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Syntheses of Tetrahydrobenzoazepinoindoles and Dihydrobenzodiazepinoindoles via Ring-Opening Cyclization of Activated Aziridines with 2-(2-Bromophenyl)-1*H*-indoles

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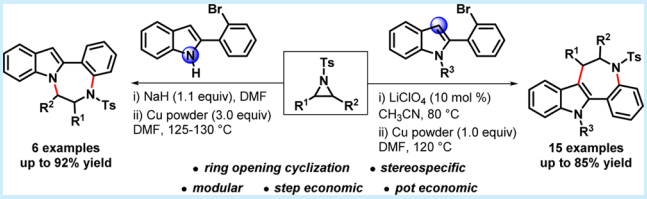
Supporting Information

ABSTRACT: Two efficient, modular, step- and pot-economic strategies to access various 5,6,7,12-tetrahydrobenzo[2,3]-azepino[4,5-*b*]indoles and 6,7-dihydro-5*H*-benzo[5,6][1,4]-diazepino[1,7-*a*]indoles are disclosed that advance via S_N2-type regioselective ring opening of enantiopure aziridines with 2-(2-bromophenyl)-1*H*-indoles at their C3 and indolyl N centers, respectively, followed by Cu-mediated C−N cyclization which furnishes the products in excellent yields with outstanding enantiomeric excesses (up to >99%).



5,6,7,12-Tetrahydrobenzo[2,3]azepino[4,5-*b*]indoles are an important class of indoloazepine often found in naturally occurring compounds with intriguing bioactivities (Figure 1). A few

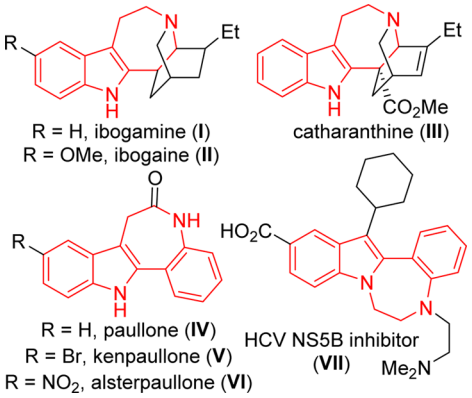


Figure 1. Representative examples of natural products containing azepino- and diazepinoindoles.

illustrative examples include the iboga alkaloids viz. ibogamine (**I**) and ibogaine (**II**) that can attenuate addiction of major drugs of abuse,[1] catharanthine (**III**) that demonstrates potent inhibition to TRPM8 activity,[2] and the paullones (**IV**−**VI**) that are cyclin-dependent and glycogen synthase kinase inhibitors.[3,4] Another structural variant of indoloazepines, the 6,7-dihydro-5*H*-benzo-[5,6][1,4]diazepino[1,7-*a*]indole **VII**, acts as an HCV NS5B-polymerase inhibitor.[5]

Despite the immense pharmacological significance of THB-[2,3]azepino[4,5-*b*]indoles and DHB-[5,6][1,4]diazepino[1,7-*a*]indoles, only a few reports are known for their syntheses that include Au-catalyzed intramolecular hydroarylation of alkynyl indoles,[6−9] Ir-catalyzed allylic dearomatization/retro-Mannich/hydrolysis cascade reaction,[10] Ni-catalyzed C−H functionalization,[1] Cu-catalyzed [4 + 2] cyclization of 2-vinylindoles,[11] fragmentation of an indole diazabicyclo[3.2.2]nonedione derivative,[12] Au-catalyzed intramolecular cyclization of indolylcyclopropenes,[13] Pd-catalyzed intramolecular oxidative C−H coupling of *N*-alkylated indoles,[14] etc. A number of existing strategies typically rely on multistep syntheses. To circumvent the shortcomings of the existing methodologies, we sought an expedient access to both of these indoloazepine skeleta with extensive scope for structural and functional diversification. Based on our longstanding interest in S_N2-type ring opening of activated aziridines[15] followed by cyclization strategies with functionalized nucleophiles to construct chiral aza-heterocycles and other targets of contemporary interest,[16] we recognized the prospect of procuring THB-[2,3]azepino[4,5-*b*]indoles and DHB-[5,6]-[1,4]diazepino[1,7-*a*]indoles through the ring opening of activated aziridines with 2-(2-bromophenyl)-1*H*-indoles by exploiting their C3 and N centers as nucleophilic sites, respectively, followed by metal-assisted C−N bond-forming cyclization. Herein, we wish to report our results as a Letter.

Our study commenced with the S_N2-type ring opening of 2-phenyl-*N*-tosylaziridine (**1a**) with 2-(2-bromophenyl)-1*H*-indole(**2a**)[17] through its C3 site in the presence of 10 mol % $LiClO_4$ as the Lewis acid (LA) in acetonitrile at 80 °C,[16e,f] and the corresponding ring-opened product formed as a single regioisomer in 89% yield (Scheme 1).[18] Next, **3a** was subjected to an intramolecular C−N cyclization in the presence of 10 mol % copper(I) iodide, 20 mol % L-proline as the ligand, and 2.5 equiv of sodium hydride in DMF at 120 °C[19] to afford the corresponding THB-[2,3]azepino[4,5-*b*]indole **4a** in moderate yield (42%, Scheme 2). The structure of **4a** was confirmed by single crystal X-ray analysis.[18]

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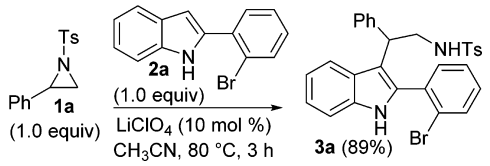
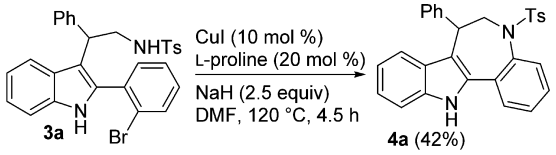
Scheme 1. $LiClO_4$-Catalyzed Ring Opening of 2-Phenyl-*N*-tosylaziridine (1a) with 2-(2-Bromophenyl)-1*H*-indole (2a)

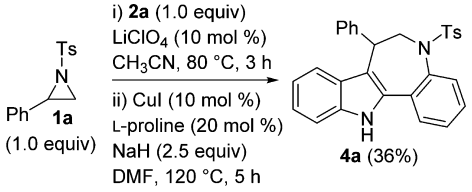


Scheme 2. Synthesis of THB-[2,3]azepino[4,5-*b*]indole 4a via Intramolecular Cyclization of 3a through Cu(I)-Catalyzed C−N Coupling



To improve the efficiency of the transformation, a one-pot (stepwise) protocol for the synthesis of **4a** through the ring opening of **1a** with **2a** followed by Cu-catalyzed cyclization was explored, and the desired THB-[2,3]azepino[4,5-*b*]indole **4a** was obtained in 36% overall yield (Scheme 3). It is noteworthy that the developed strategy does not require protection of the indolyl nitrogen,[20] thus furnishing the desired products with free N−H groups.

Scheme 3. Synthesis of THB-[2,3]azepino[4,5-*b*]indole 4a via One-Pot Ring-Opening Cyclization of 2-Phenyl-*N*-tosylaziridine with 2-(2-Bromophenyl)-1*H*-indole (2a)

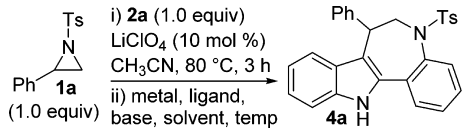


To optimize the reaction conditions with respect to the yield of the isolated product (**4a**), various metal sources, ligands, and bases in different solvents were screened. The best result was obtained under Cu-powder-mediated C−N bond forming reaction conditions[16d] to furnish **4a** in 81% overall yield (entry 5). Altering the solvent from DMF to toluene (entry 6), DMSO (entry 7), or NMP (entry 8) failed to enhance the yield of **4a** further. The results of the complete optimization study are detailed in Table 1.

To investigate the substrate tolerance of our approach, a range of racemic 2-aryl-*N*-tosylaziridines **1a−e** were studied for the one-pot ring-opening cyclization cascade with 2-(2-bromophenyl)-1*H*-indole (**2a**), and in all the cases the corresponding THB-[2,3]azepino[4,5-*b*]indoles **1a−e** formed in high yield. The results are described in detail in Table 2.

The strategy was further generalized by engaging a range of substituted 2-(2-bromophenyl)-1*H*-indoles as the nucleophiles. When aziridines **1a**, **1d**, and **1f** were subjected to the one-pot ring-opening cyclization with 2-(2-bromophenyl)-5-fluoro-1*H*-indole (**2b**) under the optimized reaction conditions, the corresponding THB-[2,3]azepino[4,5-*b*]indoles **4f−h** were obtained in excellent overall yield (up to 84%, entries 1−3). Likewise, the reaction of 5-chloro- and 5-fluoroindole derivatives **2c** and **2d**, respectively, with aziridines **1a** and **1d** afforded the corresponding

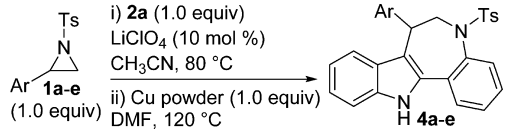
Table 1. Optimization Studies for One-Pot Synthesis of THB-[2,3]azepino[4,5-*b*]indole 4a via Ring-Opening-Cyclization of 2-Phenyl-*N*-tosylaziridine (1a) with 2-(2-Bromophenyl)-1*H*-indole (2a)



entry	metal, ligand, base, solvent, temp	*t* (h)	yield (%)
1	CuI, L-proline, NaH, DMF, 120 °C	8	36
2	CuI, L-proline, K_2CO_3, DMF, 120 °C	10	trace
3	CuI, glycine, NaH, DMF, 120 °C	9	25
4	CuBr, L-proline, NaH, DMF, 120 °C	9	28
5	Cu powder, DMF, 120 °C	6	81
6	Cu powder, toluene, 110 °C	10	35
7	Cu powder, DMSO, 120 °C	8	70
8	Cu powder, NMP, 120 °C	10	65

[a]The reaction was carried out in the presence of 10 mol % metal source, 20 mol % ligand, and 2.5 equiv of base. [b]The reaction was carried out in the presence of 1.0 equiv of the metal source.

Table 2. One-Pot Synthesis of THB-[2,3]azepino[4,5-*b*]indoles (4) via Ring-Opening Cyclization of 2-Aryl-*N*-tosylaziridine with 2-(2-Bromophenyl)-1*H*-indole (2a)



entry	aziridine (Ar, **1**)	indole (**2**)	**4**	time (h)	yield (%)
1	Ph, **1a**	**2a**	**4a**	6	81
2	4-FC_6H_4, **1b**	**2a**	**4b**	6	82
3	4-ClC_6H_4, **1c**	**2a**	**4c**	6.5	83
4	3-ClC_6H_4, **1d**	**2a**	**4d**	6	85
5	2-naphthyl, **1e**	**2a**	**4e**	6	77

THB-[2,3]azepino[4,5-*b*]indoles **4i−l** single regioisomers in excellent yield (up to 84%, entries 4−7). It is pertinent to note here that the halogen groups appended around the synthesized THB-[2,3]azepino[4,5-*b*]indoles could naturally allow further synthetic elaboration to other heterocyclic frameworks. All the results are detailed in Table 3.

The efficiency of the developed methodology was further examined by using substituted indole nucleophiles with varying electronic nature. To enhance the nucleophilicity of the C3 center, a methyl group was installed at the NH moiety.[21] When **1a** was reacted with **2e**, the corresponding THB-[2,3]azepino[4,5-*b*]indole derivative **4m** was obtained in 75% yield (Scheme 4).

To extend the scope of the methodology further by accommodating additional functionality in the products, 2-vinyl-*N*-tosylaziridine (**1g**) was employed as the substrate. When **1g** was treated with **2a** under the optimized reaction conditions, the corresponding vinyl-substituted THB-[2,3]azepino[4,5-*b*]-indole derivative **4n** formed as a single regioisomer in 75% yield (Scheme 5).

To synthesize enantioenriched THB-[2,3]azepino[4,5-*b*]-indoles, enantiopure aziridines were employed as the substrates. When enantiopure (*R*)-2-phenyl-*N*-tosylaziridine (*R*)-**1a** (ee >99%) and (*S*)-2-vinyl-*N*-tosylaziridine (*S*)-**1g** (ee 98%) were reacted with **2a−e**, the corresponding THB-[2,3]azepino[4,5-

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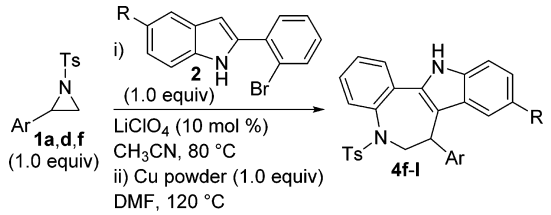
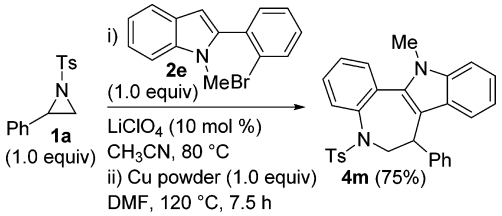
Table 3. One-Pot Synthesis of Tetrahydrobenzoazepinoindoles (4) via Ring-Opening Cyclization Cascade of 2-Aryl-*N*-tosylaziridine with 2-(2-Bromophenyl)-1*H*-indoles (2)

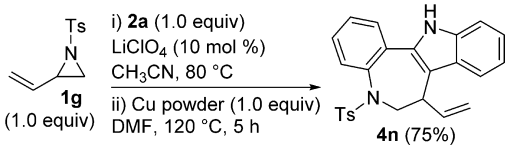


entry	1 (Ar)	2 (R)	4	time (h)	yield (%)
1	**1a** (Ph)	**2b** (F)	**4f**	6	84
2	**1d** (3-ClC_6H_4)	**2b** (F)	**4g**	6.5	80
3	**1f** (3-BrC_6H_4)	**2b** (F)	**4h**	6.5	79
4	**1a** (Ph)	**2c** (Cl)	**4i**	6	84
5	**1d** (3-ClC_6H_4)	**2c** (Cl)	**4j**	6.5	80
6	**1a** (Ph)	**2d** (Br)	**4k**	6.5	81
7	**1d** (3-ClC_6H_4)	**2d** (Br)	**4l**	7	79

Scheme 4. Synthesis of THB-[2,3]azepino[4,5-*b*]indoles via One-Pot Ring-Opening Cyclization of 2-Phenyl-*N*-tosylaziridine (1a) with 2-(2-Bromophenyl)-1-methyl-1*H*-indole (2e)



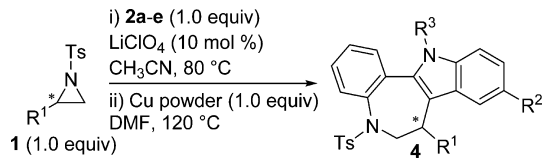
Scheme 5. Synthesis of THB-[2,3]azepino[4,5-*b*]indoles via One-Pot Ring-Opening Cyclization of 2-Vinyl-*N*-tosylaziridine (1g) with 2-(2-Bromophenyl)-1*H*-indole (2a)



b]indole derivatives were obtained in very high yields with excellent enantiomeric excesses (ee up to 98%, Scheme 6).

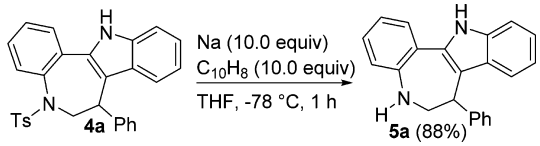
To enhance the potential and applicability of the THB-[2,3]azepino[4,5-*b*]indole derivatives in medicinal chemistry,[22,23] we attempted the deprotection of the tosyl group. As a representative example, detosylation of **4a** was accomplished in the presence of sodium naphthalenide in THF at −78 °C and the corresponding THB-[2,3]azepino[4,5-*b*]indole derivative **5a** with a free NH group was obtained in excellent yield (88%, Scheme 7).

Scheme 6. Stereospecific Synthesis of THB-[2,3]azepino[4,5-*b*]indoles via One-Pot Ring-Opening Cyclization of (*R*)-2-Aryl/Vinyl-*N*-tosylaziridines with 2-(2-Bromophenyl)-1*H*-indole (2a)[a]



[a](*R*)-**1a**: >99% ee; (*S*)-**1g**: 98% ee; R^1, R^2, R^3: Ph, H, H, (*S*)-**4a**, 96% ee; Ph, F, H, (*S*)-**4f**, 96% ee; Ph, Cl, H, (*S*)-**4i**, 94% ee; Ph, Br, H, (*S*)-**4k**, 97% ee; Ph, H, Me, (*S*)-**4m**, 98% ee; vinyl, H, H (*S*)-**4n**, 98% ee

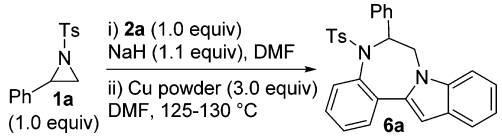
Scheme 7. Detosylation of THB-[2,3]azepino[4,5-*b*]indole with Sodium-Naphthalenide



Encouraged by our successful results for the synthesis of THB-[2,3]azepino[4,5-*b*]indoles, we next directed our efforts to synthesize another important yet rarely accessed class of heterocycles viz. DHB-[5,6][1,4]diazepino[1,7-*a*]indoles by altering the reactivity of the nucleophile under appropriate reaction conditions.

To perform the initial ring-opening reaction of 2-phenyl-*N*-tosylaziridine **1a** with the N site of the indole, **2a** was treated with a strong base (1.1 equiv of sodium hydride) in DMF and **1a** was added at rt.[16h] After complete consumption of **1a** in 3 h, 3.0 equiv of Cu powder were added to the reaction mixture in DMF portionwise and the temperature of the reaction was elevated to 125 °C. The reaction completed in 5 h, and the desired DHB-[5,6][1,4]diazepino[1,7-*a*]indoles **6a** was obtained in 73% yield as the only product (Scheme 8). It is worth noting that the ring

Scheme 8. Synthesis of DHB-[5,6][1,4]diazepino[1,7-*a*]indole 6a via One-Pot Ring-Opening Cyclization of *N*-Tosylaziridines (1a) with 2-(2-Bromophenyl)-1*H*-indole (2a)



opening primarily took place from the less hindered site of the aziridine **1a**. The structure of **6a** was confirmed by single crystal X-ray analysis.[18]

The methodology was generalized by studying a wide range of structurally different activated aziridines with 2-(2-bromophenyl)-1*H*-indoles under the above-described basic reaction conditions. Unsubstituted *N*-tosylaziridine (**1h**) smoothly underwent the transformation to furnish the corresponding DHB-[5,6][1,4]diazepino[1,7-*a*]indoles **6b** in 82% yield (entry 2). Next, to widen the scope of the strategy we engaged 2-alkyl substituted aziridines as the substrates. When 2-methyl-*N*-tosylaziridine (**1i**) and 2-*n*-octyl-*N*-tosylaziridine (**1j**) with a long hydrophobic tail were reacted with **2a**, the corresponding DHB-[5,6][1,4]diazepino[1,7-*a*]indoles **6c** and **6d** were obtained in very good yields (entries 3 and 4). Interestingly, the strategy works well with cyclopentane- and cyclohexane-fused bicyclic aziridines as well. When **1k** and **1l** were reacted with **2a** and **2c**, respectively, the corresponding products were obtained in high yields (entries 5 and 6). All the results are shown in Table 4.

To synthesize enantioenriched DHB-[5,6][1,4]diazepino[1,7-*a*]indoles, enantiopure (*R*)-**1a** was reacted with **2a** under the optimized reaction conditions and the corresponding product

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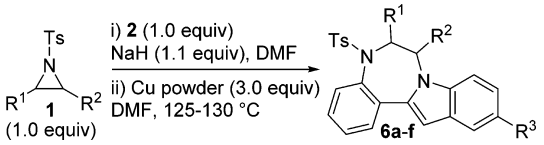
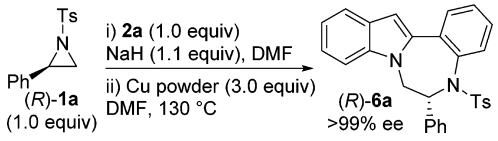
Table 4. Synthesis of DHB-[5,6][1,4]diazepino[1,7-*a*]indoles via One-Pot Ring-Opening Cyclization of *N*-Tosylaziridines (1) with 2-(2-Bromophenyl)-1*H*-indoles (2)



entry	1 (R^1, R^2)	2 (R^3)	6	time (h)	yield (%)
1	**1a** (Ph, H)	**2a** (H)	**6a**	24.5	73
2	**1h** (H, H)	**2a** (H)	**6b**	24.5	82
3	**1i** (Me, H)	**2a** (H)	**6c**	25.75	83
4	**1j** (n-C_8H_{17}, H)	**2a** (H)	**6d**	23.75	86
5	**1k** (-$(CH_2)_3$-)	**2c** (Cl)	**6e**	30.5	81
6	**1l** (-$(CH_2)_4$-)	**2a** (H)	**6f**	23.5	92

(*R*)-**6a** was obtained in high yield with excellent enantiomeric excess (ee >99%, Scheme 9).

Scheme 9. Synthesis of Enantioenriched DHB-[5,6][1,4]diazepino[1,7-*a*]indole (*R*)-6a from (*R*)-1a and 2a



Based on our experimental observations we reasoned that the reactions proceed via an S_N2-type ring opening of aziridines with indoles followed by a rearomatization process to generate the corresponding ring-opened products that further undergo a well-documented Cu-powder mediated C−N cyclization[16d] to furnish the final products.[18]

To conclude, we have successfully developed two synthetic routes to THB-[2,3]azepino[4,5-*b*]indoles and DHB-[5,6][1,4]-diazepino[1,7-*a*]indoles via one-pot ring-opening cyclization of activated aziridines with 2-(2-bromophenyl)-1*H*-indoles utilizing both C3 and N nucleophilic centers of the indoles. This simple, convenient, and efficient protocol delivers a wide range of racemic and enantioenriched products with structural and functional diversities. We believe that the practicing organic chemists will utilize these strategies for the syntheses of useful indole derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01397.

Experimental procedures, analytical data, NMR spectra, HPLC chromatograms, and crystallographic data (PDF)
X-ray data for compound **4a** (CCDC 1530701) (CIF)
X-ray data for compound **6a** (CCDC 1530700) (CIF)

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Notes

The authors declare no competing financial interest.

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