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Ring Opening/C−N Cyclization of Activated Aziridines with Carbon Nucleophiles: Highly Diastereo- and Enantioselective Synthesis of Tetrahydroquinolines

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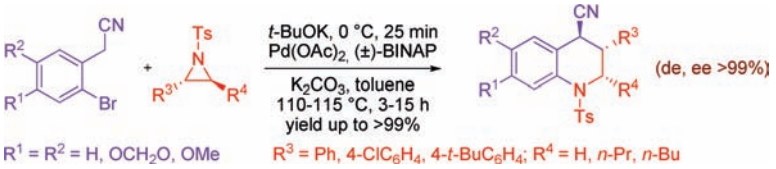
ABSTRACT



A simple strategy for the synthesis of substituted tetrahydroquinolines through regio- and stereoselective ring opening of *N*-tosyl aziridines with carbon nucleophiles generated from 2-(bromoaryl)acetonitriles followed by palladium-catalyzed intramolecular C−N cyclization is reported in excellent yields (up to >99%) and stereoselectivity (*ee* and *de* up to >99%).

Tetrahydroquinolines and their derivatives are prevalent in a number of naturally occurring and biologically active compounds. Some of the important natural products containing a tetrahydroquinoline ring system are Sumanirole maleate (PNU95666E) **1**,[1a] Angustureine **2a**,[1b] Galipinine **2b**,[1c] Cuspareine **2c**,[1d] (*S*)-flumequine **3**[1e] (Figure 1), Discorhabdin C,[1f] Dynemycin A,[1g] and Virantmycin.[1h] Several of them have been found to exhibit a wide range of pharmacological acitivities such as analgesic, antiarrhythmic, cardiovascular, immunosuppresent, antitumor, antiallergenic, anticonvulsant, antifertility, NMDA antagonist activities, etc.[2,3] Pyrrolo[3,2,1-*ij*]quinoline derivatives **4** are the basic skeleton of compounds possessing 5-lipoxygenase inhibitor properties and used for the treatment of asthma (Figure 1).[4] Tetrahydroquinoline based inhibitors are also shown as one of the most potent protein farnesyltransferase inhibitors.[5]

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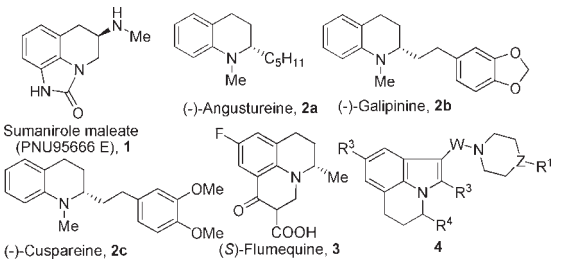

Figure 1. Some biologically active tetrahydroquinolines.

Immense synthetic and pharmacological utilities of such tetrahydroquinolines have inspired synthetic organic and medicinal chemists to develop new strategies for their syntheses. A number of methodologies have been developed for this purpose[2,6,7] including synthesis from either aniline precursors using electrophilic aromatic substitution,[8] Aza Diels–Alder reaction,[9] or nucleophilic displacement[10] or reduction of a quinolone precursor.[11] Palladium-catalyzed amination reactions allow for facile construction of C_{aryl}–N bonds to form both activated and nonactivated aryl halogenides.[12]

We anticipated that tetrahydroquinolines could easily be synthesized from the ring opening of *N*-tosyl aziridines by C-nucleophiles generated from bromoarylacetonitriles followed by Pd-catalyzed intramolecular C–N cyclization. Several reports are known for the ring opening of aziridines with heteroatoms;[13] yet, ring opening of aziridines with C-nucleophiles is still limited.[14,15]

Recently, we have reported the Lewis acid (LA) mediated S_N2-type ring opening of enantiopure 2-aryl-*N*-tosylaziridines and azetidines by a number of nucleophiles to provide nonracemic products in high enantiomeric excess.[16] In continuation of our research in this area, we have developed a simple strategy for the synthesis of tetrahydroquinolines with excellent yields (up to 99%) and stereoselectivity (*ee* and *de* up to > 99%) via the regio- and stereoselective ring opening of aziridines by C-nucleophiles generated from 2-bromoarylacetonitriles followed by Pd-catalyzed intramolecular C–N cyclization. Herein, we report our preliminary results.

Our study began with the ring opening of 2-phenyl-*N*-tosylaziridine **5a** with a C-nucleophile generated from 2-bromo-3,4-dimethoxyphenylacetonitrile **6a** by treatment of ^{t}BuOK as the base in THF at 0 °C to afford the corresponding ring opening product **7a** (Scheme 1). Other bases were studied; yet the best results (yield and reaction time) were obtained using ^{t}BuOK (Scheme 1; see Table S1). Product **7a** was characterized by ^{1}H, ^{13}C NMR and mass

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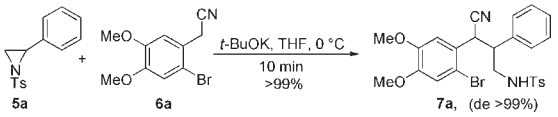
Scheme 1. Regioselective Ring Opening of **6a** with Carbon Nucleophile of 2-Bromo-3,4-dimethoxyphenylacetonitrile



spectral data. Next, **7a** was subjected to Pd-catalyzed cyclization to obtain tetrahydroquinoline **8a** (Scheme 2). To find the optimum reaction conditions, **7a** was subjected to different Pd-catalysts, solvents, ligands, and a number of bases. These optimization results are summarized in Table 1 (Scheme 2). The best result was obtained with $Pd(OAc)_2$, (±)-BINAP, and K_2CO_3 as the base in toluene at 110−115 °C (Table 1, entry 8), and this condition was employed for further studies as the optimum reaction conditions. **8a** was characterized by ^1H, ^{13}C NMR, ^1H COSY, and mass spectral data. The structure of **8a** was unequivocally confirmed by X-ray crystallographic analysis. In some cases, we also observed the formation of quinoline **9a** (Scheme 2, Table 1), and its structure was confirmed by ^1H, ^{13}C NMR and mass spectral data. To generalize this approach, several *N*-[3-(2-bromoaryl)-3-cyano-2-arylpropyl]-4-methylbenzene sulfonamides **7a**−**i** were prepared from aziridines **5a**−**c** and nitriles **6a**−**c**. Compounds **7a**−**i** were cyclized under optimized conditions

Scheme 2. Pd-Catalyzed C−N Cyclization of **7a**

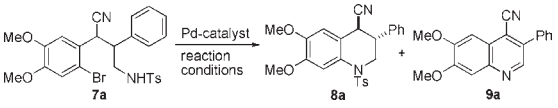


Table 1. Pd-Catalyzed Intramolecular C−N Cyclization of **7a**

entry	reaction conditions[a]	**8a** yield (%)[c]	**9a** yield (%)[c]
1[b]	$Pd(PPh_3)_4$, K_2CO_3, toluene, 12 h	–	62
2	$Pd(PPh_3)_4$, K_2CO_3, CH_3CN, reflux, 12 h	–	58
3[b]	$Pd(OAc)_2$, Xantphos, K_2CO_3, toluene, 10 h	–	61
4	$Pd(OAc)_2$, (*o*-tolyl)$_3$P, K_2CO_3, DMF, 120 °C, 10 h	–	57
5	$Pd(OAc)_2$, PPh_3, K_2CO_3, toluene, reflux, 8 h	–	66
6	$Pd(OAc)_2$, dppb, toluene, K_2CO_3, reflux, 8 h	58	12
7	$Pd(OAc)_2$, dpp, toluene, K_2CO_3, reflux, 8 h	56	10
8[b]	$Pd(OAc)_2$, (±)-BINAP, K_2CO_3, toluene, 8 h	99	–
9[b]	$Pd(OAc)_2$, (±)-BINAP, Cs_2CO_3, toluene, 3 h	62	–
10	$Pd(OAc)_2$, dppb, toluene, *t*-BuOK, reflux, 8 h	60	11

[a] All reactions were carried out with **7a** (1.0 mmol), Pd-catalyst (20 mol %), ligand (40 mmol %), base (2.5 equiv) in solvent (8 mL) under argon. [b] These reactions were reflexed at 110−115 °C for 3−12 h. [c] Yields of isolated products (%).

Scheme 3. Synthesis of Tetrahydroquinolines **8a**−**i**

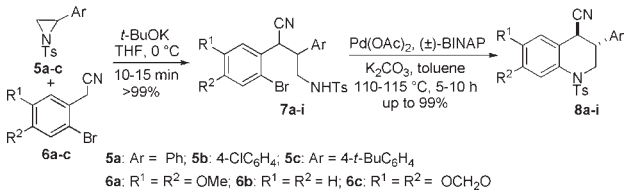


Table 2. Regioselective Ring Opening of **6** and Pd-Catalyzed Intramolecular C−N Cyclization of **7a**−**i**[a]

entry	**5** (Ar)	**6** ($R^1 = R^2$)	**7** yield (%)[b,c]	time (h)	**8** yield (%)[b]
1	**5a** (Ph)	**6a** (OMe)	**7a**, >99	10	**8a**, 83
2	**5b** (4-ClC$_6$H4)	**6a** (OMe)	**7b**, 99	12	**8b**, 90
3	**5c** (*t*-BuC$_6$H$_4$)	**6a** (OMe)	**7c**, 99	6	**8c**, 86
4	**5a** (Ph)	**6b** (H)	**7d**, >99	5	**8d**, 98
5	**5b** (4-ClC$_6$H4)	**6b** (H)	**7e**, >99	5	**8e**, 95
6	**5c** (*t*-BuC$_6$H$_4$)	**6b** (H)	**7f**, >99	10	**8f**, 86
7	**5a** (Ph)	**6c** (OCH_2O)	**7g**, 99	5	**8g**, 91
8	**5b** (4-ClC$_6$H4)	**6c** (OCH_2O)	**7h**, 99	5	**8h**, 87
9	**5c** (*t*-BuC$_6$H$_4$)	**6c** (OCH_2O)	**7i**, 99	5	**8i**, 94

[a] All reactions were carried out with **7a**−**i** (1.0 mmol), $Pd(OAc)_2$ (20 mol %), (±)BINAP (40 mmol %), K_2CO_3 (2.5 equiv) in toluene (8 mL) under argon for 4−10 h under refluxed at 110−115 °C. [b] Yields of isolated products (%), [c] de >99% in all the cases.

to afford the corresponding tetrahydroquinolines **8a**−**i** in excellent yields (Scheme 3, Table 2). The strategy was extended further for the synthesis of cyclopenta- and cyclohexa-fused tetrahydroquinolines **12a**−**f** via the ring opening of bicyclic aziridines **10a**−**b**. Aziridines **10a**−**b** were reacted with different arylacetonitriles **6a**−**c** in the presence of ^{t}BuOK in THF at 0 °C to afford the corresponding ring-opening products **11a**−**f** in almost quantitative yields. **11a**−**f** were cyclized under optimized conditions to afford the corresponding fused tetrahydroquinolines **12a**−**f** in excellent yields (Scheme 4, Table 3). After the successful demonstration of our strategy for the synthesis of a variety of racemic tetrahydroquinolines **8a**−**i** and **12a**−**f** via the ring opening of racemic aziridines, the scope of the methodology was extended to the synthesis of nonracemic tetrahydroquinolines **15a**−**e**. Chiral *N*-tosylaziridines (*S*)-**13a** and (2*S*,3*S*)-**13b**−**c** (*ee*/*de* > 99%) were

Scheme 4. Synthesis of Cyclopenta[*b*]- and Cyclohexa[*b*]-Fused Tetrahydroquinolines **12a**−**f**

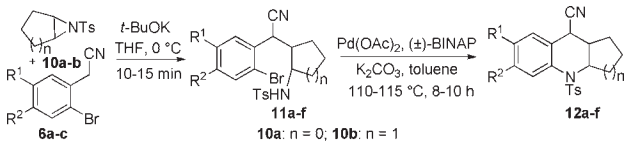


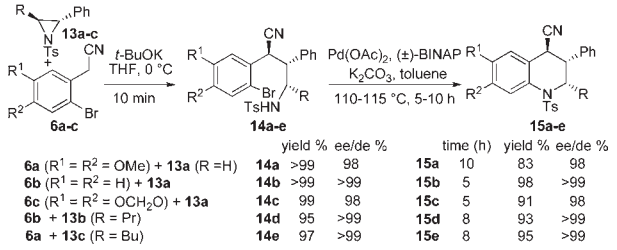
Table 3. Synthesis of Cyclopenta[*b*]- and Cyclohexa[*b*]-Fused Tetrahydroquinolines **12a**–**f**[a]

entry	**10** (*n*)	**6** ($R^1 = R^2$)	**11** yield (%)[b]	time (h)	**12** yield (%)[b]
1	**10a** (0)	**6b** (H)	**11a**, 99	6	**12a**, 97
2	**10b** (1)	**6b** (H)	**11b**, 98	6	**12b**, 93
3	**10a** (0)	**6a** (OMe)	**11c**, >99	10	**12c**, 90
4	**10b** (1)	**6a** (OMe)	**11d**, >99	15	**12d**, 98
5	**10a** (0)	**6c** (OCH_2O)	**11e**, 94	12	**12e**, 98
6	**10b** (1)	**6c** (OCH_2O)	**11f**, >99	13	**12f**, 96

[a] All reactions were carried out with **11a**–**f** (1.0 mmol), $Pd(OAc)_2$ (20 mol %), (±)BINAP (40 mmol %), and K_2CO_3 (2.5 equiv) in toluene (8 mL) under argon for 4–10 h refluxed at 110–115 °C. [b] Yields of isolated products.

reacted with C-nucleophiles derived from various bromoarylacetonitriles **6a**–**c** followed by Pd-catalyzed intramolecular C–N cyclization to produce the nonracemic tetrahydroquinolines (3*R*,4*S*)-**15a**–**b**, (7*R*,8*S*)-**15c**, and (2*S*,3*R*,4*S*)-**15d**–**e** in excellent yields (up to 99%) and stereoselectivity (*ee*, *de* up to >99%) as shown in Scheme 5.

Scheme 5. Synthesis of Nonracemic Tetrahydroquinolines **15**



		yield %	ee/de %		time (h)	yield %	ee/de %
6a ($R^1 = R^2$ = OMe) + **13a** (R =H)	**14a**	>99	98	**15a**	10	83	98
6b ($R^1 = R^2$ = H) + **13a**	**14b**	>99	>99	**15b**	5	98	>99
6c ($R^1 = R^2 = OCH_2O$) + **13a**	**14c**	99	98	**15c**	5	91	98
6b + **13b** (R = Pr)	**14d**	95	>99	**15d**	8	93	>99
6a + **13c** (R = Bu)	**14e**	97	>99	**15e**	8	95	>99

To make our strategy more attractive and straightforward as a synthetic methodology, domino and one-pot (stepwise) protocols for the synthesis of chiral tetrahydroquinolines **15** via ring opening of enantiopure mono- and *trans*-disubstituted aziridines **13a**–**c** were explored. When (*S*)-**13a** and (2*S*,3*S*)-**13b**–**c** were reacted with C-nucleophiles generated from **6a**–**c** followed by cyclization under one-pot or domino reaction conditions,[17] the corresponding substituted tetrahydroquinolines (3*R*,4*S*)-**15a**, (2*S*,3*R*,4*S*)-**15d**–**i**, and (6*S*,7*R*,8*S*)-**15g**–**h** were obtained as the only diastereomer *de* (>99%) with excellent yields (up to 98%) (Scheme 6 and Table 4).

Scheme 6. Synthesis of Nonracemic Tetrahydroquinolines **15**

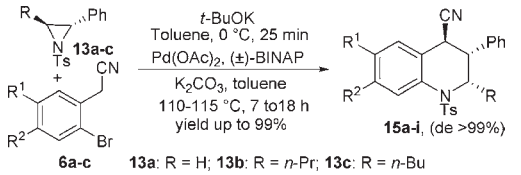


Table 4. One-Pot Ring Opening C–N Cyclization of Activated Aziridines with Carbon Nucleophiles[a]

entry	**6** ($R^1 = R^2$)	**13** (R)	time (h)	**15**	yield (%)[b]	de (%)[c]
1	**6b** (H)	**13a** (H)	5	**15a**	98	>99[d]
2	**6b** (H)	**13c** (^{n}Bu)	18	**15f**	92	99
3	**6c** (OCH_2O)	**13b** (^{n}Pr)	12	**15g**	97	99
4	**6c** (OCH_2O)	**13c** (^{n}Bu)	7	**15h**	94	99
5	**6a** (OMe)	**13b** (^{n}Pr)	11	**15i**	93	99
6	**6b** (H)	**13b** (^{n}Pr)	12	**15d**	94	99
7	**6a** (OMe)	**13c** (^{n}Bu)	10	**15e**	97	99
8	**6a** (OMe)	**13b** (^{n}Pr)[e]	8	**15i**	71	99
9	**6a** (OMe)	**13c** (^{n}Bu)[e]	11	**15e**	85	99

[a] All reactions were carried out with **13a**–**c** (1.0 mmol), **6a**–**c** (1.1 mmol), *t*-BuOK (1.1 equiv), toluene (8 mL), 0 °C, 25 min, $Pd(OAc)_2$ (20 mol %), (±)BINAP (40 mol %), K_2CO_3 (2.5 equiv), under reflux at 110–115 °C, 5–18 h. [b] Yields of isolated products (%). [c] Determined by ^1H NMR. [d] The enantiomeric excess determined by chiral HPLC using AD–H column. [e] These two reactions were carried out under domino conditions.

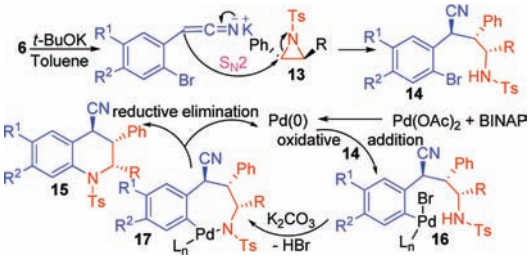


Figure 2. Proposed reaction mechanism.

A probable mechanism for the formation of chiral tetrahydroquinolines **15a**–**i** is described in Figure 2. S_N2-type ring opening of chiral *N*-tosylaziridines **13a**–**c** by the C-nucleophiles derived from **6a**–**c** at the benzylic position generate the corresponding bromoamines **14** which undergo Pd-catalyzed intramolecular C–N coupling to produce the corresponding tetrahydroquinolines **15a**–**i**.[12]

In conclusion, we have developed a simple protocol for the synthesis of substituted nonracemic tetrahydroquinolines through a ^{t}BuOK-mediated S_N2-type ring opening of *N*-activated aziridines with arylacetonitriles followed by Pd-catalyzed C–N cyclization in excellent yields and stereoselctivity (*de* and *ee* up to >99%).

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Supporting Information Available. Experimental procedure, characterization data, and NMR spectra for all new compounds and X-ray crystallographic data of **8a**, **12a**, **14e**, and **15d**. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) See Supporting Information for details.