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Article

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Stereoselective Construction of Pyrazinoindoles and Oxazinoindoles via Ring-Opening/Pictet-Spengler Reaction of Aziridines and Epoxides with 3-Methylindoles and Carbonyls

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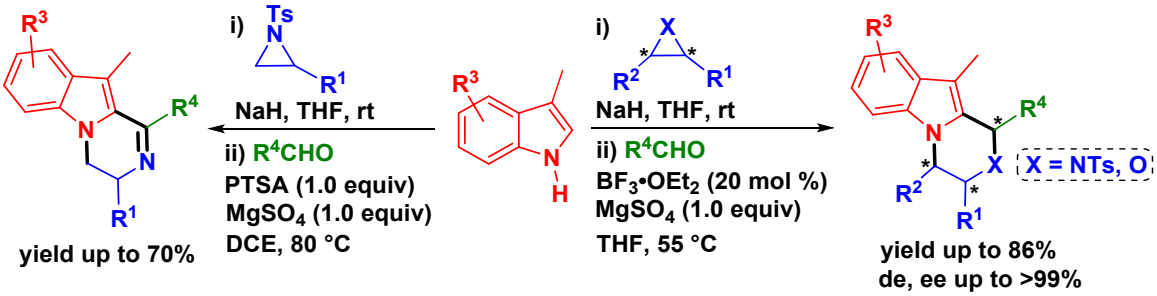


R^1, R^2 = H, Ph, 4-ClC_6H_4, 4-BrC_6H_4, 2-FC_6H_4, 3-MeC_6H_4, Bn, Me, n-octyl, -$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_5$-;
R^3 = H, Me, Br; R^4 = Ph, 4-$NO_2C_6H_4$, 4-FC_6H_4, 4-MeC_6H_4, cinnamyl, 4-BrC_6H_4, 4-CNC_6H_4, 4-ClC_6H_4, 2-naphthyl, 2-furyl, Et, cyclopentanone

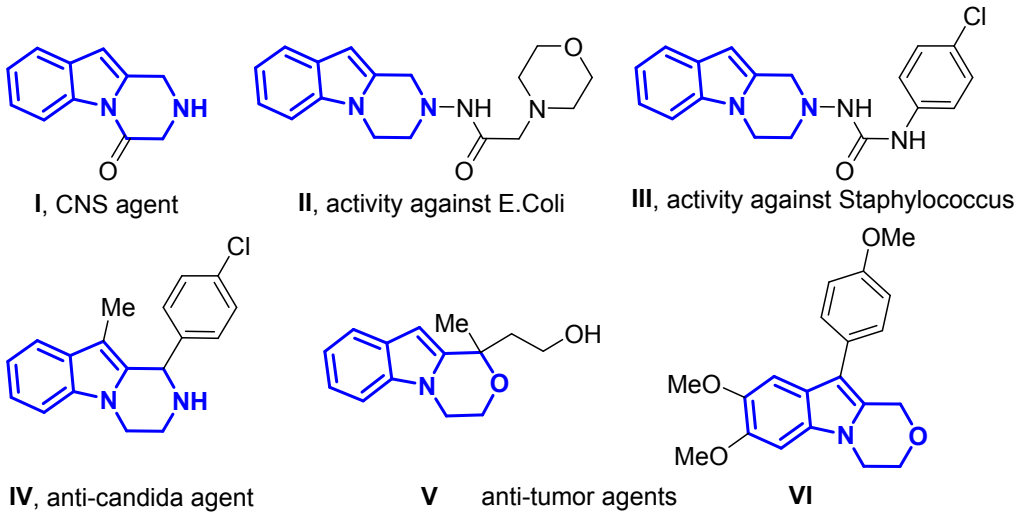
✓ *one-pot cascade* ✓ *metal-free conditions* ✓ *inexpensive catalysts* ✓ *wide substrate scope*

A highly efficient and stereoselective route to access 1,3-disubstituted 1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles and 3,4-dihydro-1H-[1,4]oxazino[4,3-*a*]indoles with excellent stereoselectivity (de, ee >99%) via base mediated ring opening of aziridines/epoxides with 3-methylindoles followed by $BF_3{\cdot}OEt_2$ catalyzed Pictet-Spengler reaction is accomplished. Interestingly, PTSA promoted cyclization led to the formation of oxidized 3,4-dihydropyrazino[1,2-*a*]indoles in excellent yields via an unprecedented Pictet-Spengler-detosylation cascade.

INTRODUCTION

Among widely distributed fused indole derivatives in natural products and alkaloids, tetrahydropyrazino[1,2-*a*]indoles and dihydro-1*H*-[1,4]oxazino[4,3-*a*]indoles are found to be of immense biological significance and pharmacological importance.[1,2] Especially, tetrahydropyrazino[1,2-*a*]indoles are known to possess 5-HT_{2C}, 5-HT_{2A} and 5-HT_4 receptor agonistic,[3] and protein kinase C inhibitors activities;[4] whereas, dihydro-1*H*-[1,4]oxazino[4,3-*a*]indoles exhibit potent anti-tumor activities.[5] Some of the biologically active alkaloids containing these two core structures are shown in Figure 1.

Figure 1. Biologically Active Alkaloids Containing Pyrazino- and Oxazinoindoles



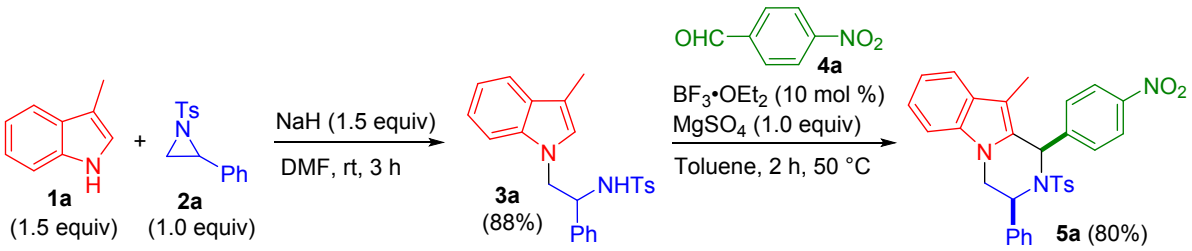
Despite their high medicinal values, only a few reports are available for the stereoselective synthesis of these indole-based heterocyclic scaffolds.[6,7] The interesting reports available in the literature for the formation of pyrazinoindoles include intramolecular aza-Michael reaction of α,β-unsaturated esters,[6b,c] Pd-catalyzed AAA reaction of indoles with vinyl aziridines,[6d] and Lewis acid promoted asymmetric iso-Pictet-Spengler reaction of aminoindoles with α-keto amides.[6e] Similarly, formation of

oxazinoindoles via base mediated addition-cyclization reaction of (1*H*-indole-2-yl)methanols with vinyl sulfonium salts,[7a] TMSOTf-mediated intramolecular oxa-Pictet-Spengler reaction of indoles with *N*-tethered vinylogous carbonate functionality,[7b] and gold-catalyzed asymmetric cascade reactions of functionalized indoles[7c] are known in the literature. However, most of these efforts rely on the use of costly metal catalysts and chiral ligands, super-stoichiometric amount of base and LAs etc. Moreover, some of these approaches suffer from reduced stereoselectivity and substrate scope. Due to said limitations, the development of a metal-free, cost-effective and catalytic synthetic route to such scaffolds with high stereoselectivity is highly desirable. In this context, Pictet-Spengler (PS) reaction[8] is one of the key routes to achieve indole-fused heterocycles.[9] Notably, aziridines[10] and epoxides[11] serve as important building blocks to realise complex heterocyclic scaffolds. Synthesis of pyrazino[1,2-*a*]indoles and oxazino[4,3-*a*]indoles via ring-opening/transformations of aziridines and epoxides, respectively, is unknown except one report by Chen et al. for the latter.[12] Our ongoing research activities on Lewis acid catalyzed S_N2-type ring-opening transformations of activated aziridines and epoxides[13] with indole based nucleophiles[14] prompted us to explore (iso/oxa)-Pictet-Spengler reaction as a tool to achieve synthesis of diastereo- and enantiopure pyrazino[1,2-*a*]indoles and oxazino[4,3-*a*]indoles in a one-pot cascade manner by engaging three components, *viz*. 3-methylindoles, aziridine/epoxide and carbonyls. Herein, we wish to report our results in detail for the synthesis of titular compounds based on the aforementioned proposal as an article.

RESULTS AND DISCUSSION

Our study commenced with the reaction of 2-phenyl-*N*-tosylaziridine (**2a**) and 3-methylindole (**1a**) in the presence of NaH as the base in DMF at rt to obtain the ring-opening product (**3a**) in 88% yield as a single regioisomer (Scheme 1).[14d,15] It is noteworthy that the nucleophile being strong and bulky attacks the aziridine at the unsubstituted side to afford **3a** as the only product. **3a** was then subject to $BF_3{\cdot}OEt_2$ (10 mol %) catalyzed PS reaction with 4-nitrobenzaldehyde (**4a**) in presence of 1.0 equiv of $MgSO_4$ in toluene at 50 °C, and the corresponding tetrahydropyrazino[1,2-*a*]indole derivative (**5a**) was formed in 80% yield as a single diastereomer (Scheme 1). Both **3a** and **5a** were characterized by spectroscopic data and the structure of **5** was further confirmed by single crystal X-ray analysis.[16]

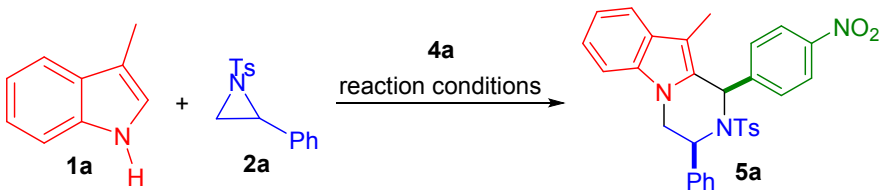
Scheme 1. Ring-Opening/Pictet-Spengler Reaction of 2-Phenyl-*N*-tosylaziridine (2a) with 3-Methylindole (1a) and 4-Nitrobenzaldehyde (4a)



Next, to increase the efficiency of our protocol for the synthesis of **5a**, we switched the two-step synthetic strategy to one-pot stepwise fashion comprising of base-mediated ring opening of **2a** with 1a followed by PS reaction of the ring-opening product with **4a** by using 10 mol % $BF_3{\cdot}OEt_2$ catalyst in toluene at 50 °C and the corresponding cyclic product **5a** was obtained in 48% overall yield as a single diastereomer (entry 2, Table 1). To improve the yield, various reaction parameters including Lewis acid, base, solvent, and temperature were screened. Altering

the Lewis acid to PTSA even lowered the yield of one-pot process drastically (entry 3). Slightly better yield

Table 1. Optimization Studies for the One-Pot Stepwise Synthesis of 1,2,3,4-Tetrahydropyrazino[1,2-*a*]indole (5a)[a]



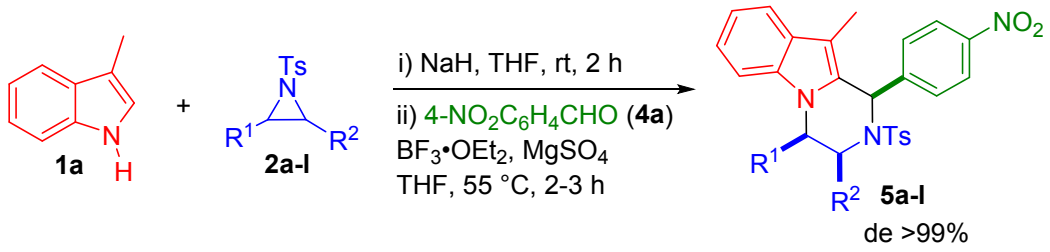
entry	reaction conditions	**5a**[b]
1	i) NaH (1.2 equiv), toluene, rt, 2 h ii) **4a**, $BF_3{\cdot}OEt_2$ (20 mol %), $MgSO_4$, toluene, rt, 10 h	25
2	i) NaH (1.2 equiv), toluene, rt, 2 h ii) **4a**, $BF_3{\cdot}OEt_2$ (10 mol %), $MgSO_4$, toluene, 50 °C, 4 h	48
3[c]	i) NaH (1.2 equiv), toluene, rt, 2 h ii) **4a**, PTSA (10 mol %), $MgSO_4$, toluene, 50 °C, 6 h	10
4	i) NaH (1.2 equiv), diethyl ether, rt, 3 h ii) **4a**, $BF_3{\cdot}OEt_2$ (10 mol %), $MgSO_4$, diethyl ether, rt, 7 h	58
5	**i) NaH (1.2 equiv), THF, rt, 2 h** **ii) 4a, $BF_3{\cdot}OEt_2$ (20 mol %), $MgSO_4$, THF, 55 °C, 2 h**	**72**
6	i) tBuOK (1.2 equiv), toluene, rt, 4 h ii) **4a**, $BF_3{\cdot}OEt_2$ (20 mol %), $MgSO_4$, toluene, 55 °C, 4 h	53
7	i) tBuOK (1.2 equiv), THF, rt, 3.5 h ii) **4a**, $BF_3{\cdot}OEt_2$ (20 mol %), $MgSO_4$, THF, 55 °C, 4.5 h	42
8	i) K_2CO_3 (1.2 equiv), THF, rt, 3 h ii) **4a**, $BF_3{\cdot}OEt_2$ (20 mol %), $MgSO_4$, THF, 55 °C, 5 h	34
9	i) tBuOK (1.2 equiv), DMF, rt, 3 h ii) **4a**, $BF_3{\cdot}OEt_2$ (20 mol %), $MgSO_4$, DMF, 100 °C, 9 h	NR[d]
10	i) NaH (1.2 equiv), DMF, rt, 2 h ii) **4a**, $BF_3{\cdot}OEt_2$ (20 mol %), $MgSO_4$, DMF, 100 °C, 10 h	NR

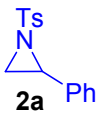
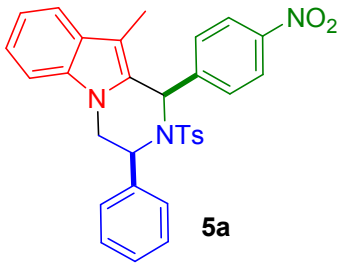
[a]Unless otherwise noted, 0.12 mmol of **1a**, 0.10 mmol of **2a**, 0.12 mmol of base, 0.11 mmol of **4a**, 0.02 mmol of $BF_3{\cdot}OEt_2$ and 0.10 mmol of $MgSO_4$ were reacted. [b]Yield of the isolated product. [c]Along with **5a**, the oxidized product 3,4-dihydropyrazino[1,2-*a*]indole was obtained in 30% yield. [d]NR = No reaction.

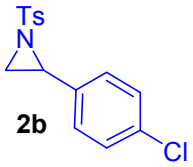
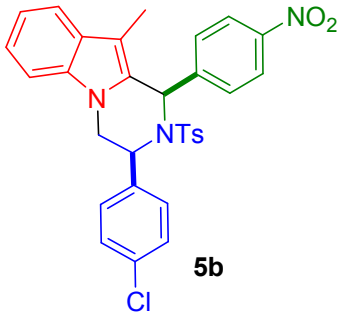
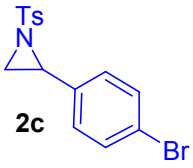
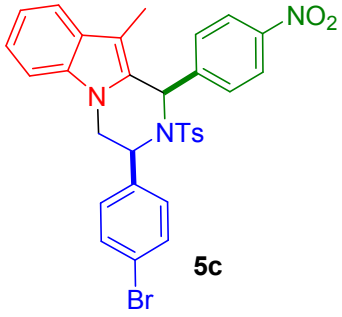
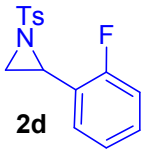
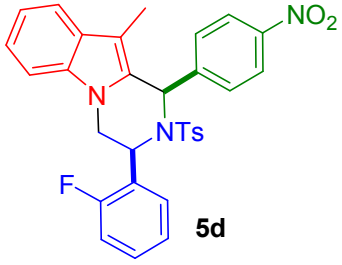
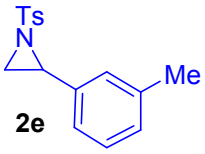
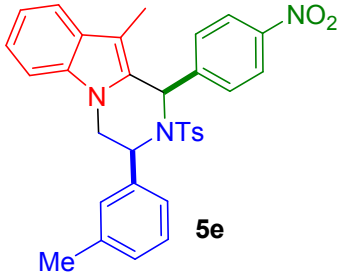
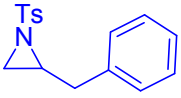
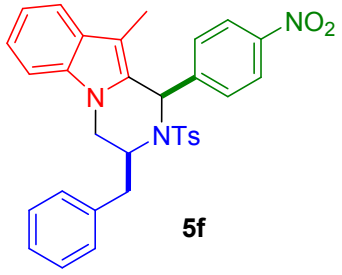
was observed when NaH in diethyl ether was employed along with $BF_3{\cdot}OEt_2$ as catalyst (entry 4). The best result was obtained by using 20 mol % $BF_3{\cdot}OEt_2$ in THF at 55 °C affording **5a** in 72% overall yield (Entry 5). When *t*BuOK and K_2CO_3 were used as bases in the ring-opening reaction, they resulted in poorer yields of the desired product (entries 6–8). Further, use of DMF, as a polar aprotic solvent, proved futile for desired product formation and the starting material was recovered back (entries 9 and 10). All results are summarized in Table 1.

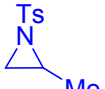
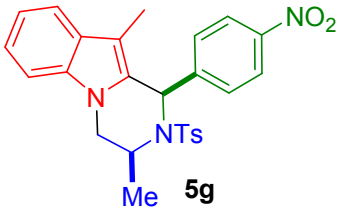
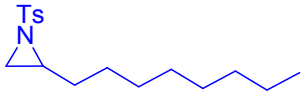
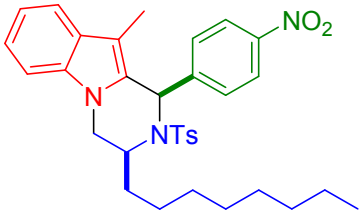
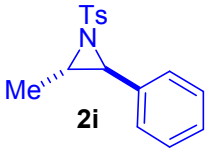
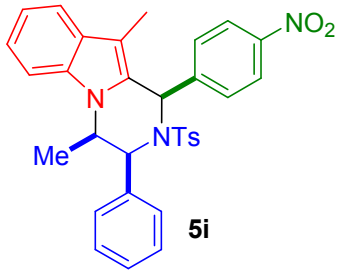
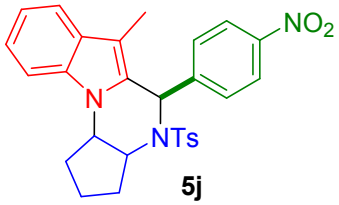
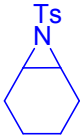
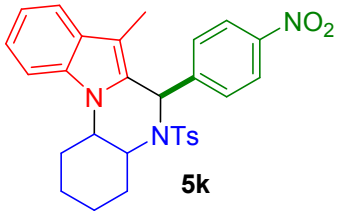
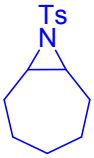
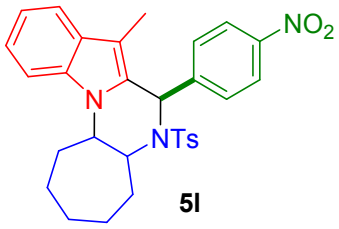
To generalize our approach, a wide range of racemic 2-(aryl/alkyl)-*N*-tosylaziridines **2a–l** were reacted with 3-methylindole **1a** and 4-nitrobenzaldehyde **4a** under optimized reaction conditions (Table 2). Both electron withdrawing groups, like halides (Cl, Br, F), and donating group like -CH_3, in the benzene ring of 2-aryl-*N*-tosylaziridines were well tolerated under the reaction conditions to yield **5b–e** in good to excellent yields as single diastereomers (entries 2–5). Among activated alkyl aziridines, 2-benzyl-*N*-tosylaziridine and 2-methyl-*N*-tosylaziridine underwent smooth transformations to produce **5f** and **5g** in good yields (entries 6,7). Interestingly,

Table 2. One-Pot Cascade Synthesis of Tetrahydropyrazino[1,2-*a*]indoles (5a–l)[a]



entry	**1a**	aziridine (**2**)	**4a**	pyrazinoindole (**5**)	yield (%)[b]	dr[c]
1	**1a**	 **2a**	**4a**	 **5a**	72	>99:1

2	**1a**	 **2b**	**4a**	 **5b**	74	>99:1
3	**1a**	 **2c**	**4a**	 **5c**	78	>99:1
4	**1a**	 **2d**	**4a**	 **5d**	58	>99:1
5	**1a**	 **2e**	**4a**	 **5e**	60	>99:1
6	**1a**	 **2f**	**4a**	 **5f**	68	>99:1

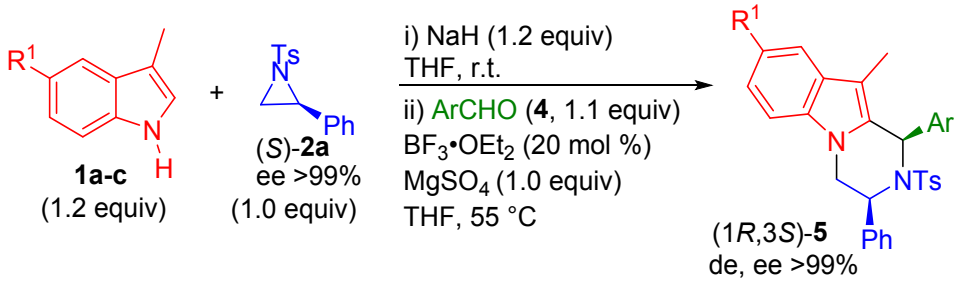
7	**1a**	 **2g**	**4a**	 **5g**	67	>99:1
8	**1a**	 **2h**	**4a**	 **5h**	75	>99:1
9	**1a**	 **2i**	**4a**	 **5i**	65	>99:1
10	**1a**	 **2j**	**4a**	 **5j**	72	>99:1
11	**1a**	 **2k**	**4a**	 **5k**	75	>99:1
12	**1a**	 **2l**	**4a**	 **5l**	86	>99:1

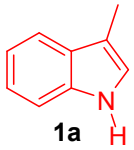
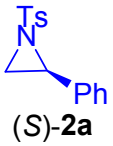
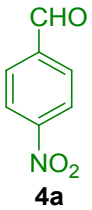
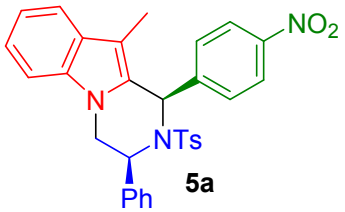
[a]Unless otherwise noted, 0.12 mmol of **1**, 0.10 mmol of **2**, 0.12 mmol of base, 0.11 mmol of **4a**, 0.02 mmol of $BF_3 \cdot OEt_2$, and 0.10 mmol of $MgSO_4$ were reacted. [b]Yields of isolated products. [c]Diastereomeric ratios have been determined by ^1H NMR analysis of the crude reaction mixture.

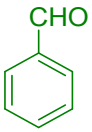
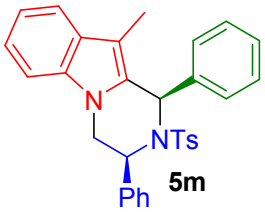
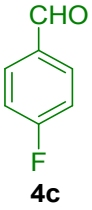
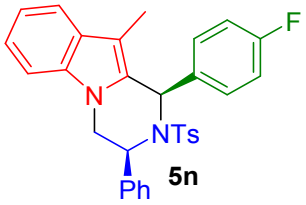
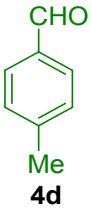
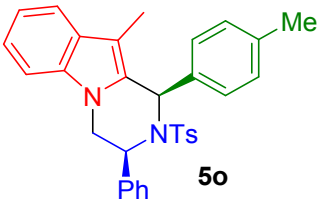
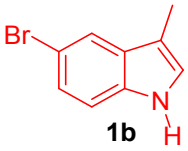
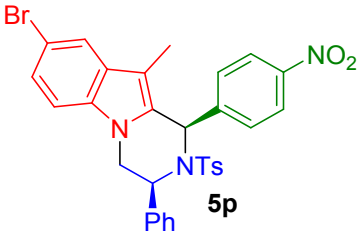
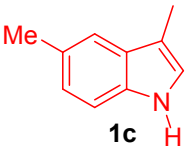
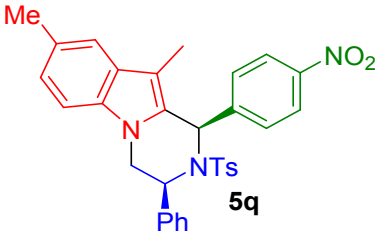
2-*n*-octyl-*N*-tosylaziridine (**2h**), with a long-tethered alkyl chain, and *trans*-disubstituted activated aziridine (**2i**), when reacted under the same reaction conditions, the desired tetrahydropyrazino[1,2-*a*]indoles, **5h** and **5i**, were obtained as single diastereomers, respectively (entries 8,9). When five to seven membered cycloalkyl-fused activated aziridines were reacted with **1a** and **4a**, the corresponding tetracyclic core of pyrazino[1,2-*a*]indoles **5j–l** were obtained as single diastereomers in excellent yields (entries 10–12). All the results are described in Table 2.

The synthetic significance of the methodology was further demonstrated by the formation of optically pure tetrahydropyrazino[1,2-*a*]indoles, (1*R*,3*S*)-**5a**,**m–q** (de, ee >99%), from enantiopure 2-phenyl-*N*-tosylaziridine (*S*)-**2a** (ee >99%), 3-methylindole **1a** and different aldehydes **4a–d** under optimized one-pot reaction conditions in good yields (Table 3). The formation of the products with enantiospecificity (ee >99%) could be rationalized by the fact that the stereocenter of enantiopure aziridine remains unperturbed during base-mediated ring-opening

Table 3. One-Pot Stereospecific Synthesis of Tetrahydropyrazino[1,2-*a*]indoles (5)[a]



entry	3-methylindole (**1**)	aziridine (*S*)-**2a**	aldehyde (**4**)	pyrazinoindole (**5**)	yield[a] (%)	de[b]/ee (%)
1[c]	 **1a**	 (*S*)-**2a**	 **4a**	 **5a**	72	>99/99

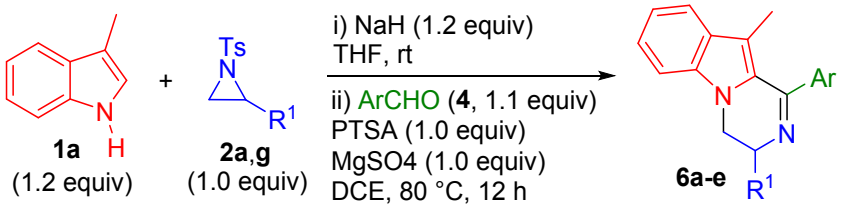
2[d]	**1a**	(*S*)-**2a**	 **4b**	 **5m**	63	>99/99
3[d]	**1a**	(*S*)-**2a**	 **4c**	 **5n**	76	>99/99
4[d]	**1a**	(*S*)-**2a**	 **4d**	 **5o**	56	>99/99
5[d]	 **1b**	(*S*)-**2a**	**4a**	 **5p**	72	>99/99
6[d]	 **1c**	(*S*)-**2a**	**4a**	 **5q**	74	>99/99

[a]Yields of isolated products. [b]The products were obtained as single diastereomers. [c]As a representative example, the ee was determined by chiral HPLC analysis. [d]Since, ring-opening doesn't disturb the chiral center, the formation of single diastereomeric product confirms that *de* equals *ee*.[14d]

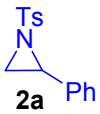
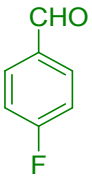
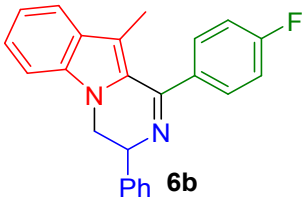
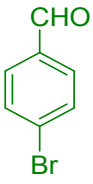
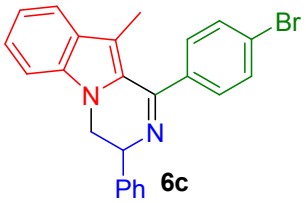
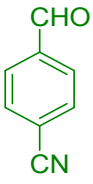
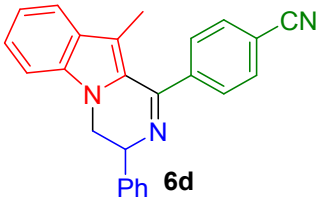
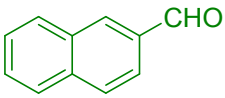
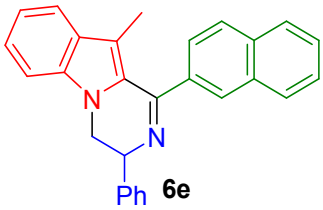
with **1a**.[14d] Successful implementation of both electron-deficient and electron-rich aldehydes to obtain desired products in enantiopure forms indicates little or no significant electronic influence on PS reaction outcomes (entries 1-4). Further, 5-bromo-3-methyl-1*H*-indole (**1b**) and 3,5-dimethylindole (**1c**) were investigated as nucleophiles with (*S*)-**2a** (ee >99%) and 4-nitrobenzaldehyde **4a** to obtain (1*R*,3*S*)-**5p**,**q** in high yields with excellent stereospecificities (de, ee >99%, entries 5,6).[17] The absolute configuration of **5** has been determined as (1*R*,3*S*) based on the crystal structure of **5n**.[16]

The synthetic utility of this strategy was further realized by the formation of another class of biologically important compounds, 3,4-dihydropyrazino[1,2-*a*]indoles **6**,[18] via a one-pot unprecedented detosylation of tetrahydropyrazino[1,2-*a*]indoles. We observed that while optimizing reaction conditions for one-pot synthesis of **5a**, PTSA-promoted PS reaction in toluene at 50 °C (entry 3, Table 1) produced **5a** only in 10% yield, along with the detosylated oxidized product dihydropyrazino[1,2-*a*]indole derivative **6** in 30% yield.

Table 4. PTSA-Promoted One-Pot Synthesis of 3,4-dihydropyrazino[1,2-*a*]indoles (6a–e)[a]



entry	**1a**	aziridine (**2**)	aldehyde (**4**)	3,4-dihydropyrazinoindole (**6**)	yield[a] (%)
1	**1a**	**2g**	**4a**	**6a**	57

2	**1a**	 **2a**	 **4c**	 **6b**	62
3	**1a**	**2a**	 **4e**	 **6c**	67
4	**1a**	**2a**	 **4f**	 **6d**	70
5	**1a**	**2a**	 **4g**	 **6e**	60

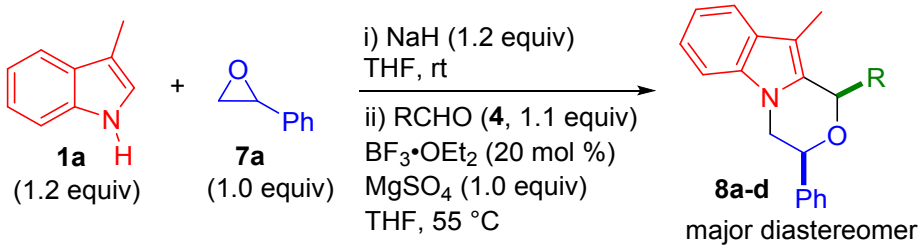
[a]Yields of isolated products.

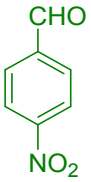
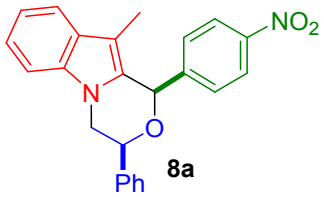
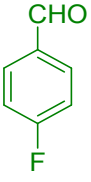
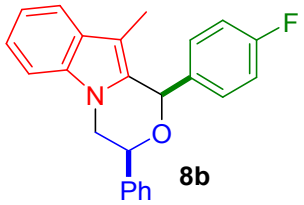
To increase the yield of dihydropyrazino[1,2-*a*]indole moiety, a set of reaction conditions were screened. The best result was obtained when ring-opening product was treated with 1.1 equiv. of aldehyde in presence of 1.0 equiv PTSA in DCE at 80 °C for overnight (Table 4). Under the optimal reaction conditions, when alkyl and aryl *N*-tosylaziridines (**2a**,**g**, respectively) were treated with 3-methylindole **1a**, the ring-opening products were formed which further underwent ring-closing transformations with various aldehydes to produce

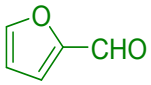
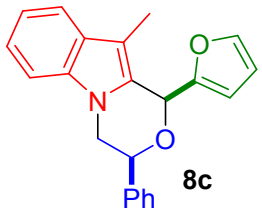
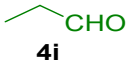
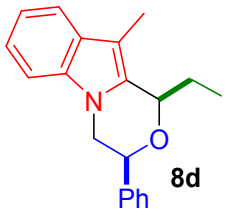
the corresponding oxidized dihydropyrazino[1,2-*a*]indole derivatives **6a**–**e** in good yields (Table 4, Entries 1–5).

Inspired by our success for the synthesis of pyrazino[1,2-*a*]indoles, we next explored the synthesis of dihydro-1*H*-[1,4]oxazino[4,3-*a*]indoles employing 2-phenyl-oxirane (**7a**) under identical reaction conditions (Table 5). When, 2-phenyloxirane **7a** was treated with 3-methylindole **1a** under basic reaction conditions followed by $BF_3{\cdot}OEt_2$ catalyzed PS reaction with **4a**, to our great pleasure, the desired product dihydro-1*H*-[1,4]oxazino[4,3-*a*]indole (**8a**) was obtained in excellent yield, although, as a mixture of diastereomers (dr 3:1, entry 1). The structure of **8a** was confirmed by single crystal X-ray analysis.[16] Generalization of this method was made by studying

Table 5. One-Pot Stepwise Synthesis of Dihydro-1H-[1,4]oxazino[4,3-*a*]indoles (8a–d)[a,b]



entry	**1a**	**7a**	aldehyde (**4**)	oxazinoindole (**8**)	yield[a] (%)	dr[b]
1	**1a**	**7a**	 **4a**	 **8a**	74	3:1
2	**1a**	**7a**	 **4c**	 **8b**	73	1.5:1

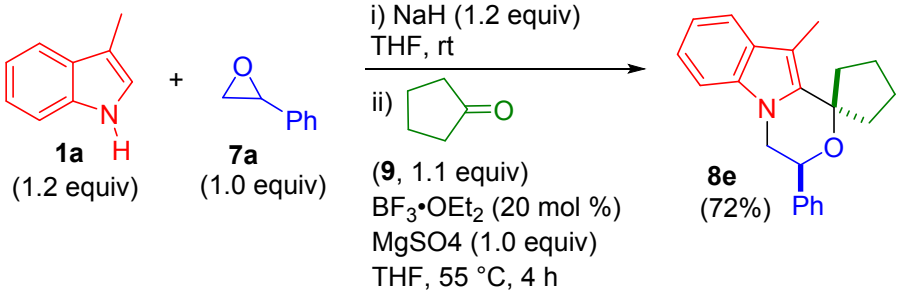
3	**1a**	**7a**	 **4h**	 **8c**	68	5:1
4	**1a**	**7a**	 **4i**	 **8d**	65	5:1

[a]Yields of isolated products. [b]Diastereomeric ratios have been determined by ^{1}H NMR analysis of the crude reaction mixture.

a series of aromatic, heteroaromatic, and alkyl aldehydes (**4**) under optimized reaction conditions to produce the corresponding oxazinoindoles derivatives **8b**–**d** in good yields with diastereomeric ratio up to 5:1 (Entries 2–4). All the results are described in Table 5.

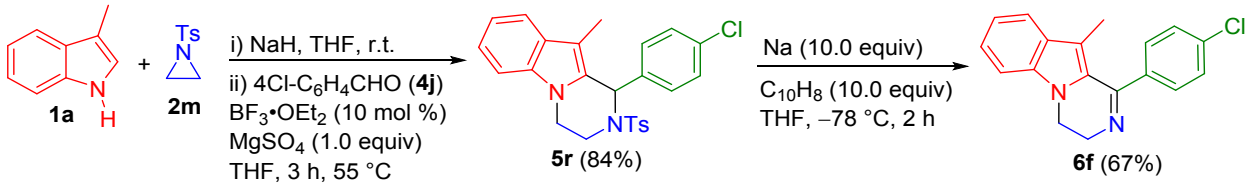
Moreover, we were delighted to observe that cyclic ketone, such as cyclopentanone (**9**), underwent smooth transformation after being introduced as an electrophile in the second step under optimal Pictet-Spengler reaction condition, to form spiro-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indole (**8e**) in 72% yield (Scheme 2). Notably, such spiro compounds with heterocyclic scaffolds are important in drug design and delivery due to their inherent three-dimensional structures.[19]

Scheme 2. One-Pot Synthesis of Spiro-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indole 8e



To demonstrate the synthetic utility of our approach, we attempted a short synthesis of pyrazinoindole derivative **IV** (Figure 1), used as anti-candida agent.[2a] One-pot synthesis of **5r** was carried out via ring-opening/Pictet-Spengler reaction of unsubstituted activated aziridine **2m** with 3-methylindole (**1a**) and 4-chlorobenzaldehyde (**4j**) under the optimized reaction conditions. However, **5r**, upon detosylation,[14e,20] produced only the more stable oxidized product, dihydropyrazino[1,2-*a*]indole (**6f**), probably due to its extended conjugation (Scheme 3).

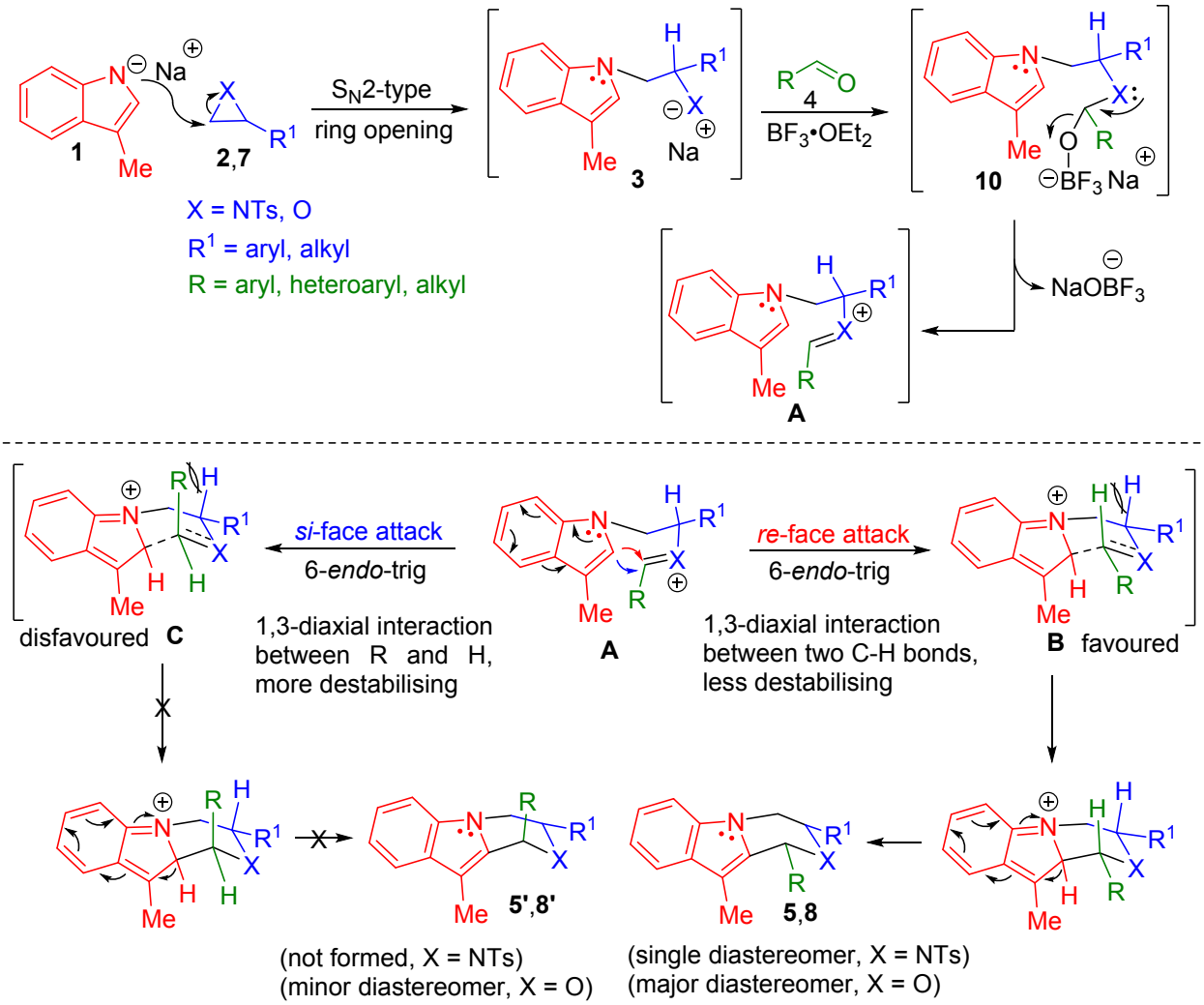
Scheme 3. **Oxidative Detosylation of Tetrahydropyrazinoindole (5r): Synthesis of Dihydropyrazino[1,2-*a*]indole (6f)**



MECHANISM

A plausible mechanism is shown in Scheme 4. Based on our experimental observations, we believe that the ring opening of activated aziridines and epoxides follows an S_N2-type pathway.[14d] Under basic reaction conditions, **1** attacks **2** and **7** from less substituted side through its N-1 site in an S_N2 fashion to produce **3**. $BF_3 \cdot OEt_2$ activates **4** to initiate nucleophilic attack by the ring opening product to generate the corresponding iminium and oxonium ion boat like TS **A**. A subsequent favorable re- face intramolecular nucleophilic attack through C-2 center of the indole ring on C=X bond in 6-*endo*-trig fashion then leads to the more stable species **B**, where bulky 1,3-substituents are present at pseudo-equatorial orientations to avoid possible destabilizing 1,3-diaxial interactions, producing the exclusive or major 1,3-*cis* diastereomers in (**5**,**8**). The exclusive formation of **5** in case of aziridines

Scheme 4. Plausible Mechanism for the Formation of Pyrazino[1,2-*a*]indoles and Oxazino[4,3-*a*]indoles



is due to the presence of bulky tosyl group in between two aryl groups which pushes them to 1,3-pseudo-diequatorial orientation to alleviate steric strain. The absence of such type of steric hinderance in case of epoxides explains the formation of minor 1,3-*trans* diastereomer **8'** through species **C**.

CONCLUSION

We have successfully developed a simple and efficient route for the synthesis of three important heterocycles, viz. tetrahydropyrazino[1,2-*a*]indoles, dihydro-1*H*-[1,4]oxazino[4,3-*a*]indoles and dihydropyrazino[1,2-*a*]indoles in high yields with excellent diastereo- and enantiomeric excess via Lewis acid catalyzed three component one-pot cascade reaction of activated aziridines and epoxides with 3-methyl indoles and carbonyl compounds under metal-free condition. We do believe that the developed strategy would find tremendous utility in synthetic organic chemistry towards the synthesis of polycyclic indole-fused heterocycles.

EXPERIMENTAL SECTION

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 were used for column chromatography using the combination of ethyl acetate and petroleum ether as an eluent. Unless otherwise noted, all reactions were carried out in oven-dried glassware under an atmosphere of nitrogen using anhydrous solvents. Where appropriate, solvents and all reagents were purified prior to use following the guidelines of Perrin, Armarego[21] and Vogel.[22] 2-aryl-*N*-tosylaziridines were prepared from different styrene derivatives following a reported procedure.[23] Chiral 2-phenyl-*N*-tosylaziridine was prepared from corresponding amino alcohol following a reported procedure.[24] All commercial reagents were used as received without prior purification unless mentioned. IR spectra were recorded in potassium bromide (KBr) pellet for solid compounds. Proton nuclear magnetic resonance (^{1}H NMR) were recorded at 500 MHz and 400 MHz. The chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethyl silane (δ 0.00) as internal standard. ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d),

doublet of doublet (dd), triplet (t), triplet of doublets (td), quartet (q), multiplet (m) etc. Carbon nuclear magnetic resonance ($^{13}C\{^1H\}$ NMR) spectra were recorded at 100 MHz and 125 MHz. HRMS were obtained using (ESI) mass spectrometer (TOF). The melting point measurements were made using a hot stage apparatus and are reported as uncorrected. The enantiomeric excess (ee) were determined by HPLC using Chiralcel OD-H column (detection at 254 nm). Optical rotations were measured using a 6.0 mL cell with a 1.0 dm path length and are reported as $[\alpha]_D^{25}$ (*c* in gm per 100 mL solvent) at 25 ºC.

General experimental procedure for the synthesis of 1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles/3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indoles (**2A**): A clean and dried double neck round bottom flask under argon was charged with NaH (0.120 mmol, 1.2 equiv) and 3-methylindole (0.120 mmol, 1.2 equiv) dissolved in (1.0 mL) of THF and was allowed to stir at rt for 1 h followed by the addition of aziridine (0.100 mmol, 1.0 equiv)/epoxide (0.100 mmol, 1.0 equiv) dissolved in (2.0 mL) of THF. The reaction mixture was then allowed to stir at the same temperature for 0.5 h. After complete consumption of starting compound, the formation of ring opening product was monitored by TLC. To this reaction mixture containing ring opening product was added the aldehyde (0.110 mmol, 1.1 equiv), $BF_3{\cdot}OEt_2$ (0.020 mmol, 0.2 equiv), $MgSO_4$ (0.100 mmol, 1.0 equiv) and then again stirred at 55 °C for appropriate time. The formation of product and the progress of reaction was monitored by TLC. The aqueous layer was extracted with ethyl acetate (3 × 10.0 mL) and dried over anhydrous Na_2SO_4. The crude product was purified by flash column chromatography on silica gel (230−400 mesh) using diethyl ether in petroleum ether as the eluent to provide the pure products.

General experimental procedure for the synthesis of 3,4-dihydropyrazino[1,2-*a*]indoles (**2B**): A clean and dried double neck round bottom flask under argon was charged with NaH (0.120

mmol, 1.2 equiv) and 3-methyl indole (0.120 mmol, 1.2 equiv) dissolved in (1.0 mL) of THF and stirred at rt for 0.5 h followed by the addition of aziridine (0.100 mmol, 1.0 equiv.) dissolved in (2.0 mL) of THF. The reaction mixture was then allowed to stir at the same temperature for 0.5 h. The formation of ring opening product was monitored by TLC, after complete consumption of starting compound. To this reaction mixture containing ring opening product was added the aldehyde (0.110 mmol, 1.1 equiv) dissolved in DCE (2.0 mL), PTSA (0.100 mmol, 1.0 equiv), $MgSO_4$ (0.100 mmol, 1.0 equiv) and then again stirred at 80 °C for appropriate time. The formation of product and the progress of reaction was monitored by TLC. The aqueous layer was extracted with ethyl acetate (3 × 10.0 mL) and dried over anhydrous Na_2SO_4. The crude product was purified by flash column chromatography on silica gel (230−400 mesh) using ethyl acetate in petroleum ether as the eluent to give the pure products.

***4-Methyl-N-(2-(3-methyl-1H-indol-1-yl)-1-phenylethyl)benzenesulfonamide* (*3a*).** To the suspension of NaH (10.9 mg, 0.273 mmol, 1.5 equiv) in dry DMF (1.0 mL) taken in a double necked round bottom flask under argon atmosphere was added a solution of 3-methylindole **1a** (35.8 mg, 0.273 mmol, 1.5 equiv) in dry DMF (0.5 mL) and stirred at room temperature for 10 min. Subsequently, a solution of 2-phenyl-*N*-tosylziridine **2a** (50.0 mg, 0.182 mmol, 1.0 equiv) in dry DMF (0.5 mL) was added to the reaction mixture and stirred at room temperature for 3 h. After the complete consumption of aziridine, the reaction mixture was quenched with saturated aqueous NH_4Cl solution. The organic layer was extracted with ethyl acetate (5 × 10.0 mL). Combined extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography on silica gel (230–400 mesh) using 15% ethyl acetate in petroleum ether to afford ring-opening product **3a** (35.6 mg, 0.088 mmol) as a thick colorless liquid in 88% yield: R_f 0.42 (20% ethyl

acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (neat, cm^{-1}) 3278, 3029, 2922, 1598, 1495, 1481, 1466, 1386, 1329, 1184, 1158, 1119, 1092, 1068, 1015, 957, 811, 739, 700, 665; ^1H NMR (400 MHz, $CDCl_3$) δ 2.18 (s, 3H), 2.32 (s, 3H), 4.28 (dd, 1H, J = 11.5, 5.0 Hz), 4.30–4.35 (m, 1H), 4.57–4.61 (m, 1H), 4.91 (d, 1H, J = 4.6 Hz), 6.45 (s, 1H), 7.00 (d, 2H, J = 6.4 Hz), 7.06–7.13 (m, 5H), 7.21–7.24 (m, 3H), 7.38 (d, 2H, J = 6.9 Hz), 7.48 (d, 1H, J = 6.0 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 9.5, 21.6, 52.3, 58.0, 109.0, 111.3, 119.0, 119.1, 122.0, 125.4, 126.7, 126.9, 128.3, 128.9, 129.0, 129.4, 136.3, 136.4, 138.5, 143.4; HRMS (ESI-TOF) calcd for $C_{24}H_{25}N_2O_2S$ $(M+H)^+$ 405.1637, found 405.1633.

***(1R,3S)-10-Methyl-1-(4-nitrophenyl)-3-phenyl-2-tosyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole* (*5a*).** The general method **2A** described above was followed when aziridine **2a** (27.3 mg, 0.10 mmol) was reacted with 3-methylindole **1a** (15.7 mg, 0.12 mmol) in presence of NaH (4.8 mg, 0.12 mmol) in THF at room temperature for 1.5 h followed by addition of 4-nitrobenzaldehyde **4a** (16.7 mg, 0.11 mmol) along with $BF_3{\cdot}OEt_2$ (2.5 μL, 20 mol %) and $MgSO_4$ (11.9 mg, 0.10 mmol) at 55 °C for 2.5 h to afford **5a** (38.7 mg, 0.072 mmol) as a white solid in 72% yield: R_f 0.5 (10% ethyl acetate in petroleum ether), mp 178–180 °C; IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3059, 2924, 2851, 1739, 1569, 1598, 1520, 1493, 1422, 1387, 1347, 1303, 1245, 1163, 1095, 1011, 997, 928, 862, 814, 745, 700, 654; ^1H NMR (400 MHz, $CDCl_3$) δ 2.03 (s, 3H), 2.32 (s, 3H), 3.75 (dd, 1H, J = 13.3, 5.5 Hz), 4.29 (dd, 1H, J = 13.3, 4.6 Hz), 5.22–5.25 (m, 1H), 6.67 (s, 1H), 6.97–7.10 (m, 5H), 7.17–7.23 (m, 5H), 7.26–7.29 (m, 2H), 7.59 (d, 1H, J = 7.8 Hz), 7.68 (d, 2H, J = 8.7 Hz), 7.87 (d, 2H, J = 9.1 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 7.7, 20.6, 41.1, 53.0, 55.2, 107.7, 107.9, 118.2, 119.2, 121.2, 122.2, 125.8, 126.2, 126.8, 127.1, 127.39, 127.44, 128.0, 129.1, 134.9, 135.2, 136.3, 143.4, 145.8, 146.0; HRMS (ESI-TOF) calcd for $C_{31}H_{28}N_3O_4S$ $(M+H)^+$ 538.1801, found 538.1806. $[\alpha]^{25}_D$ = 79.26 (c 0.16, $CHCl_3$) for a >99% ee sample. The enantiomeric excess was

determined by chiral HPLC analysis (OD-H column), n-hexane/i-propanol = 95:5, flow rate = 1 mL/min, tR (1) = 15.30 min (minor), tR (2) = 18.49 min (major).

3-(4-Chlorophenyl)-10-methyl-1-(4-nitrophenyl)-2-tosyl-1,2,3,4-tetrahydropyrazino[1,2- a]indole (***5b***). The general method **2A** described above was followed when aziridine **2b** (30.7 mg, 0.10 mmol) was reacted with 3-methylindole **1a** (15.7 mg, 0.12 mmol) in presence of NaH (4.8 mg, 0.12 mmol) in THF at room temperature for 2 h followed by addition of 4-nitrobenzaldehyde **4a** (16.7 mg, 0.11 mmol) along with $BF_3{\cdot}OEt_2$ (2.5 μL, 20 mol %) and $MgSO_4$ (11.9 mg, 0.10 mmol) at 55 °C for 2 h to afford **5b** (42.3 mg, 0.074 mmol) as a white solid in 74% yield: R_f 0.4 (10% ethyl acetate in petroleum ether), mp 193–195 °C; IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2923, 2854, 1596, 1520, 1492, 1460, 1347, 1250, 1163, 1093, 1012, 963, 855, 815, 746, 716; ^1H NMR (500 MHz, $CDCl_3$) δ 2.04 (s, 3H), 2.32 (s, 3H), 3.78 (dd, 1H, J = 13.0, 5.4 Hz), 4.18 (dd, 1H, J = 13.0, 5.4 Hz), 5.15 (t, 1H, J = 5.4 Hz), 6.65 (s, 1H), 7.01 (dd, 4H, J = 15.3, 8.4 Hz), 7.17 (d, 2H, J = 8.4 Hz), 7.21–7.29 (m, 5H), 7.59 (d, 1H, J = 8.4 Hz), 7.66 (d, 2H, J = 8.5 Hz), 7.95 (d, 2H, J = 9.2 Hz); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 8.7, 21.6, 42.4, 54.1, 56.2, 108.8, 108.9, 119.3, 120.2, 122.3, 123.3, 126.6., 127.2, 128.4, 128.5, 128.9, 129.1, 130.1, 132.9, 134.2, 135.8, 136.1, 144.6, 146.6, 147.1; HRMS (ESI-TOF) calcd for $C_{31}H_{27}ClN_3O_4S$ $(M+H)^+$ 572.1411, found 572.1415.

3-(4-Bromophenyl)-10-methyl-1-(4-nitrophenyl)-2-tosyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole **(*5c*).** The general method **2A** described above was followed when aziridine **2c** (35.1 mg, 0.10 mmol) was reacted with 3-methylindole **1a** (15.7 mg, 0.12 mmol) in presence of NaH (4.8 mg, 0.12 mmol) in THF at room temperature for 2 h followed by addition of 4-nitrobenzaldehyde **4a** (16.7 mg, 0.11 mmol) along with $BF_3{\cdot}OEt_2$ (2.5 μL, 20 mol %) and $MgSO_4$ (11.9 mg, 0.10 mmol) at 55 °C for 2.5 h to afford **5c** (48.1 mg, 0.078 mmol) as a white

solid in 78% yield: R_f 0.4 (10% ethyl acetate in petroleum ether), mp 204–206 °C; IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2927, 2923, 2854, 2851, 1739, 1696, 1598, 1569, 1520, 1464, 1431, 1427, 1367, 1345, 1309, 1295, 1163, 1093, 1035, 1017, 964, 921, 865, 818, 745, 702, 642; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04 (s, 3H), 2.32 (s, 3H), 3.77 (dd, 1H, J = 13.3, 5.5 Hz), 4.18 (dd, 1H, J = 13.3, 5.5 Hz), 5.12–5.15 (m, 1H), 6.65 (s, 1H), 6.96 (d, 2H, J = 8.7 Hz), 7.14–7.28 (m, 9H), 7.59 (d, 1H, J = 7.8 Hz), 7.66 (d, 2H, J = 8.2 Hz), 7.95 (d, 2H, J = 8.7 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 8.7, 21.6, 42.2, 54.1, 56.2, 108.8, 108.9, 119.3, 120.3, 122.3, 123.4, 126.6, 127.2, 127.9, 128.9, 129.4, 130.1, 131.5, 132.6, 132.9, 135.8, 140.9, 142.5, 146.6, 147.0; HRMS (ESI-TOF) calcd for $C_{31}H_{27}BrN_3O_4S$ $(M+H)^+$ 616.0906, found 616.0910.

***3-(2-Fluorophenyl)-10-methyl-1-(4-nitrophenyl)-2-tosyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole* (*5d*).** The general method **2A** described above was followed when aziridine **2d** (29.1 mg, 0.10 mmol) was reacted with 3-methylindole **1a** (15.7 mg, 0.12 mmol) in presence of NaH (4.8 mg, 0.12 mmol) in THF at room temperature for 2 h followed by addition of 4-nitrobenzaldehyde **4a** (16.7 mg, 0.11 mmol) along with $BF_3{\cdot}OEt_2$ (2.5 μL, 20 mol %) and $MgSO_4$ (11.9 mg, 0.10 mmol) at 55 °C for 2.5 h to afford **5d** (32.2 mg, 0.058 mmol) as a white solid in 58% yield: R_f 0.5 (10% ethyl acetate in petroleum ether), mp 171–173 °C; IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2956, 2925, 2855, 1598, 1521, 1492, 1459, 1348, 1165, 1092, 963, 844, 747, 706, 686, 665; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.13 (s, 3H), 2.30 (s, 3H), 3.86 (dd, 1H, J = 13.0, 8.6 Hz), 4.20 (dd, 1H, J = 13.5, 5.5 Hz), 5.25 (dd, 1H, J = 8.5, 5.5 Hz), 6.57 (s, 1H), 6.89–6.97 (m, 2H), 7.06–7.09 (m, 1H), 7.15–7.26 (m, 6H), 7.41 (d, 2H, J = 8.5 Hz), 7.58 (d, 1H, J = 10.9 Hz), 7.68 (d, 2H, J = 8.2 Hz), 8.07 (d, 2H, J = 8.9 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 8.6, 21.6, 43.6, 53.6, 54.4, 108.6, 108.8, 115.6 (d, $^2J_{C–F}$ = 22.0 Hz), 119.4, 119.9, 122.3, 123.7, 124.4 (d, $^4J_{C–F}$ = 3.8 Hz), 126.3, 127.1, 127.6, 128.1, 128.8, 129.9 (d, $^3J_{C–F}$ = 8.6 Hz), 130.1, 134.4, 135.3, 144.6, 146.9,

147.5, 159.9 (d, $^1J_{C-F}$ = 267.3 Hz); HRMS (ESI-TOF) calcd for $C_{31}H_{27}FN_3O_4S$ $(M+H)^+$ 556.1706, found 556.1703.

10-Methyl-1-(4-nitrophenyl)-3-(m-tolyl)-2-tosyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole (5e). The general method **2A** described above was followed when aziridine **2e** (28.7 mg, 0.10 mmol) was reacted with 3-methylindole **1a** (15.7 mg, 0.12 mmol) in presence of NaH (4.8 mg, 0.12 mmol) in THF at room temperature for 2 h followed by addition of 4-nitrobenzaldehyde **4a** (16.7 mg, 0.11 mmol) along with $BF_3{\cdot}OEt_2$ (2.5 μL, 20 mol %) and $MgSO_4$ (11.9 mg, 0.10 mmol) at 55 °C for 2 h to afford **5e** (33.1 mg, 0.060 mmol) as a colorless liquid in 60% yield: R_f 0.5 (10% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (neat, cm^{-1}) 2956, 2925, 2854, 1597, 1520, 1490, 1461, 1347, 1245, 1163, 1094, 1014, 963, 928, 845, 776, 736, 687, 655; ^1H NMR (400 MHz, $CDCl_3$) δ 2.04 (s, 6H), 2.31 (s, 3H), 3.73 (dd, 1H, J = 12.8, 5.5 Hz), 4.27 (dd, 1H, J = 13.3, 4.6 Hz), 5.22 (t, 1H, J = 5.0 Hz), 6.67 (s, 1H), 6.82–6.92 (m, 4H), 7.15–7.22 (m, 5H), 7.26–7.29 (m, 2H), 7.59 (d, 1H, J = 7.8 Hz), 7.67 (d, 2H, J = 8.7 Hz), 7.87 (d, 2H, J = 9.2 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 8.7, 21.2, 21.6, 42.0, 54.0, 56.1, 108.6, 108.9, 119.1, 120.1, 122.1, 123.0, 124.2, 126.7, 127.2, 128.3, 128.4, 128.7, 128.9, 129.0, 130.1, 135.9, 136.2, 137.0, 138.0, 144.4, 146.7, 146.9; HRMS (ESI-TOF) calcd for $(C_{32}H_{30}N_3O_4S)$ $(M+H)^+$ 552.1957, found 552.1955.

3-Benzyl-10-methyl-1-(4-nitrophenyl)-2-tosyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole (5f). The general method **2A** described above was followed when aziridine **2f** (28.7 mg, 0.10 mmol) was reacted with 3-methylindole **1a** (15.7 mg, 0.12 mmol) in presence of NaH (4.8 mg, 0.12 mmol) in THF at room temperature for 2 h followed by addition of 4-nitrobenzaldehyde **4a** (16.7 mg, 0.11 mmol) along with $BF_3{\cdot}OEt_2$ (2.5 μL, 20 mol %) and $MgSO_4$ (11.9 mg, 0.10 mmol) at 55 °C for 3 h to afford **5f** (37.5 mg, 0.068 mmol) as a white solid in 68% yield: R_f 0.55 (10% ethyl acetate in petroleum ether), mp 174–176 °C; IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3059, 3028, 2925, 2855,

1598, 1521, 1493, 1457, 1348, 1258, 1163, 1095, 1015, 966, 856, 813, 742, 703, 670; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09 (s, 3H), 2.22 (s, 3H), 2.48–2.54 (m, 1H), 3.07–3.11 (m, 1H), 3.47–3.58 (m, 2H), 4.30–4.37 (m, 1H), 6.55 (s, 1H), 7.00–7.05 (m, 5H), 7.13–7.18 (m, 2H), 7.23–7.29 (m, 3H), 7.53–7.60 (m, 5H), 8.17 (d, 2H, J = 9.2 Hz); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 8.6, 21.3, 41.2, 41.8, 53.5, 56.3, 108.7, 108.9, 118.9, 119.9, 122.0, 123.8, 126.8, 126.9, 127.1, 128.1, 128.80, 128.84, 129.1, 129.6, 135.7, 136.1, 137.0, 144.1, 147.1, 147.6; HRMS (ESI-TOF) calcd for $C_{32}H_{30}N_3O_4S$ $(M+H)^+$ 552.1957, found 552.1956.

***3,10-Dimethyl-1-(4-nitrophenyl)-2-tosyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole* (*5g*).** The general method **2A** described above was followed when aziridine **2g** (21.1 mg, 0.10 mmol) was reacted with 3-methylindole **1a** (15.7 mg, 0.12 mmol) in presence of NaH (4.8 mg, 0.12 mmol) in THF at room temperature for 2 h followed by addition of 4-nitrobenzaldehyde **4a** (16.7 mg, 0.11 mmol) along with $BF_3{\cdot}OEt_2$ (2.5 μL, 20 mol %) and $MgSO_4$ (11.9 mg, 0.10 mmol) at 55 °C for 2.5 h to afford **5g** (31.9 mg, 0.067 mmol) as a white solid in 67% yield: R_f 0.4 (10% ethyl acetate in petroleum ether), mp 155–157 °C; IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3055, 2962, 2925, 2857, 1601, 1573, 1519, 1485, 1469, 1455, 1422, 1387, 1348, 1327, 1314, 1303, 1242, 1209, 1184, 1108, 1057, 1000, 866, 857, 837, 808, 743, 732, 704; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (d, 3H, J = 6.4 Hz), 2.11 (s, 3H), 2.22 (s, 3H), 3.40 (dd, 1H, J = 12.8, 7.4 Hz), 3.84 (dd, 1H, J = 13.0, 6.2 Hz), 4.24 (td, 1H, J = 13.3, 6.6 Hz), 6.48 (s, 1H), 7.03 (d, 2H, J = 8.2 Hz), 7.12–7.16 (m, 2H), 7.18–7.22 (m, 1H), 7.51–7.57 (m, 5H), 8.17 (d, 2H, J = 8.7 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 8.6, 21.5, 22.0, 44.1, 51.1, 53.7, 108.7, 119.1, 119.8, 122.0, 123.9, 126.9, 127.2, 128.1, 128.7, 129.4, 129.6, 135.6, 135.8, 144.1, 147.4, 147.7; HRMS (ESI-TOF) calcd for $C_{26}H_{26}N_3O_4S$ $(M+H)^+$ 476.1644, found 476.1649.

***10-Methyl-1-(4-nitrophenyl)-3-octyl-2-tosyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole* (*5h*).** The general method **2A** described above was followed when aziridine **2h** (30.9 mg, 0.10

mmol) was reacted with 3-methylindole **1a** (15.7 mg, 0.12 mmol) in presence of NaH (4.8 mg, 0.12 mmol) in THF at room temperature for 2 h followed by addition of 4-nitrobenzaldehyde **4a** (15.7 mg, 0.11 mmol) along with $BF_3{\cdot}OEt_2$ (2.5 μL, 20 mol %) and $MgSO_4$ (11.9 mg, 0.10 mmol) at 55 °C for 2.5 h to afford **5h** (43.0 mg, 0.075 mmol) as a white solid in 75% yield: R_f 0.35 (10% ethyl acetate in petroleum ether), mp 180–182 °C; IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3210, 2924, 2854, 1614, 1595, 1524, 1462, 1436, 1416, 1348, 1267, 1157, 1119, 1092, 1017, 953, 852, 813, 789, 749, 731, 715, 670; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87–0.91 (m, 3H), 1.24–1.35 (m, 11H), 1.48–1.51 (m, 1H), 1.68–1.74 (m, 2H), 1.91 (s, 3H), 2.13 (s, 3H), 3.81–3.89 (m, 1H), 4.08–4.12 (m, 1H), 4.20–4.26 (m, 1H), 6.60 (d, 2H, J = 8.2 Hz), 6.76 (brs, 1H), 7.11–7.17 (m, 4H), 7.36 (t, 1H, J = 7.8 Hz), 7.48 (d, 1H, J = 8.2 Hz), 7.94 (d, 2H, J = 8.7 Hz), 8.35 (d, 2H, J = 8.7 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 11.8, 14.1, 21.5, 22.7, 25.1, 29.3, 29.5, 29.7, 31.9, 35.3, 47.8, 53.6, 110.3, 120.7, 121.2, 122.0, 123.9, 125.8, 127.2, 127.5, 128.5, 130.8, 132.1, 137.2, 138.9, 141.8, 144.5, 150.3; HRMS (ESI-TOF) calcd for $C_{33}H_{43}N_4O_4S$ $(M+NH_4)^+$ 591.3005, found 591.3011.

***4,10-Dimethyl-1-(4-nitrocyclohexa-1,5-dien-1-yl)-3-phenyl-2-tosyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole* (*5i*).** The general method **2A** described above was followed when aziridine **2i** (28.7 mg, 0.10 mmol) was reacted with 3-methylindole **1a** (15.7 mg, 0.12 mmol) in presence of NaH (4.8 mg, 0.12 mmol) in THF at room temperature for 2 h followed by addition of 4-nitrobenzaldehyde **4a** (16.7 mg, 0.11 mmol) along with $BF_3{\cdot}OEt_2$ (2.5 μL, 20 mol %) and $MgSO_4$ (11.9 mg, 0.10 mmol) at 55 °C for 3 h to afford **5i** (35.9 mg, 0.065 mmol) as colorless liquid in 65% yield: R_f 0.55 (10% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (neat, cm^{-1}) 3480, 2956, 2925, 2855, 1598, 1522, 1461, 1346, 1259, 1157, 1088, 1014, 910, 860, 813, 741, 700, 681; ^1H NMR (400 MHz, $CDCl_3$) δ 1.78 (s, 3H), 1.87 (d, 3H, J = 6.4 Hz), 2.27 (s, 3H), 4.97–5.02 (m, 1H), 5.52 (d, 1H, J = 3.2 Hz), 6.06 (s, 1H), 6.88 (d, 2H, J = 8.2 Hz), 7.05 (d, 2H, J = 7.3 Hz), 7.10 (d, 2H, J

= 8.2 Hz), 7.14 (d, 1H, *J* = 7.8 Hz), 7.17–7.24 (m, 4H), 7.31 (d, 1H, *J* = 8.2 Hz), 7.35 (d, 2H, *J* = 8.7 Hz), 7.47 (d, 1H, *J* = 7.8 Hz) 7.87 (d, 2H, *J* = 8.2 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 8.5, 21.3, 21.5, 51.8, 57.3, 62.5, 107.1, 109.0, 118.8, 119.9, 121.9, 122.9, 126.7, 127.9, 128.3, 128.75, 128.80, 128.9, 129.1, 131.0, 134.9, 137.3, 138.7, 143.3, 145.5, 147.2; HRMS (ESI-TOF) calcd for $C_{32}H_{32}N_3O_4S$ $(M+H)^+$ 554.2114, found 554.2119.

***6-Methyl-5-(4-nitrophenyl)-4-tosyl-2,3,3a,4,5,11a-hexahydro-1H-cyclopenta[5,6]pyrazino[1,2-a]indole* (*5j*).** The general method **2A** described above was followed when aziridine **2j** (23.7 mg, 0.10 mmol) was reacted with 3-methylindole **1a** (15.7 mg, 0.12 mmol) in presence of NaH (4.8 mg, 0.12 mmol) in THF at room temperature for 2 h followed by addition of 4-nitrobenzaldehyde **4a** (16.7 mg, 0.11 mmol) along with $BF_3{\cdot}OEt_2$ (2.5 μL, 20 mol %) and $MgSO_4$ (11.9 mg, 0.10 mmol) at 55 °C for 2 h to afford **5j** (36.1 mg, 0.072 mmol) as a yellow solid in 72% yield: R_f 0.5 (10% ethyl acetate in petroleum ether), mp 164–166 °C; IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2956, 2924, 2854, 1745, 1605, 1524, 1463, 1377, 1349, 1260, 1165, 1088, 1025, 993, 909, 815; ^1H NMR (400 MHz, $CDCl_3$) δ 1.88–1.97 (m, 3H), 2.10–2.17 (m, 1H), 2.28 (s, 3H), 2.35 (s, 3H), 2.54–2.63 (m, 2H), 2.87–2.94 (m, 1H), 3.79–3.87 (m, 1H), 6.38 (s, 1H), 7.07–7.15 (m, 2H), 7.22–7.30 (m, 3H), 7.48 (d, 2H, *J* = 9.2 Hz), 7.56 (d, 1H, *J* = 7.5 Hz), 7.67 (d, 2H, *J* = 8.1 Hz), 8.13 (d, 2H, *J* = 8.7 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 8.6, 19.3, 21.5, 25.8, 29.5, 56.2, 58.7, 65.3, 108.4, 110.6, 118.9, 119.7, 122.2, 123.8, 127.4, 127.8, 127.9, 129.9, 130.2, 133.6, 134.9, 144.4, 147.4, 148.3; HRMS (ESI-TOF) calcd for $(C_{28}H_{28}N_3O_4S)$ $(M+H)^+$ 502.1801, found 502.1806.

***7-Methyl-6-(4-nitrophenyl)-5-tosyl-1,2,3,4,4a,5,6,12a-octahydroindolo[1,2-a]quinoxaline* (*5k*).** The general method **2A** described above was followed when aziridine **2k** (25.1 mg, 0.10 mmol) was reacted with 3-methylindole **1a** (15.7 mg, 0.12 mmol) in presence of NaH

(4.8 mg, 0.12 mmol) in THF at room temperature for 2 h followed by addition of 4-nitrobenzaldehyde **4a** (16.7 mg, 0.11 mmol) along with $BF_3{\cdot}OEt_2$ (2.5 μL, 20 mol %) and $MgSO_4$ (11.9 mg, 0.10 mmol) at 55 °C for 2 h to afford **5k** (38.7 mg, 0.075 mmol) as a yellow solid in 75% yield: R_f 0.5 (10% ethyl acetate in petroleum ether), mp 167–169 °C; IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2964, 2934, 2896, 2812, 1735, 1698, 1567,1473, 1446, 1398, 1358, 1259, 1189, 1112, 1035, 965, 940, 849, 742, 634; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.42 (m, 2H), 1.47 (dt, 1H, J = 13.3, 3.2 Hz), 1.74–1.78 (m, 1H), 1.90–1.93 (m, 1H), 2.02 (s, 3H), 2.14–2.21 (m, 4H), 2.72–2.76 (m, 1H), 2.93–2.97 (m, 1H), 3.50–3.59 (m, 2H), 6.18 (s, 1H), 6.94 (d, 2H, J = 8.2 Hz), 7.04–7.11 (m, 2H), 7.42–7.48 (m, 4H), 7.56 (d, 2H, J = 8.7 Hz), 8.18 (d, 2H, J = 8.7 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 8.3, 21.4, 24.5, 24.8, 30.9, 35.0, 54.5, 58.5, 64.5, 111.3, 119.0, 122.1, 124.0, 126.96, 127.03, 128.0, 129.2, 130.3, 132.7, 133.8, 133.9, 134.6, 143.9, 147.0, 147.7; HRMS (ESI-TOF) calcd for $C_{29}H_{30}N_3O_4S$) $(M+H)^+$ 516.1957, found 516.1954.

***8-Methyl-7-(4-nitrophenyl)-6-tosyl-2,3,4,5,5a,6,7,13a-octahydro-1H-cyclohepta[5,6]pyrazino[1,2-a]indole* (*5l*).** The general method **2A** described above was followed when aziridine **2l** (26.5 mg, 0.10 mmol) was reacted with 3-methylindole **1a** (15.7 mg, 0.12 mmol) in presence of NaH (4.8 mg, 0.12 mmol) in THF at room temperature for 2 h followed by addition of 4-nitrobenzaldehyde **4a** (16.7 mg, 0.11 mmol) along with $BF_3{\cdot}OEt_2$ (2.5 μL, 20 mol %) and $MgSO_4$ (11.9 mg, 0.10 mmol) at 55 °C for 2 h to afford **5l** (45.5 mg, 0.086 mmol) as a white solid in 78% yield: R_f 0.5 (10% ethyl acetate in petroleum ether), mp 171–173 °C; IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3047, 2925, 2855, 1708, 1598, 1521, 1490, 1454, 1412, 1377, 1347, 1264, 1184, 1164, 1090, 1032, 1015, 981, 943, 877, 856, 812, 738, 705, 688, 665; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26–1.34 (m, 1H), 1.38–1.47 (m, 1H), 1.56–1.75 (m, 4H), 1.78–1.86 (m, 1H), 2.03 (d, 6H, J = 2.3 Hz), 2.11–2.22 (m, 1H), 2.38–2.43 (m, 1H), 2.92–2.99 (m, 1H), 3.58 (td, 1H, J = 10.5, 4.6 Hz), 3.84–3.89

(m, 1H), 6.26 (s, 1H), 6.76 (d, 2H, J = 8.2 Hz), 7.05 (t, 2H, J = 5.0 Hz), 7.32 (d, 2H, J = 8.2 Hz), 7.39–7.43 (m, 4H), 7.59 (d, 2H, J = 8.7 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 8.3, 21.2, 23.4, 23.9, 25.2, 32.2, 35.9, 54.2, 61.4, 63.9, 109.5, 112.3, 118.8, 119.1, 122.0, 124.0, 126.6, 128.4, 128.8, 130.3, 134.6, 135.1, 143.7, 146.4, 147.8; HRMS (ESI-TOF) calcd for $C_{30}H_{32}N_3O_4S$ $(M+H)^+$ 530.2114, found 530.2116.

(*1R,3S*)-*10-Methyl-1,3-diphenyl-2-tosyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole* (*5m*). The general method **2A** described above was followed when aziridine **2a** (27.3 mg, 0.10 mmol) was reacted with 3-methylindole **1a** (15.7 mg, 0.12 mmol) in presence of NaH (4.8 mg, 0.12 mmol) in THF at room temperature for 2 h followed by addition of benzaldehyde **4b** (11.2 μL, 11.7 mg, 0.11 mmol) along with $BF_3{\cdot}OEt_2$ (2.5 μL, 20 mol %) and $MgSO_4$ (11.9 mg, 0.10 mmol) at 55 °C for 2 h to afford **5m** (31.0 mg, 0.063 mmol) as a white solid in 63% yield: R_f 0.6 (10% ethyl acetate in petroleum ether), mp 163–165 °C; IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3059, 2919, 1598, 1493, 1467, 1451, 1349, 1248, 1184, 1163, 1095, 1010, 961, 925, 894, 842, 813, 740, 698; ^1H NMR (400 MHz, $CDCl_3$) δ 2.08 (s, 3H), 2.28 (s, 3H), 3.96 (dd, 1H, J = 13.3, 8.7 Hz), 4.04 (dd, 1H, J = 13.5, 5.7 Hz), 4.88–4.92 (m, 1H), 6.58 (s, 1H), 7.09–7.22 (m, 15H), 7.55 (d, 1H, J = 7.8 Hz), 7.61 (d, 2H, J = 7.8 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 8.4, 21.4, 44.0, 54.9, 59.8, 107.8, 108.4, 119.0, 119.3, 121.5. 127.27, 127.31, 127.6, 127.7, 127.8, 128.2, 128.3, 128.4, 128.9, 129.5, 135.0, 135.5, 139.2, 139.6, 143.8; HRMS (ESI-TOF) calcd for $C_{31}H_{29}N_2O_2S$ $(M+H)^+$ 493.1950, found 493.1955. $[\alpha]_D^{25}$ = +139.00 (c 0.10, $CHCl_3$) for a 99% ee sample.

(*1R,3S*)-*1-(4-Fluorophenyl)-10-methyl-3-phenyl-2-tosyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole* (*5n*). The general method **2A** described above was followed when aziridine **2a** (27.3 mg, 0.10 mmol) was reacted with 3-methylindole **1a** (15.7 mg, 0.12 mmol) in presence of NaH (4.8 mg, 0.12 mmol) in THF at room temperature for 2 h followed by addition

of 4-fluorobenzaldehyde **4c** (11.8 μL, 13.7 mg, 0.11 mmol) along with $BF_3{\cdot}OEt_2$ (2.5 μL, 20 mol %) and $MgSO_4$ (11.9 mg, 0.10 mmol) at 55 °C for 2 h to afford **5n** (38.8 mg, 0.076 mmol) as a white solid in 76% yield: R_f 0.55 (10% ethyl acetate in petroleum ether), mp 166–168 °C; IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3058, 2919, 1602, 1506, 1461, 1348, 1225, 1163, 1095, 1010, 962, 927, 895, 860, 838, 788, 740, 698, 678, 655, 599; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05 (s, 3H), 2.30 (s, 3H), 3.94 (dd, 1H, J = 13.3, 5.5 Hz), 4.09 (dd, 1H, J = 13.3, 7.3 Hz), 4.99–5.02 (m, 1H), 6.56 (s, 1H), 6.82 (t, 2H, J = 8.7 Hz), 7.08–7.19 (m, 10H), 7.22 (d, 2H, J = 4.6 Hz), 7.56 (d, 1H, J = 7.8 Hz), 7.63 (d, 2H, J = 8.2 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 8.5, 21.6, 43.4, 54.3, 58.5, 108.0, 108.6, 115.1 (d, $^2J_{C\text{-}F}$ = 21.9 Hz), 119.1, 119.7, 121.7, 127.3, 127.4, 127.9, 128.3, 128.5 (d, $^4J_{C\text{-}F}$ = 3.8 Hz), 129.8 (d, $^3J_{C\text{-}F}$ = 9.5 Hz), 135.3, 135.41, 135.44, 135.8, 135.9, 138.7, 144.0, 162.1 (d, $^1J_{C\text{-}F}$ = 246.0 Hz); HRMS (ESI-TOF) calcd for $C_{31}H_{28}FN_2O_2S$ $(M+H)^+$ 511.1856, found 511.1855. $[\alpha]_D^{25}$ = –48.00 (c 0.15, $CHCl_3$) for a >99% ee sample.

(1R,3S)-10-Methyl-3-phenyl-1-(p-tolyl)-2-tosyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole (5o). The general method **2A** described above was followed when aziridine **2a** (27.3 mg, 0.10 mmol) was reacted with 3-methylindole **1a** (15.7 mg, 0.12 mmol) in presence of NaH (4.8 mg, 0.12 mmol) in THF at room temperature for 2 h followed by addition of 4-methylbenzaldehyde **4d** (13 μL, 13.2 mg, 0.11 mmol) along with $BF_3{\cdot}OEt_2$ (2.5 μL, 20 mol %) and $MgSO_4$ (11.9 mg, 0.10 mmol) at 55 °C for 2 h to afford **5o** (28.4 mg, 0.056 mmol) as a white solid in 56% yield: R_f 0.6 (10 % ethyl acetate in petroleum ether), mp 164–166 °C; IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3028, 2957, 2924, 2854, 1739, 1598, 1510, 1494, 1464, 1378, 1349, 1260, 1185, 1163, 1095, 1019, 927, 894, 874, 812, 739, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08 (s, 3H), 2.29 (d, 6H, J = 9.2 Hz), 3.93 (dd, 1H, J = 13.5, 9.4 Hz), 4.07 (dd, 1H, J = 13.5, 5.7 Hz), 4.84 (dd, 1H, J = 9.2, 5.5 Hz), 6.53 (s, 1H), 7.03 (d, 2H, J = 8.2 Hz), 7.08 (d, 3H, J = 9.2 Hz), 7.11–7.21 (m, 9H), 7.54 (d, 1H, J = 7.8 Hz), 7.60 (d,

2H, J = 8.7 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 8.5, 21.1, 21.5, 44.4, 54.9, 60.5, 108.4, 119.1, 119.3, 121.5, 124.8, 125.7, 127.4, 127.77, 127.83, 128.2, 128.5, 129.2, 129.4, 129.6, 134.98, 135.04, 136.7, 136.6, 137.5, 139.6; HRMS (ESI-TOF) calcd for $C_{32}H_{31}N_2O_2S$ $(M+H)^+$ 507.2106, found 507.2109. $[\alpha]_D^{25}$ = +83.5 (c 0.16, $CHCl_3$) for a >99% ee sample.

***(1R,3S)-8-Bromo-10-methyl-1-(4-nitrophenyl)-3-phenyl-2-tosyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole* (*5p*).** The general method **2A** described above was followed when aziridine **2a** (27.3 mg, 0.10 mmol) was reacted with 5-bromo-3-methylindole **1b** (25.2 mg, 0.12 mmol) in presence of NaH (4.8 mg, 0.12 mmol) in THF at room temperature for 2 h followed by addition of 4-nitrobenzaldehyde **4a** (16.7 mg, 0.11 mmol) along with $BF_3{\cdot}OEt_2$ (2.5 μL, 20 mol %) and $MgSO_4$ (11.9 mg, 0.10 mmol) at 55 °C for 2 h to afford **5p** (44.3 mg, 0.072 mmol) as a white solid in 72% yield: R_f 0.4 (10% ethyl acetate in petroleum ether), mp 203–205 °C; IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2923, 1597, 1519, 1493, 1461, 1347, 1247, 1163, 1094, 1009, 959, 927, 855, 812, 749, 690, 656; ^1H NMR (500 MHz, $CDCl_3$) δ 1.98 (s, 3H), 2.33 (s, 3H), 3.73 (dd, 1H, J = 13.2, 5.2 Hz), 4.25 (dd, 1H, J = 12.9, 4.9 Hz), 5.24 (t, 1H, J = 5.2 Hz), 6.65 (s, 1H), 6.98–7.05 (m, 5H), 7.12–7.19 (m, 5H), 7.33 (dd, 1H, J = 8.6, 1.7 Hz), 7.67 (d, 2H, J = 8.1 Hz), 7.70 (d, 1H, J = 1.7 Hz), 7.87 (d, 2H, J = 8.6 Hz); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 8.5, 21.5, 41.9, 53.8, 55.9, 108.2, 110.1, 113.3, 121.8, 123.1, 124.9, 127.1, 127.6, 128.0, 128.1, 128.3, 128.8, 129.9, 130.0, 134.4, 136.0, 136.9, 144.5, 146.2, 146.9; HRMS (ESI-TOF) calcd for $C_{31}H_{27}BrN_3O_4S$ $(M+H)^+$ 616.0906, found 616.0910. $[\alpha]_D^{25}$ = +112.3 (c 0.15, $CHCl_3$) for a 99% ee sample.

***(1R,3S)-8,10-Dimethyl-1-(4-nitrophenyl)-3-phenyl-2-tosyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole* (*5q*).** The general method **2A** described above was followed when aziridine **2a** (27.3 mg, 0.10 mmol) was reacted with 3,5-dimethylindole **1c** (17.4 mg, 0.12 mmol) in presence of NaH (4.8 mg, 0.12 mmol) in THF at room temperature for 2 h followed by

addition of 4-nitrobenzaldehyde **4a** (16.7 mg, 0.11 mmol) along with $BF_3{\cdot}OEt_2$ (2.5 μL, 20 mol %) and $MgSO_4$ (11.9 mg, 0.10 mmol) at 55 °C for 2 h to afford **5q** (40.8 mg, 0.074 mmol) as a yellow solid in 74% yield: R_f 0.5 (10% ethyl acetate in petroleum ether), mp 194–196 °C; IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3031, 2920, 1597, 1520, 1488, 1455, 1347, 1301, 1249, 1211, 1163, 1095, 1009, 963, 928, 873, 858, 814, 795, 764, 749, 736, 697, 677, 662; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.00 (s, 3H), 2.33 (s, 3H), 2.50 (s, 3H), 3.68 (dd, 1H, J = 13.1, 5.3 Hz), 4.28 (dd, 1H, J = 13.1, 4.6 Hz), 5.24 (t, 1H, J = 4.8 Hz), 6.66 (s, 1H), 6.96–6.99 (m, 2H), 7.01–7.04 (m, 1H), 7.08–7.11 (m, 3H), 7.17–7.9 (m, 5H), 7.38 (s, 1H), 7.69 (d, 2H, J = 8.2 Hz), 7.85 (d, 2H, J = 8.8 Hz); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 8.6, 21.5, 41.9, 53.9, 55.8, 108.1, 108.5, 118.7, 123.0, 123.6, 126.7, 127.1, 127.7, 127.9, 128.2, 128.5, 128.8, 129.5, 130.0, 134.2, 136.2, 137.1, 144.3, 146.71, 146.73; HRMS (ESI-TOF) calcd for $C_{32}H_{30}N_3O_4S$ $(M+H)^+$ 552.1957, found 552.1953; $[\alpha]_D^{25}$ = +87.00 (c 0.10, $CHCl_3$) for a 99% ee sample.

***3,10-Dimethyl-1-(4-nitrophenyl)-3,4-dihydropyrazino[1,2-a]indole* (*6a*).** The general method **2B** described above was followed when aziridine **2g** (27.3 mg, 0.10 mmol) was reacted with 3-methylindole **1a** (15.7 mg, 0.12 mmol) in presence of NaH (4.8 mg, 0.12 mmol) in THF at room temperature for 2 h followed by addition of 4-nitrobenzaldehyde **4a** (16.7 mg, 0.11 mmol) dissolved in DCE (2.0 mL) along with PTSA (17.2 mg, 0.10 mmol, 1.0 equiv) and $MgSO_4$ (11.9 mg, 0.10 mmol) at 80 °C for 12 h to afford **6a** (22.5 mg, 0.057 mmol) as a yellow solid in 57% yield: R_f 0.3 (10 % ethyl acetate in petroleum ether), mp 133–135 °C; IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3024, 2965, 2832, 1732, 1697, 1565, 1361, 1335, 1312, 1298, 1234, 1183, 1159, 1082, 1024, 980, 934, 893, 854, 814, 748, 723, 701, 685; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (d, 3H, J = 6.8 Hz), 1.95 (s, 3H), 3.72–3.77 (m, 1H), 4.01-4.10 (m, 1H), 4.26–4.30 (m, 1H), 7.13–7.17 (m, 1H), 7.33–7.39 (m, 2H), 7.62 (d, 1H, J = 7.8 Hz), 7.80 (dt, 2H, J = 9.2, 2.3 Hz), 8.30-8.34 (m, 2H); ^{13}C{^{1}H} NMR

(100 MHz, $CDCl_3$) δ 11.1, 19.6, 44.5, 54.3, 109.1, 113.2, 120.1, 120.9, 123.8, 124.1, 125.1, 128.4, 129.7, 136.1, 145.5, 148.7, 160.2; HRMS (ESI-TOF) calcd for $C_{19}H_{18}N_3O_2$ $(M+H)^+$ 320.1399, found 320.1395 .

***1-(4-Fluorophenyl)-10-methyl-3-phenyl-3,4-dihydropyrazino[1,2-a]indole* (*6b*).** The general method **2B** described above was followed when aziridine **2a** (27.3 mg, 0.10 mmol) was reacted with 3-methylindole **1a** (15.7 mg, 0.12 mmol) in presence of NaH (4.8 mg, 0.12 mmol) in THF at room temperature for 2 h followed by addition of 4-fluorobenzaldehyde **4c** (11.8 μL, 13.7 mg, 0.11 mmol) dissolved in DCE (2.0 mL) along with PTSA (17.2 mg, 0.10 mmol, 1.0 equiv) and $MgSO_4$ (11.9 mg, 0.10 mmol) at 80 °C for 12 h to afford **6b** (21.0 mg, 0.057 mmol) as a white solid in 57% yield: R_f 0.4 (10% ethyl acetate in petroleum ether), mp 134–136 °C; IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3058, 2924, 2855, 1732, 1601, 1568, 1507, 1466, 1453, 1386, 1301, 1261, 1231, 1154, 1095, 1068, 1023, 996, 844, 813, 738, 700; ^1H NMR (500 MHz, $CDCl_3$) δ 2.02 (s, 3H), 3.91–3.95 (m, 1H), 4.45–4.48 (m, 1H), 4.95 (dd, 1H, J = 10.3, 5.2 Hz), 7.12–7.16 (m, 3H), 7.28–7.34 (m, 3H), 7.38 (t, 2H, J = 7.5 Hz), 7.48 (d, 2H, J = 6.9 Hz), 7.63 (d, 1H, J = 8.0 Hz), 7.68 (dd, 2H, J = 8.6, 5.8 Hz); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 11.0, 45.6, 62.5, 109.1, 113.5, 115.4 (d, $^2J_{C\text{-}F}$ = 22.7 Hz), 119.9, 120.9, 124.8, 125.0, 127.5, 127.7, 128.6, 128.8, 130.8 (d, $^3J_{C\text{-}F}$ = 7.2 Hz), 135.5 (d, $^4J_{C\text{-}F}$ = 3.6 Hz), 135.9, 141.2, 163.0, 163.7 (d, $^1J_{C\text{-}F}$ = 317.6 Hz); HRMS (ESI-TOF) calcd for $C_{24}H_{20}FN_2$ $(M+H)^+$ 355.1611, found 355.1614.

***1-(4-Bromophenyl)-10-methyl-3-phenyl-3,4-dihydropyrazino[1,2-a]indole* (*6c*).** The general method **2B** described above was followed when aziridine **2a** (27.3 mg, 0.10 mmol) was reacted with 3-methylindole **1a** (15.7 mg, 0.12 mmol) in presence of NaH (4.8 mg, 0.12 mmol) in THF at room temperature for 2 h followed by addition of 4-bromobenzaldehyde **4e** (20.0 mg, 0.11 mmol) dissolved in DCE (2.0 mL) along with PTSA (17.2 mg, 0.10 mmol, 1.0 equiv) and $MgSO_4$

(11.9 mg, 0.10 mmol) at 80 °C for 12 h to afford **6c** (20.0 mg, 0.057 mmol) as a white solid in 57% yield: *Rf* 0.4 (10 % ethyl acetate in petroleum ether), mp 155–157 °C; IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2924, 2854, 1578, 1557, 1487, 1466, 1451, 1419, 1386, 1321, 1301, 1261, 1231, 1181, 1070, 1012, 994, 836, 809, 737, 700; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.04 (s, 3H), 3.90–3.94 (m, 1H), 4.47 (dd, 1H, *J* = 12.6, 5.2 Hz), 4.95 (dd, 1H, *J* = 10.3, 5.2 Hz), 7.11–7.16 (m, 1H), 7.22–7.24 (m, 1H), 7.29–7.35 (m, 3H), 7.39 (t, 2H, *J* = 7.5 Hz), 7.48 (d, 2H, *J* = 6.9 Hz), 7.59 (dd, 4H, *J* = 14.9, 8.6 Hz); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 11.1, 45.6, 62.6, 109.1, 113.5, 120.0, 120.9, 124.2, 124.9, 126.2, 127.5, 127.7, 128.7, 128.8, 130.5, 131.6, 133.2, 135.9, 138.2, 141.1, 161.8; HRMS (ESI-TOF) calcd for $C_{24}H_{20}BrN_2$ $(M+H)^+$ 415.0810, found 415.0811.

***4-(10-Methyl-3-phenyl-3,4-dihydropyrazino[1,2-a]indol-1-yl)benzonitrile* (*6d*).** The general method **2B** described above was followed when aziridine **2a** (27.3 mg, 0.10 mmol) was reacted with 3-methylindole **1a** (15.7 mg, 0.12 mmol) in presence of NaH (4.8 mg, 0.12 mmol) in THF at room temperature for 2 h followed by addition of 4-cyanobenzaldehyde **4f** (14.4 mg, 0.11 mmol) dissolved in DCE (2.0 mL) along with PTSA (17.2 mg, 0.10 mmol, 1.0 equiv) and $MgSO_4$ (11.9 mg, 0.10 mmol) at 80 °C for 12 h to afford **6d** (28.3 mg, 0.070 mmol) as colorless thick liquid in 70% yield: *Rf* 0.3 (10% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (neat, cm^{-1}) 2955, 2924, 1854, 2229, 1733, 1578, 1554, 1484, 1465, 1455, 1420, 1378, 1322, 1297, 1232, 1184, 1128, 1069, 1022, 995, 848, 813, 740, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (s, 3H), 3.93 (dd, 1H, *J* = 11.9, 11.0 Hz), 4.50 (dd, 1H, *J* = 12.4, 5.0 Hz), 5.00 (dd, 1H, *J* = 11.0, 5.0 Hz), 7.16 (td, 1H, *J* = 6.9, 1.4 Hz), 7.30–7.36 (m, 3H), 7.38–7.42 (m, 2H), 7.47–7.49 (m, 2H), 7.64 (d, 1H, *J* = 7.8 Hz), 7.77 (d, 2H, *J* = 8.2 Hz), 7.81 (d, 2H, *J* = 8.2 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 11.1, 45.6, 62.8, 109.2, 113.5, 113.7, 118.7, 120.2, 121.0, 124.4, 125.2, 127.4, 127.9, 128.5, 128.9, 129.6, 132.3.

136.0, 140.8, 143.6, 161.3; HRMS (ESI-TOF) calcd for $C_{25}H_{20}N_3$ $(M+H)^+$ 362.1657, found 362.1656.

***10-Methyl-1-(naphthalen-2-yl)-3-phenyl-3,4-dihydropyrazino[1,2-a]indole* (*6e*).** The general method **2B** described above was followed when aziridine **2a** (27.3 mg, 0.10 mmol) was reacted with 3-methylindole **1a** (15.7 mg, 0.12 mmol) in presence of NaH (4.8 mg, 0.12 mmol) in THF at room temperature for 2 h followed by addition of 2-naphthaldehyde **4g** (17.2 mg, 0.11 mmol) dissolved in DCE (2.0 mL) along with PTSA (17.2 mg, 0.10 mmol, 1.0 equiv) and $MgSO_4$ (11.9 mg, 0.10 mmol) at 80 °C for 12 h to afford **6e** (23.2 mg, 0.060 mmol) as a white solid in 60% yield: *Rf* 0.4 (10% ethyl acetate in petroleum ether), mp 164–166 °C; IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3059, 3024, 2987, 2931, 2845, 1756, 1628, 1601, 1548, 1524, 1489, 1449, 1413, 1368, 1356, 1287, 1256, 1201, 1168, 1130, 1098, 1068, 1024, 987, 946, 912, 910, 856, 752, 658; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.00 (s, 3H), 3.98 (dd, 1H, J = 12.0, 10.9 Hz), 4.51 (dd, 1H, J = 12.0, 5.2 Hz), 5.03 (dd, 1H, J = 10.6, 4.9 Hz), 7.14–7.17 (m, 1H), 7.31–7.41 (m, 5H), 7.51–7.57 (m, 4H), 7.65 (d, 1H, J = 8.0 Hz), 7.82 (dd, 1H, J = 8.6, 1.2 Hz), 7.89–7.95 (m, 3H), 8.20 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 11.1, 45.8, 62.7, 109.1, 113.6, 119.9, 120.9, 124.7, 125.3, 126.2, 126.4, 126.9, 127.6, 127.7, 127.9, 128.66, 128.69, 128.7, 128.8, 133.2, 134.1, 135.9, 136.7, 141.3, 162.9; HRMS (ESI-TOF) calcd for $C_{28}H_{23}N_2$ $(M+H)^+$ 387.1861, found 387.1866

10-Methyl-1-(4-nitrophenyl)-3-phenyl-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indole* (*8a, major *cis* diastereomer**).** The general method **2A** described above was followed when epoxide **7a** (11.4 μL, 0.10 mmol) was reacted with 3-methylindole **1a** (15.7 mg, 0.12 mmol) in presence of NaH (4.8 mg, 0.12 mmol) in THF at room temperature for 2 h followed by addition of 4-nitrobenzaldehyde **4a** (16.7 mg, 0.11 mmol) along with $BF_3{\cdot}OEt_2$ (2.5 μL, 20 mol %) and $MgSO_4$ (11.9 mg, 0.10 mmol) at 55 °C for 4 h to afford **8a** (28.5 mg, 0.074 mmol) as a white solid (3:1

diastereomeric mixture, combined yield 74%): *Rf* 0.5 (20% ethyl acetate in petroleum ether), mp 133–135 °C; IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3412, 2919, 1604, 1520, 1457, 1346, 1262, 1238, 1193, 1075, 1047, 958, 898, 856, 843, 807, 742, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 (s, 3H), 3.95 (t, 1H, J = 11.4 Hz), 4.31–4.34 (m, 1H), 4.80–4.84 (m, 1H), 6.42 (s, 1H), 7.19–7.31 (m, 3H), 7.34–7.41 (m, 5H), 7.51 (d, 2H, J = 8.2 Hz), 7.64 (d, 1H, J = 7.3 Hz), 8.19 (d, 2H, J = 8.7 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 8.7, 47.9, 70.4, 72.9, 107.4, 109.0, 118.9. 120.2, 122.0, 123.9, 126.4, 127.5, 128.7, 128.8, 128.9, 129.2, 136.5, 138.3, 146.4, 148.0; HRMS (ESI-TOF) calcd for $C_{24}H_{19}N_2O_3$ $(M-H)^-$ 383.1396, found 383.1391.

1-(4-Fluorophenyl)-10-methyl-3-phenyl-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indole* (*8b, major *cis* diastereomer**).** The general method **2A** described above was followed when epoxide **7a** (11.4 μL, 12.0 mg, 0.10 mmol) was reacted with 3-methylindole **1a** (15.7 mg, 0.12 mmol) in presence of NaH (4.8 mg, 0.12 mmol) in THF at room temperature for 2 h followed by addition of 4-fluorobenzaldehyde **4c** (13.7 mg, 0.11 mmol) along with $BF_3{\cdot}OEt_2$ (2.5 μL, 20 mol %) and $MgSO_4$ (11.9 mg, 0.10 mmol) at 55 °C for 4 h to afford **8b** (26.1 mg, 0.073 mmol) as a white solid (1.5:1 diastereomeric mixture, combined yield 73%): *Rf* 0.55 (5% ethyl acetate in petroleum ether), mp 126–128 °C; IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3404, 3052, 2919, 2857, 1606, 1510, 1469, 1455, 1425, 1363, 1327, 1294, 1224, 1156, 1095, 1074, 1030, 1013, 968, 788, 835, 813, 740, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 (s, 3H), 3.91–3.97 (m, 1H), 4.29-4.33 (m, 1H), 4.88-4.91 (m, 1H), 6.35 (s, 1H), 6.98–7.03 (m, 2H), 7.17–7.30 (m, 5H), 7.32–7.40 (m, 5H), 7.62 (d, 1H, J = 7.3 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 8.6, 47.9, 69.4, 73.1, 106.7, 108.9, 115.6 (d, $^2J_{C\text{-}F}$ = 21.0 Hz), 118.7, 119.9, 121.6, 126.5, 128.5, 128.7 (d, $^4J_{C\text{-}F}$ = 3.8 Hz), 128.8, 130.2 (d, $^3J_{C\text{-}F}$ = 7.6 Hz), 135.0, 135.1, 136.4, 138.9, 162.7 (d, $^1J_{C\text{-}F}$ = 246.0 Hz); HRMS (ESI-TOF) calcd for $C_{24}H_{21}FNO$ $(M+H)^+$ 358.1607, found 358.1611.

1-(Furan-2-yl)-10-methyl-3-phenyl-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indole **(*8c,*** major *cis* diastereomer**).** The general method **2A** described above was followed when epoxide **7a** (11.4 μL, 12.0 mg, 0.10 mmol) was reacted with 3-methylindole **1a** (15.7 mg, 0.12 mmol) in presence of NaH (4.8 mg, 0.12 mmol) in THF at room temperature for 2 h followed by addition of furan-2-carbaldehyde **4h** (9.6 mg, 0.11 mmol) along with $BF_3.OEt_2$ (2.5 μL, 20 mol %) and $MgSO_4$ (11.9 mg, 0.10 mmol) at 55 °C for 5.5 h to afford **8c** (22.4 mg, 0.068 mmol) as a white solid (5:1 diastereomeric mixture, combined yield 73%) in 68% yield: *Rf* 0.36 (5% ethyl acetate in petroleum ether), mp 136–138 °C; IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3118, 3033, 2919, 2857, 1614, 1497, 1469, 1457, 1426, 1386, 1333, 1293, 1239, 1223, 1189, 1142, 1072, 1049, 1011, 959, 938, 894, 842, 794, 740, 699; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.13 (s, 3H), 3.95 (t, 1H, J = 11.2 Hz), 4.35 (dd, 1H, J = 11.6, 3.5 Hz), 5.11 (dd, 1H, J = 10.9, 3.3 Hz), 6.11 (d, 1H, J = 3.3 Hz), 6.32 (dd, 1H, J = 1.9, 3.2 Hz), 6.39 (s, 1H), 7.15–7.24 (m, 2H), 7.28 (d, 1H, J = 8.1 Hz), 7.33–7.41 (m, 3H), 7.45–7.46 (m, 3H), 7.59 (d, 1H, J = 7.8 Hz); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 8.3, 47.9, 67.9, 70.2, 106.3, 108.6, 110.1, 110.9, 118.6, 119.6, 121.4, 126.4, 127.2, 128.4, 128.5, 128.6, 135.9, 138.7, 143.4, 152.0; HRMS (ESI-TOF) calcd for $C_{22}H_{18}NO_2$ $(M-H)^-$ 328.1338, found 328.1346.

1-Ethyl-10-methyl-3-phenyl-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indole **(*8d,*** *m*ajor *cis* diastereomer**).** The general method **2A** described above was followed when epoxide **7a** (11.4 μL, 12.0 mg, 0.10 mmol) was reacted with 3-methylindole **1a** (15.7 mg, 0.12 mmol) in presence of NaH (4.8 mg, 0.12 mmol) in THF at room temperature for 2 h followed by addition of propionaldehyde **4i** (5.8 mg, 0.11 mmol) along with $BF_3{\cdot}OEt_2$ (2.5 μL, 20 mol%) and $MgSO_4$ (11.9 mg, 0.10 mmol) at 55 °C for 5.5 h to afford **8d** (18.9 mg, 0.065 mmol) as a white solid (5:1 diastereomeric mixture, combined yield 65%): *Rf* 0.6 (5% ethyl acetate in petroleum ether), mp 138–140 °C; IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3253, 2907, 1685, 1648, 1605, 1580, 1515, 1454, 1407, 1362,

1310, 1254, 1213, 1174, 1148, 1122, 1019, 960, 881, 768, 756, 714, 610; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (t, 1H, J = 7.3 Hz), 1.84 (s, 3H), 2.05–2.16 (m, 1H), 2.20–2.29 (m, 1H), 2.32 (s, 3H), 3.90–3.96 (m, 1H), 4.28 (dd, 1H, J = 11.9, 3.2 Hz), 4.85–4.89 (m, 1H), 5.23 (dd, 1H, J = 5.5, 3.2 Hz), 7.11–7.23 (m, 3H), 7.35–7.39 (m, 1H), 7.41–7.45 (m, 2H), 7.51 (d, 2H, J = 7.9 Hz), 7.56 (d, 1H, J = 7.3 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 8.8, 9.3, 27.8, 48.5, 75.4, 75.5, 103.8, 108.2, 118.2, 119.3, 120.9, 126.1, 128.3, 128.6, 128.9, 131.0, 135.2, 139.3; HRMS (ESI-TOF) calcd for ($C_{20}H_{22}NO$) $(M+H)^+$ 292.1701, found 292.1708.

***10'-Methyl-3'-phenyl-3',4'-dihydrospiro[cyclopentane-1,1'-[1,4]oxazino[4,3-a]indole]* (*8e*).** The general method **2A** described above was followed when epoxide **7a** (11.4 μL, 12.0 mg, 0.10 mmol) was reacted with 3-methylindole **1a** (15.7 mg, 0.12 mmol) in presence of NaH (4.8 mg, 0.12 mmol) in THF at room temperature for 2 h followed by addition of cyclopentanone **9** (8.4 mg, 0.11 mmol) along with $BF_3{\cdot}OEt_2$ (2.5 μL, 20 mol%) and $MgSO_4$ (11.9 mg, 0.10 mmol) at 55 °C for 4 h to afford **8e** (22.9 mg, 0.072 mmol) as a white solid in 72% yield: *Rf* 0.6 (5% ethyl acetate in petroleum ether), mp 158–160 °C; IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3031, 2953, 2869, 1606, 1496, 1470, 1454, 1421, 1374, 1326, 1284, 1236, 1181, 1076, 1029, 1011, 982, 738, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86–1.93 (m, 3H), 1.95–2.08 (m, 2H), 2.17–2.23 (m, 1H), 2.29–2.37 (m, 4H), 2.45–2.52 (m, 1H), 3.89–3.95 (m, 1H), 4.32 (dd, 1H, J = 11.4, 3.2 Hz), 5.00 (dd, 1H, J = 11.0, 2.8 Hz), 7.10–7.18 (m, 2H), 7.22 (d, 1H, J = 8.2 Hz), 7.33–7.37 (m, 1H), 7.40–7.44 (m, 2H), 7.50 (d, 2H, J = 7.8 Hz), 7.54 (d, 1H, J = 7.3 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 9.5, 24.6, 24.9, 37.9, 40.7, 47.9, 70.8, 85.4, 103.0, 108.2, 118.0, 119.3, 120.8, 126.1, 128.1, 128.5, 128.9, 133.9, 134.5, 139.5; HRMS (ESI-TOF) calcd for $C_{22}H_{24}NO$ $(M+H)^+$ 318.1858, found 318.1855.

***1-(4-Chlorophenyl)-10-methyl-2-tosyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole* (*5r*).** The general method **2A** described above was followed when aziridine **2m** (19.7 mg, 0.10 mmol) was

reacted with 3-methylindole **1a** (15.7 mg, 0.12 mmol) in presence of NaH (4.8 mg, 0.12 mmol) in THF at room temperature for 1 h followed by addition of 4-chlorobenzaldehyde **4j** (15.4 mg, 0.11 mmol) along with $BF_3{\cdot}OEt_2$ (2.5 μL, 20 mol %) and $MgSO_4$ (11.9 mg, 0.10 mmol) at 55 °C for 2 h to afford **5r** (37.8 mg, 0.084 mmol) as a white solid in 84% yield: *Rf* 0.4 (10% ethyl acetate in petroleum ether), mp 132–134 °C; IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3054, 2925, 2855, 1915, 1739, 1597, 1489, 1461, 1403, 1350, 1318, 1271, 1239, 1163, 1111, 1088, 1014, 982, 934, 891, 858, 814, 744, 716, 694, 664; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10 (s, 3H), 2.20 (s, 3H), 3.40–3.53 (m, 2H), 3.80–3.88 (m, 1H), 3.96–4.05 (m, 1H), 6.47 (s, 1H), 7.01 (d, 2H, J = 8.2 Hz), 7.06 (dd, 1H, J = 6.4, 1.4 Hz), 7.11–7.18 (m, 4H), 7.24–7.27 (m, 2H), 7.53–7.58 (m, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 8.2, 21.3, 38.5, 39.4, 54.5, 107.8, 108.6, 118.6, 119.8, 121.6, 126.7, 127.4, 128.2, 128.7, 129.4, 129.5, 134.0, 136.3, 136.99, 137.03, 143.8; HRMS (ESI-TOF) calcd for $C_{25}H_{23}ClN_2NaO_2S$ $(M+H)^+$ 473.1066, found 473.1068.

***1-(4-Chlorophenyl)-10-methyl-3,4-dihydropyrazino[1,2-a]indole* (*6f*).** To a solution of **5r** (48.5 mg, 0.10 mmol, 1.0 equiv) in tetrahydrofuran (2.0 mL) cooled in cooling bath at −78 °C, was added sodium-naphthalenide (prepared by adding naphthalene (128.2 mg, 1.0 mmol, 10.0 equiv) in one portion to a vigorously stirred suspension of sodium (22.9 mg, 1.0 mmol, 10.0 equiv) in tetrahydrofuran (2.0 mL) at 25 °C, the resulting suspension was stirred further for 2 h) portion wise until the reaction solution formed a persistent, dark-green color. The dark-green solution was stirred at −78 °C for 2 h to afford **6f** (19.7 mg, 0.067 mmol) as a white solid in 67% yield. *Rf* 0.7 (10% ethyl acetate in petroleum ether), mp 124–126 °C; IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3068, 2936, 1655, 1608, 1592, 1535, 1498, 1427, 1357, 1328, 1259, 1210, 1144, 1126, 1101, 1069, 960, 871, 762, 726, 704, 654, 623; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (s, 3H), 4.05–4.16 (m, 4H), 7.12–7.16 (m, 1H), 7.32–7.37 (m, 2H), 7.42–7.45 (m, 2H), 7.55–7.59 (m, 2H), 7.61–7.64 (m, 1H); ^{13}C{^{1}H} NMR

(100 MHz, $CDCl_3$) δ 11.0, 38.6, 48.9, 109.0, 113.2, 119.8, 120.7, 124.66, 124.72, 128.2, 128.6, 129.8, 135.76, 135.78, 137.7, 162.2; HRMS (ESI-TOF) calcd for $C_{18}H_{15}ClN_2$ $(M+H)^+$ 294.0924, found 294.0919.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Copies of ^1H and ^{13}C NMR spectra of the compounds, HPLC chromatograms for ee determination, and crystal structures (PDF)

X-ray crystallographic analysis of **5l** (CIF)

X-ray crystallographic analysis of (1*R*,3*S*)-**5n** (CIF)

X-ray crystallographic analysis of (1*R*,3*S*)-**5p** (CIF)

X-ray crystallographic analysis of **8a** (CIF)

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NOTES

The authors declare no competing financial interest.

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