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Palladium(II)-Catalyzed Formal [3 + 2] Cycloaddition of Aziridines with 3-Substituted Indoles: Synthesis of Enantioenriched Pyrroloindolines

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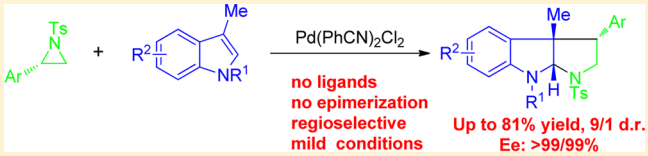
Supporting Information

ABSTRACT: A Pd-catalyzed enantiospecific formal [3 + 2] cycloaddition between chiral aziridines and indoles has been developed. With this method, chiral pyrroloindolines in enantiomerically pure forms were constructed in high yields and diastereoselectivities under mild conditions.



INTRODUCTION

Aziridines have been extensively utilized as one of the most useful three membered ring functionalities in the reactions with a variety of carbon and heteroatom nucleophiles for the construction of various amino acids, chiral ligands, nitrogen-containing heterocycles, and alkaloids.[1,2] During the past few years, with the easily accessible enantiopure aziridines, a couple of stereoselective ring-opening reactions have been reported to provide nonracemic products directly. Ghorai and co-workers[3] have reported extensive work on the Lewis acid catalyzed S_N2-type ring-opening of enantiopure *N*-activated aziridines to provide the corresponding products with partial loss of enantiopurity in almost all cases. Recently, Takeda and co-workers developed a Pd-catalyzed enantiospecific cross-coupling of chiral 2-arylaziridines with arylboronic acids for the construction of 2-arylphenethylamines in an enantiopure form using *N*-heterocyclic carbene (NHC) ligands to promote the coupling.[4] In this context, an efficient method for regioselective and stereospecific ring-opening of chiral aziridines is still in great demand.

Pyrroloindoline backbones are present in an array of fascinating natural products with interesting biological activities such as (−)-physostigmine,[5a] (−)-debromoflustramine E,[5b] (−)-gliocladin C,[5c] (+)-folicanthine,[5d] (−)-bionectin A,[5e] and (+)-nocardioazine B[5f] (Figure 1). Considerable efforts have been devoted to developing elegant strategies for the construction of hexahydropyrrolo[2,3-*b*]indoles, which, to the best of our knowledge, can be accessed through four general strategies concerning the enantioselective synthesis.

The first strategy is started with tryptophan or tryptamine derivatives by using biomimetic methods[6] (Scheme 1, route a). The second strategy by using 2-oxoindoles as the starting materials undergoes alkylation and a series of functional group interconversions and cyclization[7] (Scheme 1, route b). The third pathway is developed by Michael-type Friedel−Crafts alkylations of indoles with *N*-acylated *α,β*-dehydroamino esters[8] (Scheme 1, route c). Recently, Davies and co-workers reported the Rh-catalyzed [3 + 2]-annulation of C3-substituted indoles with 4-aryl-1-sulfonyl-1,2,3-triazoles to provided chiral didehydropyrroloindolines[9] (Scheme 1, route d). In 2000, Nakagawa's group reported the [3 + 2] cycloaddition of the unsubstituted aziridine with *N*-methyl-3-methylindoles promoted by stoichiometric amount of $Sc(OTf)_3$ with TMSCl as the additive.[10] Wang and co-workers studied the cycloaddition between mesoaziridines and C3-alkylindoles mediated by magnesium catalyst.[11] Using their methods, pyrroloindolines with no substitution or with alkyl-substituted groups in the pyrrole rings were constructed smoothly (Scheme 1, route e). However, the syntheses of pyrroloindolines with aryl-substituted groups are not sufficiently investigated; herein, we would like to present our contributions to the construction of these backbones via a [3 + 2] cycloaddition reaction between C3-substituted indoles and achiral or chiral 2-arylaziridines catalyzed by the simple Pd(II) salts.[12]

RESULTS AND DISCUSSION

Our initial investigation was commenced with the reaction between C3-methylindole **1a** and aziridine **2a** (as a racemic mixture) catalyzed by various Lewis acids in toluene (Table 1). When the commonly used $Zn(OTf)_2$, $Mg(OTf)_2$, and $Cu(OAc)_2$ were employed as the catalysts, no products were observed (Table 1, entries 1−3). Fortunately, the alternative $Cu(OTf)_2$ and $Sc(OTf)_3$ did provide the desired products, although the yields and diastereoselectivities were low (Table 1, entries 4, 5). The Pd(II) complexes, which are more popular in transition metal catalysis, have also been applied as Lewis acids to promote a variety of reactions.[13] Using $PdCl_2$ as the catalyst, the reaction indeed happened with the yield and diastereoselectivity largely improved. Thus, various Pd(II) catalysts were then examined and $Pd(PhCN)_2Cl_2$ was found to give the best results (69% yield and 6:1 dr, Table 1, entry 7). In the

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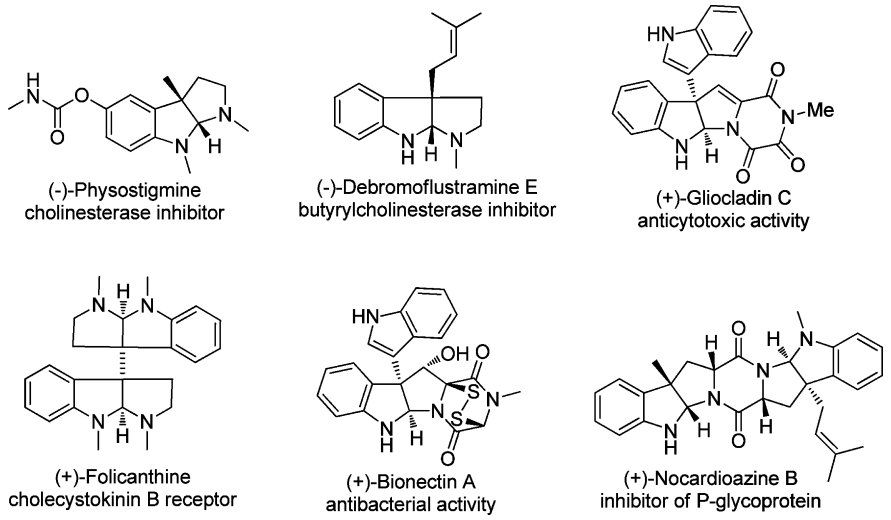
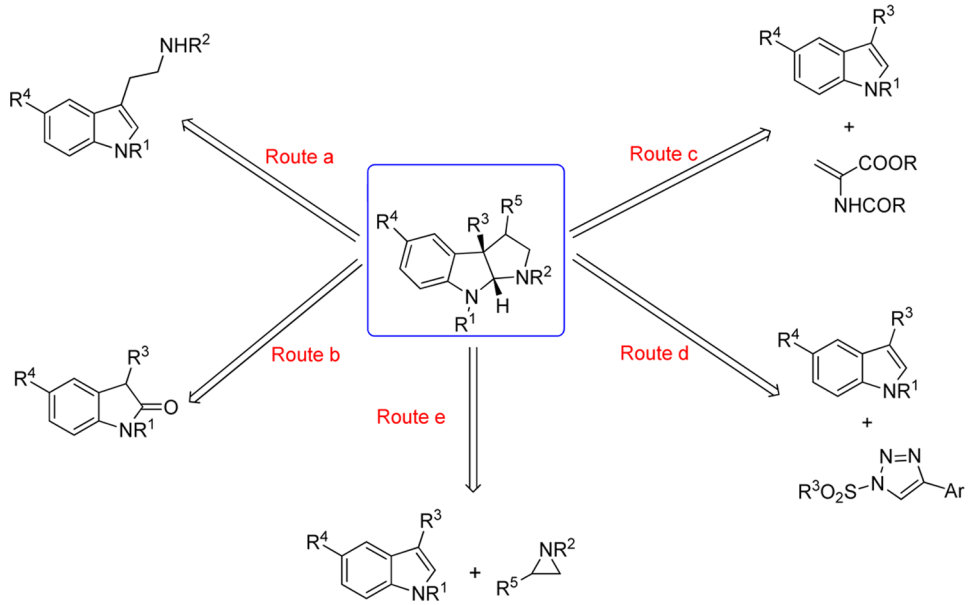


Figure 1. Representative natural products containing the pyrroloindolines.

Scheme 1. Retrosynthetic Approaches



following studies, solvents such as MeCN, DCM, THF, or DMF were screened; however, the yields and diastereoselectivities were not improved. The study of the effect of temperature on the diastereoselectivity was also made; the lower reaction temperature gave the better diastereoselectivity (see Supporting Information, page S2). Finally, when the ratio of **2a**:**1a** was increased to 2:1, the corresponding product could be obtained in 81% yield and 10:1 dr (Table 1, entries 12). In addition to the Pd(II) catalyst, another transition metal $PtCl_2$ was also evaluated, and the reaction underwent smoothly; however, only 5:1 dr was observed (Table 1, entry 13).

Under the optimized conditions, the reaction scope was examined (Table 2). The reaction worked well with a series of indoles. Using the methyl group instead of benzyl group to protect the nitrogen of indole, the yield and diastereoselectivity were preserved (**3b**). Indoles with various types of substituents on the phenyl rings provided the products with good to excellent yield, and moderate to good dr (**3c**−**3g**), regardless of their electronic nature or positions. In addition, the reactions of cyclopenta- and cyclohexa-fused indoles also proceeded smoothly, giving tetracyclic indolines **3h** and **3i** containing two quaternary bridging carbons in high yields with excellent diastereoselectivities. What is more, indole C3 substituents other than methyl group are also compatible in the reaction, albeit with moderate yields and stereoselectivities (**3j**−**3l**). As for the aziridines, the electronic nature of substituents on the 2-aryl group did not affect the reactivity significantly (**3m**−**3q**). However, the *o*-Br-substituted 2-aryl aziridine gave the corresponding product (**3r**) with decreased diastereoselectivity compared to the *p*-Br-substituted 2-aryl aziridine, probably because of the steric effect of bromine at the ortho position of the phenyl ring. In addition, reactions with aziridines protected by different sulfonyl groups also proceed smoothly (**3s**−**3u**).

Further exploration was also conducted to construct chiral hexahydropyrrolo[2,3-*b*]indole backbones. For this purpose, enantiomerically pure aziridines were employed as the substrates. To our great delight, the ring-opening reaction between chiral aziridines and indoles with various substituents

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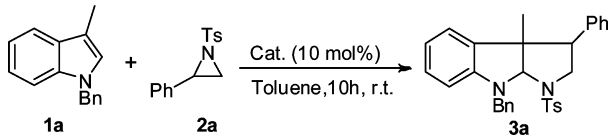
Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	catalyst	yield [%][b]	dr[c]
1	$Zn(OTf)_2$	NR	*d*
2	$Mg(OTf)_2$	NR	*d*
3	$Cu(OAc)_2$	NR	*d*
4	$Cu(OTf)_2$	40	1:1
5	$Sc(OTf)_2$	24	1:1
6	$PdCl_2$	65	6:1
7	$Pd(PhCN)_2Cl_2$	69	6:1
8	$Pd(OAc)_2$	43	9:1
9	$Pd(O_2CCF_3)_2$	24	5:1
10	$Pd(NO_3)_2$	53	5:1
11	$Pd(PPh_3)_2Cl_2$	NR	*d*
12[e]	$Pd(PhCN)_2Cl_2$	81	10:1
13[e]	$PtCl_2$	82	5:1

[a]Reaction conditions: **1a** (0.1 mol), **2a** (0.1 mol), catalyst (10 mol %), toluene (1.0 mL). [b]Yield of the isolated product after column chromatography. [c]Determined by ^{1}H NMR analysis. [d]Not determined. [e]**1a** (0.1 mol), **2a** (0.2 mol).

on the phenyl rings afforded the corresponding pyrroloindolines in enantiomerically pure form with good yields and diastereoselectivities (Table 3). The absolute configuration of (*S*,*S*,*S*)-**3c** was unambiguously determined by single-crystal X-ray analysis (see Supporting Information), confirming the complete stereoinversion at the C-2 of aziridine. Other chiral products can therefore be assigned by analogy.

In the following studies, stereochemical outcomes of the reactions were probed with electron-rich 1,3,5-trimethoxybenzene **4** and (*R*)-**2a** or (*S*)-**2a** (Schemes 2a and 2b). As predicted, both of the products could be attained as a single enantiomer. This represents great progress compared to the same initial study performed by Ghorai (Scheme 2c).[3] Therefore, we tried to explore the mechanism difference between Pd(II) and $Sc(OTf)_3$.

A variety of control experiments were first performed to verify the Pd(II) catalyst acting as the Lewis acid. Under strictly oxygen-free conditions, the reaction could go smoothly; while the reaction of C3-methylindole **1a** and benzyl-substituted aziridine was examined and no product was observed under the same conditions[14] (Scheme 3a). Using Pd(0) catalysts such as $Pd(PPh_3)_4$ or $Pd_2(dba)_3$, no desired product was observed and the two substrates were recovered quantitatively (Scheme 3b). Furthermore, when the $Pd(PPh_3)_2Cl_2$ or $PdCl_2$ coupled with phosphines or amines ligands were used as the catalysts, the reaction did not proceed probably due to the addition of ligands decreasing the Lewis acidity of palladium by resonance of unpaired electrons to the empty orbit of metal palladium (Scheme 3c).

Three more reactions of enantiopure aziridine in toluene with $Sc(OTf)_3$ or $Pd(PhCN)_2Cl_2$ were investigated, and results are shown in Scheme 4. It can be seen that the ee of (*R*)-**2a** was dropped to 39% with $Sc(OTf)_3$ after 10 min (Scheme 4a), while the racemization was not observed with $Pd(PhCN)_2Cl_2$ as the catalyst (Scheme 4b). Furthermore, in agreement with the above results, $Sc(OTf)_3$-catalyzed [3 + 2] cycloaddition of indole **1a** with chiral aziridine (*S*)-**2a** provided low stereoselectivity (Scheme 4c). These results were probably because of the difference of Lewis acidity between Sc(III) and Pd(II).

Kinetic experiments conducted showed that the reaction with electron-rich substrates, with electron-rich substituents on either the sulfonamides or the 2-aromatic rings, has a large initial reaction rate, as the electron-rich substrate is more liable to coordinate with palladium; thus the reaction is faster (Figure 2).

Based on the above results, a plausible mechanism is proposed. The Pd catalyst coordinated to the aziridine,[14] generating a highly reactive species, which undergoes nucleophilic attack by indoles in an S_N2 fashion to provide stereoinverted iminium ion, followed by cyclization to obtain the desired product (Scheme 5).

CONCLUSIONS

In summary, we have developed a Pd-catalyzed formal [3 + 2] cycloaddition of achiral and chiral aziridines with indoles. The reaction allows for preparation of chiral hexahydropyrrolo[2,3-*b*]indoles in enantiomerically pure forms. Further studies will concentrate on a detailed mechanism as well as extending the synthetic utility of this strategy.

EXPERIMENTAL SECTION

The melting points recorded are uncorrected. Nuclear magnetic resonance spectra were recorded at 400 MHz. All chemical shifts (δ) are given in ppm. Data are reported as follows: chemical shift, integration, multiplicity (s = single, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants (Hz). Ee values were determined by chiral HPLC analysis using Chiral ID-3, Chiral OD-H, or Chiral AD-H connected with Chiral PC-2. The mobile phase was a binary mixture, *n*-hexane/*i*-PrOH. Optical rotations (α) were measured on a polarimeter with a sodium lamp in the given solvent at the indicated concentration (*c*, g/100 mL) and temperature (°C). High resolution mass spectra were recorded under TOF conditions. All solvents were used after redistillation according to standard procedures. All reactions were carried out employing oven-dried glassware. 3-Substituted indoles **1** were prepared according to procedures reported previously.[15] Aziridines **2** were synthesized using reported procedures.[16] Compound **4** is commercially available.

2-(4-Chlorophenyl)-1-tosylaziridine (2b): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.34 (d, *J* = 4.0 Hz, 1H), 2.44 (s, 3H), 2.98 (d, *J* = 7.2 Hz, 1H), 3.74 (dd, *J* = 4.0 Hz, *J* = 7.2 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.25−7.27 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.85 (d, *J* = 8.4 Hz, 2H).

2-(4-Bromophenyl)-1-tosylaziridine (2c): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.34 (d, *J* = 4.4 Hz, 1H), 2.44 (s, 3H), 2.98 (d, *J* = 7.2 Hz, 1H), 3.72 (dd, *J* = 4.4 Hz, *J* = 7.2 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.86 (d, *J* = 8.4 Hz, 2H).

2-(2-Bromophenyl)-1-tosylaziridine (2g): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.27 (d, *J* = 4.4 Hz, 1H), 2.45 (s, 3H), 3.03 (d, *J* = 7.2 Hz, 1H), 3.99 (dd, *J* = 4.4 Hz, *J* = 7.2 Hz, 1H), 7.12−7.22 (m, 3H), 7.36 (d, *J* = 7.6 Hz, 2H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 2H).

1-((4-Methoxyphenyl)sulfonyl)-2-phenylaziridine (2h): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.38 (d, *J* = 4.8 Hz, 1H), 2.96 (d, *J* = 7.6 Hz, 1H), 3.75 (dd, *J* = 4.8 Hz, *J* = 7.6 Hz, 1H), 3.87 (s, 3H), 6.98 (d, *J* = 8.8 Hz, 2H), 7.21−7.23 (m, 2H), 7.26−7.30 (m, 3H), 7.92 (d, *J* = 8.8 Hz, 2H).

1-((4-Bromophenyl)sulfonyl)-2-phenylaziridine (2i): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.43 (d, *J* = 4.4 Hz, 1H), 3.02 (d, *J* = 7.2 Hz, 1H), 3.81 (dd, *J* = 4.4 Hz, *J* = 7.2 Hz, 1H), 7.21−7.23 (m, 2H), 7.30−7.31 (m, 3H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.85 (d, *J* = 8.4 Hz, 2H).

1-((4-Nitrophenyl)sulfonyl)-2-phenylaziridine (2j): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.49 (d, *J* = 4.8 Hz, 1H), 3.10 (d, *J* = 7.2 Hz, 1H), 3.88 (dd, *J* = 4.8 Hz, *J* = 7.2 Hz, 1H), 7.19−7.21 (m, 2H), 7.29−7.31 (m, 3H), 8.17 (d, *J* = 8.4 Hz, 2H), 8.36 (d, *J* = 8.4 Hz, 2H).

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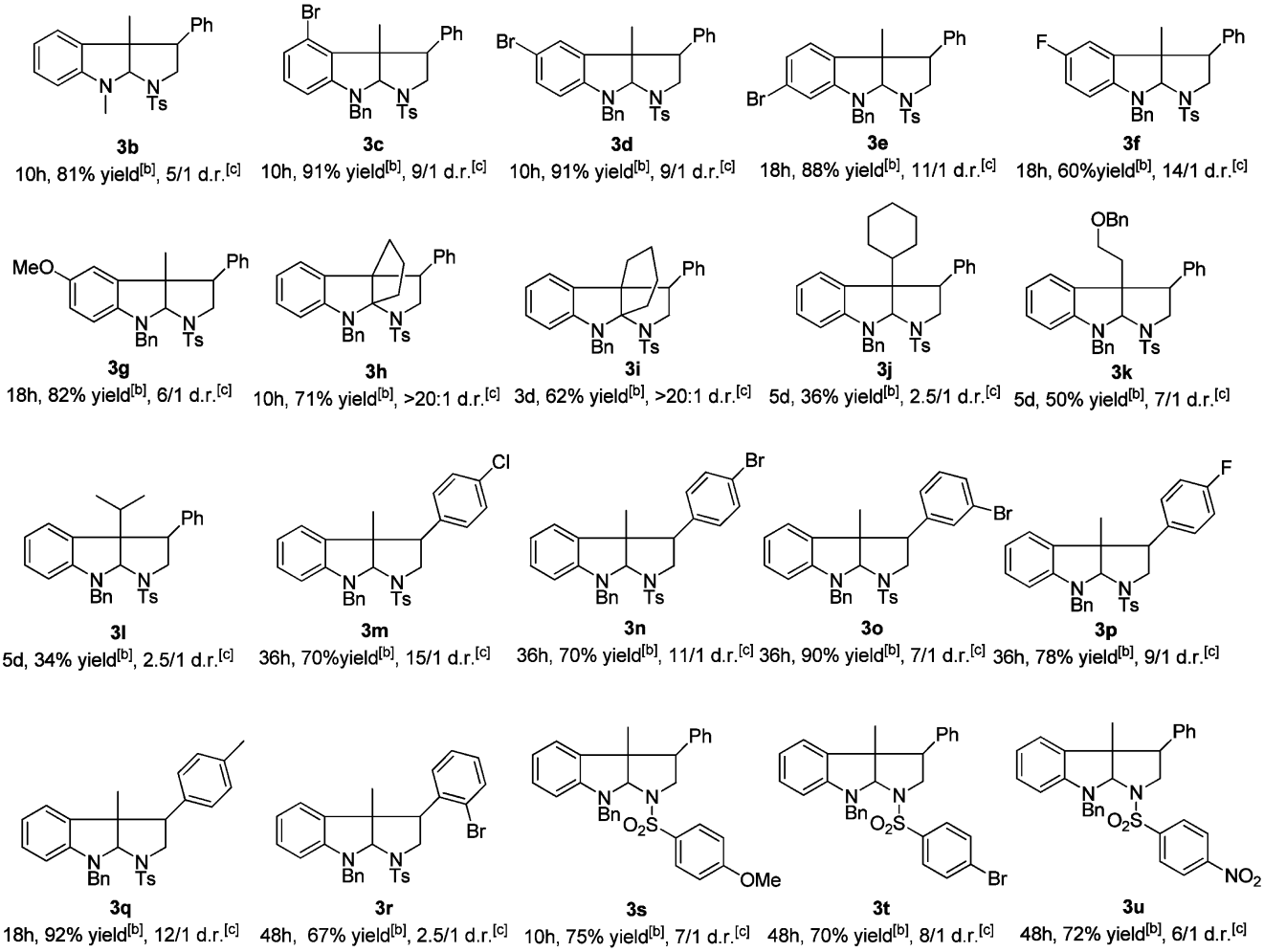
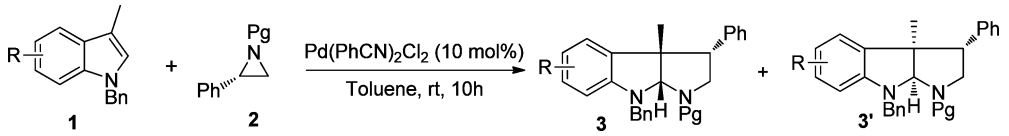
Table 2. Reaction Scope[a]



[a]Reaction conditions: **1a** (0.1 mol), **2a** (0.2 mol), $Pd(PhCN)_2Cl_2$ (10 mol %), toluene (1.0 mL). [b]Yield of the isolated product after column chromatography. [c]Determined by ^1H NMR analysis.

Table 3. Construction of Chiral Hexahydropyrrolo[2,3-*b*]indoles[a]



entry	R	2	products	yield [%][b]	dr[c]	ee [%][d]
1	H	(*S*)-**2a**	(*S*,*S*,*S*)-**3a**	81	9/1	>99/99
2	H	(*R*)-**2a**	(*R*,*R*,*R*)-**3a**	83	9/1	>−99/−99
3	H, *N*-Me	(*S*)-**2a**	(*S*,*S*,*S*)-**3b**	67	5/1	>99/99
4	4-Br	(*S*)-**2a**	(*S*,*S*,*S*)-**3c**	75	8/1	>99/99
5	6-Br	(*S*)-**2a**	(*S*,*S*,*S*)-**3e**	63	9/1	>99/99
6	5-F	(*S*)-**2a**	(*S*,*S*,*S*)-**3f**	65	8/1	>99/99
7	5-OMe	(*S*)-**2a**	(*S*,*S*,*S*)-**3g**	62	6/1	>99/99
8	H	(*S*)-**2h**	(*S*,*S*,*S*)-**3s**	75	7/1	>99/99
9	H	(*S*)-**2i**	(*S*,*S*,*S*)-**3t**	73	7/1	>99/99
10	H	(*S*)-**2j**	(*S*,*S*,*S*)-**3u**	70	6/1	>99/99

[a]Reaction conditions: **1a** (0.1 mol), **2a** (0.2 mol), $Pd(PhCN)_2Cl_2$ (10 mol %), toluene (1.0 mL). [b]Yield of the isolated product after column chromatography. [c]Determined by ^1H NMR analysis. [d]Ee % of **3**/**3′** determined by chiral HPLC analysis.

General Procedure for the [3 + 2] Cycloaddition. To a mixture of 3-substituted indole **1** (0.1 mmol, 1.0 equiv) and $Pd(PhCN)_2Cl_2$ (0.01 mmol, 0.1 equiv) in toluene (1.0 mL) was added aziridine **2** (0.2 mmol, 2.0 equiv) at room temperature. The reaction was monitored

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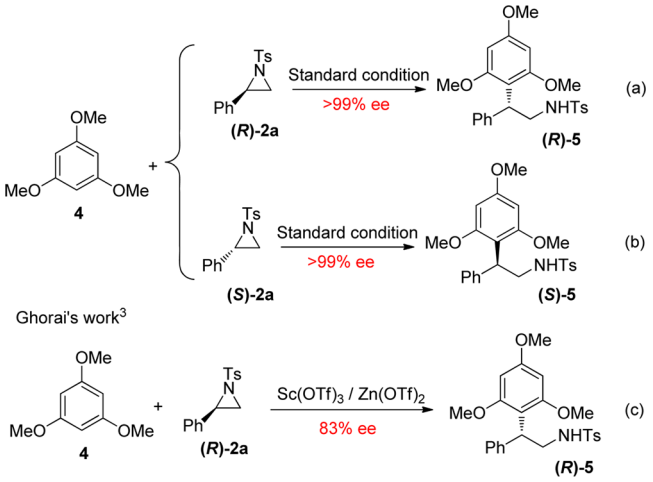
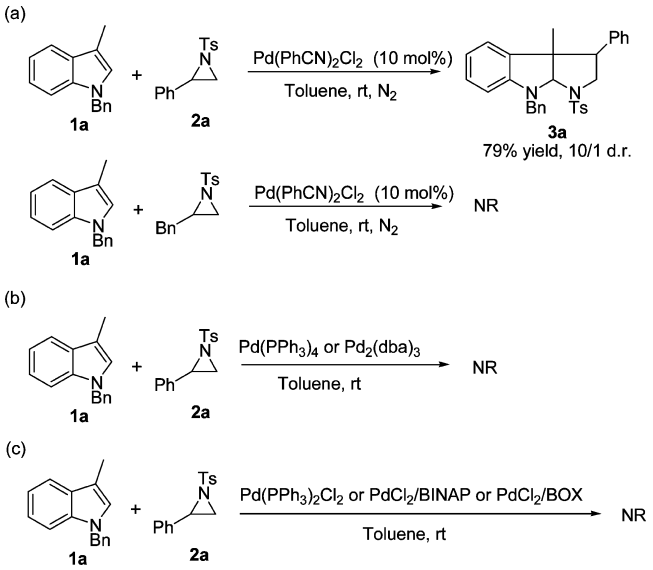
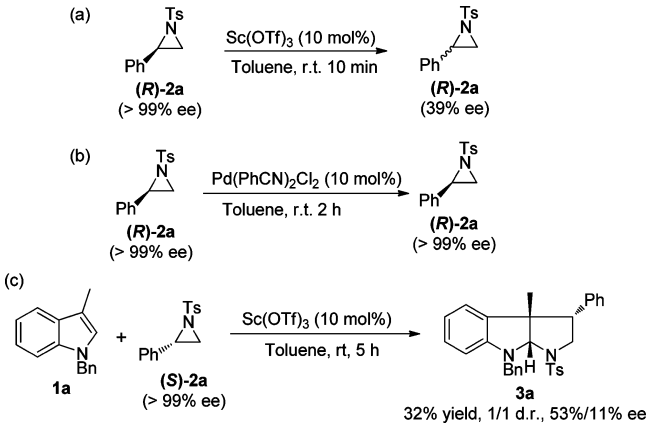
Scheme 2. Stereochemical Study with the Reaction of 1,3,5-Trimethoxybenzene



Scheme 3. Control Experiments



Scheme 4. Racemization Studies and $Sc(OTf)_3$-Catalyzed Reaction of Chiral Aziridine



by TLC analysis. At the end of the reaction, the mixture was quenched with H_2O (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated to afford the corresponding product **3** after flash column chromatography (hexanes/ethyl acetate = 10/1−5/1).

(3*S*,3a*S*,8a*S*)-8-Benzyl-3a-methyl-3-phenyl-1-tosyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (3a): 40 mg, yield 81%; white solid; mp = 98−100 °C; $[\alpha]_D^{26}$ = −52.9 (*c* = 0.9 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.24 (s, 3H), 2.44 (s, 3H), 2.76 (dd, *J* = 6.4 Hz, *J* = 12.8 Hz, 1H), 3.50 (t, *J* = 12.8 Hz, 1H), 3.87−3.92 (m, 1H), 4.70 (AB, J = 16.0 Hz, 2H), 5.48 (s, 1H), 5.56 (d, *J* = 7.2 Hz, 1H), 6.27 (t, *J* = 7.2 Hz, 1H), 6.32 (d, *J* = 8.0 Hz, 1H), 6.84 (d, *J* = 7.2 Hz, 2H), 6.94 (t, *J* = 7.6 Hz, 1H), 7.21−7.34 (m, 10H), 7.73 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.6, 26.4, 48.1, 51.2, 55.4, 56.9, 89.9, 105.4, 116.5, 125.7, 127.0, 127.3, 127.4, 127.6, 128.0, 128.4, 128.5, 128.91, 128.93, 135.8, 137.2, 138.7, 143.8, 150.2 ppm; IR (neat) ν 1603, 1494, 1455, 1349, 1162, 1088, 1036, 960 cm^{-1}; ESI-MS (*m*/*z*) 495 (M + H$^+$); MALDI/DHB calcd for $C_{31}H_{31}N_2O_2S^+$ 495.2101, found 495.2113; dr = 10/1. HPLC-separation conditions: Chiralcel AD-H/PC-2, 25 °C, 254 nm, 90/10 hexane/*i*-PrOH, 1.0 mL/min; trans diastereoisomer, *t* = 23.8 min, >99% ee; cis diastereoisomer, *t* = 22.4 min, >99% ee.

(3*R*,3a*R*,8a*R*)-8-Benzyl-3a-methyl-3-phenyl-1-tosyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (3a): 41 mg, yield 83%; $[\alpha]_D^{25}$ = +29.3 (*c* = 0.7 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.24 (s, 3H), 2.44 (s, 3H), 2.76 (dd, *J* = 6.4 Hz, *J* = 12.8 Hz, 1H), 3.50 (t, *J* = 12.8 Hz, 1H), 3.87−3.92 (m, 1H), 4.70 (AB, *J* = 16.0 Hz, 2H), 5.48 (s, 1H), 5.56 (d, *J* = 7.2 Hz, 1H), 6.27 (t, *J* = 7.2 Hz, 1H), 6.32 (d, *J* = 8.0 Hz, 1H), 6.84 (d, *J* = 7.2 Hz, 2H), 6.94 (t, *J* = 7.6 Hz, 1H), 7.21−7.34 (m, 10H), 7.73 (d, *J* = 8.0 Hz, 2H); ESI-MS (*m*/*z*) 495 (M + H$^+$); trans diastereoisomer, *t* = 20.7 min, >99% ee; cis diastereoisomer, *t* = 25.7 min, >99% ee.

(3*S*,3a*S*,8a*S*)-3a,8-Dimethyl-3-phenyl-1-tosyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (3b): 28 mg, yield 67%; white solid; mp = 110−112 °C; $[\alpha]_D^{26}$ = −10.9 (*c* = 0.35 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.27 (s, 3H), 2.47 (s, 3H), 2.73 (dd, *J* = 6.8 Hz, *J* = 12.8 Hz, 1H), 3.03 (t, *J* = 12.8 Hz, 3H), 3.39 (t, *J* = 12.8 Hz, 1H), 3.72−3.82 (m, 1H), 5.36 (s, 1H), 5.57 (d, *J* = 7.2 Hz, 1H), 6.28 (t, *J* = 7.6 Hz, 1H), 6.36 (d, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 2H), 7.01 (t, *J* = 7.6 Hz, 1H), 7.20−7.26 (m, 3H), 7.34−7.40 (m, 2H), 7.82 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.6, 26.0, 31.3, 51.2, 55.0, 56.7, 91.1, 105.0, 116.4, 125.5, 127.4, 127.5, 128.0, 128.4, 128.6, 128.9, 130.0, 135.8, 137.2, 143.8, 150.9 ppm; IR (neat) ν 1605, 1493, 1453, 1347, 1303, 1162, 1092, 1024, 1001, 957 cm^{-1}; ESI-MS (*m*/*z*) 441 (M + Na$^+$); MALDI/DHB calcd for $C_{25}H_{26}N_2O_2S^+$ 418.1710, found 418.1712; dr = 5/1. HPLC-separation conditions: Chiralcel AD-H/PC-2, 25 °C, 254 nm, 90/10 hexane/*i*-PrOH, 1.0 mL/min; trans diastereoisomer, *t* = 49.2 min, >99% ee; cis diastereoisomer, *t* = 54.2 min, >99% ee.

(3*S*,3a*S*,8a*S*)-8-Benzyl-4-bromo-3a-methyl-3-phenyl-1-tosyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (3c): 43 mg, yield 75%; white solid; mp = 129−131 °C; $[\alpha]_D^{25}$ = +25.2 (*c* = 0.78 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.42 (s, 3H), 2.43 (s, 3H), 3.19 (t, *J* = 8.0 Hz, 1H), 3.61 (dd, *J* = 8.0 Hz, *J* = 12.0 Hz, 1H), 3.96 (dd, *J* = 8.0 Hz, *J* = 12.0 Hz, 1H), 4.63 (AB, *J* = 16.8 Hz, 2H), 5.49 (s, 1H), 6.19 (d, *J* = 8.0 Hz, 1H), 6.48 (d, *J* = 8.0 Hz, 1H), 6.73 (t, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 7.6 Hz, 2H), 7.05 (t, *J* = 7.6 Hz, 2H), 7.12 (t, *J* = 7.2 Hz, 2H), 7.25−7.35 (m, 7H), 7.70 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.6, 25.1, 49.6, 54.7, 57.1, 59.1, 92.3, 105.5, 120.9, 122.3, 127.0, 127.2, 127.4, 127.6, 127.7, 128.6, 129.2, 129.7, 129.9, 130.0, 136.2, 138.1, 138.2, 144.1, 152.2 ppm; IR (neat) ν 1596, 1569, 1495, 1454, 1351, 1304, 1164, 1088, 1024, 963 cm^{-1}; ESI-MS (*m*/*z*) 573 (M + H$^+$); MALDI/DHB calcd for $C_{31}H_{30}N_2O_2SBr^+$ 573.1206, found 573.1202; dr = 8/1. HPLC-separation conditions: Chiralcel ID-3, 25 °C, 214 nm, 80/20 hexane/*i*-PrOH, 0.7 mL/min; trans diastereoisomer, *t* = 8.8 min, >99% ee; cis diastereoisomer, *t* = 10.3 min, >99% ee.

(3*S*,3a*S*,8a*S*)-8-Benzyl-5-bromo-3a-methyl-3-phenyl-1-tosyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (3d): 52 mg, yield 91%; white solid; mp = 143−145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.21 (s, 3H), 2.45 (s, 3H), 2.72 (dd, *J* = 7.0 Hz, *J* = 12.4 Hz, 1H), 3.47 (t, *J* = 12.4 Hz, 1H), 3.84 (dd, *J* = 7.0 Hz, *J* = 12.4 Hz, 1H), 4.66 (AB, *J* = 16.4 Hz, 2H), 5.47 (s, 1H), 5.53 (s, 1H), 6.17 (d, *J* = 8.4 Hz,

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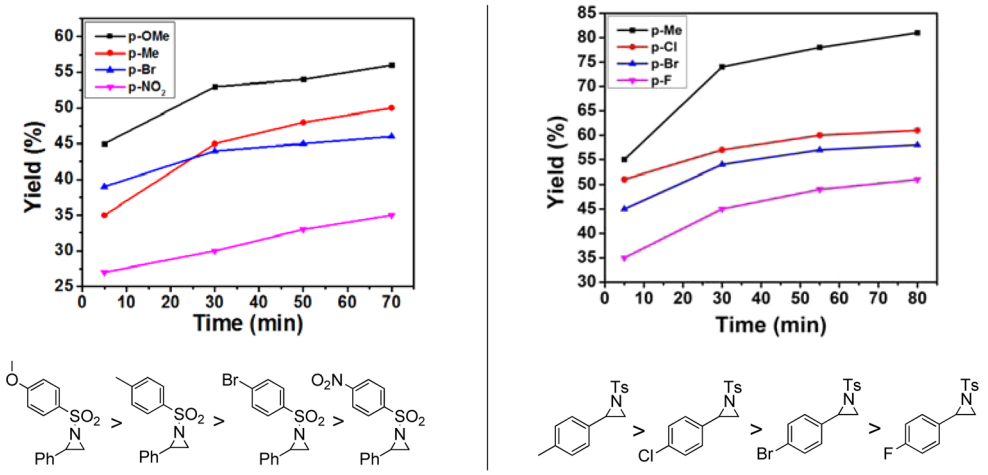
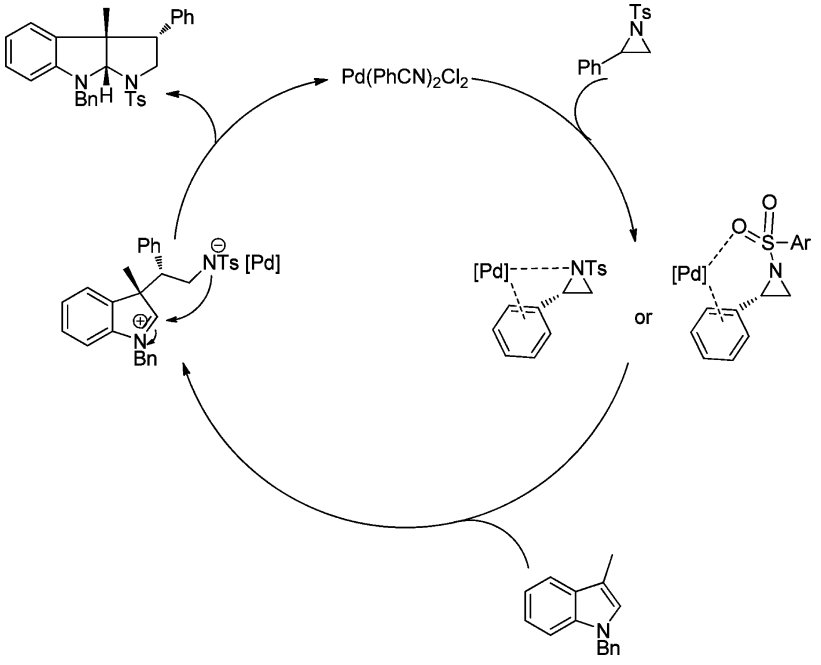


Figure 2. Impacts of sulfonamide and phenyl substituents on ring opening rate.

Scheme 5. A Plausible Mechanism



1H), 6.83 (d, J = 6.4 Hz, 2H), 7.02 (dd, J = 2.0 Hz, J = 8.4 Hz, 1H), 7.25−7.34 (m, 10H), 7.73 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.6, 26.2, 48.1, 51.0, 55.3, 56.9, 89.8, 106.8, 107.9, 127.2, 127.4, 127.9, 128.1, 128.7, 128.8, 130.0, 130.7, 130.9, 135.2, 137.0, 138.1, 144.0, 149.0 ppm; IR (neat) ν 1703, 1599, 1490, 1453, 1345, 1304, 1257, 1160, 1093, 1050, 963 cm^{-1}; ESI-MS (m/z) 573 (M + H$^+$); MALDI/DHB calcd for $C_{31}H_{30}N_2O_2SBr^+$ 573.1206, found 573.1218; dr = 9/1.

(3*S*,3a*S*,8a*S*)-8-Benzyl-6-bromo-3a-methyl-3-phenyl-1-tosyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (3e): 36 mg, yield 63%; white solid; mp = 152−154 °C; $[\alpha]_D^{26}$ = −6.67 (c = 0.22 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.21 (s, 3H), 2.45 (s, 3H), 2.75 (dd, J = 2.8 Hz, J = 12.8 Hz, 1H), 3.47 (t, J = 12.8 Hz, 1H), 3.83 (dd, J = 6.4 Hz, J = 12.8 Hz, 1H), 4.66 (AB, J = 16.4 Hz, 2H), 5.35 (d, J = 7.6 Hz, 1H), 5.47 (s, 1H), 6.38 (d, J = 8.4 Hz, 1H), 6.45 (d, J = 0.8 Hz, 1H), 6.83 (d, J = 6.8 Hz, 2H), 7.22−7.35 (m, 10H), 7.71 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.6, 26.3, 47.8, 51.0, 55.2, 56.5, 89.8, 108.3, 119.3, 122.6, 126.9, 127.18, 127.2, 127.4, 127.7, 128.1, 128.7, 128.8, 130.0, 135.4, 137.0, 137.9, 144.0, 151.4 ppm; IR (neat) ν 1598, 1494, 1453, 1349, 1259, 1162, 1089, 1053, 1035, 961, 899 cm^{-1}; ESI-MS (m/z) 573 (M + H$^+$); MALDI/DHB calcd for $C_{31}H_{30}N_2O_2SBr^+$ 573.1206, found 573.1224; dr = 9/1. HPLC-separation conditions: Chiralcel ID-3, 25 °C, 214 nm, 80/20 hexane/*i*-PrOH, 0.7 mL/min; trans diastereoisomer, t_{major} = 8.1 min, t_{minor} = 7.8 min, >99% ee; cis diastereoisomer, t_{major} = 8.5 min, t_{minor} = 9.0 min, >99% ee.

(3*S*,3a*S*,8a*S*)-8-Benzyl-5-fluoro-3a-methyl-3-phenyl-1-tosyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (3f): 34 mg, yield 65%; white solid; mp = 127−129 °C; $[\alpha]_D^{26}$ = −22.2 (c = 0.42 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.21 (s, 3H), 2.45 (s, 3H), 2.74 (dd, J = 6.4 Hz, J = 12.4 Hz, 1H), 3.48 (t, J = 12.4 Hz, 1H), 3.84 (dd, J = 6.4 Hz, J = 12.4 Hz, 1H), 4.67 (AB, J = 16.4 Hz, 2H), 5.47 (s, 1H), 5.54 (s, 1H), 6.17 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 6.8 Hz, 2H), 7.02 (d, J = 6.8 Hz, 1H), 7.25−7.37 (m, 10H), 7.73 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.6, 26.2, 48.1, 51.0, 55.3, 56.9, 89.8, 106.8, 108.0, 127.1, 127.2, 127.4, 127.9, 128.1, 128.6, 128.7 (J_{C-F} = 207 Hz),128.8 130.0, 130.7, 130.9, 135.2, 137.0, 138.1, 144.0, 149.0 ppm; IR (neat) ν 1598, 1495, 1454, 1348, 1305, 1259, 1212, 1186, 1092, 1035, 960, 911 cm^{-1}; IR (neat) ν 1598, 1492, 1454, 1416, 1349, 1290, 1162, 1089, 1052, 960 cm^{-1}; IR (neat) ν 1699, 1598, 1490, 1454, 1416, 1349, 1262, 1205, 1170, 1090, 1051, 961, 913 cm^{-1}; MALDI/DHB (m/z) 513 (M + H$^+$); MALDI/DHB calcd for

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$C_{31}H_{29}N_2O_2SFNa^+$ 535.1825, found 535.1824; dr = 8/1. HPLC-separation conditions: Chiralcel ID-3, 25 °C, 214 nm, 80/20 hexane/*i*-PrOH, 0.7 mL/min; trans diastereoisomer, *t* = 26.4 min, >99% ee; cis diastereoisomer, *t* = 23.0 min, >99% ee.

(3*S*,3a*S*,8a*S*)-8-Benzyl-5-methoxy-3a-methyl-3-phenyl-1-tosyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (3g): 32 mg, yield 62%; white solid; mp = 61−63 °C; $[\alpha]_D^{26}$ = −22.7 (*c* = 0.67 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.26 (s, 3H), 2.44 (s, 3H), 2.81 (dd, *J* = 6.4 Hz, *J* = 12.4 Hz, 1H), 3.34 (s, 3H), 3.51 (t, *J* = 12.4 Hz 1H), 3.83 (dd, *J* = 6.4 Hz, *J* = 12.4 Hz, 1H), 4.65 (dd, *J* = 16.4 Hz, 2H), 5.19 (dd, *J* = 2.0 Hz, 1H), 5.48 (s, 1H), 6.20 (d, *J* = 8.8 Hz, 1H), 6.51 (dd, *J* = 2.4 Hz, *J* = 8.8 Hz, 1H), 6.88 (d, *J* = 6.0 Hz, 2H), 7.24−7.31 (m, 10H), 7.74 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.6, 26.2, 49.2, 51.0, 55.3, 55.8, 57.0, 90.5, 106.1, 112.4, 114.2, 126.9, 127.3, 127.4, 127.6, 128.1, 128.9, 129.8, 129.9, 135.9, 137.2, 138.9, 143.7, 144.6, 151.6 ppm; IR (neat) ν 1597, 1495, 1454, 1429, 1347, 1262, 1219, 1160, 1093, 1038, 956, 909 cm^{-1}; ESI-MS (*m*/*z*) 525 (M + H$^+$); MALDI/DHB calcd for $C_{32}H_{32}N_2O_3SNa^+$ 547.2026, found 547.2026; dr = 6/1. HPLC-separation conditions: Chiralcel PC-2/AD-H, 25 °C, 254 nm, 90/10 hexane/*i*-PrOH, 1.0 mL/min; trans diastereoisomer, *t* = 38.6 min, >99% ee; cis diastereoisomer, *t* = 22.5 min, >99% ee.

4-Benzyl-9-phenyl-11-tosyl-1,2,3,4-tetrahydro-3a,8b-(epiminoethano)cyclopenta[*b*]indole (3h): 37 mg, yield 71%; white solid; mp = 99−100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.52−1.55 (m, 2H), 1.71−1.75 (m, 1H), 1.91−1.94 (m, 1H), 2.36 (s, 3H), 2.45−2.49 (m, 1H), 2.75−2.79 (m, 1H), 3.45−3.54 (m, 2H), 3.87 (t, *J* = 8.8 Hz, 1H), 4.48 (d, *J* = 16.8 Hz, 1H), 5.40 (d, *J* = 16.8 Hz, 1H), 6.15 (d, *J* = 8.0 Hz, 1H), 6.64 (t, *J* = 7.2 Hz, 1H), 6.83 (d, *J* = 7.2 Hz, 1H), 7.12 (t, *J* = 7.2 Hz, 1H), 7.15−7.27 (m, 4H), 7.32−7.40 (m, 4H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.39 (d, *J* = 7.2 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.5, 26.7, 34.0, 38.0, 49.4, 51.5, 53.5, 70.5, 104.7, 107.0, 117.7, 122.5, 126.5, 126.8, 127.4, 127.7, 128.4, 128.5, 128.7, 129.4, 133.7, 137.1, 137.7, 139.7, 143.5, 150.5 ppm; IR (neat) ν 1703, 1603, 1486, 1464, 1453, 1384, 1324, 1217, 1160, 1088, 1032, 996, 932, 918 cm^{-1}; ESI-MS (*m*/*z*) 521 (M + H$^+$); MALDI/DHB calcd for $C_{33}H_{33}N_2O_2S^+$ 521.2257, found 521.2263; dr > 20/1.

9-Benzyl-12-phenyl-10-tosyl-6,7,8,9-tetrahydro-5*H*-8a,4b-(epiminoethano)carbazole (3i): 33 mg, yield 62%; white solid; mp = 186−188 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.00−1.05 (m, 1H), 1.16−1.21 (m, 1H), 1.41−1.48 (m, 3H), 1.61−1.68 (m, 1H), 2.34 (s, 3H), 3.23 (d, *J* = 14.8 Hz, 1H), 3.71−3.82 (m, 2H), 4.06 (t, *J* = 9.2 Hz, 1H), 4.14 (d, *J* = 16.8 Hz, 1H), 5.28 (d, *J* = 4.0 Hz, 1H), 6.19 (d, *J* = 7.6 Hz, 1H), 6.65−6.71 (m, 2H), 7.00−7.04 (m, 3H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.22−7.35 (m, 7H), 7.67 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 20.7, 21.0, 21.4, 25.2, 28.9, 48.2, 50.4, 51.8, 58.4, 98.7, 108.4, 117.6, 122.2, 126.7, 127.2, 127.9, 128.3, 128.4, 128.8, 129.4, 131.1, 139.6, 143.3, 148.7 ppm; IR (neat) ν 1607, 1495, 1481, 1454, 1338, 1170, 1096, 1065, 1025, 991 cm^{-1}; MALDI/DHB (*m*/*z*) 535 (M + H$^+$); MALDI/DHB calcd for $C_{34}H_{35}N_2O_2S^+$ 535.2414, found 535.2419; dr > 20/1.

8-Benzyl-3a-cyclohexyl-3-phenyl-1-tosyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (3j): 20 mg, yield 36%; white solid; mp = 74−75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.66−1.06 (m, 6H), 1.35−1.73 (m, 5H), 2.42 (s, 3H), 3.44−3.58 (m, 2H), 3.77−3.81 (m, 1H), 4.74 (AB, *J* = 16.8 Hz, 2H), 5.54 (d, *J* = 7.2 Hz, 1H), 5.60 (s, 1H), 6.23−6.31 (m, 2H), 6.84 (d, *J* = 6.8 Hz, 1H), 6.94 (t, *J* = 7.2 Hz, 1H), 7.02−7.33 (m, 1H), 7.19−7.33 (m, 10H), 7.71 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.4, 21.5, 25.6, 25.8, 26.1 26.2, 26.3, 26.5, 26.7, 27.7, 28.1, 28.2, 28.6, 29.7, 41.3, 43.5, 48.4, 48.6, 50.0, 53.8, 54.8, 64.7, 65.0, 68.0, 84.5, 87.3, 105.1, 107.2, 116.1, 117.3, 124.3, 126.3, 126.6, 126.8, 126.9, 127.1, 127.2, 127.3, 127.4, 127.6, 127.8, 128.1, 128.2, 128.3, 128.4, 128.9, 129.2, 129.5, 129.7, 130.9, 136.5, 137.2, 138.2, 138.5, 138.9, 143.0 149.7, 151.1 ppm; IR (neat) ν 1703, 1601, 1488, 1466, 1452, 1402, 1345, 1260, 1203, 1165, 1092, 1051, 928 cm^{-1}; ESI-MS (*m*/*z*) 563 (M + H$^+$); MALDI/DHB calcd for $C_{36}H_{39}N_2O_2S^+$ 563.2727, found 563.2738; dr = 2.5/1.

8-Benzyl-3a-(2-(benzyloxy)ethyl)-3-phenyl-1-tosyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (3k): 31 mg, yield 50%; white solid; mp = 58−60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.65−1.70 (m, 1H), 2.02−2.07 (m, 1H), 2.43 (s, 3H), 2.77 (dd, *J* = 6.4 Hz, *J* = 12.8 Hz, 1H), 3.01−3.03 (m, 2H), 3.46 (t, *J* = 8.8 Hz, 1H), 3.80 (dd, *J* = 6.4 Hz, *J* = 12.8 Hz, 1H), 4.16 (s, 2H), 4.60 (AB, *J* = 16.4 Hz, 2H), 5.48 (d, *J* = 7.2 Hz, 1H), 5.86 (s, 1H), 6.25 (t, *J* = 7.2 Hz, 1H), 6.33 (d, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 7.2 Hz, 2H), 6.96 (t, *J* = 7.6 Hz, 1H), 7.16−7.39 (m, 15H), 7.72 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.6, 39.0, 48.4, 50.2, 55.7, 59.4, 67.2, 87.4, 105.3, 116.3, 125.6, 126.1, 127.0, 127.4, 127.5, 127.6, 127.9, 128.4, 128.5, 128.6, 129.2, 129.9, 135.5, 137.2, 138.3, 143.8, 138.8, 151.0 ppm; IR (neat) ν 1602, 1494, 1454, 1349, 1270, 1162, 1095, 1030, 969, 912 cm^{-1}; MALDI/DHB (*m*/*z*) 637 (M + Na$^+$); MALDI/DHB calcd for $C_{39}H_{38}N_2O_3SNa^+$ 637.2495, found 637.2508; dr = 7/1.

8-Benzyl-3a-isopropyl-3-phenyl-1-tosyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (3l): 18 mg, yield 34%; white solid; mp = 65−66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.52 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H), 1.96−2.00 (m, 1H), 2.42 (s, 3H), 3.37−3.58 (m, 2H), 3.77−3.81 (m, 1H), 4.70 (AB, *J* = 16.4 Hz, 2H), 5.56 (d, *J* = 7.2 Hz, 1H), 5.60 (s, 1H), 6.26−6.31 (m, 2H), 6.87 (d, *J* = 6.8 Hz, 1H), 6.96 (t, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 6.8 Hz, 1H), 7.19−7.63 (m, 10H), 7.71 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 15.0, 15.6, 15.8, 16.2, 18.87, 18.94, 28.2, 30.7, 45.8, 47.2, 48.5, 51.4, 52.3, 62.2, 81.3, 84.9, 102.5, 104.6, 113.6, 114.9, 121.9, 123.7, 123.9, 124.2, 124.5, 124.71, 124.75, 124.8, 125.0, 125.2, 125.7, 125.8, 126.3, 126.6, 126.9, 127.2, 133.8, 134.6, 136.0, 136.8, 141.6, 148.5 ppm; IR (neat) ν 1702, 1602, 1487, 1467, 1454, 1390, 1342, 1261, 1204, 1168, 1092, 1031, 919 cm^{-1}; MALDI/DHB (*m*/*z*) 508 (M + H$^+$); MALDI/DHB calcd for $C_{32}H_{32}N_2O_2S^+$ 508.2166, found 508.2172; dr = 2.5/1.

8-Benzyl-3-(4-chlorophenyl)-3a-methyl-1-tosyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (3m): 37 mg, yield 70%; white solid; mp = 146−148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.22 (s, 3H), 2.44 (s, 3H), 2.78 (dd, *J* = 6.4 Hz, *J* = 12.4 Hz, 1H), 3.42 (t, *J* = 12.4 Hz, 1H), 3.81 (dd, *J* = 6.4 Hz, *J* = 12.4 Hz, 1H), 4.68 (AB, *J* = 16.4 Hz, 2H), 5.49 (s, 1H), 5.64 (d, *J* = 7.2 Hz, 1H), 6.32 (t, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 6.96 (t, *J* = 7.6 Hz, 1H), 7.19−7.34 (m, 9H), 7.72 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.6, 26.4, 48.2, 55.0, 56.9, 89.9, 105.6, 116.7, 125.6, 127.0, 127.3, 127.4, 130.0, 128.2, 128.6, 128.8, 129.9, 130.0, 133.4, 134.4, 137.1, 138.6, 143.9, 150.2 ppm; IR (neat) ν 1603, 1485, 1453, 1349, 1216, 1170, 1091, 1036, 1015, 960, 899 cm^{-1}; ESI-MS (*m*/*z*) 529 (M + H$^+$); MALDI/DHB calcd for $C_{31}H_{30}N_2O_2SCl^+$ 529.1711, found 529.1710; dr = 15/1.

8-Benzyl-3-(4-bromophenyl)-3a-methyl-1-tosyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (3n): 40 mg, yield 70%; white solid; mp = 149−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.22 (s, 3H), 2.44 (s, 3H), 2.76 (dd, *J* = 6.4 Hz, *J* = 12.4 Hz, 1H), 3.42 (t, *J* = 12.4 Hz, 1H), 3.81 (dd, *J* = 6.4 Hz, *J* = 12.4 Hz, 1H), 4.67 (AB, *J* = 16.4 Hz, 2H), 5.49 (s, 1H), 5.65 (d, *J* = 7.2 Hz, 1H), 6.32 (t, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 8.0 Hz, 2H), 6.85 (d, *J* = 8.0 Hz, 2H), 6.96 (t, *J* = 8.0 Hz, 1H), 7.24−7.76 (m, 9H), 7.85 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.6, 26.4, 48.2, 51.2, 55.1, 56.8, 89.9, 105.6, 116.7, 121.5, 125.6, 127.0, 127.3, 127.4, 128.1, 128.57, 128.6, 130.0, 130.7, 131.1, 134.9, 137.1, 138.5, 143.9, 150.2 ppm; IR (neat) ν 1703, 1603, 1489, 1453, 1409, 1349, 1261, 1162, 1090, 1010, 961, 899 cm^{-1}; ESI-MS (*m*/*z*) 573 (M + H$^+$); MALDI/DHB calcd for $C_{31}H_{30}N_2O_2SBr^+$ 573.1206, found 573.1193; dr = 11/1.

8-Benzyl-3-(3-bromophenyl)-3a-methyl-1-tosyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (3o): 51 mg, yield 90%; white solid; mp = 151−153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.24 (s, 3H), 2.45 (s, 3H), 2.77 (dd, *J* = 6.4 Hz, *J* = 12.4 Hz, 1H), 3.43 (t, *J* = 12.4 Hz, 1H), 3.82 (dd, *J* = 6.4 Hz, *J* = 12.4 Hz, 1H), 4.68 (AB, *J* = 16.4 Hz, 2H), 5.49 (s, 1H), 5.64 (d, *J* = 7.2 Hz, 1H), 6.38 (t, *J* = 7.6 Hz, 2H), 6.74 (d, *J* = 8.0 Hz, 1H), 6.91−6.96 (m, 2H), 7.04−7.16 (m, 1H), 7.24−7.41 (m, 8H), 7.72 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.6, 26.4, 48.3, 51.2, 55.3, 57.0, 89.8, 105.7, 116.7, 122.1, 125.6, 127.0, 127.3, 127.4, 127.5, 128.0, 128.6, 128.7, 129.5, 130.0, 130.6, 132.0, 137.1, 138.4, 138.6, 144.0, 150.1 ppm; IR (neat) ν 1702, 1602, 1567, 1493, 1453, 1402, 1348, 1260, 1203, 1170, 1089, 961, 904 cm^{-1}; ESI-MS (*m*/*z*) 573 (M + H$^+$); MALDI/DHB calcd for $C_{31}H_{30}N_2O_2SBr^+$ 573.1206, found 573.1202; dr = 7/1.

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8-Benzyl-3-(4-fluorophenyl)-3a-methyl-1-tosyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (3p): 40 mg, yield 78%; white solid; mp = 131−133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.22 (s, 3H), 1.45 (s, 3H), 2.79 (dd, J = 6.4 Hz, J = 12.4 Hz, 1H), 3.42 (t, J = 12.4 Hz, 1H), 3.82 (dd, J = 6.4 Hz, J = 12.4 Hz, 1H), 4.68 (AB, J = 16.4 Hz, 2H), 5.49 (s, 1H), 5.60 (d, J = 7.6 Hz, 1H), 6.28−6.34 (m, 2H), 6.78−6.81 (m, 2H), 6.90−6.97 (m, 3H), 6.24−6.32 (m, 7H), 7.72 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.6, 26.4, 48.2, 51.4, 54.9, 56.8, 89.8, 105.6, 114.9 (J_{C-F} = 21.4 Hz), 116.6, 125.6, 127.0, 127.3, 127.4, 128.3, 128.5, 128.6, 129.9, 130.4 (J_{C-F} = 7.9 Hz), 131.6, 137.1, 138.6, 143.9, 150.2, 162.3 (J_{C-F} = 245 Hz) ppm; IR (neat) ν 1604, 1512, 1494, 1453, 1349, 1260, 1225, 1163, 1106, 1088, 1059, 1036, 960, 900 cm^{-1}; MALDI/DHB (m/z) 513 (M + H$^+$); MALDI/DHB calcd for $C_{31}H_{30}N_2O_2SF^+$ 513.2007, found 513.2006; dr = 9/1.

8-Benzyl-3a-methyl-3-(p-tolyl)-1-tosyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (3q): 47 mg, yield 92%; white solid; mp = 57−59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.22 (s, 3H), 2.32 (s, 3H), 2.44 (s, 3H), 2.70 (dd, J = 6.8 Hz, J = 12.8 Hz, 1H), 3.46 (t, J = 12.8 Hz, 1H), 3.79 (dd, J = 6.8 Hz, J = 12.8 Hz, 1H), 4.71 (AB, J = 16.4 Hz, 2H), 5.46 (s, 1H), 5.63 (d, J = 7.2 Hz, 1H), 6.27−6.32 (m, 2H), 6.73 (d, J = 7.6 Hz, 2H), 6.94 (d, J = 7.6 Hz, 1H), 7.03−7.10 (m, 3H), 7.74 (d, J = 8.0 Hz, 2H), 7.23−7.34 (m, 6H), 7.72 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.1, 21.6, 26.4, 48.1, 51.3, 55.0, 56.8, 89.9, 105.4, 116.5, 125.8, 126.9, 127.3, 127.4, 128.3, 128.5, 128.7, 129.9, 132.6, 137.2, 138.7, 143.8, 150.2 ppm; IR (neat) ν 1603, 1516, 1494, 1454, 1402, 1348, 1260, 1217, 1185, 1163, 1091, 1036, 960, 900 cm^{-1}; ESI-MS (m/z) 509 (M + H$^+$); MALDI/DHB calcd for $C_{32}H_{33}N_2O_2S^+$ 509.2257, found 509.2262; dr = 12/1.

8-Benzyl-3-(2-bromophenyl)-3a-methyl-1-tosyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (3r): 38 mg, yield 67%; white solid; mp = 63−65 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.22 (s, 3H), 2.45 (s, 3H), 3.40−3.45 (m, 1.4H), 3.57−3.75 (m, 0.3H), 3.75−3.84 (m, 1H), 4.28−4.31 (m, 0.3H), 4.66−4.71 (m, 2H), 5.40 (s, 0.3H), 5.46 (s, 0.7H), 5.85 (d, J = 7.6 Hz, 0.7H), 6.30−6.35 (m, 1.4H), 6.43 (d, J = 8.0 Hz, 0.3H), 6.55 (dd, J = 2.0 Hz, J = 7.2 Hz, 0.7H), 6.72 (t, J = 7.2 Hz, 0.3H), 6.94−7.11 (m, 3H), 7.18−7.27 (m, 3H), 7.32−7.36 (m, 4H), 7.46−7.55 (m, 1.5H), 7.71 (d, J = 8.0 Hz, 0.6H), 7.78 (d, J = 8.0 Hz, 1.4H), 7.78 (d, J = 8.0 Hz, 0.2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 20.6, 21.6, 27.0, 48.2, 50.7, 52.6, 53.8, 57.8, 58.1, 89.5, 90.7, 105.6, 108.3, 116.4, 118.8, 122.9, 125.8, 125.9, 126.4, 127.0, 127.1, 127.2, 127.4, 127.7, 128.0, 128.4, 126.5, 128.6, 128.7, 128.8, 129.6, 130.2, 131.0, 133.0, 133.1, 135.4, 136.9, 138.5, 138.6, 144.0, 150.1 ppm; IR (neat) ν 1651, 1603, 1538, 1494, 1488, 1471, 1455, 1349, 1163, 1091, 1026, 958 cm^{-1}; ESI-MS (m/z) 573 (M + H$^+$); DART Positive calcd for $C_{31}H_{30}N_2O_2BrS^+$ 573.1211, found 573.1196; dr = 2.5/1.

(3*S*,3a*S*,8a*S*)-8-Benzyl-1-((4-methoxyphenyl)sulfonyl)-3a-methyl-3-phenyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (3s): 38 mg, yield 75%; white solid; mp = 69−70 °C; $[\alpha]_D^{26}$ = −39.5 (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.26 (s, 3H), 2.88 (dd, J = 6.4 Hz, J = 12.4 Hz, 1H), 3.49 (t, J = 12.4 Hz, 1H), 3.79−3.87 (m, 4H), 4.70 (AB, J = 16.4 Hz, 2H), 5.47 (s, 1H), 5.57 (d, J = 7.6 Hz, 1H), 6.27 (t, J = 7.6 Hz, 1H), 6.32 (d, J = 8.0 Hz, 1H), 6.85 (d, J = 7.2 Hz, 2H), 6.91−6.96 (m, 3H), 7.21−7.32 (m, 7H), 7.77 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 26.5, 48.2, 51.2, 55.5, 55.7, 56.9, 89.9, 105.4, 114.5, 116.5, 125.7, 127.0, 127.3, 127.6, 128.0, 128.4, 128.5, 128.9, 129.5, 131.8, 135.9, 138.7, 150.2, 163.2 ppm; IR (neat) ν 1597, 1495, 1455, 1348, 1260, 1159, 1095, 1027, 960 cm^{-1}; ESI-MS (m/z) 511 (M + H$^+$); MALDI/DHB calcd for $C_{31}H_{31}N_2O_3S^+$ 511.2050, found 511.2056; dr = 7/1. HPLC-separation conditions: Chiralcel AD-H/PC-2, 25 °C, 254 nm, 90/10 hexane/*i*-PrOH, 1.0 mL/min; trans diastereoisomer, t = 43.9 min, >99% ee; cis diastereoisomer, t = 34.1 min, >99% ee.

(3*S*,3a*S*,8a*S*)-8-Benzyl-1-((4-bromophenyl)sulfonyl)-3a-methyl-3-phenyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (3t): 41 mg, yield 73%; white solid; mp = 68−70 °C; $[\alpha]_D^{26}$ = −31.8 (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.28 (s, 3H), 2.88 (dd, J = 6.4 Hz, J = 12.4 Hz, 1H), 3.49 (t, J = 12.4 Hz, 1H), 3.78−3.83 (m, 1H), 4.68 (AB, J = 16.4 Hz, 2H), 5.49 (s, 1H), 5.59 (d, J = 7.2 Hz, 1H), 6.28−6.35 (m, 2H), 6.87 (d, J = 6.8 Hz, 2H), 6.96 (t, J = 7.2 Hz, 1H), 7.24−7.29 (m, 7H), 7.60−7.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 26.5, 48.5, 51.1, 55.6, 57.0, 90.0, 105.6, 116.8, 125.8, 127.2, 127.7, 127.9, 128.1, 128.4, 128.6, 128.8, 128.9, 132.5, 135.5, 138.5, 139.3, 150.1 ppm; IR (neat) ν 1603, 1574, 1494, 1453, 1389, 1353, 1164, 1087, 1067, 1009, 960 cm^{-1}; ESI-MS (m/z) 559 (M + H$^+$); MALDI/DHB calcd for $C_{30}H_{28}N_2O_2SBr^+$ 559.1049, found 559.1062; dr = 7/1. HPLC-separation conditions: Chiralcel AD-H/PC-2, 25 °C, 254 nm, 90/10 hexane/*i*-PrOH, 1.0 mL/min; trans diastereoisomer, t = 19.0 min, >99% ee; cis diastereoisomer, t = 17.2 min, >99% ee.

(3*S*,3a*S*,8a*S*)-8-benzyl-3a-methyl-1-((4-nitrophenyl)-sulfonyl)-3-phenyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]-indole (3u): 37 mg, yield 70%; white solid; mp = 78−79 °C; $[\alpha]_D^{26}$ = −41.2 (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.31 (s, 3H), 2.99 (dd, J = 6.4 Hz, J = 12.4 Hz, 1H), 3.52 (t, J = 12.4 Hz, 1H), 3.85−3.91 (m, 1H), 4.65 (s, 2H), 5.56 (s, 1H), 5.61 (d, J = 7.6 Hz, 1H), 6.30−6.35 (m, 2H), 6.88 (d, J = 6.8 Hz, 2H), 6.97 (t, J = 7.6 Hz, 2H), 7.23−7.29 (m, 7H), 7.94 (d, J = 8.4 Hz, 2H), 8.26 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 26.6, 49.2, 51.0, 56.0, 57.2, 90.3, 106.0, 117.3, 124.4, 125.8, 127.0, 127.2, 127.8, 128.1, 128.3, 128.6, 128.64, 128.9, 135.2, 138.2, 146.1 150.05, 105.08 ppm; IR (neat) ν 1604, 1531, 1494, 1454, 1401, 1350, 1311, 1261, 1166, 1087, 1055, 1012, 960, 900 cm^{-1}; ESI-MS (m/z) 526 (M + H$^+$); MALDI/DHB calcd for $C_{30}H_{28}N_3O_4S^+$ 526.1795, found 526.1793; dr = 6/1. HPLC-separation conditions: Chiralcel AD-H/PC-2, 25 °C, 254 nm, 90/10 hexane/*i*-PrOH, 1.0 mL/min; trans diastereoisomer, t = 99.9 min, >99% ee; cis diastereoisomer, t = 53.3 min, >99% ee.

4-Methyl-*N*-(2-phenyl-2-(2,4,6-trimethoxyphenyl)ethyl)-benzenesulfonamide (5): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.41 (s, 3H), 3.60 (s, 6H), 3.66−3.73 (m, 2H), 3.78 (s, 3H), 4.41 (t, J = 6.4 Hz, 1H), 4.66 (dd, J = 8.8, 7.2 Hz, 1H), 6.05 (s, 2H), 7.09−7.29 (m, 5H), 7.24 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H). HPLC-separation conditions: Chiralcel OD-H, 25 °C, 254 nm, 90/10 hexane/*i*-PrOH, 1.0 mL/min; For (*S*)-**5**: t = 27.9 min, >99% ee, (*R*)-**5**: t = 31.9 min, >99% ee.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01931.

3c (CIF)

^{1}H and ^{13}C NMR spectra and HPLC traces (PDF)

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Notes

The authors declare no competing financial interest.

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