J* = 16.1 Hz, 1H), 5.83 (d, *J* = 16.1 Hz, 1H), 3.79 (d, *J* = 13.0 Hz, 1H), 3.63 (d, *J* = 13.0 Hz, 1H), 2.43 (s, 3H), 2.32 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 149.8, 144.6, 141.2, 135.2, 134.6, 132.7, 130.0, 128.8, 128.8, 128.8, 128.7, 126.9, 125.3, 122.5, 122.5, 118.2, 116.9, 104.5, 89.6, 58.4, 21.7 , 21.6. **HRMS** (EI-TOF): calcd for, $C_{25}H_{23}NO_4S$ $[M]^+$, 433.1348; found, 433.1344.

4.3.26 *Compound* ***3kk***. Yellow solid, 86 mg, 54% yield, MP: 165-167°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.62 (d, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.37-7.27 (m, 2H), 7.20 (d, *J* = 7.5 Hz, 1H), 7.02 (t, *J* = 8.2 Hz, 3H), 6.59 (s, 1H), 6.32 (d, *J* = 8.4 Hz, 1H), 6.20 (d, *J* = 8.2 Hz, 1H), 4.18 (dd, *J* = 10.3, 5.2 Hz, 1H), 3.87 (s, 3H), 2.92-2.79 (m, 2H), 2.54 (dq, *J* = 13.4, 4.4 Hz, 1H), 2.31 (s, 3H), 2.03 (dtd, *J* = 13.3, 10.1, 6.1 Hz, 1H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 155.5, 152.3, 143.3, 139.1, 135.8, 131.9, 130.6, 130.0, 129.0, 127.9, 127.7, 127.3, 127.0, 110.6, 108.2, 104.9, 103.2, 83.5, 66.3, 55.7, 30.5, 27.4, 21.6. **HRMS** (EI-TOF): calcd for, $C_{25}H_{23}NO_5S$ $[M]^+$, 449.1297; found, 449.1299.

4.3.27 *Compound* ***3ad'***. Unstable exposed to air (water). Light yellow solid, 127 mg, 85 % yield, MP: 67-69 °C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 8.1 Hz, 2H), 7.40-7.33 (m, 3H), 7.32-7.27 (m, 4H), 7.20-7.15 (m, 1H), 6.98 (s, 1H), 6.89-6.85 (m, 2H), 6.53 (s, 1H), 6.04 (s, 1H), 3.90 (s, 3H), 2.39 (s, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 147.9, 146.8, 144.7, 143.8, 132.2, 129.9, 129.1, 128.5, 128.3, 128.0, 124.8, 123.5, 119.9, 119.5, 111.9, 103.4, 89.6, 56.3, 21.8. **HRMS** (EI-TOF): calcd for, $C_{23}H_{21}NO_5S$ $[M]^+$, 423.1140; found, 423.1141.

4.3.28 *Compound* ***3le'***. White solid, 61 mg, 74% yield, MP: 88-90°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.49 (s, 1H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.11 (s, 1H), 2.77 (t, *J* = 3.3 Hz, 2H), 2.66 (t, *J* = 3.4 Hz, 2H), 2.43 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 162.6, 156.2, 144.7, 144.2, 135.1, 129.9, 128.3, 29.9, 28.6, 21.8. **HRMS** (EI-TOF): calcd for, $C_{12}H_{13}NO_2S$ $[M]^+$, 235.0667; found, 235.0668.

4.4 General procedure for the Rh(II)-catalyzed reaction of *N*-sulfonyl-1,2,3-triazoles with 2-methanesulfonamidly benzaldehyde

To an oven-dried Schlenk tube was added 0.35 mmol (1 eq) *N*-sulfonyl-1,2,3-triazoles, 0.39 mmol (1.1 eq) Salicylaldehyde and 0.007 mmol (2 mol%) Rh(II) octanoate. The Schlenk tube was sealed with a Rubber plug and the atmosphere was replaced using standard Schlenk techniques under nitrogen atmosphere. Then 1 mL dried solvent was added and the reaction mixture was heated at 75°C, with vigorous stirring, for 30 min. Once *N*-sulfonyl-1,2,3-triazoles consumped, the reaction tube was transferred to 120°C oil-bath for a further stirring. After reaction, the reaction mixture was cooled to ambient temperature and 1 mL DCM was added. The mixture was purified by flash chromatography (Petroleum ether/EtOAc= 5:1~3:1) directly to provide the title compound.

4.4.1 *Compound* ***5a***. Yellow solid, 62 mg, 55% yield, MP: 191-193°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 11.32 (s, 1H), 8.14 (d, *J* = 7.9 Hz, 1H), 7.81 (d, *J* = 8.3 Hz, 1H), 7.74 (d, *J* = 7.7 Hz, 2H), 7.50-7.46 (m, 4H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 3.07 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 159.6, 150.8, 137.1, 131.8, 129.2, 129.2, 127.5, 127.3, 124.5, 123.5, 122.1, 118.5, 114.1, 39.9. **HRMS** (EI-TOF): calcd for, $C_{16}H_{14}N_2O_3S$ $[M]^+$, 314.0725; found, 314.0724.

4.4.2 *Compound* ***5g***. Yellow solid, 53 mg, 44% yield, MP: 175-177°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 11.34 (s, 1H), 8.11 (d, *J* = 7.9 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.34 (s, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 2H), 3.87 (s, 3H), 3.06 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 160.3, 158.9, 150.9, 136.9, 131.6, 127.4, 126.1, 123.5, 120.6, 120.1, 118.5, 114.6, 114.2, 55.5, 39.9. **HRMS** (EI-TOF): calcd for, $C_{17}H_{16}N_2O_4S$ $[M]^+$, 344.0831; found, 344.0832.

4.4.3 *Compound* ***5k***. White solid, 86 mg, 72% yield, MP: 105-107°C, **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 11.35 (s, 1H), 8.13 (d, *J* = 7.9 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.51 (d, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.26 – 7.19 (m, 3H), 3.14 (t, *J* = 8.1 Hz, 2H), 3.07 (s, 3H), 2.96 (t, *J* = 8.1 Hz, 2H). **13C NMR** (100 MHz, Chloroform-d) δ 158.9, 145.7, 136.8, 136.1, 134.8, 131.5, 128.5, 128.0, 127.4, 127.1, 125.7, 123.4, 119.9, 118.3, 114.3, 39.9, 28.9, 21.7. **HRMS** (EI-TOF): calcd for, $C_{18}H_{16}N_2O_3S$ $[M]^+$, 340.0882; found, 340.0883.

4.5 General procedure for one-pot synthesis of 5k'

To an oven-dried Schlenk tube was added 0.35 mmol (1 eq) *N*-sulfonyl-1,2,3-triazoles, 0.39 mmol (1.1 eq) Salicylaldehyde and 0.007 mmol (2 mol%) Rh(II) octanoate. The Schlenk tube was sealed with a Rubber plug and the atmosphere was replaced using standard Schlenk techniques under nitrogen atmosphere. Then 1 mL dried solvent was added and the reaction mixture was heated at 75°C, with vigorous stirring, for 2 h. After reaction, DDQ 0.7 mmol (2 eq) was added and the reaction mixtures was stirred at the same temperature. After reaction, the mixture was

purified by flash chromatography (Petroleum ether/EtOAc= 5:1~3:1) directly to provide the title compound.

4.5.1 *Compound **5k'***. Orange solid, 67 mg, 57% yield, MP: 218-220 ^{o}C, **^{1}H NMR** (400 MHz, Chloroform-d) δ 11.55 (s, 1H), 8.38 (dd, J = 7.9, 1.2 Hz, 1H), 8.31 (d, J = 8.2 Hz, 1H), 8.00 (d, J = 8.2 Hz, 1H), 7.89-7.82 (m, 2H), 7.68 (t, J = 7.5 Hz, 1H), 7.60-7.52 (m, 2H), 7.30 (t, J = 7.6 Hz, 1H), 3.12 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-d) δ 160.8, 145.2, 137.9, 137.2, 132.7, 132.1, 128.9, 128.6, 127.3, 126.3, 126.2, 123.5, 120.3, 120.1, 118.4, 118.3, 113.9, 40.1. **HRMS** (EI-TOF): calcd for, $C_{18}H_{14}N_2O_3S$ $[M]^+$, 338.0725; found, 338.0724.

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17. During the preparation of this manuscript, Li reported $Rh_2(piv)_4$-catalyzed synthesis of 2,5-epoxybenzo[*f*][1,4]oxazepines by

tandem reaction of salicylaldehydes and triazoles. By contrast, Our $Rh_2(oct)_4$ catalytic system provides an more efficient access to oxa-bridged 2,5-epoxy-1,4-benzoxazepines in broad reaction scope under mild conditions, and clearly experimental mechanistic study was illustrated. For details see: Shi, Y.-P.; Yu, X.; Li, C.-Y. *Eur. J. Org. Chem*., **2015**, *29*, 6429-6433.
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