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FULL PAPER

Accessing Quinoxalines via Ring Opening-Cyclization-Detosylation-Aromatization of Activated Aziridines with 2-Bromoanilines: Synthesis of Tyrphostin AG 1296

Chandan Kumar Shahi,[a] Sajan Pradhan,[a] Aditya Bhattacharyya,[a] Raushan Kumar[a] and Manas K. Ghorai*[a]

Dedicated to Prof. Ganesh Pandey on the occasion of his 63rd birthday.

Abstract: Synthesis of substituted 2-arylquinoxalines via an unprecedented Cu(I) catalyzed ring-opening-cyclization followed by detosylation-aromatization of activated aziridines with 2-bromoanilines has been accomplished. The transformation efficiently accommodates a wide range of aziridines and 2-bromoanilines to afford the desired quinoxaline frameworks in excellent yields (up to 86%) as a single regioisomer. The methodology has also been conveniently applied for the synthesis of tyrphostin AG 1296, a PDGF-receptor tyrosine kinase inhibitor.

Introduction

Quinoxalines are an important class of heterocycles found in numerous biologically active compounds and are of immense pharmacological significance and synthetic utility. A few representative quinoxaline-based drug candidates are depicted in Figure 1. For example, **I** (RPR 101511A)[1] and **II** (tyrphostin AG 1296)[2] are PDGF-receptor tyrosine kinase inhibitors, **III** (CP 99,711) is a non-peptide glucagon receptor antagonist,[3] and echinomycin (**IV**) is a well-known peptide antibiotic.[4] Quinoxaline derivatives are also used in the preparation of dyes,[5] electroluminescent materials,[6] organic semiconductors,[7] dehydroannulenes,[8] cavitands,[9] and chemically controllable switches.[10] Owing to their valuable applications, a number of interesting strategies have been developed for the synthesis of substituted and functionalized quinoxalines. The general synthetic routes to quinoxalines[11] comprise condensation of various two-carbon unit suppliers with 1,2-diaminobenzenes,[12] *o*-benzoquinone diimines and diimides, and condensation of *N*,*N*-dimethyl(dibenzyl) ethylenediamine with 1,2- and 1,4-dihydroxybenzenes.[11] Other routes include visible-light photoredox catalysis,[13] sp^3 and sp^2 C–H cross-dehydrogenative coupling,[14] copper-catalyzed cycloamination of α-Csp^3–H bond of N-aryl ketimines with sodium azide,[15] aerobic oxidative aromatization of N-heterocycles[16] etc. For more than a decade, we are involved in exploring the S_N2-type ring-opening

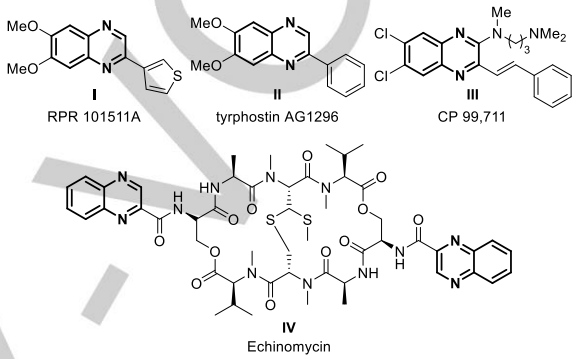


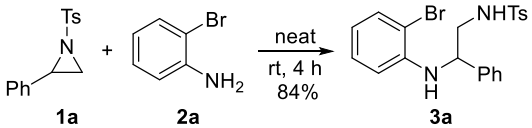
Figure 1. A few representative examples of biologically active quinoxaline derivatives

transformations of activated aziridines and azetidines to produce a diverse array of nitrogen-containing high-value functional motifs.[17] Cognizant of the synthetic importance and usefulness of quinoxaline skeletons, we envisaged an effective approach to access such moieties from activated aziridines via ring opening with 2-bromoanilines[18] followed by an unprecedented copper(I)-catalyzed C-N cyclization-detosylation-aromatization cascade. In this article, we wish to report our results in detail.

Results and Discussion

The study was initiated with the ring-opening reaction of racemic 2-phenyl-*N*-tosylaziridine (**1a**) with 2-bromoaniline (**2a**) in neat condition at room temperature following our earlier report.[18] The reaction completed in 4 h and the corresponding ring-opened product **3a** was obtained in 84% yield as a single regioisomer (Scheme 1).

To investigate the viability of our approach, we carried out the metal-assisted C-N bond formation of **3a** in the presence of 10 mol % CuI, 20 mol % glycine, and 2.5 equiv of NaH in DMF at 125 °C and the transformation predominantly furnished the corresponding product, 2-phenylquinoxaline (**4a**), in 62% yield in 15 h, evidently following a sequence of consecutive cyclization,



Scheme 1. Regioselective ring-opening of 2-phenyl-*N*-tosylaziridine (**1a**) with 2-bromoaniline (**2a**).

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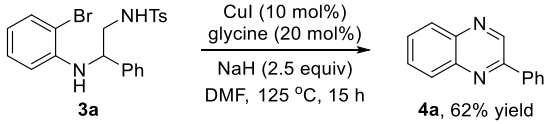


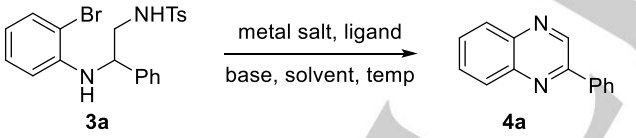
Scheme 2. Synthesis of 2-phenylquinoxaline (**1a**) with 2-bromoaniline (**2a**).

detosylation, and aromatization reactions in a step-economic fashion (Scheme 2). The structure of the product was unambiguously determined and confirmed with the help of spectroscopic and analytical data.[19]

Subsequently, several combinations of metal salts, ligands, and bases were examined in order to obtain the desired quinoxaline derivative **4a** in increased yield and the screening results are shown in Table 1. Other copper salts such as CuBr (entry 2) and Cu_2O with either glycine (entry 3) or 1,10-phenanthroline (entry 4) as ligands were found to be ineffective to enhance the efficiency of the transformation. Using 10 mol % CuI and altering the ligand from glycine (entry 1) to 20 mol % L-proline (entry 5) in the presence of 2.5 equiv of NaH markedly improved the yield of the reaction (75%, entry 5). $Pd(OAc)_2$ coupled with (±)-BINAP as ligand in the presence of either Cs_2CO_3 (2.5 equiv, entry 6) or K_2CO_3 (2.5 equiv, entry 7) resulted in inferior yields of the desired product **4a** (56 and 58%, respectively).

Under the optimized reaction conditions, the generality of our strategy was next explored by employing different 2-aryl-*N*-tosylaziridines bearing different alkyl and halogen-substitutions at different positions of the 2-aryl rings. When aziridines **1b–g** reacted with 2-bromoaniline (**2a**) in neat condition at room temperature, the corresponding ring-opened products, 1,2-diamine derivatives **3b–g**, formed in very high yields (up to 81% yield). Subsequently, when **3b–g** were treated with 10 mol % CuI and 20 mol % L-proline in the presence of 2.5 equiv of NaH in DMF at 125 °C, the corresponding 2-arylquinoxalines **4b–g** were obtained in good yields (up to 72%) in all the cases. The methodology was found to be amenable to a wide range of activated aziridines harboring different alkyl (4-CH_3; **1b**, entry 2) and halogen substituents either at 4- (F, Cl, Br; **1c–e**, entries 3–5) or 3-positions of the 2-aryl group (Cl, Br; **1f–g**, entries 6-7), thereby providing handles for further synthetic manipulations. All of the results are shown in Table 2 in detail.

Table 1. Optimization of the reaction conditions for the synthesis of quinoxaline **4a**[a]

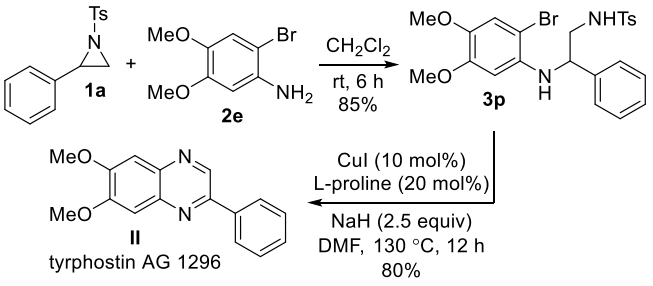


entry	metal salt, ligand, base, solvent	T (°C)	*t* (h)	yield (%)
1	CuI, glycine, NaH, DMF	125	15	62
2	CuBr, glycine, NaH, DMF	125	15	60
3	Cu_2O, glycine, NaH, DMF	125	15	50
4	Cu_2O, 1,10-phenanthroline, NaH, DMF	125	15	52
5	CuI, L-proline, NaH, DMF	125	15	75
6	$Pd(OAc)_2$, (±)-BINAP, Cs_2CO_3, DMF	125	15	56
7	$Pd(OAc)_2$, (±)-BINAP, K_2CO_3, DMF	125	15	58

[a] Unless noted otherwise, all the reactions were carried out with 10 mol % metal salt, 20 mol % ligand, and 2.5 equiv of the base.

With a view to expanding the scope of our methodology various substituted 2-aryl-*N*-tosylaziridines and 2-bromoaniline derivatives **2b–d** were undertaken. When 4-methyl-2-bromoaniline (**2b**) was reacted with aziridine **1a** followed by Cu(I)-catalyzed cyclization/detosylation/aromatization cascade, 6-methyl-2-phenylquinoxaline (**4h**) formed in very high yield through the intermediacy of the corresponding ring-opened product **3h** (entry 1). Comparable results were obtained when other 2-aryl-*N*-tosylaziridines with halogen substituents at 4- (F, **1c**, entry 2; Br, **1e**, entry 3) and 3-positions (Cl, **1f**, entry 4; Br, **1g**, entry 5) of the aryl ring were engaged as substrates in the ring-opening cyclization process with **2b**. In all of the cases, the corresponding quinoxaline derivatives **4i–l** were obtained in very good yields (up to 78%) as single regioisomers. When the relative steric crowding was enhanced in the nucleophile (e. g. 2-bromo-4-isopropylaniline **2c**), a marginal increase in the efficiency of both of the ring opening and subsequent cyclization/detosylation/aromatization of aziridines (**1a** and **1d)** was observed and the corresponding quinoxalines (**4m** and **4n)** were obtained in excellent yields (up to 86%, entries 6 and 7). On the other hand, when slightly electron-deficient 2-bromoaniline derivative **2d** was employed as a nucleophile (4-ClC_6H_3), the corresponding quinoxaline derivative **4o** formed in slightly reduced yield (64%, entry 8). All of the results are detailed in Table 3.

To demonstrate the synthetic utility of our developed methodology synthesis of tyrphostin AG 1296 (**II**), a potent and selective inhibitor of PDGF receptor kinase,[19] has been accomplished in excellent yield via ring opening of 2-phenyl-*N*-tosylaziridine (**1a**) with 4,5-dimethoxy-2-bromoaniline (**2e**) in dichloromethane followed by Cu(I) catalyzed C-N cyclization-detosylation-aromatization cascade under the optimized reaction condition (Scheme 3).



Scheme 3. Synthesis of tyrphostin AG 1296 via ring opening of **1a** with **2e** followed by cyclization-detosylation-aromatization cascade

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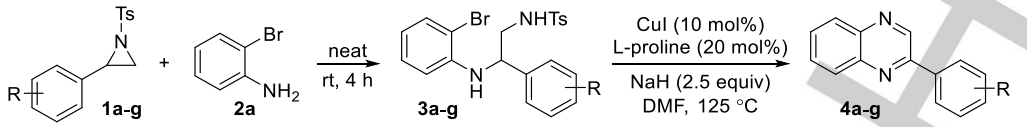
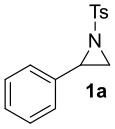
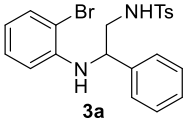
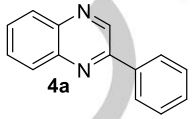
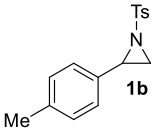
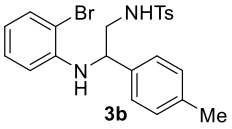
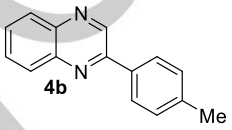
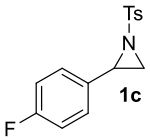
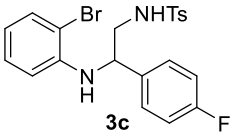
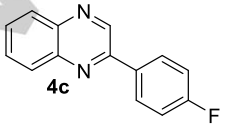
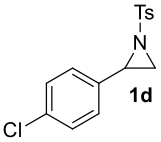
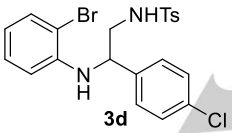
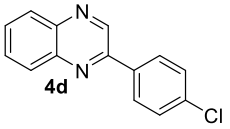
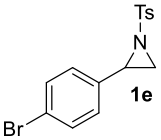
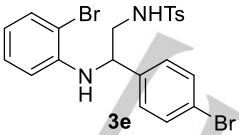
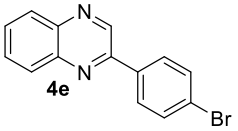
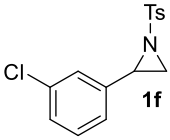
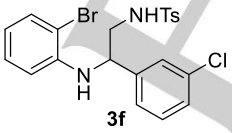
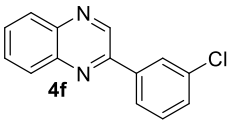
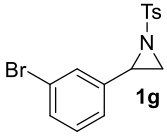
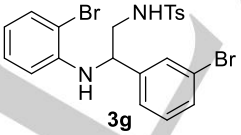
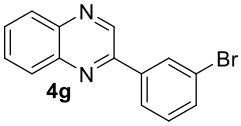
Table 2. Synthesis of 2-arylquinoxalines from 2-aryl-*N*-tosylaziridines



entry	**1**, R	*t* (h)	**3**	yield (%)	*t* (h)	**4**	yield (%)
1	 **1a**	4	 **3a**	84	12	 **4a**	70
2	 **1b**	6	 **3b**	81	12	 **4b**	72
3	 **1c**	4	 **3c**	80	16	 **4c**	68
4	 **1d**	5	 **3d**	78	15	 **4d**	69
5	 **1e**	4	 **3e**	77	14	 **4e**	70
6	 **1f**	5	 **3f**	80	14	 **4f**	67
7	 **1g**	6	 **3g**	76	13	 **4g**	72

[a] Unless noted otherwise, all the reactions were carried out with 10 mol % metal salt, 20 mol % ligand, and 2.5 equiv of the base.

Mechanism

Based on our observations we propose that the transformation proceeds via an initial S_N2-type ring opening of *N*-tosylaziridines with 2-bromoanilines regioselectively at the benzylic position (Scheme 4).[18,20] Subsequently, the ring-opened product **3** enters into a well-documented Cu(I) catalytic cycle to effect a second C–N bond formation via oxidative addition and reductive elimination pathway to form the tetrahydroquinoxaline intermediate **D** through the generation of the intermediates **B** and **C**.[21] Subsequent base-mediated detosylation of **D** and rearomatization of **E** produce another dihydroquinoxaline derivative **F** with two free amine groups. **F** concomitantly participates in a SET process in the presence of Cu catalyst to afford the corresponding radical cation **G** that further undergoes cross dehydrogenation to produce the iminium intermediate **H**.[17e] **H** then undergoes deprotonation in the basic condition to deliver the desired 2-arylquinoxaline derivative **4**.[22]

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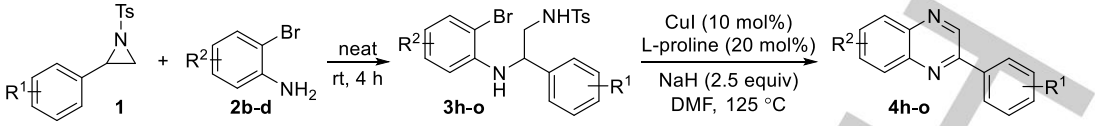
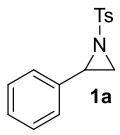
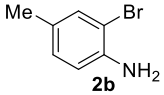
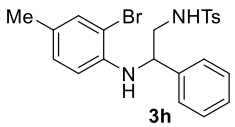
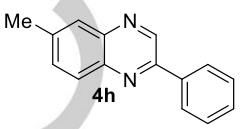
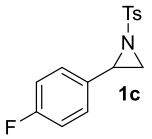
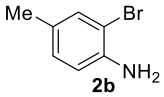
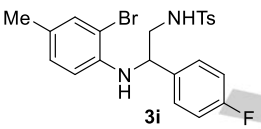
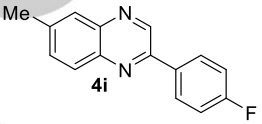
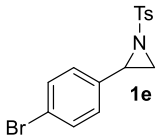
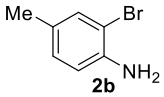
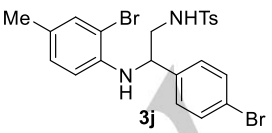
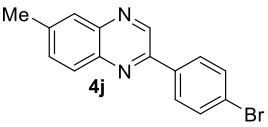
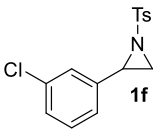
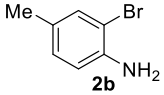
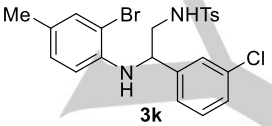
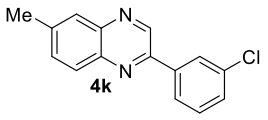
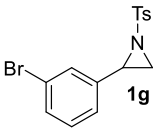
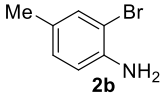
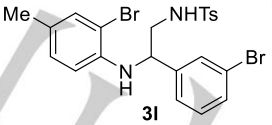
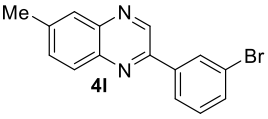
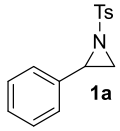
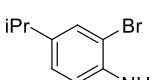
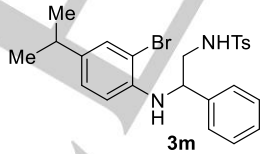
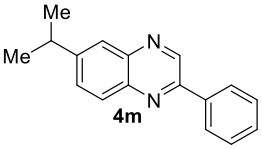
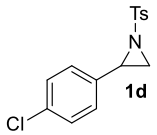
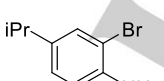
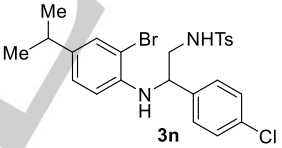
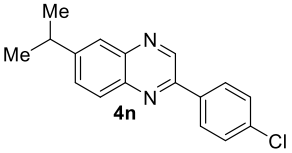
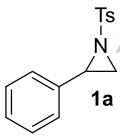
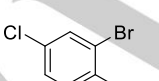
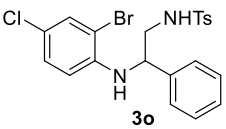
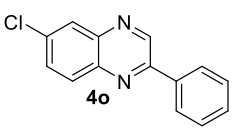
Table 3. Synthesis of Substituted 2-Arylquinoxalines from 2-Aryl-*N*-tosylaziridines



entry	1	2	*t* (h)	3	yield (%)	*t* (h)	4	yield (%)
1	 **1a**	 **2b**	5	 **3h**	80	11	 **4h**	81
2	 **1c**	 **2b**	5	 **3i**	78	13	 **4i**	77
3	 **1e**	 **2b**	6	 **3j**	79	12	 **4j**	78
4	 **1f**	 **2b**	6	 **3k**	78	14	 **4k**	78
5	 **1g**	 **2b**	6	 **3l**	76	14	 **4l**	76
6	 **1a**	 **2c**	5	 **3m**	84	12	 **4m**	86
7	 **1d**	 **2c**	5	 **3n**	83	12	 **4n**	84
8	 **1a**	 **2d**	6	 **3o**	73	16	 **4o**	64

Conclusions

In summary, we have developed a direct and expedient synthetic route to a wide range of 2-arylquinoxalines in excellent yields from readily available 2-aryl-*N*-tosylaziridines and 2-bromoanilines following a ring opening-cyclization-detosylation-aromatization cascade in the presence of Cu(I) catalyst. It is a significant advancement in the area of synthesis of quinoxalines considering the use of low-cost alternative of Cu-salt in place of other expensive transition metal catalysts to effect the C-N coupling

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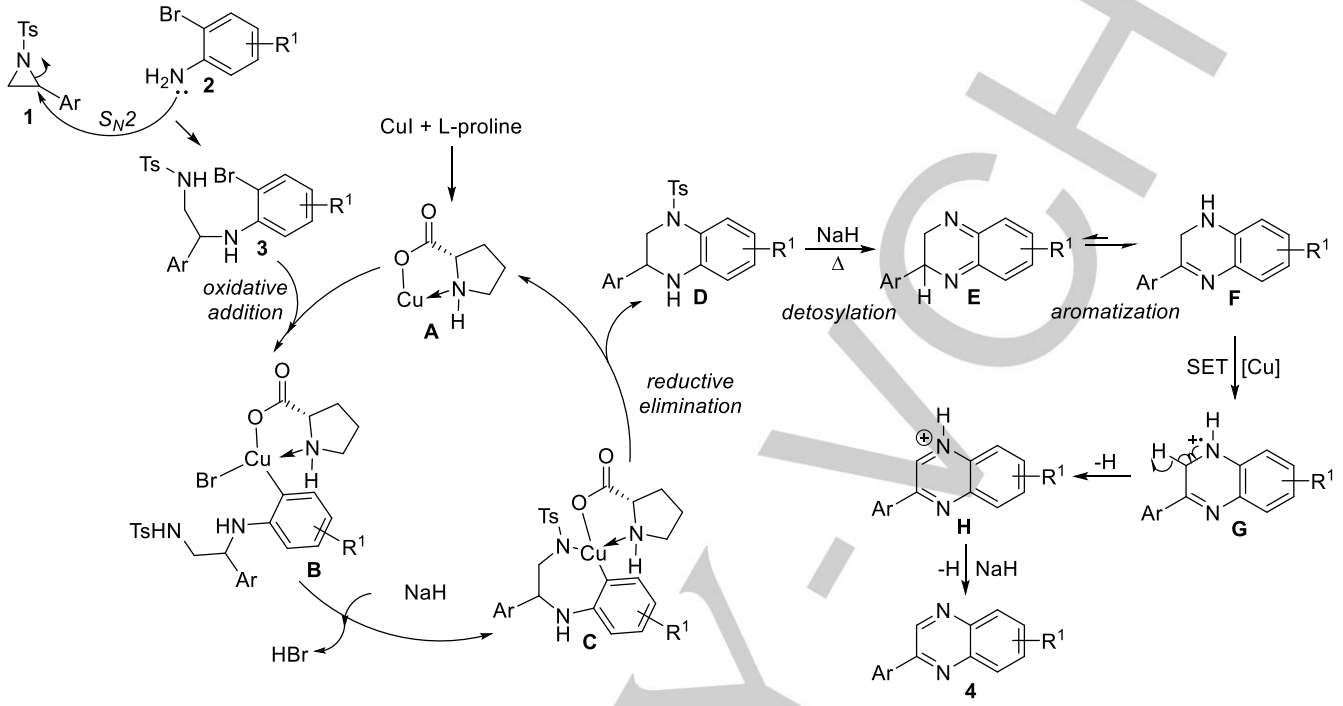
reaction and subsequent detosylation and aromatization. Considering the ubiquity and usefulness of the aromatic pharmaceutical agents, we believe that the present methodology will be helpful for the practicing synthetic and medicinal chemists.



Scheme 4. Plausible mechanistic pathway for the formation of 2-arylquinoxalines from 2-aryl-*N*-tosylaziridines via ring opening-cyclization-detosylation-aromatization cascade

Experimental Section

General Procedures. Analytical thin layer chromatography (TLC) was carried out using silica gel 60 F_{254} pre-coated plates. Visualization was accomplished with UV lamp or I_2 stain. Silica gel 230−400 mesh size was used for flash column chromatography using the combination of ethyl acetate and petroleum ether as eluent. Unless noted, all reactions were carried out in oven-dried glassware under an atmosphere of nitrogen/argon using anhydrous solvents. Where appropriate, all reagents were purified prior to use following the guidelines of Armerego and Chai.[23] All mono-substituted aziridines were prepared from the corresponding amino alcohol following earlier report. All other commercial reagents were used without further purification. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 400 MHz/500 MHz. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethyl silane (δ 0.00). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), doublet of doublets (dd), triplet of doublets (td), triplet (t), quartet (q), multiplet (m). Proton-decoupled carbon nuclear magnetic resonance (^{13}C{^{1}H} NMR) spectra were recorded at 100 MHz/125 MHz. Mass spectra (MS) were obtained using ESI-TOF mass spectrometers. IR spectra were recorded as neat for liquid and in KBr for solids.

General Procedure for the Ring Opening reaction of Aziridines.

Method A. A solution of aziridines (1.0 equiv) in 2-bromoanilines (3.0 equiv.) was taken under N_2 atmosphere in a two-necked round bottom flask. The reaction mixture was stirred for appropriate time. The reaction was monitored by TLC and quenched with water. The aqueous layer was extracted with EtOAc (3 × 10.0 mL). The combined organic extract was washed with brine (15.0 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give crude product which was purified by flash column chromatography on silica gel (230–400 mesh) using ethyl acetate in petroleum ether to afford the pure products as white solids.

Method B. A solution of the aziridine ring opening product (1.0 eqiv.) in 1.0 mL of DMF solvent was added to a suspension of CuI (10 mol %), L-proline (20 mol %), and NaH (2.5 equiv.) in 1.0 mL of DMF under argon atmosphere and the mixture was heated to 125−130 °C for 8−16 h. The reaction was monitored by TLC. It was cooled to room temperature and quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate (4 × 8.0 mL). The combined organic extract was washed with brine (15.0 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude product, which was purified by flash column chromatography on silica gel (230−400 mesh) using ethyl acetate in petroleum ether to afford the pure product.

2-Phenylquinoxaline (4a). The general method B described above was followed when **3a** (50 mg, 0.112 mmol) in 1.0 mL of DMF solvent was added to a suspension of CuI (2.1 mg, 0.011 mmol), L-proline (2.6 mg, 0.022 mmol), and NaH (6.7 mg, 0.281 mmol) in 1.0 mL of DMF under argon atmosphere and the mixture was heated to 130 °C for 12 hrs to afford **4a** (16.2 mg, 0.079 mmol) as a light yellow solid in 70% yield; mp 78–80 °C; R_f 0.60 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3059, 2925, 1549, 1491, 1446, 1350, 1317, 1077, 958, 840, 763; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.59 (m, 3H), 7.73–7.80 (m, 2H), 8.11–8.21 (m, 4H), 9.33 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 127.6, 129.2,

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129.6, 129.7, 130.3, 130.4, 136.9, 141.7, 142.4, 143.4, 151.9; HRMS (ESI-TOF) calcd for $C_{14}H_{11}N_2$ (M + H)$^+$ 207.0922, found 207.0926.

2-(*p*-Tolyl)quinoxaline (4b). The general method B described above was followed when **3b** (50 mg, 0.110 mmol) in 1.0 mL of DMF solvent was added to a suspension of CuI (2.1 mg, 0.011 mmol), L-proline (2.6 mg, 0.022 mmol), and NaH (6.5 mg, 0.272 mmol) in 1.0 mL of DMF under argon atmosphere and the mixture was heated to 130 °C for 12 h to afford **4b** (17.3 mg, 0.079 mmol) as a yellow solid in 72% yield; mp 92–94 °C; R_f 0.65 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3056, 2934, 1544, 1446, 1317, 1079, 1065, 956, 841, 763; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.36 (d, J = 8.2 Hz, 2H), 7.69–7.78 (m, 2H), 8.08–8.14 (m, 4H), 9.30 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.5, 127.5, 129.2, 129.4, 129.6, 130.0, 130.3, 134.1, 140.6, 141.5, 142.4, 143.4, 151.9; HRMS (ESI-TOF) calcd for $C_{15}H_{13}N_2$ (M + H)$^+$ 221.1079, found 221.1075.

***N*-(2-((2-Bromophenyl)amino)-2-(4-fluorophenyl)ethyl)-4-methylbenzenesulfonamide (3c).** The general method A described above was followed when **1c** (50 mg, 0.172 mmol) was reacted with **2a** (56 μL, 0.515 mmol) at rt for 4 h to afford **3c** (63.6 mg, 0.137 mmol) as a white semi-solid in 80% yield; mp 116–118 °C; R_f 0.30 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3373, 3284, 3068, 2859, 1931, 1702, 1589, 1511, 1478, 1461, 1432, 1321, 1278, 1256, 1179, 1158, 1092, 1074, 1046, 1027, 954, 881, 821, 747, 703, 663, 550; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 3.17–3.24 (m, 1H), 3.33–3.40 (m, 1H), 4.43–4.47 (m, 1H), 4.78 (t, J = 6.9 Hz, 1H), 4.92 (d, J = 5.9 Hz, 1H), 6.25 (dd, J = 1.4, 8.2 Hz, 1H), 6.54 (td, J = 1.4, 7.8 Hz, 1H), 6.94–7.00 (m, 3H), 7.20–7.26 (m, 4H), 7.39 (dd, J = 1.4, 7.8 Hz, 1H), 7.71 (d, J = 8.3 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.6, 49.1, 56.9, 110.4, 110.5, 112.8, 116.0, 116.2, 118.9, 127.1, 128.1, 128.2, 128.4, 129.9, 132.5, 143.3, 143.9, 162.4 (d, $^1J_{C-F}$ = 246.8 Hz); HRMS (ESI-TOF) calcd for $C_{21}H_{21}BrFN_2O_2S$(M + H)$^+$ 463.0491, found 463.0494.

2-(4-Fluorophenyl)quinoxaline (4c). The general method B described above was followed when **3c** (50 mg, 0.108 mmol) in 1.0 mL of DMF solvent was added to a suspension of CuI (2.1 mg, 0.011 mmol), L-proline (2.5 mg, 0.022 mmol), and NaH (6.5 mg, 0.270 mmol) in 1.0 mL of DMF under argon atmosphere and the mixture was heated to 130 °C for 16 h to afford **4c** (16.5 mg, 0.073 mmol) as a light yellow solid in 68% yield; mp 120–122 °C; R_f 0.55 (20% ethyl acetate in petroleum ether); mp: 120-122 ^{0}C; IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3063, 2961, 1591, 1497, 1454, 1366, 1169, 1078, 962, 836, 819; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.50 (m, 2H), 7.73–7.81 (m, 2H), 8.03–8.06 (m, 1H), 8.10–8.16 (m, 2H), 8.21–8.22 (m, 1H), 9.28 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 116.2, 116.4, 129.2, 129.5, 129.6, 129.6, 129.7, 130.5, 132.4, 133.0, 141.5, 142.3, 143.0, 150.8, 164.3 (d, $^1J_{C-F}$ = 250.1 Hz); HRMS (ESI-TOF) calcd for $C_{14}H_{10}FN_2$ (M + H)$^+$ 225.0828, found 225.0824.

2-(4-Chlorophenyl)quinoxaline (4d). The general method B described above was followed when **3d** (50 mg, 0.104 mmol) in 1.0 mL of DMF solvent was added to a suspension of CuI (2.0 mg, 0.010 mmol), L-proline (2.4 mg, 0.021 mmol), and NaH (6.3 mg, 0.261 mmol) in 1.0 mL of DMF under argon atmosphere and the mixture was heated to 130 °C for 15 h to afford **4d** (17.3 mg, 0.072 mmol) as a white solid in 69% yield; mp 134–136 °C; R_f 0.5 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2965, 2941, 2789, 1588, 1476, 1449, 1421, 1350, 1312, 1250, 1164, 958, 840, 763, 683; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.54 (m, 2H), 7.73–7.80 (m, 2H), 8.10–8.15 (m, 4H), 9.29 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 128.8, 129.2, 129.5, 129.7, 129.9, 130.6, 135.2, 136.7, 141.7, 142.3, 142.9, 150.6.; HRMS (ESI-TOF) calcd for $C_{14}H_{10}ClN_2$ (M + H)$^+$ 241.0533, found 241.0539.

***N*-(2-(4-Bromophenyl)-2-((2-bromophenyl)amino)ethyl)-4-methylbenzenesulfonamide (3e).** The general method A described above was followed when **1e** (50 mg, 0.142mmol) was reacted with **2a** (46 μL, 0.426 mmol) at rt for 4 h to afford **3e** (57.3 mg, 0.109 mmol) as a white solid in 77% yield; mp 112–114 °C; R_f 0.35 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3371, 3281, 3063, 2924, 2855, 1913, 1732, 1596, 1510, 1488, 1460, 1430, 1405, 1322, 1290, 1264, 1185, 1159, 1092, 1072, 1047, 1020, 1010, 956, 882, 814, 742, 705, 665, 551; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 3.16–3.23 (m, 1H), 3.34–3.40 (m, 1H), 4.40–4.44 (m, 1H), 4.79 (t, J = 6.6 Hz, 1H), 4.95 (d, J = 5.9 Hz, 1H), 6.22 (dd, J = 1.5, 8.4 Hz, 1H), 6.54 (td, J = 1.5, 7.7 Hz, 1H), 6.94–6.98 (m, 1H), 7.13 (d, J = 8.4 Hz, 2H), 7.23–7.25 (m, 2H), 7.38–7.42 (m, 3H), 7.70 (d, J = 8.1 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.6, 48.9, 57.1, 110.5, 112.8, 118.9, 122.0, 127.1, 128.3, 128.4, 129.9, 132.3, 132.6, 136.7, 138.5, 143.2, 143.9; HRMS (ESI-TOF) calcd for $C_{21}H_{21}Br_2N_2O_2S$(M + H)$^+$ 522.9690, found 522.9696.

2-(4-Bromophenyl)quinoxaline (4e). The general method B described above was followed when **3e** (50 mg, 0.095 mmol) in 1.0 mL of DMF solvent was added to a suspension of CuI (1.8 mg, 0.009 mmol), L-proline (2.2 mg, 0.019 mmol), and NaH (5.7 mg, 0.238 mmol) in 1.0 mL of DMF under argon atmosphere and the mixture was heated to 130 °C for 14 h to afford **4e** (19.1 mg, 0.067 mmol) as a pale yellow solid in 70% yield; mp 134–136 °C; R_f 0.5 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3058, 2923, 1548, 1491, 1446, 1350, 1317, 1207, 1150, 1077, 1058, 958, 840, 763, 683; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.71 (m, 2H), 7.73–7.81 (m, 2H), 8.06–8.14 (m, 4H), 9.29 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 125.1, 129.1, 129.3, 129.7, 129.9, 130.6, 132.5, 135.7, 141.8, 142.3, 142.9, 150.7; HRMS (ESI-TOF) calcd for $C_{14}H_{10}BrN_2$ (M + H)$^+$ 285.0027, found 285.0032.

2-(3-Chlorophenyl)quinoxaline (4f). The general method B described above was followed when **3f** (50 mg, 0.104 mmol) in 1.0 mL of DMF solvent was added to a suspension of CuI (2.0 mg, 0.010 mmol), L-proline (2.4 mg, 0.021 mmol), and NaH (6.3 mg, 0.261 mmol) in 1.0 mL of DMF under argon atmosphere and the mixture was heated to 130 °C for 14 h to afford **4f** (16.8 mg, 0.070 mmol) as a white solid in 67% yield; mp 130–132 °C; R_f 0.5 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3057, 2948, 1544, 1497, 1459, 1366, 1271, 1058, 963, 876, 836, 764; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.50 (m, 2H), 7.73–7.81 (m, 2H), 8.03–8.06(m, 1H), 8.10–8.16 (m, 2H), 8.21–8.22 (m, 1H), 9.28 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 125.6, 127.7, 129.3, 129.7, 130.1, 130.3, 130.4, 130.6, 135.4, 138.6, 141.9, 142.3, 143.0, 150.4; HRMS (ESI-TOF) calcd for $C_{14}H_{10}ClN_2$ (M + H)$^+$ 241.0533, found 241.0538.

2-(3-Bromophenyl)quinoxaline (4g). The general method B described above was followed when **3g** (50 mg, 0.095 mmol) in 1.0 mL of DMF solvent was added to a suspension of CuI (1.8 mg, 0.009 mmol), L-proline (2.2 mg, 0.019 mmol), and NaH (5.7 mg, 0.238 mmol) in 1.0 mL of DMF under argon atmosphere and the mixture was heated to 130 °C for 13 h to afford **4g** (19.6 mg, 0.069 mmol) as a brown solid in 72% yield; mp 132–134 °C; R_f 0.55 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3060, 2949, 1546, 1497, 1488, 1459, 1365, 1277, 1025, 1058, 961, 876, 841, 763; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.45 (t, J = 6.4 Hz, 1H), 7.64 (m, 1H), 7.75–7.82 (m, 2H), 8.10–8.16 (m, 3H), 8.38–8.39 (m, 1H), 9.29 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 123.5, 126.1, 127.6, 129.3, 129.7, 130.1, 130.6, 130.7, 133.2, 138.8, 141.9, 142.3, 143.0, 150.3; HRMS (ESI-TOF) calcd for $C_{14}H_{10}BrN_2$ (M + H)$^+$ 285.0027, found 285.0031.

6-Methyl-2-phenylquinoxaline (4h). The general method B described above was followed when **3h** (50 mg, 0.109 mmol) in 1.0 mL of DMF solvent was added to a suspension of CuI (2.1 mg, 0.011 mmol), L-proline (2.5 mg, 0.022 mmol), and NaH (6.5 mg, 0.272 mmol) in 1.0 mL of DMF

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under argon atmosphere and the mixture was heated to 130 °C for 11 h to afford **4h** (19.4 mg, 0.088 mmol) as a yellow solid in 81% yield; mp 92–94 °C; R_f 0.60 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3061, 2920, 2855, 1548, 1455, 1421, 1350, 1303, 1025, 972, 828, 765, 683; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.59 (s, 3H), 7.47–7.61 (m, 4H), 7.87 (s, 1H), 8.03 (d, J = 8.7 Hz, 1H), 8.15–8.17 (m,2H), 9.26 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.9, 127.5, 128.1, 129.2, 130.1, 132.7, 137.1, 140.2, 140.8, 141.7, 143.3, 151.1; HRMS (ESI-TOF) calcd for $C_{15}H_{13}N_2$ $(M + H)^+$ 221.1079, found 221.1074.

2-(4-Fluorophenyl)-6-methylquinoxaline (4i). The general method B described above was followed when **3i** (50 mg, 0.106 mmol) in 1.0 mL of DMF solvent was added to a suspension of CuI (2.0 mg, 0.011 mmol), L-proline (2.4 mg, 0.021 mmol), and NaH (6.3 mg, 0.264 mmol) in 1.0 mL of DMF under argon atmosphere and the mixture was heated to 130 °C for 13 h to afford **4i** (19.6 mg, 0.082 mmol) as a pale yellow solid in 77% yield; mp 120–122 °C; R_f 0.55 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3053, 2928, 1601, 1541, 1498, 1459, 1366, 1271, 1057, 944, 836, 766, 619; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.59 (s, 3H), 7.20–7.25 (m, 2H), 7.58–7.61 (m, 1H), 7.86 (s, 1H), 8.01 (d, J = 8.2 Hz, 1H), 8.14–8.18 (m, 2H), 9.22 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.9, 116.1, 116.3, 128.1, 129.1, 129.4, 129.5, 132.8, 133.2, 140.3, 140.7, 141.6, 142.9, 150.1, 164.2 (d, $^1J_{C-F}$ = 249.8 Hz); HRMS (ESI-TOF) calcd for $C_{15}H_{12}FN_2$ $(M + H)^+$ 239.0985, found 239.0989.

N-(2-((2-Bromo-4-methylphenyl)amino)-2-(4-bromophenyl)ethyl)-4-methylbenzenesulfonamide (3j). The general method A described above was followed when **1e** (50 mg, 0.142 mmol) was reacted with **2b** (53 μL, 0.426 mmol) at rt for 6 h to afford **3j** (60.4 mg, 0.112 mmol) as a white solid in 79% yield; mp 128–130 °C; R_f 0.40 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3372, 3271, 3035, 2920, 2859, 1741, 1614, 1597, 1579, 1517, 1472, 1321, 1268, 1193, 1155, 1097, 1032, 1017, 997, 956, 831, 812, 786, 739, 692, 664, 551; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 (s, 3H), 2.38 (s, 3H), 3.14–3.21 (m, 1H), 3.32–3.38 (m, 1H), 4.39 (br s, 1H), 4.75 (br s, 1H), 4.82 (t, J = 6.9 Hz, 1H), 6.14 (d, J = 8.0 Hz, 1H), 6.76 (dd, J = 1.5, 8.4 Hz, 1H), 7.11 (d, J = 8.4 Hz, 2H), 7.22–7.25 (m, 3H), 7.40 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 20.1, 21.6, 48.9, 57.2, 110.4, 112.9, 121.9, 127.1, 128.3, 128.6, 128.9, 129.9, 132.2, 132.9, 136.7, 138.7, 140.8, 143.8; HRMS (ESI-TOF) calcd for $C_{22}H_{23}Br_2N_2O_2S(M + H)^+$ 536.9847, found 536.9843.

2-(4-Bromophenyl)-6-methylquinoxaline (4j). The general method B described above was followed when **3j** (50 mg, 0.093 mmol) in 1.0 mL of DMF solvent was added to a suspension of CuI (1.8 mg, 0.009 mmol), L-proline (2.1 mg, 0.019 mmol), and NaH (5.6 mg, 0.232 mmol) in 1.0 mL of DMF under argon atmosphere and the mixture was heated to 130 °C for 12 h to afford **4j** (21.8 mg, 0.073 mmol) as a yellow solid in 78% yield; mp 124–126 °C; R_f 0.50 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3048, 2913, 1635, 1588, 1549, 1350, 1207, 1164, 1077, 1058, 763, 683; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.59 (s, 3H), 7.58–7.62 (m, 1H), 7.65–7.69 (m, 2H), 7.86 (s, 1H), 8.01 (d, J = 8.7 Hz, 1H), 8.02–8.07 (m, 2H), 9.23 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.9, 124.8, 128.1, 128.9, 129.2, 132.4, 132.9, 135.9, 140.6, 140.8, 141.8, 142.8, 149.9; HRMS (ESI-TOF) calcd for $C_{15}H_{12}BrN_2$ $(M + H)^+$ 299.0184, found 299.0186.

2-(3-Chlorophenyl)-6-methylquinoxaline (4k). The general method B described above was followed when **3k** (50 mg, 0.101 mmol) in 1.0 mL of DMF solvent was added to a suspension of CuI (1.9 mg, 0.010 mmol), L-proline (2.3 mg, 0.020 mmol), and NaH (6.1 mg, 0.253 mmol) in 1.0 mL of DMF under argon atmosphere and the mixture was heated to 130 °C for 14 h to afford **4k** (20.1 mg, 0.079 mmol) as a yellow solid in 78% yield; mp 108–110 °C; R_f 0.5 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3050, 2915, 1456, 1621, 1488, 1378, 1207, 1250, 1166, 1072, 833, 745; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 (s, 3H), 7.46–7.48 (m, 2H), 7.62 (d, J = 8.7 Hz, 1H), 7.87 (s, 1H), 8.01–8.03 (m, 2H), 8.19 (s, 1H), 9.24 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.9, 125.4, 127.6, 128.1, 129.2, 130.0, 130.4, 132.9, 135.4, 138.8, 140.7, 141.9, 142.9, 149.6; HRMS (ESI-TOF) calcd for $C_{15}H_{12}ClN_2$ $(M + H)^+$ 255.0689, found 255.0686.

***N*-(2-((2-Bromo-4-methylphenyl)amino)-2-(3-bromophenyl)ethyl)-4-methylbenzenesulfonamide (3l).** The general method A described above was followed when **1g** (50 mg, 0.142 mmol) was reacted with **2b** (53 μL, 0.425 mmol) at rt for 6 h to afford **3l** (58.1 mg, 0.107 mmol) as a white solid in 76% yield; mp 126–128 °C; R_f 0.35 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3377, 3276, 3031, 2922, 2855, 1731, 1612, 1596, 1570, 1516, 1472, 1427, 1317, 1265, 1190, 1159, 1092, 1038, 1018, 997, 954, 835, 811, 786, 737, 697, 663, 550; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 3H), 2.38 (s, 3H), 3.14–3.21 (m, 1H), 3.33–3.39 (m, 1H), 4.36–4.38 (m, 1H), 4.75–4.78 (m, 1H), 4.85 (t, J = 6.6 Hz, 1H), 6.14 (d, J = 8.4 Hz, 1H), 6.77 (dd, J = 1.1, 8.0 Hz, 1H), 7.14–7.18 (m, 2H), 7.23–7.25 (m, 3H), 7.35–7.38 (m, 2H), 7.72 (d, J = 8.4 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 20.1, 21.6, 49.1, 57.3, 110.4, 112.8, 123.3, 125.2, 127.1, 128.6, 128.9, 129.5, 129.9, 130.7, 131.3, 132.9, 136.7, 140.8, 142.2, 143.9; HRMS (ESI-TOF) calcd for $C_{22}H_{23}Br_2N_2O_2S$ $(M + H)^+$ 536.9847, found 536.9846.

2-(3-Bromophenyl)-6-methylquinoxaline (4l). The general method B described above was followed when **3l** (50 mg, 0.093 mmol) in 1.0 mL of DMF solvent was added to a suspension of CuI (1.8 mg, 0.009 mmol), L-proline (2.1 mg, 0.019 mmol), and NaH (5.6 mg, 0.232 mmol) in 1.0 mL of DMF under argon atmosphere and the mixture was heated to 130 °C for 14 h to afford **4l** (21.1 mg, 0.071 mmol) as a cream brown solid in 76% yield; mp 102–104 °C; R_f 0.55 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3054, 2923, 1622, 1548, 1445, 1250, 1286, 1077, 1057, 958, 840, 763, 683; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.61 (s, 3H), 7.41 (t, J = 7.8 Hz, 1H), 7.61–7.63 (m, 2H), 7.87 (s, 1H), 8.02–8.08 (m, 2H), 8.02 (d, J = 8.7 Hz, 1H), 8.06–8.08 (m,1H), 8.34–8.35 (m, 1H), 9.23 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.9, 123.5, 125.9, 128.1, 129.3, 130.5, 130.7, 132.9, 139.0, 140.7, 141.9, 142.9, 149.5; HRMS (ESI-TOF) calcd for $C_{15}H_{12}BrN_2$ $(M + H)^+$ 299.0184, found 299.0187.

***N*-(2-((2-Bromo-4-isopropylphenyl)amino)-2-phenylethyl)-4-methylbenzenesulfonamide (3m).** The general method A described above was followed when **1a** (50 mg, 0.183 mmol) was reacted with **2c** (87 μL, 0.549 mmol) at rt for 5 h to afford **3m** (74.9 mg, 0.154 mmol) as a white semi-solid in 84% yield; R_f 0.45 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3372, 3283, 3062, 3030, 2958, 2925, 2867, 1916, 1739, 1608, 1514, 1494, 1454, 1404, 1381, 1324, 1265, 1207, 1185, 1160, 1119, 1093, 1034, 954, 878, 812, 738, 702, 664, 551; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, J = 6.9 Hz, 6H), 2.39 (s, 3H), 2.68–2.74 (m, 1H), 3.18–3.25 (m, 1H), 3.34–3.40 (m, 1H), 4.41–4.46 (m, 1H), 4.71–4.75 (m, 2H), 6.26 (d, J = 8.4 Hz, 1H), 6.84 (dd, J = 2.2, 8.4 Hz, 1H), 7.23–7.33 (m, 8H), 7.72 (d, J = 8.0 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.6, 24.1, 33.0, 49.1, 57.6, 110.4, 112.8, 126.4, 126.5, 127.2, 128.1, 129.1, 129.9, 130.4, 136.8, 139.5, 139.6, 141.3, 143.7; HRMS (ESI-TOF) calcd for $C_{24}H_{28}BrN_2O_2S$ $(M + H)^+$ 487.1055, found 487.1053.

6-Isopropyl-2-phenylquinoxaline (4m). The general method B described above was followed when **3m** (50 mg, 0.103 mmol) in 1.0 mL of DMF solvent was added to a suspension of CuI (2.0 mg, 0.010 mmol), L-proline (2.4 mg, 0.021 mmol), and NaH (6.2 mg, 0.256 mmol) in 1.0 mL of DMF under argon atmosphere and the mixture was heated to 130 °C for 12 h to afford **4m** (21.9 mg, 0.088 mmol) as a light yellow solid in 86% yield; mp 114–116 °C; R_f 0.65 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3060, 2959, 2924, 2873, 1543, 1490, 1442, 1385, 1145, 1169, 1026,

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963, 764, 819, 687; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 (d, J = 6.8 HZ, 6H), 3.13–3.19 (m, 1H), 7.48–7.51 (m, 1H), 7.54–7.57 (m, 2H), 7.69 (dd, J = 2.3, 9.2 Hz, 1H), 7.92–7.93 (m, 1H), 8.08 (d, J = 8.5 Hz, 1H), 8.16–8.18 (m, 2H), 9.28 (s, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 23.8, 34.3, 125.3, 127.5, 129.2, 129.4, 130.0, 130.4, 137.1, 141.1, 141.8, 143.3, 150.9, 151.3; HRMS (ESI-TOF) calcd for $C_{17}H_{17}N_2$ $(M + H)^+$ 249.1392, found 249.1398.

N-(2-((2-Bromo-4-isopropylphenyl)amino)-2-(4-chlorophenyl)ethyl)-4-methylbenzenesulfonamide (3n). The general method A described above was followed when **1d** (50 mg, 0.163 mmol) was reacted with **2c** (77 μL, 0.487 mmol) at rt for 5 h to afford **3n** (70.4 mg, 0.135 mmol) as a white semi-solid in 83% yield; R_f 0.40 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3372, 3280, 3030, 2958, 2925, 2868, 1910, 1737, 1608, 1578, 1513, 1490, 1458, 1406, 1381, 1362, 1322, 1273, 1207, 1185, 1159, 1119, 1092, 1034, 1013, 956, 878, 812, 738, 717, 705, 662, 553; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, J = 6.9 Hz, 6H), 2.39 (s, 3H), 2.68–2.75 (m, 1H), 3.15–3.22 (m, 1H), 3.31–3.37 (m, 1H), 4.38–4.43 (m, 1H), 4.75–4.79 (m, 2H), 6.19 (d, J = 8.4 Hz, 1H), 6.83 (dd, J = 1.8, 8.0 Hz, 1H), 7.17–7.20 (m, 2H), 7.24–7.27 (m, 5H), 7.70 (d, J = 8.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 21.6, 24.1, 33.0, 49.1, 57.2, 110.5, 112.8, 126.3, 127.1, 127.9, 129.3, 129.9, 130.4, 133.8, 136.7, 138.2, 139.9, 141.1, 143.8; HRMS (ESI-TOF) calcd for $C_{24}H_{27}BrClN_2O_2S$ $(M + H)^+$ 521.0665, found 521.0669.

2-(4-Chlorophenyl)-6-isopropylquinoxaline (4n). The general method B described above was followed when **3n** (50 mg, 0.096 mmol) in 1.0 mL of DMF solvent was added to a suspension of CuI (1.8 mg, 0.009 mmol), L-proline (2.2 mg, 0.020 mmol), and NaH (5.7 mg, 0.239 mmol) in 1.0 mL of DMF under argon atmosphere and the mixture was heated to 130 °C for 12 h to afford **4n** (22.9 mg, 0.081 mmol) as a pale yellow solid in 84% yield; mp 128–130 °C; R_f 0.60 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3063, 2962, 2924, 2874, 1540, 1497, 1454, 1362, 1169, 1088, 963, 836, 819; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 (d, J = 6.8 HZ, 6H), 3.13–3.19 (m, 1H), 7.52 (d, J = 8.6 Hz, 2H), 7.69 (dd, J = 1.7, 8.6 Hz, 1H), 7.92–7.93 (m, 1H), 8.05 (d, J = 8.6 Hz, 1H), 8.13 (d, J = 8.6 Hz, 2H), 9.24 (s, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 23.7, 34.5, 125.3, 128.7, 129.3, 129.4, 130.6, 135.5, 136.3, 141.1, 141.9, 142.7, 149.9, 151.2; HRMS (ESI-TOF) calcd for $C_{17}H_{16}ClN_2$ $(M + H)^+$ 283.1002, found 283.1000.

***N*-(2-((2-Bromo-4-chlorophenyl)amino)-2-phenylethyl)-4-methylbenzenesulfonamide (3o).** The general method A described above was followed when aziridine **1a** (50 mg, 0.183 mmol) was reacted with **2d** (113.3 mg, 0.549 mmol) in 2.0 mL of CH_2Cl_2 solvent at rt for 6 h to afford **3o** (64.1 mg, 0.133 mmol) as a white solid in 73% yield; mp 124–126 °C; R_f 0.30 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3370, 3282, 3063, 3029, 2924, 2854, 1733, 1593, 1565, 1504, 1454, 1392, 1354, 1321, 1269, 1158, 1092, 1032, 968, 867, 812, 757, 732, 701, 663, 564, 551; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 3.18–3.25 (m, 1H), 3.36–3.42 (m, 1H), 4.39–4.41 (m, 1H), 4.84 (t, J = 6.6 Hz, 1H), 5.02 (d, J = 6.2 Hz, 1H), 6.17 (d, J = 6.8 Hz, 1H), 6.90 (dd, J = 2.2, 8.8 Hz, 1H), 7.21–7.33 (m, 7H), 7.38 (d, J = 2.2 Hz, 1H), 7.71 (d, J = 2.2 Hz, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 21.6, 49.1, 57.5, 110.2, 113.2, 122.4, 126.4, 127.1, 128.2, 128.3, 129.2, 129.9, 131.8, 136.8, 138.9, 142.3, 143.9; HRMS (ESI-TOF) calcd for $C_{21}H_{21}BrClN_2O_2S(M + H)^+$ 479.0196, found 479.0190.

6-Chloro-2-phenylquinoxaline (4o). The general method B described above was followed when **3o** (50 mg, 0.104 mmol) in 1.0 mL of DMF solvent was added to a suspension of CuI (2.0 mg, 0.010 mmol), L-proline (2.4 mg, 0.021 mmol), and NaH (6.3 mg, 0.261 mmol) in 1.0 mL of DMF under argon atmosphere and the mixture was heated to 130 °C for 16 h to afford **4o** (16.1 mg, 0.067 mmol) as a yellow solid in 64% yield; mp 118–120 °C; R_f 0.6 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2953, 2923, 2853, 2482, 1615, 1481, 1464, 1289, 1172, 1069, 884, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.59 (m, 3H), 7.71 (dd, J = 2.3, 8.7 Hz, 1H), 8.07 (s, 1H), 8.09–8.11 (m, 1H), 8.16–8.19 (m, 2H), 9.31 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 127.6, 128.2, 129.3, 130.5, 130.9, 131.4, 135.3, 136.4, 140.9, 141.9, 144.2, 152.0; HRMS (ESI-TOF) calcd for $C_{14}H_{10}ClN_2$ $(M + H)^+$ 241.0533, found 241.0538.

***N*-(2-((2-Bromo-4,5-dimethoxyphenyl)amino)-2-phenylethyl)-4-methylbenzenesulfonamide (3p)** The general method A described above was followed when **1a** (50 mg, 0.183 mmol) was reacted with **2e** (127 mg, 0.549 mmol) in 1.0 mL of CH_2Cl_2 solvent at rt for 6 h to afford **3p** (78.9 mg, 0.156 mmol) as a white semi-solid in 85% yield; R_f 0.32 (20% ethyl acetate in petroleum ether); IR ṽmax (KBr, cm−1) 3369, 3271, 2933, 1599, 1518, 1463, 1449, 1402, 1330, 1288, 1269, 1237, 1209, 1160, 1093, 1031, 847, 812, 736, 702, 663, 551; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.39 (s, 3H), 3.23–3.28 (m, 1H), 3.32–3.37 (m, 1H), 3.59 (s, 3H), 3.75 (s, 3H), 4.44 (s, 1H), 4.54 (s, 1H), 4.82 (t, J = 6.3 Hz, 1H), 6.05 (s, 1H), 6.93 (s, 1H), 7.25–7.27 (m, 5H), 7.30–7.33 (m, 2H), 7.72 (d, J = 8.0 Hz, 2H); $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$) δ 21.4, 48.9, 55.8, 56.7, 58.5, 98.8, 99.4, 116.4, 126.5, 127.0, 128.1, 129.1, 129.8, 136.8, 138.1, 139.6, 141.6, 143.6, 149.3; HRMS (ESI-TOF) calcd for $C_{23}H_{26}BrN_2O_4S$ $(M + H)^+$ 505.0797, found 505.0791.

6,7-Dimethoxy-2-phenylquinoxaline (II) The general method B described above was followed when **3p** (50 mg, 0.099 mmol) in 1.0 mL of DMF solvent was added to a suspension of CuI (1.9 mg, 0.009 mmol), L-proline (2.3 mg, 0.020 mmol), and NaH (5.9 mg, 0.247 mmol) in 1.0 mL of DMF under argon atmosphere and the mixture was heated to 130 °C for 12 h to afford **II** (21.1 mg, 0.079 mmol) as a white solid in 80% yield; mp 130–132 °C; R_f 0.35 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2924, 1618, 1497, 1460, 1434, 1418, 1337, 1251, 1219, 1145, 1005, 867, 844, 693; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.06 (s, 3H), 4.07 (m, 3H), 7.37 (s, 1H), 7.42 (s, 1H), 7.46–7.49 (m, 1H), 7.52–7.55 (m, 2H), 8.12 (d, J = 7.4 Hz, 2H), 9.12 (s, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 56.3, 56.4, 106.6, 107.1, 127.1, 129.1, 129.5, 137.2, 138.8, 139.5, 140.7, 149.8, 152.6, 153.0; HRMS (ESI-TOF) calcd for $C_{16}H_{15}N_2O_2$ $(M + H)^+$ 267.1134, found 267.1139.

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Keywords: aromaticity • cyclization • nitrogen heterocycles • nucleophilic substitution • small ring systems

[1] G. Bilder, T. Wentz, R. Leadley, D. Amin, L. Byan, B. O'Conner, S. Needle, H. Galczenski, J. Bostwick, C. Kasiewski, M. Myers, A. Spada, L. Merkel, C. Ly, P. Persons, K. Page, M. Perrone, C. Dunwiddie, *Circulation* **1999**, *99*, 3292–3299.

[2] Y. Li, Y. Li, Q. Liu, A. Wang, *OncoTargets and therapy* **2015**, *8*, 1043–1051.

[3] J. L. Collins, P. J. Dambek, S. W. Goldstein, W. S. Faraci, *Bioorg. Med. Chem. Lett.* **1992**, *2*, 915–918.

[4] M. Josipa, T. Lidija-Marija, S. Marijana Radić, P. Ivo, *Curr. Protein Pept. Sci.* **2016**, *17*, 127–134.

[5] A. Katoh, T. Yoshida, J. Ohkanda, *Heterocycles* **2000**, *52*, 911–920.

[6] K. R. Justin Thomas, M. Velusamy, J. T. Lin, C.-H. Chuen, Y.-T. Tao, *Chemistry of Materials* **2005**, *17*, 1860–1866.

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[7] S. Dailey, W. J. Feast, R. J. Peace, I. C. Sage, S. Till, E. L. Wood, *J. Mater. Chem.* **2001**, *11*, 2238–2243.
[8] S. Ott, R. Faust, *Synlett* **2004**, *2004*, 1509–1512.
[9] J. L. Sessler, H. Maeda, T. Mizuno, V. M. Lynch, H. Furuta, *J. Am. Chem. Soc.* **2002**, *124*, 13474–13479.
[10] M. J. Crossley, L. A. Johnston, *Chem. Commun.* **2002**, 1122-1123.
[11] V. A. Mamedov, *Quinoxalines: Synthesis, Reactions, Mechanisms and Structure*; Springer, 2016.
[12] a) G. Li, L. Tang, H. Liu, Y. Wang, G. Zhao, Z. Tang, *Org. Lett.* **2016**, *18*, 4526–4529; b) X. Ji, D. Li, X. Zhou, H. Huang, G.-J. Deng, *Green Chem.* **2017**, *19*, 619–622; c) R. P. Pandit, S. H. Kim, Y. R. Lee, *Adv. Synth. Catal.* **2016**, *358*, 3586–3599; d) K. Gopalaiah, A. Saini, S. N. Chandrudu, D. C. Rao, H. Yadav, B. Kumar, *Org. Biomol. Chem.* **2017**, *15*, 2259–2268.
[13] Z. He, M. Bae, J. Wu, T. F. Jamison, *Angew. Chem., Int. Ed.* **2014**, *53*, 14451–14455.
[14] Z. Zhang, C. Xie, X. Tan, G. Song, L. Wen, H. Gao, C. Ma, *Org. Chem. Front.* **2015**, *2*, 942–946.
[15] T. Chen, X. Chen, J. Wei, D. Lin, Y. Xie, W. Zeng, *Org. Lett.* **2016**, *18*, 2078–2081.
[16] K. Mullick, S. Biswas, A. M. Angeles-Boza, S. L. Suib, *Chem. Commun.* **2017**, *53*, 2256–2259.
[17] a) C. K. Shahi, A. Bhattacharyya, Y. Nanaji, M. K. Ghorai, *J. Org. Chem.* **2017**, *82*, 37–47; b) M. K. Ghorai, A. Bhattacharyya, S. Das, N. Chauhan, *Top. Heterocycl. Chem.* **2016**, *41*, 49–142 and references cited therein; c) A. Bhattacharyya, C. V. Kavitha, M. K. Ghorai, *J. Org. Chem.* **2016**, *81*, 6433–6443; d) M. K. Ghorai, C. K. Shahi, A. Bhattacharyya, M. Sayyad, A. Mal, I. A. Wani, N. Chauhan, *Asian J. Org. Chem.* **2015**, *4*, 1103–1111; e) M. K. Ghorai, A. K. Sahoo, A. Bhattacharyya, *J. Org. Chem.* **2014**, *79*, 6468–6479; f) M. K. Ghorai, D. Shukla, A. Bhattacharyya, *J. Org. Chem.* **2012**, *77*, 3740–3753; g) M. Sayyad, I. A. Wani, R. Babu, Y. Nanaji, M. K. Ghorai, *J. Org. Chem.* **2017**, *82*, 2364–2374; h) M. Sayyad, A. Mal, I. A. Wani, M. K. Ghorai, *J. Org. Chem.* **2016**, *81*, 6424–6432; i) M. Sayyad, Y. Nanaji, M. K. Ghorai, *J. Org. Chem.* **2015**, *80*, 12659–12667; j) M. K. Ghorai, M. Sayyad, Y. Nanaji, S. Jana, *Chem. Asian J.* **2015**, *10*, 1480–1489.
[18] M. K. Ghorai, A. K. Sahoo, S. Kumar, *Org. Lett.* **2011**, *13*, 5972–5975.
[19] See the Supporting Information for details.
[20] S. Pradhan, C. K. Shahi, A. Bhattacharyya, N. Chauhan, M. K. Ghorai, *ChemistrySelect* **2017**, *2*, 550–556.
[21] H. Zhang, Q. Cai, D. Ma, *J. Org. Chem.* **2005**, *70*, 5164–5173.
[22] a) N. K. Garg, R. Sarpong, B. M. Stoltz, *J. Am. Chem. Soc.* **2002**, *124*, 13179–13184; b) E. J. Gilbert, J. D. Chisholm, D. L. Van Vranken, *J. Org. Chem.* **1999**, *64*, 5670–5676; c) J. S. Bajwa, G.-P. Chen, K. Prasad, O. Repič, T. J. Blacklock, *Tetrahedron Lett.* **2006**, *47*, 6425–6427.
[23] W. L. F. Armarego, C. Chai, *Purification of Laboratory Chemicals*, Butterworth-Heinemann, **2012**.
[24] J. U. Jeong, B. Tao, I. Sagasser, H. Henniges, K. B. Sharpless, *J. Am. Chem. Soc.* **1998**, *120*, 6844-6845.

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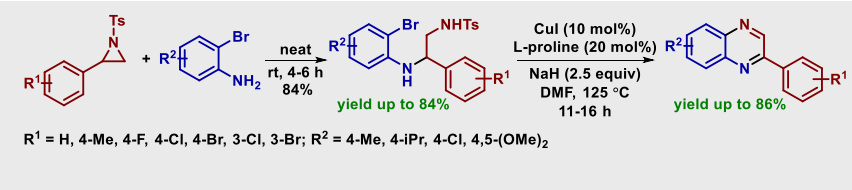

2-Arylquinoxalines have been synthesized via an unprecedented Cu(I) catalyzed ring-opening-cyclization-detosylation-aromatization cascade of activated aziridines with 2-bromoanilines. The regioselective, high-yielding transformation is amenable to a variety of aziridines and 2-bromoanilines. Tyrphostin AG 1296, a PDGF-receptor tyrosine kinase inhibitor, has also been synthesized.

Methodology*

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Accessing Quinoxalines via Ring Opening-Cyclization-Detosylation-Aromatization of Activated Aziridines with 2-Bromoanilines: Synthesis of Tyrphostin AG 1296

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