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An Efficient Approach for the Construction of Benzazepine and Benzoxepine Derivatives

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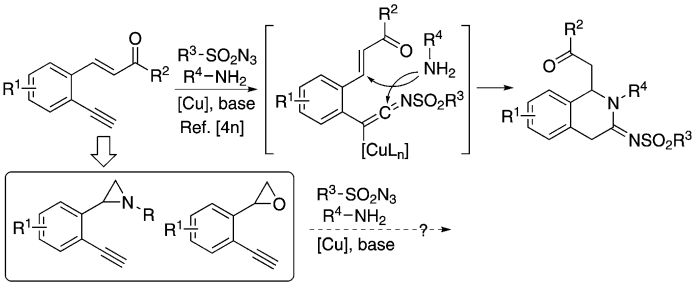
Abstract: A novel and facile synthetic protocol for the construction of benzazepine and benzoxepine derivatives through a copper(I)-catalyzed reaction of 2-(2-ethynylphenyl)-1-tosylaziridine or 2-(2-ethynylphenyl)oxirane with sulfonyl azides is disclosed. A ketenimine is the key intermediate during the reaction process.

Keywords: benzazepine · benzoxepine · copper · cyclization · homogeneous catalysis

Introduction

Tandem reactions have been recognized as an efficient approach for the generation of *N*-heterocycles.[1] As part of our ongoing research program for the preparation of natural product-like compounds in different biological evaluations, we are interested in the development of tandem reactions for the generation of *N*-heterocycles with privileged scaffolds.[2] As pioneered by the research groups of Chang and Wang, the ketenimine intermediate generated from the copper(I)-catalyzed reaction of terminal alkynes with sulfonyl azides has been extensively used for the construction of heterocycles.[3–5] A number of nucleophilic reagents such as amines and alcohols have been successfully employed in the transformations. We are also involved in ketenimine chemistry. For example, a three-component reaction of (*E*)-2-ethynylphenylchalcone, sulfonyl azide, and amine catalyzed by copper(I) chloride in the presence of triethylamine delivered the 1,2-dihydroisoquinolin-3(4*H*)-imines in good to excellent yields (Scheme 1).[4n] Prompted by this result, we envisioned that the alkenyl moiety of (*E*)-2-ethynylphenylchalcone could be replaced by other electrophiles, such as aziridine and epoxide (Scheme 1). Therefore, we started to explore the related transformation using 2-(2-ethynylphenyl)-aziridine or 2-(2-ethynylphenyl)oxirane as the starting material in the reaction of sulfonyl azide with amine.



Scheme 1. Tandem reaction of 2-(2-ethynylphenyl)aziridine or 2-(2-ethynylphenyl)oxirane with sulfonyl azide.

Results and Discussion

We chose 2-(2-ethynylphenyl)-1-tosylaziridine (**1a**), 4-methylbenzenesulfonyl azide (**2a**), and aniline as the substrates to commence our studies. Initially, the reaction was catalyzed by copper(I) iodide (10 mol%) in the presence of triethylamine as a base in 1,4-dioxane at room temperature. To our surprise, we found that the reaction afforded a complex mixture, and a small amount of product was obtained. After structural elucidation by X-ray diffraction analysis, the product was identified as compound **3a** (see the Supporting Information).[6] From this result, it seemed that aniline did not take part in the reaction. Therefore, a control experiment was performed without the addition of aniline. As expected, compound **3a** was obtained in 52% isolated yield (Table 1, entry 1). This result and the attractiveness of the benzazepine scaffold encouraged us to further investigate. So far, significant efforts have been made to construct seven-membered heterocyclic skeletons owing to their abundance in a large number of bioactive natural products and pharmaceutical molecules. Among these compounds, benzazepine and benzoxepine derivatives are of great importance. Some commercial drugs such as galantamine contain the benzaze-

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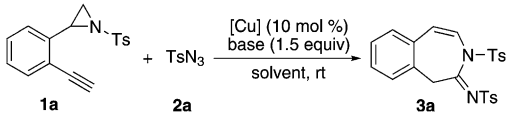
Table 1. Initial studies for the copper(I)-catalyzed reaction of 2-(2-ethynylphenyl)-1-tosylaziridine **1a** with 4-methylbenzenesulfonyl azide **2a**.



Entry	[Cu]	Base	Solvent	Yield [%][a]
1	CuI	Et_3N	1,4-dioxane	52
2	CuBr	Et_3N	1,4-dioxane	78
3	CuCl	Et_3N	1,4-dioxane	72
4[b]	CuBr	Et_3N	1,4-dioxane	73
5	CuBr	iPr_2NEt	1,4-dioxane	65
6	CuBr	Pyridine	1,4-dioxane	38
7	CuBr	K_2CO_3	1,4-dioxane	29
8	CuBr	K_3PO_4	1,4-dioxane	35
9	CuBr	Et_3N	$(CH_2Cl)_2$	85
10	CuBr	Et_3N	THF	70
11	CuBr	Et_3N	MeCN	28
12	CuBr	Et_3N	Toluene	77
13	CuBr	Et_3N	DMSO	ND

[a] Yield of isolated product based on 2-(2-ethynylphenyl)-1-tosylaziridine **1a**. [b] In the presence of 5 mol% CuBr.

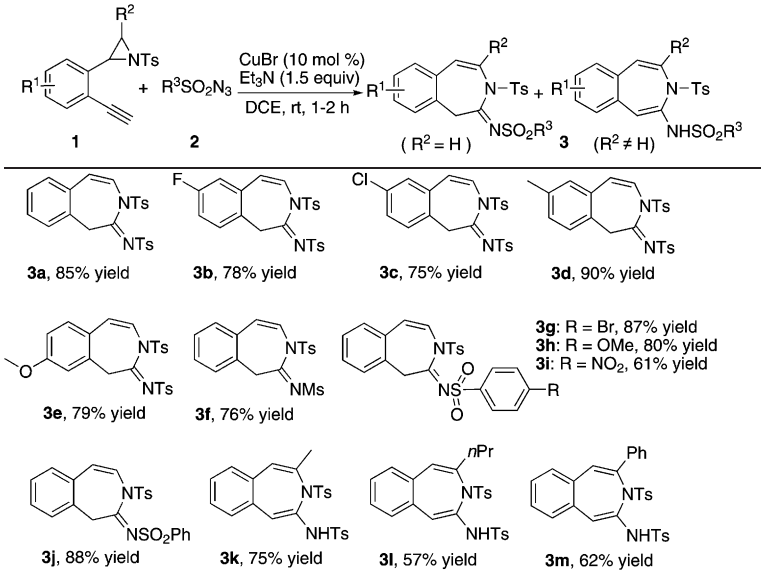
pine framework,[7] and a recent research indicates that many compounds containing this moiety appear to be novel and prominent dopamine D1/D5 receptor antagonists.[8] Meanwhile, several benzoxepines are found to possess antibiotic activities[9] and potentially considered as bronchodilators and antihypertensives.[9d] Despite their prominent importance, less attention has been paid to the synthesis of benzazepine and benzoxepine derivatives. The general method to access these scaffolds usually involves a 7-*endo* heterocyclization of aromatic ynamines and alkynols. For example, Liu and coworkers reported a strategy for the synthesis of 3-benzazepinones by a $Au(PPh_3)Cl/AgSbF_6$-catalyzed intramolecular hydroamidation of 2-(1-alkynyl)phenylacetamides.[10] However, the poor substrate sustainability and high temperatures restricted the prospects of this methodology. Recently, Saá and co-workers disclosed an osmium-catalyzed 7-*endo* heterocyclization of aromatic alkynols into benzoxepines, which was only suitable for the terminal alkynes.[11] Therefore, the development of an efficient strategy toward the preparation of benzazepine and benzoxepine derivatives is highly desirable.

As aniline was not involved in the reaction, we re-investigated the reaction of 2-(2-ethynylphenyl)-1-tosylaziridine **1a** with 4-methylbenzenesulfonyl azide **2a** (Table 1). Screening of the copper(I) salt revealed that copper(I) bromide was the best choice, thus affording the corresponding product **3a** in 78% yield (Table 1, entry 2). A lower yield was obtained when 5 mol% of copper(I) bromide was used (Table 1, entry 4). Inferior results were observed when other bases such as iPr_2NEt, pyridine, K_2CO_3, and K_3PO_4 were employed in the transformation (Table 1, entries 5–8). The yield was improved to 85% when 1,2-dichloroethane was used as the solvent (Table 1, entry 9). No improvement in the results is observed when other solvents were tested (Table 1, entries 10–13).

Under the optimized reaction conditions (Table 1, entry 9), we next set out to explore the substrate scope of this copper(I)-catalyzed reaction of 2-(2-ethynylphenyl)-1-tosylaziridines **1** with sulfonyl azides **2** (Table 2). All reactions proceeded smoothly to afford the expected products **3** in good yields. Different substituents including fluoro, chloro, methyl, methoxy, bromo, and nitro groups were compatible under the standard reaction conditions. Interestingly, isomerized products were isolated in moderate yields when R^2 was changed to an alkyl or aryl group (Table 2, compound **3k**–**3m**). The deuteroxide exchange experiment of compound **3k** identified the existence of an active hydrogen atom.

With the above results in hand, we proposed a possible process, which is illustrated in Scheme 2. We reasoned that 2-(2-ethynylphenyl)-1-tosylaziridine **1** would react with sulfonyl azide **2** catalyzed by the copper(I) salt, thereby affording the triazole intermediate **A**, which is then transferred into the reactive ketenimine **B** after the release of molecular nitrogen. An intramolecular nucleophilic attack of tosylaziridine to the ketenimine would furnish the intermediate **C**, which would undergo a rearrangement to produce the corresponding product **3**.

Table 2. Scope investigation for the copper(I)-catalyzed reaction of 2-(2-ethynylphenyl)-1-tosylaziridine **1** with sulfonyl azide **2**.



[a] Yield of isolated product based on 2-(2-ethynylphenyl)-1-tosylaziridine **1**.

Based on the above results, we then shifted our focus to 2-(2-ethynylphenyl)oxiranes, with the aim of synthesizing 3-benzoxepine derivatives. The reaction of 2-(2-ethynylphenyl)-3-propyloxirane **4a** with 4-methylbenzenesulfonyl azide **2a** catalyzed by copper(I) bromide was performed in the presence of triethylamine in 1,4-dioxane at room tempera-

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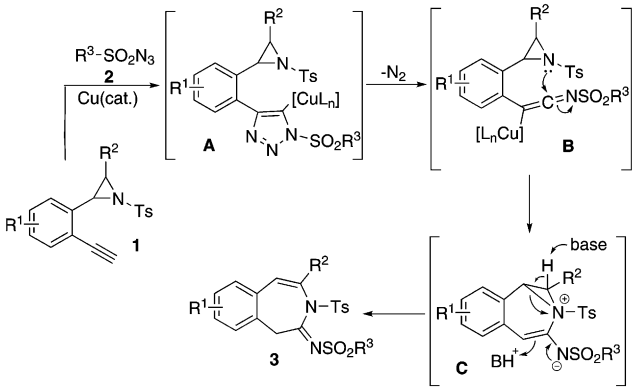
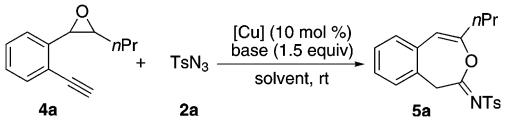


Scheme 2. A possible route for the copper(I)-catalyzed reaction of 2-(2-ethynylphenyl)-1-tosylaziridine **1** with sulfonyl azide **2**.

ture, the desired 3-benzoxepine derivative **5a** was produced in 61% yield (Table 3, entry 1). The structure of compound **5a** was further verified by X-ray diffraction analysis (see the Supporting Information).[6] With this promising result in hand, we continued to screen for optimal reaction conditions. After an extensive investigation of catalysts, bases, and solvents (Table 3, entries 2–12), we found the reaction worked efficiently when the reaction was catalyzed by 10 mol% of CuCl in the presence of diisopropylethylamine as the base in 1,4-dioxane, thus leading to the corresponding product **5a** in 83% yield (Table 3, entry 4).

Table 3. Optimization studies for the reaction of 2-(2-ethynylphenyl)-3-propyloxirane **4a** with 4-methylbenzenesulfonyl azide **2a**.

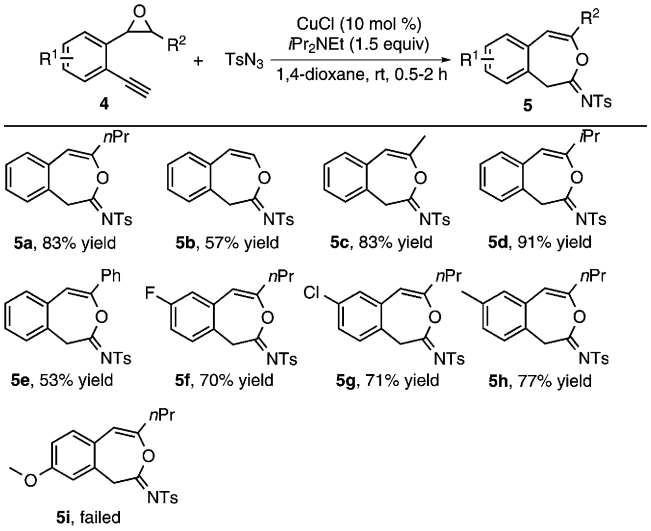


Entry	[Cu]	Base	Solvent	Yield [%][a]
1	CuBr	Et_3N	1,4-dioxane	61
2	CuI	Et_3N	1,4-dioxane	45
3	CuCl	Et_3N	1,4-dioxane	70
4	CuCl	iPr_2NEt	1,4-dioxane	83
5	CuCl	Pyridine	1,4-dioxane	60
6	CuCl	K_2CO_3	1,4-dioxane	35
7	CuCl	K_3PO_4	1,4-dioxane	38
8	CuCl	iPr_2NEt	THF	33
9	CuCl	iPr_2NEt	$(CH_2Cl)_2$	47
10	CuCl	iPr_2NEt	MeCN	25
11	CuCl	iPr_2NEt	Toluene	51
12	CuBr	Et_3N	DMSO	16

[a] Yield of isolated product based on 2-(2-ethynylphenyl)-3-propyloxirane **4a**.

After establishing the optimal reaction conditions, the scope and generality of this copper(I)-catalyzed reaction of 2-(2-ethynylphenyl)oxirane **4** with 4-methylbenzenesulfonyl azide **2** were explored (Table 4). It was found that various 2-(2-ethynylphenyl)oxiranes **4** participated successfully in the reaction and generated good results, except for the methoxy-substituted substrate.

Table 4. Scope investigation for the copper(I)-catalyzed reaction of 2-(2-ethynylphenyl)oxirane **4** with 4-methylbenzenesulfonyl azide **2a.**



[a] Yield of isolated product based on 2-(2-ethynylphenyl)oxirane **4**.

This was mainly due to the stability issue of the methoxy-substituted product **5i**, as it decomposed extremely quickly during the process of purification. Interestingly, compared with the results obtained from the reactions of 2-(2-ethynylphenyl)-1-tosylaziridines **1** with sulfonyl azides **2** (Table 2), no isomerized products were found in the reactions. The presence of a tosyl group on the nitrogen atom of the aziridine might force the subsequent isomerization, thus resulting in a different outcome.

Conclusions

In conclusion, we have described a novel and efficient approach for the concise synthesis of benzazepine and benzoxepine derivatives through a copper-catalyzed reaction of (2-ethynylphenyl)-1-tosylaziridine or 2-(2-ethynylphenyl)oxirane with sulfonyl azide. The mild reaction conditions and short reaction time enable the protocol to be attractive for further library construction. Applications of ketenimine chemistry for the formation of other heterocycles are ongoing.

Experimental Section

*General experimental procedure for the copper(I)-catalyzed reaction of 2-(2-ethynylphenyl)-1-tosylaziridine **1** with sulfonyl azide **2***

Triethylamine (45 mg, 0.45 mmol) was added to a solution of 2-(2-ethynylphenyl)-1-tosylaziridine **1** (0.3 mmol), sulfonyl azide **2** (0.36 mmol), and copper(I) bromide (4.2 mg, 0.03 mmol) in 1,2-dichloroethane (3.0 mL). The resulting mixture was stirred at room temperature under N_2 atmosphere. After completion of the reaction as indicated by TLC, the mixture was diluted with CH_2Cl_2 (10 mL) and filtered through a thin layer of silica gel. The solvent was evaporated and the residue was purified by column chromatography on silica gel (eluted with petroleum ether (b.p. 60/90)/EtOAc = 4:1) to provide products **3**.

*4-Methyl-N-(3-tosyl-1H-benzo[d]azepin-2(3H)-ylidene)benzenesulfonamide (**3a**)*

Yield: 85%; White solid; M.p.: 152.3–153.3°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.27 (s, 3H), 2.45 (s, 3H), 4.09 (s, 2H), 6.63 (d, J = 9.6 Hz, 1H), 6.89 (d, J = 8.0 Hz, 2H), 7.25–7.37 (m, 8H), 7.57 (d, J = 7.2 Hz, 1H), 7.74 ppm (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 38.9, 120.4, 122.6, 127.0, 127.6, 128.1, 128.8, 129.2, 129.3, 129.9, 130.0, 131.2, 133.0, 134.7, 138.7, 143.4, 145.3 ppm; IR: $\tilde{\nu}$ = 3061, 1631, 1593, 1492, 1303, 1188 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{22}N_2O_4S_2$: 467.1094 [M+H$^+$]; found: 467.1108.

*N-(7-Fluoro-3-tosyl-1H-benzo[d]azepin-2(3H)-ylidene)-4-methylbenzenesulfonamide (**3b**)*

Yield: 78%; White solid; M.p.: 168.5–169.5°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 3H), 2.47 (s, 3H), 4.09 (s, 2H), 6.55 (d, J = 9.6 Hz, 1H), 6.90–6.97 (m, 3H), 7.05–7.09 (m, 1H), 7.29–7.34 (m, 5H), 7.54–7.57 (m, 1H), 7.74 ppm (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 21.7, 38.1, 113.7 (d, $^2J_{CF}$ = 22.0 Hz), 117.1 (d, $^2J_{CF}$ = 21.9 Hz), 119.2, 123.7, 126.9, 127.0, 127.0, 128.8, 129.2, 131.8 (d, $^3J_{CF}$ = 7.7 Hz), 134.5, 134.7 (d, $^3J_{CF}$ = 8.6 Hz), 138.5, 143.6, 145.4, 159.5, 162.3 ppm (d, $^1J_{CF}$ = 245.0 Hz); IR: $\tilde{\nu}$ = 1632, 1595, 1152 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{21}FN_2O_4S_2$: 485.1000 [M+H$^+$]; found: 485.1011.

*N-(7-Chloro-3-tosyl-1H-benzo[d]azepin-2(3H)-ylidene)-4-methylbenzenesulfonamid (**3c**)*

Yield: 75%; White solid; M.p.: 169.9–170.9°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 3H), 2.47 (s, 3H), 4.10 (s, 2H), 6.53 (d, J = 10.6 Hz, 1H), 6.91 (d, J = 7.6 Hz, 2H), 7.25 (s, 1H), 7.32–7.34 (m, 6H), 7.52 (d, J = 8.4 Hz, 1H), 7.73 ppm (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 38.3, 118.8, 123.8, 127.0, 127.2, 127.2, 128.9, 129.3, 129.4, 129.5, 129.9, 131.4, 134.0, 134.5, 134.5, 138.5, 143.6, 145.5, 159.2 ppm; IR: $\tilde{\nu}$ = 2923, 1627, 1594 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{21}ClN_2O_4S_2$: 501.0704 [M+H$^+$]; found: 501.0707.

*4-Methyl-N-(7-methyl-3-tosyl-1H-benzo[d]azepin-2(3H)-ylidene)benzenesulfonamide (**3d**)*

Yield: 90%; White solid; M.p.: 153.8–154.8°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.28 (s, 3H), 2.32 (s, 3H), 2.46 (s, 3H), 4.09 (s, 2H), 6.59 (d, J = 10.0 Hz, 1H), 6.90 (d, J = 8.0 Hz, 2H), 7.07 (s, 1H), 7.18 (d, J = 7.6 Hz, 1H), 7.24 (d, J = 9.6 Hz, 1H), 7.30–7.33 (m, 4H), 7.46 (d, J = 9.6 Hz, 1H), 7.74 ppm (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 21.7, 38.6, 120.4, 122.5, 127.0, 127.9, 128.0, 128.4, 128.8, 129.2, 129.4, 129.8, 130.9, 132.9, 134.7, 137.9, 138.8, 143.4, 145.2, 159.9 ppm; IR: $\tilde{\nu}$ = 2968, 1616, 1323, 1158 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{24}N_2O_4S_2$: 481.1250 [M+H$^+$]; found: 481.1253.

*N-(8-Methoxy-3-tosyl-1H-benzo[d]azepin-2(3H)-ylidene)-4-methylbenzenesulfonamide (**3e**)*

Yield: 79%; White solid; M.p.: 163.7–164.7°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.28 (s, 3H), 2.46 (s, 3H), 3.80 (s, 3H), 4.10 (s, 2H), 6.58 (d, J = 9.6 Hz, 1H), 6.85–6.87 (m, 1H), 6.91 (d, J = 8.0 Hz, 2H), 7.10–7.13 (m, 1H), 7.15–7.18 (m, 2H), 7.32–7.34 (m, 4H), 7.75 ppm (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 21.7, 39.2, 55.5, 113.8, 115.5, 120.2, 120.8, 125.9, 127.0, 128.8, 128.9, 129.2, 129.3, 132.6, 134.7, 138.8, 143.4, 145.2, 159.2, 161.2 ppm; IR: $\tilde{\nu}$ = 2952, 1607, 1594, 1499, 1174 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{24}N_2O_5S_2$: 497.1199 [M+H$^+$]; found: 497.1195.

*N-(3-Tosyl-1H-benzo[d]azepin-2(3H)-ylidene)methanesulfonamide (**3f**)*

Yield: 76%; White solid; M.p.: 173.8–174.7°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 3H), 2.93 (s, 3H), 4.01 (s, 2H), 6.66 (d, J = 9.6 Hz, 1H), 7.23–7.35 (m, 6H), 7.50 (d, J = 9.2 Hz, 1H), 7.70 ppm (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 38.8, 42.8, 120.6, 122.6, 127.6, 128.2, 128.5, 129.6, 129.9, 131.1, 132.9, 135.3, 145.8, 160.2 ppm; IR: $\tilde{\nu}$ = 2926, 1595, 1368, 1136 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{18}N_2O_4S_2$: 391.0781 [M+H$^+$]; found: 391.0805.

*4-Bromo-N-(3-tosyl-1H-benzo[d]azepin-2(3H)-ylidene)benzenesulfonamide (**3g**)*

Yield: 87%; White solid; M.p.: 180.2–180.9°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (s, 3H), 4.17 (s, 2H), 6.68 (d, J = 9.6 Hz, 1H), 6.92 (d, J = 7.2 Hz, 2H), 7.26–7.39 (m, 6H), 7.57 (d, J = 6.8 Hz, 1H), 7.64–7.71 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 39.1, 120.8, 122.6, 127.5, 127.6, 128.2, 128.5, 128.6, 129.3, 130.0, 130.1, 130.1, 132.0, 132.9, 134.7, 140.6, 145.5, 160.1 ppm; IR: $\tilde{\nu}$ = 3055, 2911, 1637, 1592, 1365, 1148 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{19}BrN_2O_4S_2$: 531.0042 [M+H$^+$]; found: 531.0066.

*4-Methoxy-N-(3-tosyl-1H-benzo[d]azepin-2(3H)-ylidene)benzenesulfonamide (**3h**)*

Yield: 80%; White solid; M.p.: 149.8–150.8°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.28 (s, 3H), 3.88 (s, 3H), 4.17 (s, 2H), 6.63 (d, J = 9.6 Hz, 1H), 6.93 (d, J = 8.0 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H), 7.25–7.37 (m, 6H), 7.58 (d, J = 7.2 Hz, 1H), 7.79 ppm (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 38.8, 55.7, 113.8, 120.3, 122.7, 127.6, 128.1, 128.8, 129.1, 129.2, 129.9, 130.0, 131.2, 133.1, 133.5, 134.8, 145.3, 159.7, 163.0 ppm; IR: $\tilde{\nu}$ = 3080, 2916, 1627, 1593, 1493 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{22}N_2O_5S_2$: 483.1043 [M+H$^+$]; found: 483.1046.

*4-Nitro-N-(3-tosyl-1H-benzo[d]azepin-2(3H)-ylidene)benzenesulfonamide (**3i**)*

Yield: 61%; Yellow solid; M.p.: 209.0–210.0°C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.26 (s, 3H), 4.10 (s, 2H), 6.96 (d, J = 9.2 Hz, 1H), 7.11 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 9.2 Hz, 1H), 7.36–7.43 (m, 6H), 7.88 (d, J = 7.6 Hz, 2H), 8.41 ppm (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 21.7, 38.9, 122.3, 123.4, 125.1, 128.3, 128.4, 128.8, 129.9, 130.1, 130.4, 131.5, 133.3, 134.5, 146.2, 146.3, 150.4, 161.6 ppm; IR: $\tilde{\nu}$ = 3065, 2926, 1632, 1593, 1529 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{19}N_3O_6S_2$: 498.0788 [M+H$^+$]; found: 498.0814.

*N-(3-tosyl-1H-benzo[d]azepin-2(3H)-ylidene)benzenesulfonamide (**3j**)*

White solid; M.p.: 169.5–170.5°C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.27 (s, 3H), 4.12 (s, 2H), 6.65 (d, J = 9.6 Hz, 1H), 6.88 (d, J = 7.2 Hz, 2H), 7.27–7.40 (m, 6H), 7.52–7.54 (m, 2H), 7.58–7.63 (m, 2H), 7.86 ppm (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 21.7, 39.1, 120.5, 122.7, 127.0, 127.6, 128.1, 128.7, 128.8, 129.2, 130.0, 130.0, 131.1, 132.7, 133.0, 134.7, 141.5, 145.4, 160.0 ppm; IR: $\tilde{\nu}$ = 3060, 2921, 1627, 1592, 1447 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{20}N_2O_4S_2$: 453.0937 [M+H$^+$], found: 453.0947.

*4-Methyl-N-(4-methyl-3-tosyl-3H-benzo[d]azepin-2-yl)benzenesulfonamide (**3k**)*

Yield: 75%; White solid; M.p.: 164.0–165.0°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.66 (s, 3H), 2.06 (s, 3H), 2.44 (s, 3H), 6.24 (s, 1H), 6.63 (d, J = 7.2 Hz, 2H), 6.77–6.79 (m, 3H), 6.87 (s, 1H), 6.93–6.95 (m, 2H), 7.17 (d, J = 7.2 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.73 ppm (d, J = 7.2 Hz, 2H); ^{1}H NMR (400 MHz, $CDCl_3$+D_2O): δ = 1.66 (s, 3H), 2.06 (s, 3H), 2.44 (s, 3H), 6.24 (s, 1H), 6.63 (d, J = 7.2 Hz, 2H), 6.77–6.79 (m, 3H), 6.93–6.95 (m, 2H), 7.17 (d, J = 7.6 Hz, 2H), 7.29 (d, J = 7.2 Hz, 2H), 7.73 ppm (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 21.6, 24.1, 121.2, 126.3, 126.5, 127.2, 127.4, 127.8, 128.5, 129.3, 129.7, 129.7, 130.3, 132.0, 133.2, 134.5, 136.4, 138.7, 143.9, 144.4 ppm; IR: $\tilde{\nu}$ = 3264, 3060, 1597, 1353, 1165 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{24}N_2O_4S_2$: 481.1250 [M+H$^+$]; found: 481.1249.

*4-Methyl-N-(4-propyl-3-tosyl-3H-benzo[d]azepin-2-yl)benzenesulfonamide (**3l**)*

Yield: 57%; White solid; M.p.: 167.7–168.7°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82 (t, J = 6.4 Hz, 3H), 1.28–1.30 (m, 2H), 1.77–1.84 (m, 1H), 2.04 (s, 3H), 2.35–2.42 (m, 4H), 6.21 (s, 1H), 6.58 (d, J = 6.8 Hz, 2H), 6.71–6.73 (m, 2H), 6.81 (s, 1H), 6.91–6.93 (m, 3H), 7.06 (d, J = 6.4 Hz, 2H), 7.29 (d, J = 6.8 Hz, 2H), 7.76 ppm (d, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 20.6, 21.2, 21.6, 39.9, 117.8, 126.2, 127.5, 127.5, 127.9, 128.2, 128.5, 129.6, 129.6, 129.7, 130.1, 132.2, 133.1,

134.5, 136.4, 142.7, 143.8, 144.4 ppm; IR: $\tilde{\nu}$ = 3268, 3049, 1591, 1354, 1164 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{28}N_2O_4S_2$: 509.1563 [$M+H^+$]; found: 509.1565.

*4-Methyl-N-(4-phenyl-3-tosyl-3H-benzo[d]azepin-2-yl)benzenesulfonamide (**3m**)*

Yield: 62%; White solid; M.p.: 162.6–162.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.07 (s, 3H), 2.10 (s, 3H), 6.64 (d, J = 7.6 Hz, 2H), 6.79–6.83 (m, 3H), 6.97–6.99 (m, 2H), 7.04–7.05 (m, 2H), 7.10 (s, 1H), 7.19–7.21 (m, 5H), 7.34 (s, 1H), 7.44–7.47 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 21.5, 121.4, 125.3, 126.0, 126.7, 127.1, 127.2, 127.5, 127.8, 127.9, 128.2, 128.6, 129.3, 130.4, 130.7, 132.6, 133.4, 134.7, 135.8, 136.6, 138.0, 144.0 ppm; IR: $\tilde{\nu}$ = 3269, 3057, 1597, 1354, 1164 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{26}N_2O_4S_2$: 543.1407 [$M+H^+$]; found: 543.1408.

*General experimental procedure for the copper(I)-catalyzed reaction of 2-(2-ethynylphenyl)oxirane **4** with sulfonyl azide **2***

Diisopropylethylamine (58 mg, 0.45 mmol) was added to a solution of 2-(2-ethynylphenyl)oxirane **4** (0.3 mmol), 4-methylbenzenesulfonyl azide **2a** (71 mg, 0.36 mmol), and copper(I) chloride (3 mg, 0.03 mmol) in 1,4-dioxane (3.0 mL). The resulting mixture was stirred at room temperature under N_2 atmosphere. After completion of the reaction as indicated by TLC, the mixture was diluted with CH_2Cl_2 (10 mL) and filtered through a thin layer of silica gel. The solvent was evaporated and the residue was purified by column chromatography on silica gel (eluted with petroleum ether (b.p. 60/90)/EtOAc = 4:1) to provide the products **5**.

*4-Methyl-N-(4-propylbenzo[d]oxepin-2(1H)-ylidene)benzenesulfonamide (**5a**)*

Yield: 83%; White solid; M.p.: 158.0–159.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (t, J = 6.4 Hz, 3H), 1.46–1.58 (m, 2H), 2.31–2.37 (m, 5H), 3.55 (s, 2H), 6.23 (s, 1H), 7.17–7.30 (m, 6H), 7.78 ppm (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 20.5, 21.6, 37.0, 40.7, 111.7, 127.3, 127.8, 128.3, 128.9, 129.1, 129.3, 130.1, 132.4, 138.5, 143.5, 152.9, 164.8 ppm; IR: $\tilde{\nu}$ = 2962, 1648, 1602, 1501 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{21}NO_3S$: 356.1315 [$M+H^+$]; found: 356.1314.

*N-(benzo[d]oxepin-2(1H)-ylidene)-4-methylbenzenesulfonamide (**5b**)*

Yield: 57%; White solid; M.p.: 83.5–84.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3H), 3.61 (s, 2H), 6.39 (d, J = 6.0 Hz, 1H), 6.70 (d, J = 6.0 Hz, 1H), 7.23–7.25 (m, 4H), 7.34–7.36 (m, 2H), 7.79 ppm (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 40.9, 115.6, 127.2, 127.3, 128.4, 128.5, 129.3, 129.5, 129.9, 138.2, 143.6, 151.4, 164.6 ppm; IR: $\tilde{\nu}$ = 2961, 1610, 1321 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{15}NO_3S$: 314.0845 [$M+H^+$]; found: 314.0863.

*4-Methyl-N-(4-methylbenzo[d]oxepin-2(1H)-ylidene)benzenesulfonamide (**5c**)*

Yield: 83%; White solid; M.p.: 156.7–157.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.11 (s, 3H), 2.39 (s, 3H), 3.57 (s, 2H), 6.23 (d, J = 6.0 Hz, 1H), 7.16–7.31 (m, 6H), 7.79 ppm (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 21.6, 40.7, 112.1, 127.5, 127.6, 128.2, 128.5, 129.2, 129.3, 129.4, 132.4, 138.3, 143.6, 149.2, 164.4 ppm; IR: $\tilde{\nu}$ = 2961, 1610, 1154 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{17}NO_3S$: 328.1002 [$M+H^+$]; found: 328.1032.

*N-(4-Isopropylbenzo[d]oxepin-2(1H)-ylidene)-4-methylbenzenesulfonamide (**5d**)*

Yield: 91%; White solid; M.p.: 114.0–115.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (d, J = 6.4 Hz, 6H), 2.39 (s, 3H), 2.63–2.67 (m, 1H), 3.55 (s, 2H), 6.26 (s, 1H), 7.22–7.33 (m, 6H), 7.79 ppm (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.2, 20.6, 21.6, 33.9, 40.6, 109.4, 127.1, 128.1, 128.3, 128.5, 128.8, 129.1, 129.3, 138.5, 143.4, 158.4, 165.4 ppm; IR: $\tilde{\nu}$ = 2967, 1653, 1616, 1565 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{21}NO_3S$: 356.1315 [$M+H^+$]; found: 356.1337.

*4-Methyl-N-(4-phenylbenzo[d]oxepin-2(1H)-ylidene)benzenesulfonamide (**5e**)*

Yield: 53%; White solid; M.p.: 160.1–161.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3H), 3.70 (s, 2H), 7.06 (s, 1H), 7.21–7.28 (m, 3H), 7.35–7.44 (m, 6H), 7.74–7.82 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 40.7, 111.4, 125.5, 127.1, 128.6, 128.9, 129.4, 129.6, 129.7, 130.3, 130.4, 132.5, 133.2, 138.4, 143.5, 149.6, 160.7 ppm; IR: $\tilde{\nu}$ = 2922, 1655, 1448 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{19}NO_3S$: 390.1158 [$M+H^+$]; found: 390.1171.

*N-(7-Fluoro-4-propylbenzo[d]oxepin-2(1H)-ylidene)-4-methylbenzenesulfonamide (**5f**)*

Yield: 70%; Brown solid; M.p.: 145.0–146.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, J = 7.2 Hz, 3H), 1.50–1.56 (m, 2H), 2.33–2.35 (m, 2H), 2.39 (s, 3H), 3.53 (s, 2H), 6.17 (s, 1H), 6.87–7.26 (m, 5H), 7.78 ppm (d, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 20.4, 21.6, 37.0, 39.9, 110.7, 116.0 (d, $^2J_{CF}$ = 22.0 Hz), 116.3 (d, $^2J_{CF}$ = 20.9 Hz), 126.0, 127.0, 127.3, 129.2, 129.5, 130.4, 134.3, 138.3, 143.6, 153.9, 162.5 (d, $^1J_{CF}$ = 246.0 Hz), 164.3 ppm; IR: $\tilde{\nu}$ = 2962, 1615, 1495, 1322, 1158 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{20}FNO_3S$: 374.1221 [$M+H^+$]; found: 374.1240.

*N-(7-Chloro-4-propylbenzo[d]oxepin-2(1H)-ylidene)-4-methylbenzenesulfonamide (**5g**)*

Yield: 71%; Brown solid; M.p.: 101.2–102.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, J = 6.8 Hz, 3H), 1.53–1.61 (m, 2H), 2.35–2.43 (m, 5H), 3.54 (s, 2H), 6.15 (s, 1H), 7.18–7.27 (m, 5H), 7.79 ppm (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 20.4, 21.6, 37.0, 40.1, 110.6, 127.3, 127.6, 128.6, 128.8, 129.2, 129.5, 134.1, 138.2, 143.7, 154.0, 164.2 ppm; IR: $\tilde{\nu}$ = 2962, 1616, 1485, 1323, 1162 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{20}ClNO_3S$: 390.0925 [$M+H^+$]; found: 390.0947.

*4-Methyl-N-(7-methyl-4-propylbenzo[d]oxepin-2(1H)-ylidene)benzenesulfonamide (**5h**)*

Yield: 77%; White solid; M.p.: 100.5–101.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, J = 7.6 Hz, 3H), 1.49–1.53 (m, 2H), 2.30–2.41 (m, 2H), 2.33 (s, 3H), 2.39 (s, 3H), 3.52 (s, 2H), 6.18 (s, 1H), 6.98–7.25 (m, 5H), 7.79 ppm (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 20.5, 21.1, 21.6, 37.0, 40.3, 111.7, 127.3, 128.2, 128.8, 129.3, 130.0, 132.2, 138.1, 138.5, 143.4, 152.7, 164.9 ppm; IR: $\tilde{\nu}$ = 2961, 1613, 1450, 1303 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{23}FNO_3S$: 370.1471 [$M+H^+$]; found: 370.1492.

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[6] CCDC 900860 (**3a**) and CCDC 887777 (**5a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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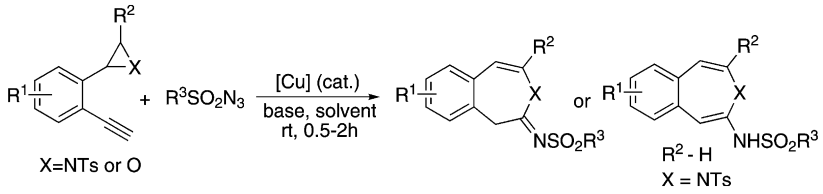

Copper on the beat: An efficient and facile synthetic protocol for the construction of benzazepine and benzoxepine derivatives through a copper(I)-catalyzed reaction of 2-(2-ethynylphenyl)-1-tosylaziridine or 2-(2-ethynylphenyl)oxirane with sulfonyl azides is disclosed.

Tandem Cyclizations

*Shaoyu Li, Shaowu Zou, Jie Wu** ——— ▮▮▮▮–▮▮▮▮

An Efficient Approach for the Construction of Benzazepine and Benzoxepine Derivatives

