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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]

(1) (a) Eary, C. T.; Jones, Z. S.; Groneberg, R. D.; Burgess, L. E.; Mareska, D. A.; Drew, M. D.; Blake, J. F.; Laird, E. R.; Balachari, D.; O'Sullivan, M.; Allen, A.; Marsh, V. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2608. (b) Ohtake, Y.; Naito, A.; Hasegawa, H.; Kawano, K.; Marizono, D.; Taniguchi, M.; Tanaka, Y.; Matsukawa, H.; Naito, K.; Oguma, T.; EzureY.; Tsuriya, Y. *Bioorg. Med. Chem.* **1999**, *7*, 1247. (c) Torisu, K.; Kobayashi, K.; Iwahashi, M.; Nakai, Y.; Onoda, T.; Sugimoto, I.; Okada, Y.; Matsumoto, R.; Nanbu, F.; Ohuchida, S.; Nakai, H.; Toda, M. *Bioorg. Med. Chem.* **2004**, *12*, 5361. (d) Sikorski, J. A. *J. Med. Chem.* **2006**, *49*, 1. (e) Jacobsen, E. J.; Stelzer, L. S.; Belonga, K. L.; Carter, D. B.; Im, W. B.; Sethy, V. H.; Tang, A. H.; Von-Voigtlander, P. F.; Petke, J. D. *J. Med. Chem.* **1996**, *39*, 3820. (f) Barrows, T. H.; Farina, P. R.; Chrzanowski, R. L.; Benkovic, P. A.; Benkovic, S. J. *J. Am. Chem. Soc.* **1976**, *98*, 3678.

(2) (a) Merişor, E.; Conrad, J.; Klaiber, I.; Mika, S.; Beifuss, U. *Angew. Chem., Int. Ed.* **2007**, *46*, 3353. (b) Yang, S.-C.; Liu, P.-C.; Feng, W.-H. *Tetrahedron Lett.* **2004**, *45*, 4951. (c) Mukhopadhyay, R.; Kundu, N. G. *Synlett* **2001**, 1143. (d) Nair, V.; Dhanya, R.; Rajesh, C.; Bhadbhade, M. M.; Manoj, K. *Org. Lett.* **2004**, *6*, 4743. (e) Majumdar, K. C.; Ray, K.; Ponra, S. *Tetrahedron Lett.* **2010**, *51*, 5437. (f) Bunce, R. A.; Herron, D. M.; Hale, L. Y. *J. Heterocycl. Chem.* **2003**, *40*, 1031. (g) Krchňák, V.; Smith, J.; Vágner, J. *Tetrahedron Lett.* **2001**, *42*, 2443. (h) Bunce, R. A.; Herron, D. M.; Ackerman, M. L. *J. Org. Chem.* **2000**, *65*, 2847. (i) Renaud, T.; Hurvois, J.-P.; Uriac, P. *Eur. J. Org. Chem.* **2001**, 987. (j) Zheng, L. Y.; Bai, X. *Chin. Chem. Lett.* **2006**, *17*, 165.

(3) (a) Massacret, M.; Lhoste, P.; Sinou, D. *Eur. J. Org. Chem.* **1999**, 129. (b) Kim, J. C.; Choi, H. G.; Kim, M. S.; Ha, H.-J.; Lee, W. K. *Tetrahedron* **2010**, *66*, 8108. (c) Li, J.-L.; Han, B.; Jiang, K.; Du, W.; Chen, Y.-C. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3952. (d) Abraham, C. J.; Paull, D. H.; Scerba, M. T.; Grebinski, J. W.; Lectka, T. *J. Am. Chem. Soc.* **2006**, *128*, 13370. (e) Samanta, K.; Panda, G. *Org. Biomol. Chem.* **2010**, *8*, 2823.

(4) (a) Chen, Q.-A.; Wang, D.-S.; Zhou, Y.-G.; Duan, Y.; Fan, H.-J.; Yang, Y.; Zhang, Z. *J. Am. Chem. Soc.* **2011**, *133*, 6126. (b) Cartigny, D.; Nagano, T.; Ayad, T.; Genêt, J.-P.; Ohshima, T.; Mashima, K.; Ratovelomanana-Vidal, V. *Adv. Synth. Catal.* **2010**, *352*, 1886. (c) Mršić, N.; Jerphagnon, T.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *Adv. Synth. Catal.* **2009**, *351*, 2549. (d) Rueping, M.; Tato, F.; Schoepke, F. R. *Chem.—Eur. J.* **2010**, *16*, 2688. (e) Tang, W.; Xu, L.; Fan, Q.-H.; Wang, J.; Fan, B.; Zhou, Z.; Lam, K.; Chan, A. S. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 9135. (f) Wang, D.-W.; Wang, D.-S.; Chen, Q.-A.; Zhou, Y.-G. *Chem.—Eur. J.* **2010**, *16*, 1133.

(5) (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (c) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125. (d) Shekhar, S.; Ryberg, P.; Hartwig, J. F.; Mathew, J. S.; Blackmond, D. G.; Strieter, E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 3584. (e) Charles, M. D.; Schultz, P.; Buchwald, S. L. *Org. Lett.* **2005**, *7*, 3965. (f) Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 13552. (g) Shen, Q.; Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 6586. (h) Zheng, Z.; Alper, H. *Org. Lett.* **2008**, *10*, 4903. (i) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423. (j) Brain, C. T.; Steer, J. T. *J. Org. Chem.* **2003**, *68*, 6814. (k) Lebedev, A. Y.; Khartulyari, A. S.; Voskoboynikov, A. Z. *J. Org. Chem.* **2005**, *70*, 596. (l) Takenaka, K.; Itoh, N.; Sasai, H. *Org. Lett.* **2009**, *11*, 1483. (m) Hernández, S.; Moreno, I.; SanMartin, R.; Herrero, M. T.; Domínguez, E. *Org. Biomol. Chem.* **2011**, *9*, 2251. (n) Erb, W.; Neuville, L.; Zhu, J. *J. Org. Chem.* **2009**, *74*, 3109. (o) Willis, M. C.; Snell, R. H.; Fletcher, A. J.; Woodward, R. L. *Org. Lett.* **2006**, *8*, 5089. (p) Nakhla, J. S.; Wolfe, J. P. *Org. Lett.* **2007**, *9*, 3279. (q) Nakhla, J. S.; Schultz, D. M.; Wolfe, J. S. *Tetrahedron* **2009**, *65*, 6549.

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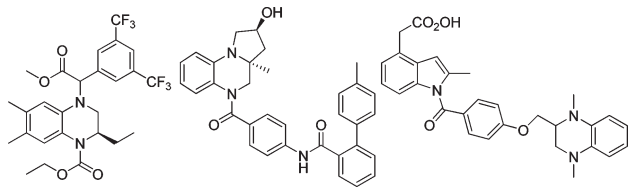


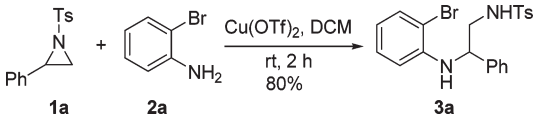
Figure 1. Selected biologically active 1,2,3,4-tetrahydroquinoxalines.

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

(6) (a) Minakata, S.; Okada, Y.; Komastu, M. *Org. Lett.* **2005**, *7*, 3509. (b) Couty, F.; Evano, G.; Prim, D. *Tetrahedron Lett.* **2005**, *46*, 2253. (c) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701 and references therein. (d) Forbeck, E. M.; Evans, C. D.; Gilleran, J. A.; Li, P.; Joullié, M. M. *J. Am. Chem. Soc.* **2007**, *129*, 14463. (e) Ochoa-Terán, A.; Concellón, J. M.; Rivero, I. A. *ARKIVOC* **2009**, No. ii, 288. (f) Concellon, J. M.; Bernad, P. L.; Suárez, J. R. *J. Org. Chem.* **2005**, *70*, 9411. (g) Minakata, S.; Hotta, T.; Oderaotoshi, Y.; Komatsu, M. *J. Org. Chem.* **2006**, *71*, 7471. (h) Joullié, M. M.; Kelley, B. T. *Org. Lett.* **2010**, *12*, 4244. (i) De Rycke, N.; David, O.; Couty, F. *Org. Lett.* **2011**, *13*, 1836. (j) D'hooghe, M.; Kenis, S.; Vervisch, K.; Lategan, C.; Smith, P. J.; Chibale, K.; De Kimpe, N. *Eur. J. Med. Chem.* **2011**, *46*, 579. (k) Yadav, J. S.; Satheesh, G.; Murthy, C. V. S. R. *Org. Lett.* **2010**, *12*, 2544. (l) Concellon, J. M.; Rodriguez-Solla, H.; Amo, V.; Diaz, P. *J. Org. Chem.* **2010**, *75*, 2407. (m) Zeng, F.; Alper, H. *Org. Lett.* **2010**, *12*, 5567. (n) Karikomi, M.; D'hooghe, M.; Verniest, G.; De Kimpe, N. *Org. Biomol. Chem.* **2008**, *6*, 1902. (o) Catak, S.; D'hooghe, M.; De Kimpe, N.; Waroquier, M; Speybroeck, V. V. *J. Org. Chem.* **2010**, *75*, 885. (p) Singh, G. S.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2007**, *107*, 2080. (q) Bhadra, S.; Adak, L.; Samanta, S.; Islam, A. K. M. M.; Mukherjee, M.; Ranu, B. C. *J. Org. Chem.* **2010**, *75*, 8533. (r) Bera, M.; Pratihar, S.; Roy, S. *J. Org. Chem.* **2011**, *76*, 1475. (s) D'hooghe, M.; Rottiers, M.; Kerkaert, I.; De Kimpe, N. *Tetrahedron* **2005**, *61*, 8746. (t) D'hooghe, M.; Waterinckx, A.; Vanlangendonck, T.; De Kimpe, N. *Tetrahedron* **2006**, *62*, 2295.

(7) (a) Minakata, S.; Murakami, Y.; Satake, M.; Hidaka, I.; Okada, Y.; Komatsu, M. *Org. Biomol. Chem.* **2009**, *7*, 641. (b) Ding, C.-H.; Dai, L.-X.; Hou, X.-L. *Tetrahedron* **2005**, *61*, 9586. (c) D'hooghe, M.; De Kimpe, N. *Chem. Commun.* **2007**, 1275. (d) D'hooghe, M.; Kerkaert, I.; Rottiers, M.; De Kimpe, N. *Tetrahedron* **2005**, *60*, 3637.

(8) (a) Blyumin, E. V.; Gallon, H. J.; Yudin, A. K. *Org. Lett.* **2007**, *9*, 4677. (b) Moss, T. A.; Fenwick, D. R.; Dixon, D. J. *J. Am. Chem. Soc.* **2008**, *130*, 10076. (c) Paixão, M. W.; Nielsen, M.; Jacobsen, C. B.; Jørgensen, K. A. *Org. Biomol. Chem.* **2008**, *6*, 3467. (d) Enders, D.; Janeck, C. F.; Raabe, G. *Eur. J. Org. Chem.* **2000**, 3337. (e) Xu, Y; Lin, L.; Kanai, M.; Matsunaga, S; Shibasaki, M. *J. Am. Chem. Soc.* **2011**, *133*, 5791.

(9) For some recent examples of aziridine mediated heterocycle synthesis, see: (a) Kiss, L.; Mangelinckx, S.; Fülöp, F.; De Kimpe, N. *Org. Lett.* **2007**, *9*, 4399. (b) Ghorai, M. K.; Nanaji, Y.; Yadav, A. K. *Org. Lett.* **2011**, *13*, 4256. (c) Du, X.; Yang, S.; Yang, J.; Liu, Y. *Chem.—Eur. J.* **2011**, *17*, 4981. (d) Wu, Y.-C.; Zhu, J. *Org. Lett.* **2009**, *11*, 5558. (e) Baktharaman, S.; Afagh, A.; Vandersteen, A.; Yudin, A. K. *Org. Lett.* **2010**, *12*, 240. (f) Prasad, D. J. C.; Sekar, G. *Org. Biomol. Chem.* **2009**, *7*, 5091. (g) Bisol, T. B.; Bortoluzzi, A. J.; Sá, M. M. *J. Org. Chem.* **2011**, *76*, 948. (h) Wang, J.-Y.; Guo, X.-F.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *J. Org. Chem.* **2008**, *73*, 1979. (i) Wang, L.; Liu, Q.-B.; Wang, D.-S.; Li, X.; Han, X.-W.; Xiao, W.-J.; Zhou, Y.-G. *Org. Lett.* **2009**, *11*, 1119. (j) Hong, D.; Lin, X.; Zhu, Y.; Lei, M.; Wang, Y. *Org. Lett.* **2009**, *11*, 5678. (k) Rao, R. K.; Naidu, A. B.; Sekar, G. *Org. Lett.* **2009**, *11*, 1923. (l) D'hooghe, M.; Aelterman, W.; De Kimpe, N. *Org. Biomol. Chem.* **2009**, *7*, 135. (m) Brabandt, W. V.; Dejaegher, Y.; Landeghem, R. V.; De Kimpe, N. *Org. Lett.* **2006**, *8*, 1101. (n) Žukauskaite, A.; Mangelinckx, S.; Buinauskaite, V.; Šačkus, A.; De Kimpe, N. *Amino Acids* **2011**, *41*, 541.

(10) (a) Ghorai, M. K.; Tiwari, D. P. *J. Org. Chem.* **2010**, *75*, 6173. (b) Ghorai, M. K.; Kumar, A.; Tiwari, D. P. *J. Org. Chem.* **2010**, *75*, 137. (c) Ghorai, M. K.; Shukla, D.; Das, K. *J. Org. Chem.* **2009**, *74*, 7013. (d) Ghorai, M. K.; Das, K.; Shukla, D. *J. Org. Chem.* **2007**, *72*, 5859. (e) Ghorai, M. K.; Kumar, A.; Das, K. *Org. Lett.* **2007**, *9*, 5441. (f) Ghorai, M. K.; Das, K.; Kumar, A. *Tetrahedron Lett.* **2007**, *48*, 4373. (g) Ghorai, M. K.; Ghosh, K. *Tetrahedron Lett.* **2007**, *48*, 3191. (h) Ghorai, M. K.; Das, K.; Kumar, A. *Tetrahedron Lett.* **2009**, *50*, 1105.

(11) See the Supporting Information for details.

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

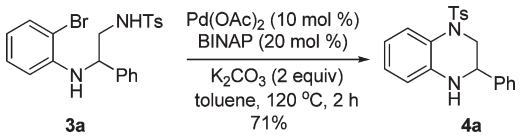


Table 1. Optimization of Reaction Conditions for the Formation of **4a**

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.

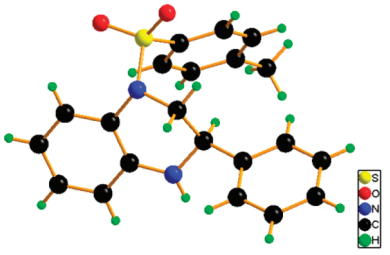
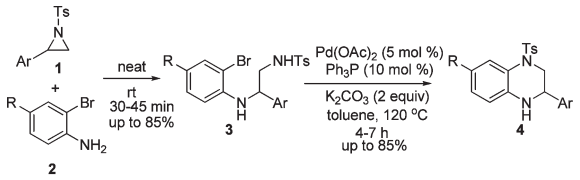


Figure 2. Diamond diagram of compound **4a**.

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**

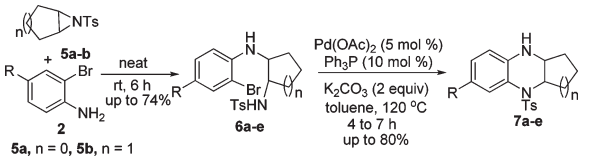
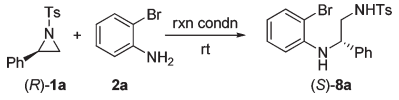


Table 3. Regioselective Ring-Opening of **5** and Pd-Catalyzed Intramolecular C–N Cyclization of **6a**–**e**[a]

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**



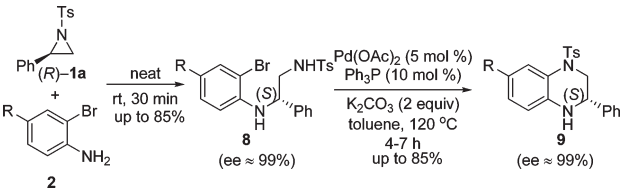
entry	equiv **2a**	LA (mol %)	solvent	time (h)	yield **8a** (%)[a]	ee **8a**[b]
1	1	$Cu(OTf)_2$ (30)	CH_2Cl_2	2	80	0
2	4	$Cu(OTf)_2$ (30)		2	78	98
3	4		neat	0.5	86	>99

[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.

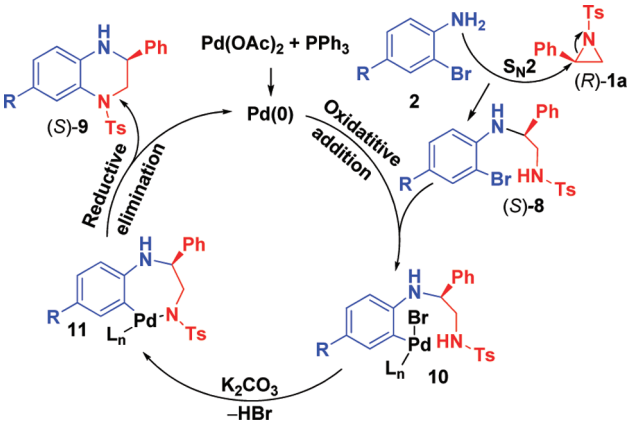


Figure 3. Proposed reaction mechanism.

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.