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Synthetic Route to Chiral Tetrahydroquinoxalines via Ring-Opening of Activated Aziridines

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ABSTRACT

A highly regio- and stereoselective route for the synthesis of racemic and nonracemic tetrahydroquinoxalines via the S_N2-type ring-opening of activated aziridines with 2-bromoanilines followed by the Pd-catalyzed intramolecular C−N bond formation is described.

The 1,2,3,4-tetrahydroquinoxaline motif is present in numerous biologically active and pharmacologically important compounds.[1] Several racemic as well as chiral 1,2,3,4-tetrahydroquinoxalines have been found to exhibit a diverse range of biological activities; e.g., compounds **1**, **2**, and **3** have found applications as potent cholesteryl ester transfer protein inhibitors,[1a] vasopressin V2 receptor antagonists,[1b] and prostaglandin D_2 receptor antagonists,[1c] respectively (Figure 1). Although several reports are available for the construction of 1,2,3,4-tetrahydroquinoxalines,[2] efficient routes for the enantioselective synthesis of such compounds are limited.[3] The most common approach for the synthesis of chiral tetrahydroquinoxalines is based on the asymmetric hydrogenation of quinoxalines.[4]

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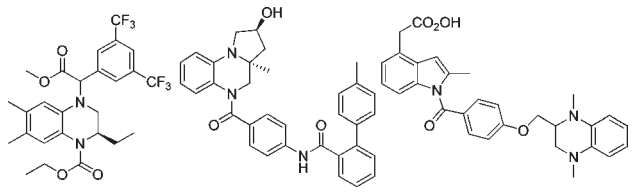


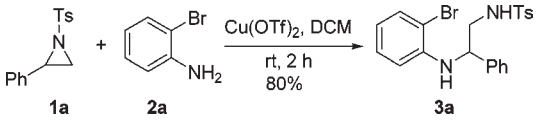
Figure 1. Selected biologically active 1,2,3,4-tetrahydroquinoxalines.

Palladium-catalyzed amination reactions made a large contribution in organic synthesis for the construction of C_{aryl}–N bonds.[5] We envisioned that substituted 1,2,3,4-tetrahydroquinoxalines could easily be accessed by the ring-opening of aziridines with 2-bromo anilines followed by Pd-catalyzed intramolecular C–N bond formation. Different heteroatomic and C-nucleophiles have been used for the ring-opening of aziridines,[6–8] and a number of examples of aziridine-mediated heterocycle syntheses have also been reported.[9]

Recently, we have reported the Lewis acid (LA)-mediated ring-opening of racemic and enantiopure 2-aryl-*N*-tosylaziridines by a number of nucleophiles to generate racemic and nonracemic products in high enantiomeric excess.[10] We have demonstrated that the LA-mediated nucleophilic ring-opening of 2-aryl-*N*-tosylaziridines does proceed through an S_N2-type pathway instead of a stable 1,3-dipolar intermediate as invoked earlier.

In continuation of our research activities in this area, we have developed a simple strategy for the synthesis of 1,2,3,4-tetrahydroquinoxalines with excellent yields (up to 85%) and enantiomeric excess (ee) (up to >99%) via the regio- and stereoselective ring-opening of aziridines by 2-bromo anilines followed by palladium-catalyzed intramolecular C–N cyclization. We report herein our preliminary results as a communication.

Scheme 1. Regioselective Ring-Opening of **1a** with 2-Bromoaniline **2a**



First, we explored the ring-opening of racemic 2-phenyl-*N*-tosylaziridine (**1a**) with 2-bromo aniline (**2a**) under varying reaction conditions to afford the corresponding racemic ring-opened product **3a** (Scheme 1). When **1a** was treated with 2-bromo aniline (**2a**) in the presence of $Cu(OTf)_2$ as the LA in DCM medium, **3a** was produced in 80% yield (Scheme 1) within 2 h. The reaction was found to be successful with other LAs ($Zn(OTf)_2$, $Sc(OTf)_3$, and $Yb(OTf)_3$) and under solvent free conditions.[11] Interestingly, the best yield of **3a** was obtained when 4 equiv of 2-bromoaniline **2a** were used in the absence of any LA and organic solvent. (Scheme 1; see Table S1, Supporting Information).

Next, we evaluated the palladium-catalyzed cyclization of **3a** to form the product **4a** under diverse reaction conditions, and the results are shown in Table 1. Initially, we used 10 mol % of palladium catalyst, 20 mol % of the ligand (PPh_3), and K_2CO_3 as the base (Scheme 2, Table 1, entry 2). K_2CO_3 was found to be a better base than Cs_2CO_3 (Table 1, entry 1 vs 2), and toluene was a better solvent than DMF (Table 1, entry 2 vs 3). When we reduced the amount of catalyst (5 mol %) and ligand (10 mol %) to

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(11) See the Supporting Information for details.

Scheme 2. Pd-Catalyzed C−N Cyclization of **3a**

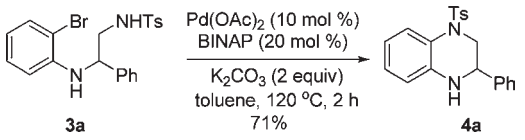


Table 1. Optimization of Reaction Conditions for the Formation of **4a**

entry	$Pd(OAc)_2$ (mol %), ligand (mol %), base (2 equiv), solvent, temp (°C), time (h)	**4a** yield (%)[a]
1	(10), BINAP (20), Cs_2CO_3, toluene, 120, 2	62
2	(10), BINAP (20), K_2CO_3, toluene, 120, 2	71
3	(10), BINAP (20), K_2CO_3, DMF, 120, 2	46
4	(5), BINAP (10), K_2CO_3, toluene, 120, 3	61
5	(5), BINAP (10), K_3PO_4, toluene, 120, 2	54
6	(5), BINAP (10), NaH, toluene, 120, 15	34
7	(5), BINAP (10), KO*t*-Bu, toluene, 120, 15	nr
8	(5), BINAP (10), K_2CO_3, CH_3CN, 80, 15	nr
9	(5), BINAP (10), K_2CO_3, THF, 60, 15	nr
10	(5), DPPF (10), K_2CO_3, toluene, 120 , 2	60
11	(5), Xantphos (10), K_2CO_3, toluene, 120, 2	73
12	(5), PPh_3 (10), K_2CO_3, toluene, 120, 4	85
13	(5), PPh_3 (10), NaO*t*-Bu, toluene, 120, 15	nr
14	(5), PPh_3 (10), K_3PO_4, toluene, 120, 15	10
15	(5), PPh_3 (10), K_2CO_3, DMF, 120, 15	nr
16[b]	$Pd(PPh_3)_4$ (5), K_2CO_3, toluene, 120, 15	nr

[a] Yields of isolated products.

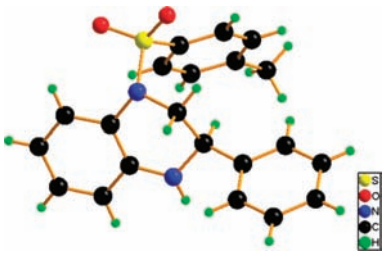
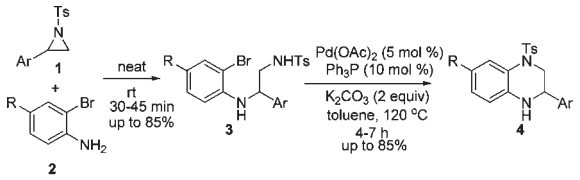


Figure 2. Diamond diagram of compound **4a**.

half, the desired product **4a** was obtained with a slightly reduced yield (Table 1, entry 4 vs 2). Replacing K_2CO_3 with K_3PO_4 or NaH provided **4a** in moderate yield (Table 1, entries 5−6). No reaction was observed when ^{t}BuOK was used as a base, toluene was replaced with THF, or CH_3CN was used as the solvent (Table 1, entries 7−9). Replacing 2,2^1-bis(diphenylphosphino)-1,1^1-binaphthyl (BINAP) and 1,1^1-bis(diphenylphosphino)ferrocene (DPPF) provided **4a** in 60% yield (Table 1, entry 10); however, use of 4,5-bis (diphenylphosphino)-9,9-dimethylxanthene (XANTPHOS) as the ligand furnished **4a** in an improved yield of 71% (Table 1, entry 11). The best result was obtained using PPh_3

Scheme 3. Synthesis of 1,2,3,4-Tetrahydroquinoxalines **4a**−**f**



1a, Ar = C_6H_5, **1b**, 4-ClC_6H_5; **2a**, R = H, **2b**, R = Me, **2c**, R = F

Table 2. Regioselective Ring-Opening of **1** and Pd-Catalyzed Intramolecular C−N Cyclization of **3a**−**f**[a]

entry	**1** (Ar)	**2** (R)	**3** yield (%)[b]	time (h)	**4** yield (%)[b]
1	**1a** (Ph)	**2a** (H)	**3a**, 85	4	**4a**, 85
2	**1a**(Ph)	**2b** (Me)	**3b**, 80	6	**4b**, 81
3	**1a** (Ph)	**2c** (F)	**3c**, 79	7	**4c**, 80
4	**1b** (4-ClC_6H_4)	**2a** (H)	**3d**, 84	4	**4d**, 77
5	**1b** (4-ClC_6H_4)	**2b** (Me)	**3e**, 82	4.5	**4e**, 76
6	**1b** (4-ClC_6H_4)	**2c** (F)	**3f**, 81	4	**4f**, 72

[a] All reactions were carried out with **3a**−**f** (1.0 mmol), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mmol %), and K_2CO_3 (2 equiv) in toluene (8 mL) under argon for 4−7 h under refluxed conditions at 120 °C. [b] Yields of isolated products (%).

in toluene (Table 1, entry 12). Further attempts to improve the yield of **4a** by changing the base or palladium source were not successful (Table 1, entries 13−16). **4a** was characterized by analytical data. The structure of **4a** was further confirmed by X-ray crystallographic analysis (Figure 2).

To generalize this approach and study the substrate scope, several *N*-[(2-aryl-2-(2-bromoarylamino)ethyl]-4-methylbenzenesulfonamides **3a**−**f** were prepared from aziridines **1a**−**b** and bromoanilines **2a**−**c**. Compounds **3a**−**f** were cyclized under optimized conditions ($Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), K_2CO_3 (2 equiv), toluene, 120 °C) to afford the corresponding tetrahydroquinoxalines **4a**−**f** in excellent yields (Scheme 3, Table 2).

Bicyclic *N*-tosylcyclohexene and cyclopentene aziridines (**5a**−**b**) underwent ring-opening smoothly with a number of 2-bromoanilines (Table 3, entries 1−5) and the resulting ring-opened products **6a**−**e** could be successfully transformed to cyclohexa- and cyclopenta-annulated tetrahydroquinoxalines **7a**−**e** (Scheme 4, Table 3, entries 1−5). The structure of compounds **7a** and **7d** were confirmed by single crystal X-ray analysis.[11]

Next, we studied ring-opening of chiral aziridine (*R*)-**1a** with 2-bromoanilines **2**, and the best ee (>99%) was obtained when 4 equiv of 2-bromoanilines were used in the absence of any LA or solvent (Table 4). Using our protocol, compounds **8** were cyclized to the corresponding tetrahydroquinoxalines **9** in excellent ee (Table 5).

A probable mechanism for the formation of chiral tetrahydroquinoxalines **9a**−**c** is described in Figure 3.

Scheme 4. Synthesis of Cyclopenta [b]- and Cyclohexa [c]-Fused Tetrahydroquinoxalines **7a**–**e**

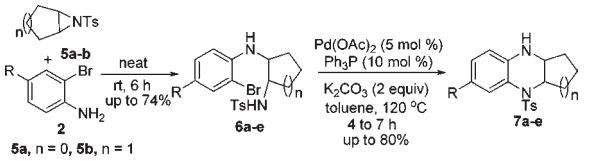
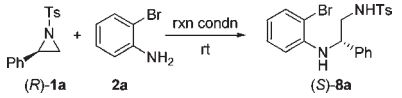


Table 3. Regioselective Ring-Opening of **5** and Pd-Catalyzed Intramolecular C–N Cyclization of **6a**–**e**[a]

entry	**5** (n)	**2** (R)	**6** yield (%)[b]	time (h)	**7** yield (%)[b]
1	**5a** (0)	**2a** (H)	**6a**, 72	8	**7a**, 78
2	**5a** (0)	**2b** (Me)	**6b**, 70	8	**7b**, 73
3	**5b** (1)	**2a** (H)	**6c**, 74	10	**7c**, 80
4	**5b** (1)	**2b** (Me)	**6d**, 71	8	**7d**, 76
5	**5b** (1)	**2c** (F)	**6e**, 73	8	**7e**, 76

[a] All reactions were carried out with **6a**–**e** (1.0 mmol), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mmol %), and K_2CO_3 (2 equiv) in toluene (8 mL) under argon for 8–10 h refluxed at 120 °C, [b] Yields of isolated products.

Table 4. Enantioselective Ring-Opening of Chiral Aziridine (*R*)-**1a**



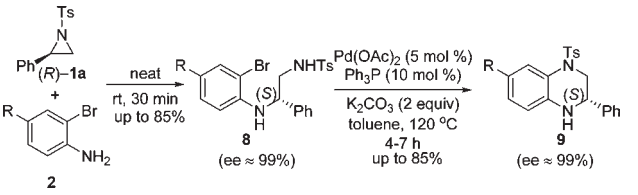
entry	equiv **2a**	LA (mol %)	solvent	time (h)	yield **8a** (%)[a]	ee **8a**[b]
1	1	$Cu(OTf)_2$ (30)	CH_2Cl_2	2	80	0
2	4	$Cu(OTf)_2$ (30)		2	78	98
3	4		neat	0.5	86	>99

[a] Yields of isolated products. [b] ee was determined using a Chiralpak AD-H column.

S_N2-type ring-opening of chiral aziridine (*R*)-**1a** by 2-bromoanilines generates the corresponding bromoamines **8**, which undergo Pd-catalyzed intramolecular C–N coupling to produce the corresponding tetrahydroquinoxalines **9a**–**c**.

In conclusion, we have developed a simple and practical protocol for the synthesis of racemic and nonracemic substituted and fused tetrahydroquinoxalines. The reaction proceeds through a solvent and catalyst free S_N2-type ring-opening of N-activated aziridines with 2-bromo anilines

Table 5. Synthesis of Chiral 1,2,3,4-Tetrahydroquinoxalines **9**



entry	R	**8**	yield **8** (%)[a]	ee **8** (%)[b]	**9**	yield **9** (%)[a]	ee **9** (%)[b]
1	H	**8a**	85	>99	**9a**	85	>99
2	Me	**8b**	80	>99	**9b**	79	>99
3	F	**8c**	79	98	**9c**	62	98

[a] Yield of isolated products. [b] ee was determined using Chiralpak AD-H and AS-H columns.

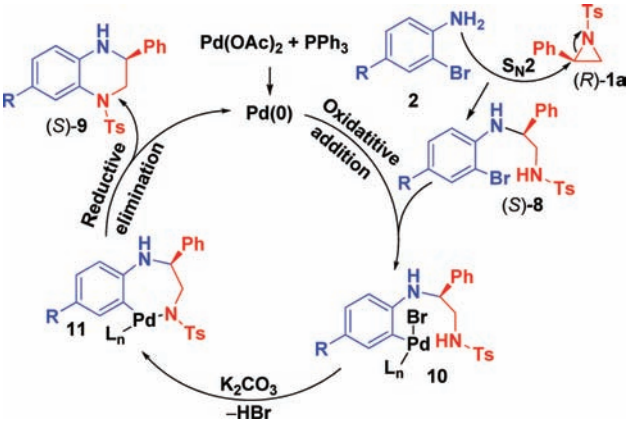


Figure 3. Proposed reaction mechanism.

followed by Pd catalyzed intramolecular C–N bond formation. This method allows the use of a wide range of aziridines and 2-bromo anilines to construct tetrahydroquinoxalines in excellent yields and enantioselectivities. Further work is in progress.

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Supporting Information Available. General procedures, X-ray crystallographic data of **4a**, copies of ^1H and ^{13}C spectra for all compounds, and HPLC chromatograms for ee determination. This material is available free of charge via the Internet at http://pubs.acs.org.