

Chapter 2

Construction of 2-(Aminomethyl)indoles Through Copper-Catalyzed Domino Three-Component Coupling and Cyclization

2.1 Introduction

As described in preface, the author found that the reaction of *N*-tosylated 2-ethynylaniline **1a** with paraformaldehyde **2a** and diisopropylamine **3a** in dioxane in the presence of copper(I) bromide afforded a 2-(aminomethyl)indole derivative **7a** in 92% yield (Scheme 1). This reaction can be rationalized by Mannich-type MCR followed by indole formation through intramolecular hydroamination toward the activated alkyne moiety of a plausible intermediate **6**. Actually, the reaction of the identically prepared propargyl amine **8** with CuBr (5 mol.%) gave the expected indole **7b** in quantitative yield (Scheme 2).

To improve the original reaction conditions using a stoichiometric amount of CuBr and 3 equiv of (*i*-Pr)₂NH (Scheme 1), the initial attempt was made by reacting with *N*-tosyl-2-ethynylaniline **1a**, paraformaldehyde **2a** (2 equiv), piperidine **3b** (1.1 equiv), and CuBr (100 mol.%) in the presence of Et₃N (2 equiv) which would decrease the loading of piperidine (Table 1, entry 1).¹ The reaction proceeded rapidly to give the desired 2-(aminomethyl)indole **7b** in 71% yield. While use of a catalytic amount of CuBr (10 or 1 mol.%) with respect to **1a** increased the yield of **7b** (entries 2 and 3), the reaction without CuBr led to the recovery of **1a**. The reaction in the absence of Et₃N also showed efficient conversion into **7b** (entry 4). This result can be explained by the plausible reaction mechanism depicted in Scheme 1, in which the sulfonamide proton is presumably transferred to the 3-position of indole. This step could be mediated by piperidine or the basic substituent in the product and/or intermediate. The decreased use of **2a** also produced the desired indole **7b**, although a prolonged reaction time (1–12 h) was necessary (entries 5 and 6). Use of CuBr₂, CuCl, or CuI as the catalyst was also tolerated in this three-component indole formation (entries 7–9).

¹ The author considered decreasing of the amount of amine component is important and economical especially when using more valuable amines such as **11** (Scheme 4).

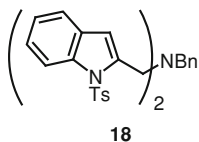
2.1.1 Synthesis of 2-(Aminomethyl)indoles Using Several Amines and Aldehydes

Next, the author examined the scope of the 2-(aminomethyl)indole formation with various symmetrical secondary amines (Table 2) under the optimized conditions (Table 1, entry 4). The reaction of 2-ethynylaniline **1a** with bulky diisopropylamine **3a** (1.1 equiv) and paraformaldehyde **2a** (2 equiv) in the presence of CuBr (1 mol.%) gave the expected indole derivatives **7a** in 81% yield (entry 1). Pyrrolidine **3c** also showed efficient conversion into the corresponding indoles **7c** (entry 3). The use of volatile diethylamine **3d** successfully afforded **7d**, although 2 equiv of Et₂NH were needed (entry 4). Secondary amines containing removable allyl and benzyl groups **3e** and **3f**, respectively, were also acceptable as amine components when the reactions were conducted with a prolonged reaction time (entries 5 and 6).²

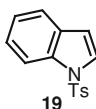
The author also investigated the three-component synthesis of 2-(aminomethyl)indoles using various aldehyde components (Table 3). The reaction of 2-ethynylaniline **1a** with butanal **2b** and piperidine **3b** in the presence of CuBr efficiently gave the indole **7g** bearing a branched substituent in an excellent yield (quant., entry 1). The bulky *i*-butyraldehyde **2c** required an elevated reaction temperature and prolonged reaction time leading to a slightly decreased yield of **7h** (77%, entry 2). Benzaldehyde **2d** was tolerated for this indole formation (entry 3). Similarly, use of a variety of substituted aryl aldehydes afforded the desired indoles **7j–7l** in good yields (entries 4–6).³

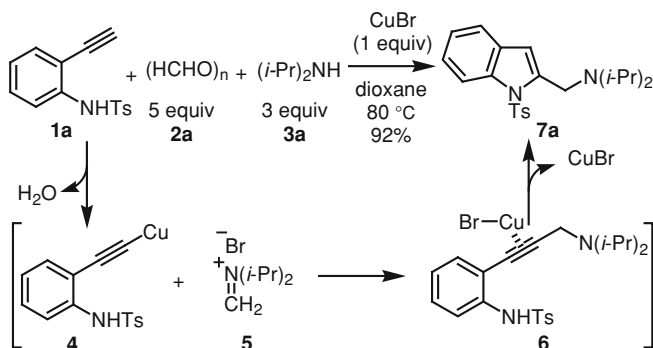
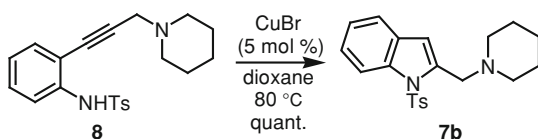
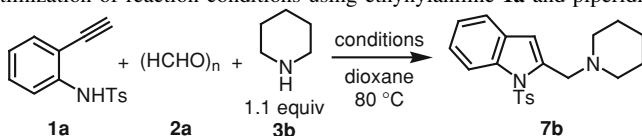
The author expected that a reaction with a chiral ligand which coordinates to a copper atom could produce optically active 2-(aminomethyl)indoles. Knochel recently developed a novel asymmetric synthesis of chiral propargylamines with excellent ee values through a copper-catalyzed asymmetric Mannich-type reaction of alkynes with an aldehyde and a secondary amine using QUINAP as a chiral ligand (up to 98% ee) [1–3]. Carreira reported the similar synthesis of propargylic amine in up to 99% ee with PINAP [4, 5]. The author initially examined the

² When benzylamine was used instead of a secondary amine, dimeric compound **18** was produced in 82% yield (100 °C, 3 h, then reflux, 1 h).



³ When acetone was used instead of an aldehyde, Mannich-type reaction did not proceed and compound **19** was produced.



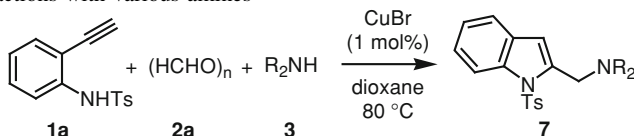
**Scheme 1** Domino three-component coupling-cyclization**Scheme 2** Indole formation from the proposed intermediate **8****Table 1** Optimization of reaction conditions using ethynylaniline **1a** and piperidine **3b**

Entry	CuX (mol.%)	(HCHO) _n (equiv)	Additive (equiv)	Time (h)	Yield ^a (%)
1	CuBr (100)	2.0	Et ₃ N (2)	0.25	71
2	CuBr (10)	2.0	Et ₃ N (2)	0.25	84
3 ^b	CuBr (1)	2.0	Et ₃ N (2)	0.25	92
4	CuBr (1)	2.0	–	0.25	87
5	CuBr (1)	1.5	–	1	75
6	CuBr (1)	1.1	–	12	70
7	CuBr ₂ (1)	2.0	–	0.25	79
8	CuCl (1)	2.0	–	0.25	87
9	CuI (1)	2.0	–	0.25	83

Unless otherwise stated, reaction was carried out with **1a** (0.18 mmol, 1 equiv), **2a** (equiv shown), **3b** (1.1 equiv), and a copper salt (catalyst amount shown) in 1,4-dioxane (3 mL) at 80 °C

^a Yields of isolated products. ^b The reaction was conducted on 1.25 mmol scale

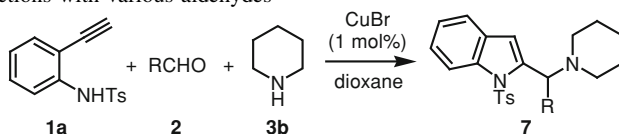
asymmetric three-component construction of the 2-(aminomethyl)indole motif with *n*-butyraldehyde **2b** in dioxane in the presence of CuBr (5 mol.%) and QUINAP (5.5 mol.%) (Table 4). The reaction proceeded smoothly even at rt to give the desired **7g** in a quantitative yield but with only 47% ee (entry 1). It was reported that the copper-catalyzed Mannich reaction of alkynes in the presence of (*R*)-QUINAP gave (*S*)-propargylamines, while the reaction with (*S*)-PINAP gave

Table 2 Reactions with various amines

Entry	Amine 3	Time (h)	Product	Yield (%) ^b
1	(<i>i</i> -Pr) ₂ NH (3a)	0.25	7a	81
2	Piperidine (3b)	0.25	7b	87
3	Pyrrolidine (3c)	0.25	7c	89
4	Et ₂ NH (3d) ^a	0.25	7d	89
5	(allyl) ₂ NH (3e)	0.5	7e	78
6	Bn ₂ NH (3f)	2	7f	78

Unless otherwise stated, reactions were carried out with **1a** (0.18 mmol), **2a** (2.0 equiv), **3** (1.1 equiv), and CuBr (1 mol.%) in 1,4-dioxane (3 mL) at 80 °C

^a 2 equiv of **3d** were used, ^b yields of isolated products

Table 3 Reactions with various aldehydes

Entry	Aldehyde 2	Conditions	Product yield (%) ^a
1	<i>n</i> -PrCHO (2b)	80 °C 0.25 h	7g (R = <i>n</i> -Pr) quant.
2	<i>i</i> -PrCHO (2c)	Reflux 3 h	7h (R = <i>i</i> -Pr) 77
3	PhCHO (2d)	Reflux 10 h	7i (R = Ph) 70
4	(4-CO ₂ Me)C ₆ H ₄ CHO (2e)	Reflux 3 h	7j [R = (4-CO ₂ Me)C ₆ H ₄] 76
5	(4-Me)C ₆ H ₄ CHO (2f)	Reflux 3 h	7k [R = (4-Me)C ₆ H ₄] 85
6	(2-Br)C ₆ H ₄ CHO (2g)	Reflux 4 h	7l [R = (2-Br)C ₆ H ₄] 65

Reactions were carried out with **1a** (0.18 mmol), **2** (2.0 equiv), **3b** (1.1 equiv), and CuBr (1 mol.%) in 1,4-dioxane (1.5 mL) at 80 °C

^a Yields of isolated products

the corresponding (*R*)-isomers, see Refs. 1–5. Screening of the reaction solvent did not improve the asymmetric induction (entries 2–4). When the reaction was carried out with PINAP in dioxane, **7g** was obtained with a slightly higher ee (59%, ee, entry 5). Use of PINAP in benzene gave the most promising result (63% ee), although a prolonged reaction time was necessary (entry 7). These results suggest that 2-ethynylaniline **1a** is a less effective alkyne component for an asymmetric Mannich reaction. Knochel and Carreira reported that phenylacetylene is a good component for enantioselective synthesis of propargylic amine using QUINAP or PINAP, see Refs. 1–5.

Table 4 Asymmetric synthesis of 2-(aminomethyl)indoles

$\text{1a} + \text{2b} + \text{3b} \xrightarrow[\text{solvent}]{\text{CuBr, ligand}}$ **7g**

Entry	Ligand	Solvent	Conditions	Yield ^a (%)	Product (% ee) ^b
1	(<i>R</i>)-QUINAP	Dioxane	rt, 24 h	quant.	(+)- 7g (47)
2	(<i>R</i>)-QUINAP	THF	rt, 72 h	86	(+)- 7g (30)
3	(<i>R</i>)-QUINAP	benzene	rt, 72 h	86	(+)- 7g (43)
4	(<i>R</i>)-QUINAP	Toluene	rt, 72 h	94	(+)- 7g (22)
5	(<i>S</i>)-PINAP	Dioxane	rt, 10 h	quant.	(-)- 7g (59)
6	(<i>S</i>)-PINAP	Toluene	rt, 120 h	93	(-)- 7g (56)
7	(<i>S</i>)-PINAP	Benzene	rt, 120 h	quant.	(-)- 7g (63)

$(R)\text{-QUINAP}$ $(S)\text{-PINAP}$

Reactions were carried out with **1a**, CuBr (5 mol.%), ligand (5.5 mol.%) in solvent (2 mL)

^a Yields of isolated products, ^b determined by chiral HPLC (CHIRALCEL OD-H)

2.1.2 Synthesis of Substituted 2-(Aminomethyl)indoles Using Various Ethynylanilines and Secondary Amines

Various substituted 2-ethynylanilines and asymmetrical secondary amines were then applied to the domino three-component coupling–cyclization (Table 5). 2-Ethynylanilines **1b** and **1c** substituted by electron-withdrawing trifluoromethyl or methoxycarbonyl group at the para position to the amino group were reacted with paraformaldehyde **2a** and dibenzylamine **3f** in the presence of CuBr (1 mol.%) to yield indoles **7m** (90% yield) and **7n** (91% yield), respectively (entries 1 and 2). Ethynylaniline **1d** bearing an electron-donating methyl group at the para position to the amino group also showed efficient compatibility leading to the corresponding indole **7o**. The reaction using 2-ethynylanilines **1e** and **1f** containing an electron-withdrawing group such as a trifluoromethyl or methoxycarbonyl group at the meta position were similarly converted into the corresponding indoles **7p** (61% yield) and **7q** (79% yield), respectively (entries 4, 5). The asymmetrical 2-bromoallylamine **3g** and 2-bromobenzylamine **3h** were also applicable to this indole formation using various 2-ethynylanilines (entries 6–11), although Et₃N was necessary for the cyclization step when using 2-ethynylanilines **1a** and **1d**.

2.1.3 Construction of Polycyclic Indoles by Palladium-Catalyzed C–H Functionalization

A polycyclic indole motif is an important core framework which is widely found in biologically active compounds. For biologically active polycyclic indoles having a 2-(aminomethyl) moiety, see [6–10]. Therefore, development of a convenient and reliable method for the construction of these frameworks is strongly required. For recent synthesis of polycyclic indoles, see [11–13]. The author expected that the present synthesis of 2-(aminomethyl)indoles via domino three-component coupling–cyclization would bring about an extremely useful synthetic route to this class of compounds. Thus, the author surveyed the construction of polycyclic indole skeletons by three-component indole formation followed by palladium-catalyzed C–H functionalization at the C-3 position of indoles. First, 2-(aminomethyl)indole **7r** synthesized by the three-component indole formation (Table 5, entry 6) was subjected to Pd(OAc)₂ (10 mol.%), PPh₃ (20 mol.%), and CsOAc (2 equiv) in DMF (Table 6, entry 1). The reaction proceeded cleanly to afford tetrahydropyridine-fused indole **9a** in 47% yield. When DMA was used as the reaction solvent, a higher yield of **9a** was observed (65%, entry 2). Further investigation of the palladium catalyst, ligand, and base (entries 3–5) revealed that the conditions shown in entry 2 were most effective.

Encouraged by this result, the author investigated the reaction with several 2-(aminomethyl)indoles containing an electron-withdrawing and -donating group to obtain variously substituted tetrahydropyridine-fused indoles **9b–f** in moderate to good yields (Table 7).

The author next examined construction of polycyclic indoles by palladium-catalyzed C–H arylation using 2-(aminomethyl)indole **7x**, which was prepared from ethynylaniline **1a** and amine **3h** (Table 5, entry 11). By treatment with 20 mol.% of Pd(OAc)₂ and 40 mol.% of PPh₃, dihydrobenzazepine-fused indole **10** was efficiently obtained in 80% yield over 2 steps (Scheme 3). One-pot three-component indole formation/Pd-catalyzed C–H arylation also provided polycyclic indole **10** in 84% yield from **1a**.

2.1.4 Synthetic Application to Calindol, Benzo[e][1,2]thiazines, and Indene

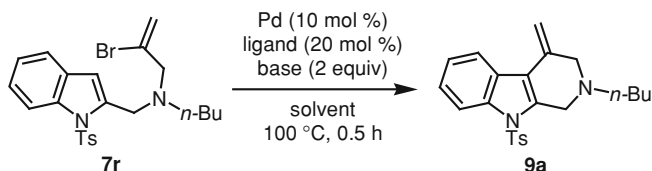
Calindol (**13**), which contains a 2-(aminomethyl)indole motif, is a positive modulator of the human Ca²⁺ receptor showing a calcimimetic activity [1–3]. This compound could be easily synthesized using this domino three-component indole formation (Scheme 4). As the author expected, the reaction of 2-ethynylaniline **1a** with paraformaldehyde **2a** and 1-(1-naphthyl)ethylamine **11** in presence of CuBr directly produced a protected calindol **12**. The allyl and tosyl groups on the nitrogen atoms of **12** were easily removed by successive treatment with Pd(PPh₃)₄ (2 mol.%)/NDMBA and TBAF [14] to give calindol **13** in 90% yield over 2 steps.

Table 5 Synthesis of variously substituted 2-(aminomethyl)indoles

Entry	2-ethynylaniline	Amine	Conditions	Product (yield ^c)
1	1b (R = CF ₃)	3f	80 °C, 3 h	7m (R = CF ₃ , 90%)
2	1c (R = CO ₂ Me)		80 °C, 5 h	7n (R = CO ₂ Me, 91%)
3	1d (R = Me)		80 °C, 5 h, then reflux, 1 h	7o (R = Me, 78 %)
4	1e (R = CF ₃)		80 °C, 3 h	7p (R = CF ₃ , 61%)
5	1f (R = CO ₂ Me)		80 °C, 5 h	7q (R = CO ₂ Me, 79%)
6 ^a	1a (R = H)	3g	80 °C, 3 h, then reflux, ^b 1 h	7r (R = H, 98%)
7 ^a	1b (R = CF ₃)		80 °C, 3 h	7s (R = CF ₃ , 91%)
8 ^a	1c (R = CO ₂ Me)		80 °C, 3 h	7t (R = CO ₂ Me, 98%)
9 ^a	1d (R = Me)		80 °C, 3 h, then reflux, ^b 3 h	7u (R = Me, 98%)
10 ^a	1e (R = CF ₃)	3g	80 °C, 3 h, then reflux, 1 h	7v (R = CF ₃ , 94%)
11 ^a	1f (R = CO ₂ Me)		80 °C, 3 h, then reflux, 1.5 h	7w (R = CO ₂ Me, 99%)
12	1a	3h	80 °C, 3 h, then reflux, 1 h	7x (80%)

Unless otherwise stated, reactions were carried out with **1** (0.18 mmol), **2a** (2.0 equiv), **3** (1.1 equiv), and CuBr (1 mol.%) in 1,4-dioxane (3 mL) ^a 0.37 mmol scale, ^b 4 equiv of Et₃N were added before reflux, ^c yields of isolated products

The author next envisioned the preparation of benzothiazine-1,1-dioxide derivatives **15** through domino MCR and cyclization. Since benzo[e][1,2]thiazine-1,1-dioxides are widely found in biologically active compounds including non-steroidal anti-inflammatory drugs (NSAIDs) [15–22], various approaches to construct this structure have been reported [23–33]. The author expected that the use of such a sulfonamide as **14**, an aldehyde, and a secondary amine in the presence of a copper catalyst would bring about a Mannich-type reaction followed by 6-*endo-dig* cyclization (related synthesis of thiazines has been already reported, see [34, 35]) to afford a benzo[e][1,2]thiazine **15**. The reaction of *N*-methyl and *N*-ethylsulfonamides **14a** and **14b** under standard conditions gave the desired benzothiazines **15a** and **15b**, respectively, but in low yields (34 and 37%, respectively, entries 1 and 2, Table 8). Considering that acidity of the amide proton in **14a** and

Table 6 Palladium-catalyzed C–H olefination

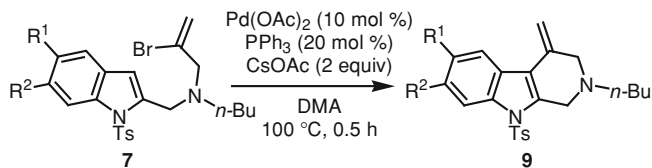
Entry	Catalyst	Ligand	Base	Solvent	Yield (%) ^a
1	Pd(OAc) ₂	PPh ₃	CsOAc	DMF	47
2	Pd(OAc) ₂	PPh ₃	CsOAc	DMA	65
3	Pd(PPh ₃) ₄	–	CsOAc	DMA	7
4	Pd(OAc) ₂	PPh ₃	KOAc	DMA	35
5	Pd(OAc) ₂	dppm	CsOAc	DMA	32

Reactions were carried out with 2-(aminomethyl)indole **7r**, palladium catalyst (10 mol.%), ligand (20 mol.%), and base (2 equiv) in solvent (2 mL) at 100 °C for 0.5 h

^a Yields of isolated products

14b would be insufficient for the cyclization step, the author next examined the reaction of sulfonanilide derivatives bearing a related structure to 2-ethynylanilines **1**. As the author expected, the reaction of sulfonanilide **14c** gave the benzothiazine **15c** in high yield (90%, entry 3). Other sulfonanilides **14d–14f** were also good reactants in this three-component thiazine synthesis (entries 4–6).

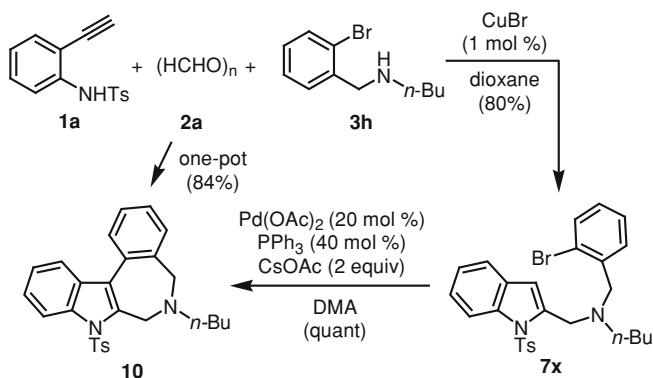
Finally, the author investigated the synthesis of 2-(aminomethyl)indene-1,1-dicarboxylate **17** using this domino Mannich-type reaction/cyclization strategy (Table 9). Disappointingly, the reaction of malonate derivative **16** with (HCHO)_n **2a** and (*i*-Pr)₂NH **3a** in dioxane in the presence of CuBr (5 mol.%) did not afford

Table 7 Palladium-catalyzed C–H olefination

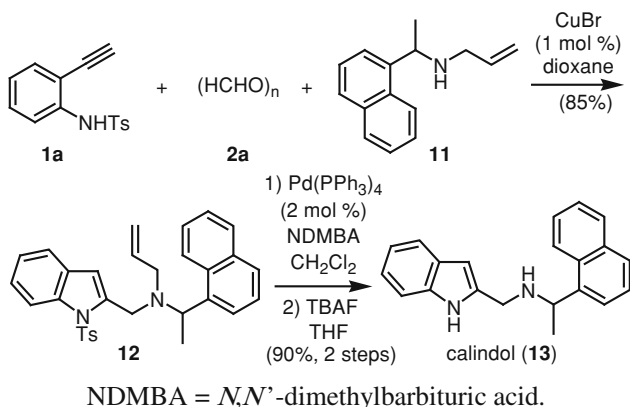
Entry	R ¹	R ²	Indole	Product	Yield (%) ^a
1	CF ₃	H	7s	9b	64
2	CO ₂ Me	H	7t	9c	54
3	CH ₃	H	7u	9d	62
4	H	CF ₃	7v	9e	62
5	H	CO ₂ Me	7w	9f	77

Reactions were carried out with 2-(aminomethyl)indole **7**, Pd(OAc)₂ (10 mol.%), PPh₃ (20 mol.%), and CsOAc (2 equiv) in DMA (2 mL) at 100 °C for 0.5 h

^a Yields of isolated products



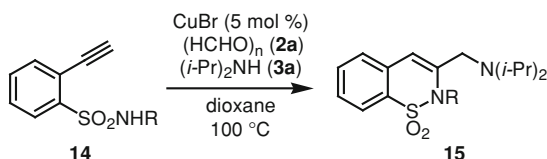
Scheme 3 Palladium-catalyzed C–H arylation and one-pot formation of polycyclic indoles from ethynylaniline



Scheme 4 Synthesis of calindol

the desired indene **17**, only to give the Mannich adduct in 90% yield (entry 1). A careful evaluation of the reaction conditions revealed that the use of more polar DMF as the solvent converted **16** into the desired 2-(aminomethyl)indene **17** in 39% yield. Addition of $(i\text{-Pr})_2\text{NEt}$ after completion of the Mannich reaction efficiently promoted the indene formation leading to **17** in 70% yield.

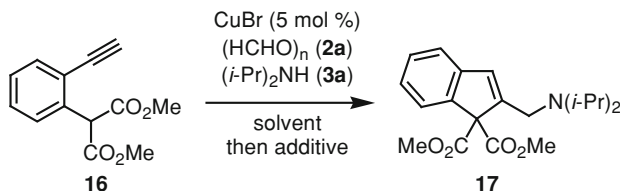
In conclusion, the author has developed a novel synthesis of 2-(aminomethyl)indoles through a copper-catalyzed domino three-component coupling–cyclization. This domino reaction forming two carbon–nitrogen bonds and one carbon–carbon bond is the first catalytic multi-component indole construction producing water as the only theoretical waste. The use of the chiral ligand PINAP in the reaction with alkyl aldehydes produced the corresponding indole bearing a

Table 8 Synthesis of benzo[*e*][1,2]thiazine-1,1-dioxide motif by three-component coupling and cyclization

Entry	R	Time (h)	Product	Yield (%) ^a
1	Me (14a)	16	15a	34
2	Et (14b)	22	15b	37
3	(4-CH ₃)C ₆ H ₄ (14c)	3.5	15c	90
4	Ph (14d)	4	15d	92
5	(4-MeO)C ₆ H ₄ (14e)	3.5	15e	89
6	(4-Cl)C ₆ H ₄ (14f)	3	15f	95

Reactions were carried out with **2a** (2.0 equiv) and **3a** (1.2 equiv) in the presence of CuBr (5 mol.%) in 1,4-dioxane (3 mL) at 100 °C

^a Yields of isolated products

Table 9 Synthesis of 2-(aminomethyl)indene **17**

Entry	Solvent	Additive ^a	Temperature (°C)	Time (h)	Yield (%) ^b
1	Dioxane	—	80	2	0
2	DMF	—	150	5	39
3	DMF	(<i>i</i> -Pr) ₂ NEt	110	10	70

Reactions were carried out with **2a** (2.0 equiv) and **3a** (1.2 equiv) in solvent (2 mL) in the presence of CuBr (5 mol.%)

^a Added after completion of the Mannich-type reaction (ca. 30 min, monitored by TLC), ^b yields of isolated products

branched substituent **7g** with moderate ee values. This reaction is synthetically useful for diversity-oriented synthesis of not only 2-(aminomethyl)indoles but also tetrahydropyridine- and benzazepine-fused indoles, using readily available reaction components. The benzo[*e*][1,2]thiazine and indene motif could also be constructed using a similar domino three-component coupling and cyclization strategy.

2.2 Experimental Section

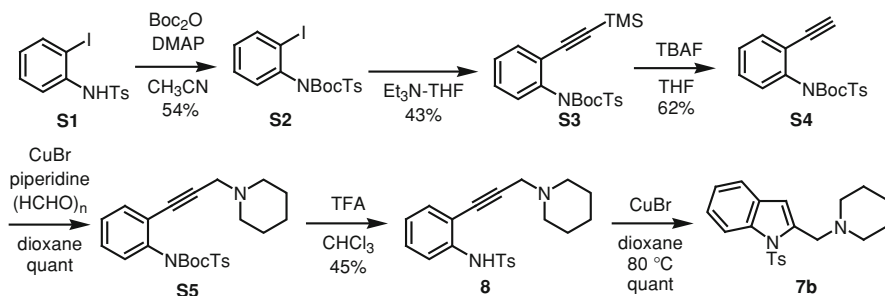
2.2.1 General Methods

^1H NMR spectra were recorded at 400 or 500 MHz frequency, respectively. Chemical shifts are reported in δ (ppm) relative to Me_4Si (in CDCl_3) as internal standard. ^{13}C NMR spectra were referenced to the residual CHCl_3 signal. Melting points were measured by a hot stage melting points apparatus (uncorrected). COSY spectra (for confirmation of the NMR peak assignments) were recorded at 500 MHz frequency.

The compound **1a** [see footnote 1, 36], **S1** [see footnote 2, 37], and **S12** [see footnote 3, 38], were synthesized according to the literature.

The compounds **S7a–e**, **S9**, and **S10a, b** are commercially available.

The compounds **S7a** [39], **S7b** [40], **S7c** [41], **S7d** [42], **S9d** [43], and **S12** [44] are known.



2.2.1.1 *N*-(*tert*-Butoxycarbonyl)-2-iodo-*N*-tosylaniline (**S2**)

To a stirred solution of **S1** (0.82 g, 2.19 mmol), DMAP (54.0 mg, 0.44 mmol) in acetonitrile (9 mL) was added Boc_2O (0.72 g, 3.29 mmol) at rt under argon, and the reaction mixture was stirred for 0.5 h at this temperature. The reaction mixture was stirred at 80 °C for 15 h. After concentration under reduced pressure, the residue was extracted with Et_2O . The extract was washed successively with aqueous saturated NaHCO_3 and brine, and dried over MgSO_4 . The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography over alumina with hexane– EtOAc (3:1) to give **S2** (561 mg, 54%) as a colorless solid which was recrystallized from hexane– CHCl_3 to give pure **S2** as colorless crystals: mp 113 °C; IR (neat) cm^{-1} 1734 (C=O); ^1H NMR (500 MHz, CDCl_3) δ 1.38 (s, 9H, $\text{C}(\text{CH}_3)_3$), 2.46 (s, 3H, ArCH_3), 7.08–7.11 (m, 1H, Ar), 7.34–7.37 (m, 3H, Ar), 7.39–7.43 (m, 1H, Ar), 7.91 (dd, $J = 8.0, 1.7$ Hz, 1H, Ar), 8.01 (d, $J = 8.6$ Hz, 2H, Ar); ^{13}C NMR (125 MHz, CDCl_3) δ 21.7, 27.9 (3C), 84.6, 101.1, 129.0, 129.2 (2C), 129.5 (2C), 130.3, 130.8, 136.6, 139.6, 139.9, 144.8, 149.7. Anal. Calcd for $\text{C}_{18}\text{H}_{20}\text{INO}_4\text{S}$: C, 45.68; H, 4.26; N, 2.96. Found: C, 45.71; H, 4.18; N, 2.72.

2.2.1.2 *N*-(*tert*-Butoxycarbonyl)-*N*-tosyl-2-[(trimethylsilyl)ethynyl]aniline (S3)

To a stirred suspension of **S2** (0.51 g, 1.08 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (38.0 mg, 0.054 mmol) and CuI (10.2 mg, 0.054 mmol) in a mixed solvent of THF (5 mL) and Et_3N (5 mL) was added TMS-acetylene (0.18 mL, 1.30 mmol) at rt under argon, and the reaction mixture was stirred for at 80 °C 12 h. The mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography over silica gel with hexane–EtOAc (10:1) to give **S3** (206 mg, 43%) as a colorless solid. Recrystallization from hexane– CHCl_3 gave pure **S3** as colorless crystals: mp 79–80 °C; IR (neat) cm^{-1} 2162 ($\text{C}\equiv\text{C}$), 1736 ($\text{C}=\text{O}$); ^1H NMR (500 MHz, CDCl_3) δ 0.05 (s, 9H, $\text{Si}(\text{CH}_3)_3$), 1.35 (s, 9H, $\text{C}(\text{CH}_3)_3$), 2.44 (s, 3H, ArCH_3), 7.29–7.42 (m, 5H, Ar), 7.52–7.54 (m, 1H, Ar), 7.96 (d, $J = 8.6$ Hz, 2H, Ar); ^{13}C NMR (125 MHz, CDCl_3) δ 0.22 (3C), 22.2, 28.4 (3C), 84.5, 100.1, 101.4, 124.2, 129.2, 129.6, 129.7 (2C), 130.0 (2C), 131.5, 134.1, 137.7, 138.4, 144.8, 150.7. Anal. Calcd for $\text{C}_{23}\text{H}_{29}\text{NO}_4\text{SSi}$: C, 62.27; H, 6.59; N, 3.16. Found: C, 62.28; H, 6.58; N, 3.10.

2.2.1.3 *N*-(*tert*-Butoxycarbonyl)-2-ethynyl-*N*-tosylaniline (S4)

To a solution of **S3** (140 mg, 0.32 mmol) in THF (2 mL) was added TBAF (1 M in THF, 0.34 mL, 0.33 mmol) at –78 °C and the reaction mixture was stirred for 2 min at this temperature. After quenching with aqueous saturated citric acid, the whole was extracted with Et_2O . The extract was washed with water, aqueous saturated NaHCO_3 and brine, and dried over MgSO_4 . Usual workup followed by purification by column chromatography over silica gel with hexane–EtOAc (5:1) gave **S4** (73.4 mg, 62%) as a colorless solid, which was recrystallized from hexane– CHCl_3 to give pure **S4** as colorless crystals: mp 133–133 °C; IR (neat) cm^{-1} 2110 ($\text{C}\equiv\text{C}$), 1732 ($\text{C}=\text{O}$); ^1H NMR (500 MHz, CDCl_3) δ 1.34 (s, 9H, $\text{C}(\text{CH}_3)_3$), 2.45 (s, 3H, ArCH_3), 2.91 (s, 1H, CH), 7.31 (d, $J = 8.6$ Hz, 2H, Ar), 7.35–7.45 (m, 3H, Ar), 7.53–7.55 (m, 1H, Ar), 7.95–7.97 (m, 2H, Ar); ^{13}C NMR (125 MHz, CDCl_3) δ 21.7, 27.8 (3C), 79.9, 82.1, 84.3, 122.7, 128.8, 129.0 (2C), 129.4 (2C), 129.5, 130.9, 133.3, 136.6, 138.5, 144.5, 150.2. Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_4\text{S}$: C, 64.67; H, 5.70; N, 3.77. Found: C, 64.40; H, 5.61; N, 3.72.

2.2.1.4 *N*-(*tert*-Butoxycarbonyl)-2-[3-(piperidin-1-yl)propy-1-nyl]-*N*-tosylaniline (S5)

To a stirred solution of **S4** (200 mg, 0.54 mmol), $(\text{HCHO})_n$ (32.4 mg, 1.08 mmol), and CuBr (3.9 mg, 0.027 mmol) in dioxane (5 mL) was added piperidine (64.0 μL , 0.65 mmol) at rt under argon. The reaction mixture was stirred at 80 °C for 10 min. Concentration under reduced pressure followed by purification by column chromatography over silica gel with hexane–EtOAc (3:1) gave **S5**

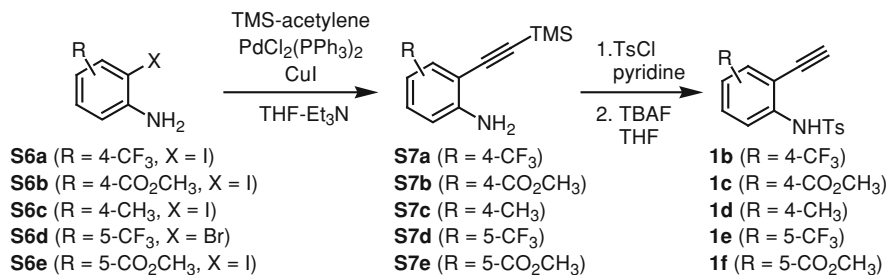
(253 mg, quant) as a pale yellow solid, which was recrystallized from hexane–CHCl₃ to give pure **S5** as pale yellow oil: IR (neat) cm⁻¹ 2233 (C≡C), 1733 (C=O); ¹H NMR (500 MHz, CDCl₃) δ 1.34 (s, 9H, C(CH₃)₃), 1.40–1.44 (m, 2H, CH₂), 1.57–1.61 (m, 4H, 2 × CH₂), 2.41–2.47 (s, 7H, 2 × CH₂ and ArCH₃), 3.15 (s, 2H, CH₂), 7.28–7.37 (m, 5H, Ar), 7.51 (d, *J* = 7.4 Hz, 1H, Ar), 7.97 (d, *J* = 8.6 Hz, 2H, Ar); ¹³C NMR (125 MHz, CDCl₃) δ 21.5, 23.6, 25.8 (2C), 27.7 (3C), 48.2, 53.2 (2C), 81.4, 83.9, 90.2, 123.7, 128.5, 128.7, 128.9 (2C), 129.2 (2C), 130.6, 132.9, 136.9, 137.7, 144.1, 150.2; MS (FAB) *m/z*: 469 (MH⁺, 100); HRMS (FAB) calcd for C₂₆H₃₃N₂O₄S (MH⁺), 469.2161; found, 469.2161.

2.2.1.5 2-[3-(Piperidin-1-yl)prop-1-ynyl]-*N*-tosylaniline (**8**)

To a stirred mixture of **S5** (150 mg, 0.32 mmol) and water (75 μL) in chloroform (1.5 mL) was added TFA (1.5 mL) at 0 °C. The reaction mixture was stirred for 2.5 h at this temperature. After concentration under reduced pressure, the residue was quenched with aqueous saturated NaHCO₃. The whole was extracted with CH₂Cl₂, and the extract was dried over MgSO₄. Usual workup followed by purification by column chromatography over alumina with hexane–EtOAc (7:1) then CHCl₃–CH₃OH (10:1) gave **8** (53.8 mg, 45%) as a colorless solid which was recrystallized from hexane–CHCl₃ to give pure **8** as colorless crystals: mp 111 °C; IR (neat) cm⁻¹ 3266 (NH), 2256 (C≡C); ¹H NMR (500 MHz, CDCl₃) δ 1.45–1.49 (m, 2H, CH₂), 1.64–1.68 (m, 4H, 2 × CH₂), 2.37 (s, 3H, ArCH₃), 2.51–2.55 (s, 4H, 2 × CH₂), 3.50 (s, 2H, CH₂), 6.98–7.01 (m, 1H, Ar), 7.20–7.31 (m, 5H, Ar), 7.58 (d, *J* = 8.0 Hz, 1H, Ar), 7.67 (d, *J* = 8.6 Hz, 1H, Ar); ¹³C NMR (125 MHz, CDCl₃) δ 21.6, 23.8, 25.9 (2C), 48.5, 53.5 (2C), 79.8, 92.4, 113.9, 119.2, 124.1, 127.2 (2C), 129.4, 129.6 (2C), 132.2, 136.2, 137.8, 144.0. Anal. Calcd for C₂₁H₂₄N₂O₂S: C, 68.45; H, 6.56; N, 7.60. Found: C, 68.25; H, 6.56; N, 7.50.

2.2.1.6 Synthesis of 2-[(Piperidin-1-yl)methyl]-1-tosylindole **7b** from **8**

To a stirred solution of **8** (25.0 mg, 0.068 mmol) in dioxane (1 mL) was added CuBr (0.5 mg, 0.0034 mmol) at rt under argon. The reaction mixture was stirred at 80 °C for 50 min. Concentration under reduced pressure followed by purification by column chromatography over silica gel with hexane–EtOAc (5:1) gave **7b** (25.0 mg, quant) as a colorless solid: mp 99 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.43–1.47 (m, 2H, CH₂), 1.51–1.56 (m, 4H, 2 × CH₂), 2.33 (s, 3H, CH₃), 2.46–2.54 (m, 4H, 2 × CH₂), 3.84 (s, 2H, ArCH₂), 6.54 (s, 1H, 3-H), 7.17–7.27 (m, 4H, Ar), 7.43–7.45 (m, 1H, Ar), 8.03 (d, *J* = 8.0 Hz, 2H, Ar), 8.07 (d, *J* = 8.0 Hz, 1H, Ar); ¹³C NMR (100 MHz, CDCl₃) δ 21.5, 24.3, 25.9 (2C), 54.6 (2C), 56.2, 111.2, 114.5, 120.4, 123.2, 124.0, 127.2 (2C), 129.0, 129.4 (2C), 136.5, 137.1, 138.4, 144.4; MS (FAB) *m/z* (%): 369 (MH⁺, 100), 284 (20); HRMS (FAB) calcd for C₂₁H₂₅N₂O₂S (MH⁺): 369.1637; found: 369.1632.



2.2.1.7 2-Ethynyl-N-(p-toluenesulfonyl)-4-(trifluoromethyl)aniline (**1b**)

To a stirred suspension of **S6a** (1.50 g, 5.23 mmol), PdCl₂(PPh₃)₂ (91.7 mg, 0.13 mmol) and CuI (24.9 mg, 0.13 mmol) in THF (1 mL) and Et₃N (20 mL) was added TMS-acetylene (0.86 mL, 6.27 mmol) at rt under argon, and the reaction mixture was stirred for 0.5 h at this temperature. The mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography over silica gel with hexane–EtOAc (20:1) to give the known compound **S7a** (1.30 g, 96%).

To a stirred solution of **S7a** (1.50 g, 5.82 mmol) in pyridine (10 mL) was added TsCl (1.66 g, 8.73 mmol) at 0 °C under argon and the reaction mixture was stirred overnight at rt. After concentration under reduced pressure, the residue was extracted with EtOAc. The extract was washed successively with 3 N HCl and brine, and dried over MgSO₄. Usual workup followed by purification over silica gel with hexane–EtOAc (20:1) gave crude tosylate as a pale yellow solid, which was used in the next step without further purification. To a stirred mixture of the tosylate in THF (10 mL) and water (0.5 mL) was treated with TBAF (1 M in THF, 5.2 mL, 5.20 mmol) at 0 °C for 5 min. The reaction mixture was quenched with aqueous saturated citric acid, and the whole was extracted with EtOAc. The extract was washed successively with H₂O, aqueous saturated NaHCO₃, and brine, and dried over MgSO₄. Concentration under reduced pressure followed by purification through a pad of silica gel with hexane–EtOAc (5:1) gave **1b** (1.76 g, 89%) as a colorless solid, which was recrystallized from *n*-hexane–EtOAc to give pure **1b** as colorless crystals: mp 99 °C; IR (neat) cm^{−1} 3295 (NH), 2112 (C≡C); ¹H NMR (500 MHz, CDCl₃) δ 2.39 (s, 3H, CH₃), 3.51 (s, 1H, C≡CH), 7.27 (d, *J* = 8.0 Hz, 2H, Ar), 7.45 (br s, 1H, NH), 7.51 (dd, *J* = 8.6, 2.3 Hz, 1H, Ar), 7.61 (d, *J* = 2.3 Hz, 1H, Ar), 7.67 (d, *J* = 8.6 Hz, 1H, Ar), 7.73–7.75 (m, 2H, Ar); ¹³C NMR (125 MHz, CDCl₃) δ 21.6, 77.3, 86.0, 112.1, 117.9, 123.4 (q, *J* = 272.3 Hz), 126.0 (q, *J* = 33.6 Hz), 127.0 (q, *J* = 3.6 Hz), 127.3 (2C), 129.7 (q, *J* = 3.6 Hz), 130.0 (2C), 135.7, 141.4, 144.7. Anal. Calcd for C₁₆H₁₂F₃NO₂S: C, 56.63; H, 3.56; N, 4.13. Found C, 56.88; H, 3.54; N, 4.14.

2.2.1.8 2-Ethynyl-4-(methoxycarbonyl)-*N*-(*p*-toluenesulfonyl)aniline (1c)

By a procedure identical to that described for of 2-(trimethylsilylethynyl)aniline **S7a**, 2-iodoaniline **S6b** (1.00 g, 3.61 mmol) was converted into the known compound **S7b** (2.80 g, 77%).

By a procedure similar to that described for of 2-ethynylaniline **1b**, **S7b** (1.64 g, 6.63 mmol) was converted into 2-ethynylaniline **1c** (1.92 g, 88%) as colorless crystals: mp 120 °C; IR (neat) cm^{-1} 3299 (NH), 2104 ($\text{C}\equiv\text{C}$), 1717 ($\text{C}=\text{O}$); ^1H NMR (500 MHz, CDCl_3) δ 2.38 (s, 3H, ArCH_3), 3.49 (s, 1H, $\text{C}\equiv\text{CH}$), 3.87 (s, 3H, OMe), 7.25 (d, $J = 8.0$ Hz, 2H, Ar), 7.52 (br s, 1H, NH), 7.62 (d, $J = 8.8$ Hz, 1H, Ar), 7.73–7.76 (m, 2H, Ar), 7.93 (dd, $J = 8.8, 2.0$ Hz, 1H, Ar), 8.04 (d, $J = 2.0$ Hz, 1H, Ar); ^{13}C NMR (125 MHz, CDCl_3) δ 21.5, 52.2, 77.6, 85.4, 111.6, 117.2, 125.5, 127.3 (2C), 129.9 (2C), 131.4, 134.1, 135.6, 142.2, 144.6, 165.6. Anal. Calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_4\text{S}$: C, 61.99; H, 4.59; N, 4.25. Found C, 62.09; H, 4.61; N, 4.31.

2.2.1.9 2-Ethynyl-4-methyl-*N*-(*p*-toluenesulfonyl)aniline (1d)

By a procedure identical to that described for 2-(trimethylsilylethynyl)aniline **S7a**, 2-iodoaniline **S6c** (2.03 g, 3.61 mmol) was converted into the known compound **S7c** (1.77 g, quant).

By a procedure identical to that described for 2-ethynylaniline **1b**, **S7c** (0.93 g, 4.57 mmol) was converted into 2-ethynylaniline **1d** (1.17 g, 90%) as colorless crystals: mp 104 °C; IR (neat) cm^{-1} 3284 (NH), 2109 ($\text{C}\equiv\text{C}$); ^1H NMR (500 MHz, CDCl_3) δ 2.23 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.29 (s, 1H, $\text{C}\equiv\text{CH}$), 7.09–7.13 (m, 3H, Ar), 7.20 (d, $J = 8.6$ Hz, 2H, Ar), 7.48 (d, $J = 8.6$ Hz, 1H, Ar), 7.66 (d, $J = 8.0$ Hz, 2H, Ar); ^{13}C NMR (125 MHz, CDCl_3) δ 20.5, 21.6, 78.8, 83.8, 112.9, 119.9, 127.4 (2C), 129.6 (2C), 131.0, 132.8, 134.2, 135.9, 136.0, 144.0. Anal. Calcd for $\text{C}_{16}\text{H}_{15}\text{NO}_2\text{S}$: C, 67.34; H, 5.30; N, 4.91. Found C, 67.42; H, 5.18; N, 4.91.

2.2.1.10 2-Ethynyl-*N*-(*p*-toluenesulfonyl)-5-(trifluoromethyl)aniline (1e)

By a procedure identical to that described for the 2-(trimethylsilylethynyl)aniline **S7a**, 2-bromoaniline **S6d** (2.09 g, 8.69 mmol) was converted into the known compound **S7d** (1.70 g, 76%) by the reaction under reflux for 16 h.

By a procedure similar to that described for 2-ethynylaniline **1b**, **S7d** (2.22 g, 8.63 mmol) was converted into 2-ethynylaniline **1e** (1.69 g, 58%) as colorless crystals: mp 162 °C; IR (neat) cm^{-1} 3266 (NH), 2111 ($\text{C}\equiv\text{C}$); ^1H NMR (500 MHz, CDCl_3) δ 2.38 (s, 3H, CH_3), 3.51 (s, 1H, $\text{C}\equiv\text{CH}$), 7.24–7.26 (m, 3H, Ar), 7.35 (br s, 1H, NH), 7.45 (d, $J = 8.0$ Hz, 1H, Ar), 7.70–7.72 (m, 2H, Ar), 7.86 (s, 1H, Ar); ^{13}C NMR (125 MHz, CDCl_3) δ 21.6, 77.5, 86.6, 115.6 (m, 2C), 120.5 (q, $J = 3.6$ Hz), 123.3 (q, $J = 272.3$ Hz), 127.4 (2C), 129.9 (2C), 132.1 (q,

$J = 33.6$ Hz), 133.0, 135.5, 139.1, 144.7. Anal. Calcd for $C_{16}H_{12}F_3NO_2S$: C, 56.63; H, 3.56; N, 4.13. Found C, 56.77; H, 3.74; N, 4.12.

2.2.1.11 2-Ethynyl-5-(methoxycarbonyl)-*N*-(*p*-toluenesulfonyl)aniline (**1f**)

By a procedure identical to that described for 2-(trimethylsilylethynyl)aniline **S7a**, 2-iodoaniline **S6e** (3.00 g, 10.8 mmol) was converted into **S7e** (2.40 g, 90%) as colorless crystals.

Compound **S7e**: mp 64 °C; IR (neat) cm^{-1} 3480, 3378 (NH_2), 2145 ($C\equiv C$), 1713 ($C=O$); 1H NMR (500 MHz, $CDCl_3$) δ 0.27 (s, 9H, $3 \times CH_3$), 3.88 (s, 3H, OMe), 4.34 (s, 2H, NH_2), 7.30–7.36 (m, 3H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 0.00 (3C), 52.1, 100.9, 102.7, 112.0, 114.9, 118.6, 131.0, 132.2, 148.1, 166.8. Anal. Calcd for $C_{13}H_{17}NO_2Si$: C, 63.12; H, 6.93; N, 5.66. found C, 63.12; H, 6.93; N, 5.66.

By a identical similar to that described for 2-ethynylaniline **1b**, **S7e** (2.40 g, 9.66 mmol) was converted into 2-ethynylaniline **1f** (2.46 g, 77%) as colorless crystals: mp 160 °C; IR (neat) cm^{-1} 3268 (NH), 2105 ($C\equiv C$), 1720 ($C=O$); 1H NMR (500 MHz, $CDCl_3$) δ 2.37 (s, 3H, $ArCH_3$), 3.51 (s, 1H, $C\equiv CH$), 3.92 (s, 3H, OMe), 7.23 (d, $J = 8.6$ Hz, 2H, Ar), 7.27 (br s, 1H, NH), 7.40 (d, $J = 8.0$ Hz, 1H, Ar), 7.68 (dd, $J = 8.0, 1.7$ Hz, 1H, Ar), 7.72 (d, $J = 8.6$ Hz, 2H, Ar), 8.23 (d, $J = 1.7$ Hz, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 52.5, 78.0, 86.8, 116.7, 119.9, 125.0, 127.5 (2C), 129.8 (2C), 131.7, 132.5, 135.8, 138.7, 144.4, 165.8. Anal. Calcd for $C_{17}H_{15}NO_4S$: C, 61.99; H, 4.59; N, 4.25. Found C, 62.25; H, 4.56; N, 4.30.

2.2.2 General Procedure for Synthesis of 2-(Aminomethyl)indole

2.2.2.1 Synthesis of 2-[(*N,N*-Diisopropylamino)methyl]-1-tosylindole (**7a**)

To a stirred mixture of 2-ethynylaniline **1a** (50.0 mg, 0.18 mmol), ($HCHO$)_n (11.1 mg, 0.37 mmol), and CuBr (0.3 mg, 0.0018 mmol) in dioxane (3.0 mL) was added diisopropylamine **3a** (28.6 μ L, 0.20 mmol) at rt under argon, and the reaction mixture was stirred at 80 °C for 15 min. Concentration under reduced pressure followed by purification by column chromatography over silica gel with hexane–EtOAc (10:1) afforded the indole **7a** (57.3 mg, 81%) as a colorless solid: mp 105 °C; 1H NMR (400 MHz, $CDCl_3$) δ 0.98 (d, $J = 6.6$ Hz, 12H, $4 \times CHCH_3$), 2.33 (s, 3H, $ArCH_3$), 3.01–3.11 (m, 2H, $2 \times CH$), 3.92 (d, $J = 1.5$ Hz, 2H, CH_2), 6.79 (s, 1H, 3-H), 7.18–7.25 (m, 4H, Ar), 7.41–7.43 (m, 1H, Ar), 7.64–7.67 (m, 2H, Ar), 8.16 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8 (4C), 21.5, 44.4, 49.3 (2C), 110.1, 114.4, 120.2, 123.3, 123.5, 126.3 (2C), 129.8 (2C), 129.9, 136.4, 137.8, 144.4, 144.6; MS (FAB) m/z (%): 385

(MH⁺, 100), 284 (75); HRMS (FAB) calcd for C₂₂H₂₉N₂O₂S (MH⁺): 385.1950; found: 385.1953.

2.2.2.2 2-[(Piperidin-1-yl)methyl]-1-tosylindole (7b) from 1a

By a procedure similar to that described for indole **7a**, **1a** (50.0 mg, 0.18 mmol) was converted into **7b** (59.2 mg, 87%) using piperidine **3b** (20.0 μL, 0.20 mmol).

2.2.2.3 2-[(Pyrrolidin-1-yl)methyl]-1-tosylindole (7c)

By a procedure similar to that described for indole **7a**, **1a** (50.0 mg, 0.18 mmol) was converted into **7c** (59.2 mg, 89%) as a colorless solid using pyrrolidine **3c** (16.8 μL, 0.20 mmol): mp 114 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.71–1.77 (m, 4H, 2 × CH₂), 2.32 (s, 3H, CH₃), 2.56–2.60 (m, 4H, 2 × CH₂), 4.04 (s, 2H, ArCH₂), 6.58 (d, *J* = 0.5 Hz, 1H, 3-H), 7.15–7.29 (m, 4H, Ar), 7.43–7.45 (m, 1H, Ar), 7.87–7.90 (m, 2H, Ar), 8.12 (dd, *J* = 8.3, 1.0 Hz, 1H, Ar); ¹³C NMR (100 MHz, CDCl₃) δ 21.5, 23.6 (2C), 53.1, 54.0 (2C), 110.4, 114.6, 120.4, 123.2, 124.1, 126.9 (2C), 129.2, 129.4 (2C), 136.5, 137.1, 139.3, 144.4; MS (FAB) *m/z* (%): 355 (MH⁺, 100), 284 (20); HRMS (FAB) calcd for C₂₀H₂₃N₂O₂S (MH⁺): 355.1480; found: 355.1485.

2.2.2.4 2-[(*N,N*-Diethylamino)methyl]-1-tosylindole (7d)

By a procedure similar to that described for of indole **7a**, **1a** (50.0 mg, 0.18 mmol) was converted into **7d** (58.2 mg, 89%) as a colorless solid using diethylamine **3d** (38.1 μL, 0.37 mmol): mp 51 °C; ¹H NMR (400 MHz, CDCl₃) δ 0.99 (t, *J* = 7.1 Hz, 6H, 2 × CH₂CH₃), 2.33 (s, 3H, ArCH₃), 2.60 (q, *J* = 7.1 Hz, 4H, 2 × CH₂CH₃), 3.94 (s, 2H, ArCH₂), 6.62 (s, 1H, 3-H), 7.17–7.27 (m, 4H, Ar), 7.44 (d, *J* = 7.1 Hz, 1H, Ar), 7.85 (d, *J* = 8.3 Hz, 2H, Ar), 8.12 (d, *J* = 8.3 Hz, 1H, Ar); ¹³C NMR (100 MHz, CDCl₃) δ 11.2 (2C), 21.5, 46.7 (2C), 51.5, 111.0, 114.6, 120.4, 123.3, 124.0, 126.8 (2C), 129.3, 129.5 (2C), 136.4, 137.3, 139.7, 144.5; MS (FAB) *m/z* (%): 357 (MH⁺, 100), 284 (60); HRMS (FAB) calcd for C₂₀H₂₅N₂O₂S (MH⁺): 357.1637; found: 357.1633.

2.2.2.5 2-[(*N,N*-Diallylamino)methyl]-1-tosylindole (7e)

By a procedure similar to that described for indole **7a**, **1a** (50.0 mg, 0.18 mmol) was converted into **7e** (54.8 mg, 78%) as a colorless solid using diallylamine **3e** (25.0 μL, 0.20 mmol) (30 min): mp 42 °C; ¹H NMR (500 MHz, CDCl₃) δ 2.33 (s, 3H, CH₃), 3.18–3.23 (m, 4H, 2 × NCH₂), 4.02 (s, 2H, ArCH₂), 5.14–5.22 (m, 4H,

$2 \times \text{CH}=\text{CH}_2$), 5.82–5.89 (m, 2H, $2 \times \text{CH}=\text{CH}_2$), 6.71 (s, 1H, 3-H), 7.17 (d, $J = 8.6$ Hz, 2H, Ar), 7.19–7.22 (m, 1H, Ar), 7.25–7.28 (m, 1H, Ar), 7.45 (d, $J = 7.4$ Hz, 1H, Ar), 7.75 (d, $J = 8.6$ Hz, 2H, Ar), 8.13 (d, $J = 8.0$ Hz, 1H, Ar); ^{13}C NMR (125 MHz, CDCl_3) δ 21.5, 51.2, 56.5 (2C), 110.7, 114.6, 117.8 (2C), 120.5, 123.4, 124.1, 126.7 (2C), 129.4, 129.6 (2C), 135.1 (2C), 136.2, 137.4, 139.8, 144.6; MS (FAB) m/z (%): 381 (MH^+ , 100), 284 (75); HRMS (FAB) calcd for $\text{C}_{22}\text{H}_{25}\text{N}_2\text{O}_2\text{S}$ (MH^+): 381.1637; found: 381.1640.

2.2.2.6 2-[(*N,N*-Dibenzylamino)methyl]-1-tosylindole (7f)

By a procedure similar to that described for indole **7a**, **1a** (50.0 mg, 0.18 mmol) was converted into **7f** (69.2 mg, 78%) as a colorless solid by treatment with dibenzylamine **3f** (39 μL , 0.20 mmol) for 2 h: mp 118 $^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 2.29 (s, 3H, CH_3), 3.73 (s, 4H, $2 \times \text{CH}_2$), 4.03 (s, 2H, CH_2), 6.93 (s, 1H, 3-H), 7.02 (d, $J = 8.3$ Hz, 2H, Ar), 7.18–7.46 (m, 15H, Ar), 8.12 (d, $J = 8.3$ Hz, 1H, Ar); ^{13}C NMR (100 MHz, CDCl_3) δ 21.5, 52.0, 58.5 (2C), 109.8, 114.7, 120.4, 123.6, 123.9, 126.2 (2C), 126.9 (2C), 128.3 (4C), 128.4 (4C), 129.7 (2C), 129.9, 135.6, 137.4, 139.2 (2C), 140.1, 144.5; MS (FAB) m/z (%): 481 (MH^+ , 100), 284 (40); HRMS (FAB) calcd for $\text{C}_{30}\text{H}_{29}\text{N}_2\text{O}_2\text{S}$ (MH^+): 481.1950; found: 481.1942.

2.2.2.7 2-[1-(Piperidin-1-yl)butyl]-1-tosylindole (7g)

By a procedure similar to that described for indole **7b**, **1a** (50.0 mg, 0.18 mmol) was converted into **7g** (75.7 mg, quant) as a colorless solid using butanal **2b** (33.2 μL , 0.37 mmol): mp 109 $^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 0.91 (t, $J = 7.3$ Hz, 3H, CH_2CH_3), 1.21–1.54 (m, 8H, $4 \times \text{CH}_2$), 1.62–1.71 (m, 1H, CHH), 1.80–1.89 (m, 1H, CHH), 2.31 (s, 3H, ArCH_3), 2.47–2.59 (m, 4H, $2 \times \text{NCH}_2$), 4.70 (dd, $J = 9.8$, 4.6 Hz, 1H, NCH), 6.51 (s, 1H, 3-H), 7.13–7.26 (m, 4H, Ar), 7.44–7.46 (m, 1H, Ar), 7.92 (d, $J = 8.3$ Hz, 2H, Ar), 8.08 (d, $J = 8.3$ Hz, 1H, Ar); ^{13}C NMR (100 MHz, CDCl_3) δ 14.2, 20.1, 21.5, 24.7, 26.2 (2C), 30.3, 49.5 (2C), 59.8, 109.4, 115.2, 120.4, 123.3, 124.0, 127.0 (2C), 129.1, 129.3 (2C), 136.5, 137.1, 141.8, 144.3; MS (FAB) m/z (%): 411 (MH^+ , 90), 367 (100), 326 (50); HRMS (FAB) calcd for $\text{C}_{24}\text{H}_{31}\text{N}_2\text{O}_2\text{S}$ (MH^+): 411.2106; found: 411.2115.

2.2.2.8 2-[2-Methyl-1-(piperidin-1-yl)propyl]-1-tosylindole (7h)

By a procedure similar to that described for indole **7b**, **1a** (50.0 mg, 0.18 mmol) was converted into **7h** (58.3 mg, 77%) as a colorless solid by treatment with *i*-butyraldehyde **2c** (33.6 μL , 0.37 mmol) under reflux for 3 h: mp 98 $^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 0.75 (d, $J = 6.6$ Hz, 3H, CCH_3), 1.12 (d, $J = 6.6$ Hz, 3H, CCH_3), 1.23–1.29 (m, 2H, CH_2), 1.46–1.52 (m, 4H, $2 \times \text{CH}_2$), 2.08–2.19 (m, 1H, CH), 2.29 (s, 3H, ArCH_3), 2.32–2.38 (m, 4H, $2 \times \text{CH}_2$), 4.36 (d, $J = 10.7$ Hz, 1H,

NCH), 6.40 (s, 1H, 3-H), 7.11 (d, $J = 8.0$ Hz, 2H, Ar), 7.20–7.29 (m, 2H, Ar), 7.45 (d, $J = 7.8$ Hz, 1H, Ar), 7.59 (d, $J = 8.0$ Hz, 2H, Ar), 8.16 (d, $J = 7.8$ Hz, 1H, Ar); ^{13}C NMR (100 MHz, CDCl_3) δ 20.7, 21.1, 21.5, 24.7, 26.7 (2C), 29.7, 49.9 (2C), 66.5, 109.9, 115.8, 120.4, 123.6, 123.9, 126.7 (2C), 129.4, (2C), 129.6, 136.2, 137.3, 140.3, 144.5; MS (FAB) m/z (%): 411 (MH^+ , 70), 367 (100), 326 (35); HRMS (FAB) calcd for $\text{C}_{24}\text{H}_{31}\text{N}_2\text{O}_2\text{S}$ (MH^+): 411.2106; found: 411.2112.

2.2.2.9 2-[Phenyl(piperidin-1-yl)methyl]-1-tosylindole (7i)

By a procedure similar to that described for indole **7b**, **1a** (50.0 mg, 0.18 mmol) was converted into **7i** (57.1 mg, 70%) as an yellow oil by treatment with benzaldehyde **2d** (37.6 μL , 0.37 mmol) under reflux for 10 h: ^1H NMR (400 MHz, CDCl_3) δ 1.38–1.57 (m, 6H, $3 \times \text{CH}_2$), 2.23–2.30 (m, 5H, ArCH_3 and $2 \times \text{CHH}$), 2.41–2.46 (m, 2H, $2 \times \text{CHH}$), 5.34 (s, 1H, NCH), 6.95 (s, 1H, 3-H), 7.00 (d, $J = 8.0$ Hz, 2H, Ar), 7.18–7.30 (m, 7H, Ar), 7.37–7.39 (m, 2H, Ar), 7.46–7.48 (m, 1H, Ar), 8.08 (d, $J = 8.0$ Hz, 1H, Ar); ^{13}C NMR (100 MHz, CDCl_3) δ 21.4, 24.7, 26.4 (2C), 53.1 (2C), 67.5, 110.6, 115.2, 120.6, 123.5, 124.0, 126.5 (2C), 127.2, 128.0 (2C), 129.4 (2C), 129.6 (2C), 129.8, 136.0, 137.2, 140.1, 143.9, 144.4; MS (FAB) m/z (%): 445 (MH^+ , 90), 360 (100); HRMS (FAB) calcd for $\text{C}_{27}\text{H}_{29}\text{N}_2\text{O}_2\text{S}$ (MH^+): 445.1950; found: 445.1956.

2.2.2.10 2-[[4-(Methoxycarbonyl)phenyl](piperidin-1-yl)methyl]-1-tosylindole (7j)

By a procedure similar to that described for indole **7b**, **1a** (50.0 mg, 0.18 mmol) was converted into **7j** (70.2 mg, 76%) as a colorless solid by treatment with 4-methoxycarbonylbenzaldehyde **2e** (60.5 mg, 0.37 mmol) under reflux for 3 h: mp 167 $^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 1.38–1.56 (m, 6H, $3 \times \text{CH}_2$), 2.25–2.31 (m, 5H, ArCH_3 and $2 \times \text{CHH}$), 2.39–2.44 (m, 2H, $2 \times \text{CHH}$), 3.90 (s, 3H, OMe), 5.42 (s, 1H, NCH), 6.90 (s, 1H, 3-H), 7.03 (d, $J = 8.0$ Hz, 2H, Ar), 7.20–7.28 (m, 2H, Ar), 7.35 (d, $J = 8.0$ Hz, 2H, Ar), 7.43 (d, $J = 8.0$ Hz, 2H, Ar), 7.47–7.50 (m, 1H, Ar), 7.89 (d, $J = 8.0$ Hz, 2H, Ar), 8.13 (d, $J = 8.0$ Hz, 1H, Ar); ^{13}C NMR (100 MHz, CDCl_3) δ 21.4, 24.6, 26.4 (2C), 52.0, 53.0 (2C), 67.0, 111.2, 115.3, 120.7, 123.7, 124.3, 126.3 (2C), 129.0, 129.31 (2C), 129.34 (2C), 129.5 (2C), 129.6, 136.0, 137.5, 142.7, 144.6, 145.6, 166.9; MS (FAB) m/z (%): 503 (MH^+ , 55), 418 (100); HRMS (FAB) calcd for $\text{C}_{29}\text{H}_{31}\text{N}_2\text{O}_4\text{S}$ (MH^+): 503.2005; found: 503.2008.

2.2.2.11 2-[(Piperidin-1-yl)(*p*-tolyl)methyl]-1-tosylindole (7k)

By a procedure similar to that described for indole **7b**, **1a** (50.0 mg, 0.18 mmol) was converted into **7k** (68.3 mg, 85%) as an yellow oil by treatment with

4-methylbenzaldehyde **2f** (43.6 μ L, 0.37 mmol) under reflux for 3 h: ^1H NMR (400 MHz, CDCl_3) δ 1.37–1.56 (m, 6H, $3 \times \text{CH}_2$), 2.24–2.34 (m, 8H, $2 \times \text{ArCH}_3$ and $2 \times \text{CHH}$), 2.39–2.46 (m, 2H, $2 \times \text{CHH}$), 5.28 (s, 1H, NCH), 6.94 (s, 1H, 3-H), 6.99 (d, $J = 8.0$ Hz, 2H, Ar), 7.04 (d, $J = 7.8$ Hz, 2H, Ar), 7.18–7.31 (m, 6H, Ar), 7.46–7.48 (m, 1H, Ar), 8.08 (d, $J = 8.0$ Hz, 1H, Ar); ^{13}C NMR (100 MHz, CDCl_3) δ 21.1, 21.4, 24.7, 26.4 (2C), 53.2 (2C), 67.2, 110.4, 115.2, 120.6, 123.5, 123.9, 126.5 (2C), 128.7 (2C), 129.3 (2C), 129.5 (2C), 129.8, 136.1, 136.8, 137.0, 137.3, 144.1, 144.3; MS (FAB) m/z (%): 459 (MH^+ , 50), 374 (100); HRMS (FAB) calcd for $\text{C}_{28}\text{H}_{31}\text{N}_2\text{O}_2\text{S}$ (MH^+): 459.2106; found: 459.2114.

2.2.2.12 2-[(2-Bromophenyl)(piperidin-1-yl)methyl]-1-tosylindole (**7l**)

By a procedure similar to that described for indole **7b**, **1a** (50.0 mg, 0.18 mmol) was converted into **7l** (62.7 mg, 65%) as a colorless solid by treatment with 2-bromobenzaldehyde **2f** (42.7 μ L, 0.37 mmol) under reflux for 4 h: mp 190 $^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 1.43–1.50 (m, 6H, $3 \times \text{CH}_2$), 2.29 (s, 3H, ArCH_3), 2.41–2.46 (m, 2H, $2 \times \text{CHH}$), 2.60–2.65 (m, 2H, $2 \times \text{CHH}$), 5.82 (s, 1H, NCH), 6.96 (s, 1H, 3-H), 7.04–7.14 (m, 4H, Ar), 7.20–7.29 (m, 3H, Ar), 7.45–7.51 (m, 3H, Ar), 7.58–7.61 (m, 1H, Ar), 8.11 (d, $J = 8.0$ Hz, 1H, Ar); ^{13}C NMR (100 MHz, CDCl_3) δ 21.5, 24.7, 26.9 (2C), 51.9 (2C), 65.5, 112.1, 115.0, 120.7, 123.4, 124.2, 126.5 (2C), 126.8, 127.1, 128.6, 129.2, 129.4 (2C), 131.0, 133.1, 136.3, 137.7, 139.2, 143.3, 144.4; MS (FAB) m/z (%): 525 [MH^+ (^{81}Br), 15], 523 [MH^+ (^{79}Br), 15], 440 (15), 438 (15); HRMS (FAB) calcd for $\text{C}_{27}\text{H}_{28}\text{BrN}_2\text{O}_2\text{S}$ [MH^+ (^{79}Br)]: 523.1055; found: 523.1052.

2.2.2.13 Enantioselective Synthesis of 2-[1-(Piperidin-1-yl)butyl]-1-tosylindole (**7g**)

To a stirred suspension of CuBr (1.3 mg, 0.0092 mmol) in benzene (2 mL) was added (*S*)-PINAP (5.7 mg, 0.010 mmol) at rt under argon. After the reaction mixture was stirred for 0.5 h at this temperature, piperidine **3b** (20.0 μ L, 0.20 mmol), butanal **2b** (33.2 μ L, 0.37 mmol), and **1a** (50.0 mg, 0.18 mmol) were successively added and the reaction mixture was additionally stirred for 5 d at rt. Concentration under reduced pressure followed by purification by column chromatography over silica gel with hexane–EtOAc (5:1) gave **7g** (quant, 63% ee): $[\alpha]_{\text{D}}^{23} -23.2$ (c 1.00, CHCl_3).

2.2.2.14 2-[(*N,N*-Dibenzylamino)methyl]-1-tosyl-5-(trifluoromethyl)indole (**7m**)

By a procedure identical to that described for of indole **7f**, **1b** (62.5 mg, 0.18 mmol) was converted into **7m** (91.0 mg, 90%) as a colorless solid by the reaction at 80 $^\circ\text{C}$ for 3 h: mp 95 $^\circ\text{C}$; ^1H NMR (500 MHz, CDCl_3) δ 2.31 (s, 3H,

ArCH₃), 3.73 (s, 4H, 2 × NCH₂), 4.04 (d, J = 1.1 Hz, 2H, NCH₂), 7.00 (s, 1H, 3-H), 7.06 (d, J = 8.0 Hz, 2H, Ar), 7.23–7.26 (m, 2H, Ar), 7.29–7.32 (m, 4H, Ar), 7.39–7.42 (m, 6H, Ar), 7.48 (dd, J = 8.6, 1.7 Hz, 1H, Ar), 7.75 (s, 1H, Ar), 8.22 (d, J = 8.6 Hz, 1H, Ar); ¹³C NMR (125 MHz, CDCl₃) δ 21.6, 51.9, 58.6 (2C), 109.4, 114.8, 117.9 (q, J = 3.6 Hz), 120.6 (q, J = 3.6 Hz), 124.6 (q, J = 272.3 Hz), 125.9 (q, J = 32.4 Hz), 126.2 (2C), 127.1 (2C), 128.40 (4C), 128.42 (4C), 129.6, 129.9 (2C), 135.4, 138.89, 138.94 (2C), 142.2, 145.1; MS (FAB) m/z (%): 547 (M–H⁺, 70), 393 (100); HRMS (FAB) calcd for C₃₁H₂₆F₃N₂O₂S (M–H⁺): 547.1667; found: 547.1665.

2.2.2.15 2-[(*N,N*-Dibenzylamino)methyl]-5-(methoxycarbonyl)-1-tosylindole (7n)

By a procedure identical to that described for of indole **7f**, **1c** (60.7 mg, 0.18 mmol) was converted into **7n** (90.7 mg, 91%) as a colorless solid by the reaction at 80 °C for 3 h: mp 104 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.30 (s, 3H, ArCH₃), 3.73 (s, 4H, 2 × CH₂), 3.91 (s, 3H, OMe), 4.03 (s, 2H, CH₂), 7.00 (s, 1H, 3-H), 7.05 (d, J = 8.3 Hz, 2H, Ar), 7.23–7.42 (m, 12H, Ar), 7.94 (dd, J = 8.8, 1.5 Hz, 1H, Ar), 8.15–8.18 (m, 2H, Ar); ¹³C NMR (100 MHz, CDCl₃) δ 21.5, 51.9, 52.1, 58.6 (2C), 109.8, 114.2, 122.6, 125.2, 125.5, 126.2 (2C), 127.0 (2C), 128.36 (4C), 128.38 (4C), 129.6, 129.8 (2C), 135.4, 139.0 (2C), 140.0, 141.6, 144.9, 167.2; MS (FAB) m/z (%): 537 (M–H⁺, 85), 383 (100); HRMS (FAB) calcd for C₃₂H₂₉N₂O₄S (M–H⁺): 537.1848; found: 537.1859.

2.2.2.16 2-[(*N,N*-Dibenzylamino)methyl]-5-methyl-1-tosylindole (7o)

By a procedure identical to that described for indole **7f**, **1d** (52.6 mg, 0.18 mmol) was converted into **7o** (71.2 mg, 78%) as a colorless solid by the reaction at 80 °C for 5 h, then reflux, 1 h): mp 140 °C; ¹H NMR (500 MHz, CDCl₃) δ 2.28 (s, 3H, ArCH₃), 2.38 (s, 3H, ArCH₃), 3.72 (s, 4H, 2 × NCH₂), 4.01 (s, 2H, NCH₂), 6.86 (s, 1H, 3-H), 7.01 (d, J = 8.0 Hz, 2H, Ar), 7.05 (d, J = 8.6 Hz, 1H, Ar), 7.22–7.25 (m, 3H, Ar), 7.28–7.31 (m, 4H, Ar), 7.37–7.41 (m, 6H, Ar), 7.99 (d, J = 8.6 Hz, 1H, Ar); ¹³C NMR (125 MHz, CDCl₃) δ 21.2, 21.5, 51.9, 58.4 (2C), 109.8, 114.4, 120.4, 125.3, 126.2 (2C), 126.9 (2C), 128.3 (4C), 128.4 (4C), 129.6 (2C), 130.2, 133.1, 135.6 (2C), 139.2 (2C), 140.1, 144.4; MS (FAB) m/z (%): 495 (MH⁺, 100), 298 (55); HRMS (FAB) calcd for C₃₁H₃₁N₂O₂S (MH⁺): 495.2106; found: 495.2099.

2.2.2.17 2-[(*N,N*-Dibenzylamino)methyl]-1-tosyl-6-(trifluoromethyl)indole (7p)

By a procedure identical to that described for of indole **7f**, **1e** (62.5 mg, 0.18 mmol) was converted into **7p** (61.7 mg, 61%) as a colorless solid by the

reaction at 80 °C, 3 h: mp 104 °C; ^1H NMR (500 MHz, CDCl_3) δ 2.31 (s, 3H, ArCH_3), 3.73 (s, 4H, $2 \times \text{NCH}_2$), 4.04 (s, 2H, NCH_2), 6.98 (s, 1H, 3-H), 7.06 (d, $J = 8.0$ Hz, 2H, Ar), 7.23–7.26 (m, 2H, Ar), 7.29–7.32 (m, 4H, Ar), 7.39–7.42 (m, 6H, Ar), 7.45 (dd, $J = 8.0, 1.1$ Hz, 1H, Ar), 7.53 (d, $J = 8.0$ Hz, 1H, Ar), 8.43 (s, 1H, Ar); ^{13}C NMR (125 MHz, CDCl_3) δ 21.5, 51.9, 58.6 (2C), 109.1, 112.0 (q, $J = 3.6$ Hz), 120.3 (q, $J = 3.6$ Hz), 120.7, 124.7 (q, $J = 272.3$ Hz), 126.0 (q, $J = 32.4$ Hz), 126.2 (2C), 127.1 (2C), 128.38 (4C), 128.40 (4C), 129.9 (2C), 132.4, 135.3, 136.5, 138.9 (2C), 143.2, 145.1; MS (FAB) m/z (%): 547 ($\text{M}-\text{H}^+$, 65), 393 (100); HRMS (FAB) calcd for $\text{C}_{31}\text{H}_{26}\text{F}_3\text{N}_2\text{O}_2\text{S}$ ($\text{M}-\text{H}^+$): 547.1667; found: 547.1672.

2.2.2.18 2-[(*N,N*-Dibenzylamino)methyl]-6-(methoxycarbonyl)-1-tosylindole (7q)

By a procedure identical to that described for indole **7f**, **1f** (60.7 mg, 0.18 mmol) was converted into **7q** (78.3 mg, 79%) as a colorless solid by the reaction at 80 °C for 5 h: ^1H NMR (400 MHz, CDCl_3) δ 2.30 (s, 3H, ArCH_3), 3.73 (s, 4H, $2 \times \text{NCH}_2$), 3.94 (s, 3H, OMe), 4.06 (s, 2H, NCH_2), 6.98 (s, 1H, 3-H), 7.05 (d, $J = 8.5$ Hz, 2H, Ar), 7.23–7.49 (m, 14H, Ar), 7.91 (dd, $J = 8.3, 1.5$ Hz, 1H, Ar); ^{13}C NMR (100 MHz, CDCl_3) δ 21.5, 52.0, 52.1, 58.6 (2C), 109.4, 116.3, 120.1, 124.9, 125.8, 126.3 (2C), 127.0 (2C), 128.4 (8C), 129.8 (2C), 133.6, 135.4, 136.9, 139.0 (2C), 143.7, 144.9, 167.4; MS (FAB) m/z (%): 539 (MH^+ , 100); HRMS (FAB) calcd for $\text{C}_{32}\text{H}_{31}\text{N}_2\text{O}_4\text{S}$ (MH^+): 539.2005; found: 539.2007.

2.2.2.19 2-[[*N*-(2-Bromoprop-2-en-1-yl)-*N*-butylamino]methyl]-1-tosylindole (7r)

By a procedure similar to that described for indole **7a**, **1a** (100 mg, 0.37 mmol) was converted into **7r** (171 mg, 98%) as a yellow oil by treatment with *N*-(2-bromoprop-2-en-1-yl)-*N*-butylamine **3g** (77.8 mg, 0.41 mmol) at 80 °C for 3 h, then in the presence of Et_3N (205.5 μL , 1.47 mmol) under reflux for 1 h: ^1H NMR (500 MHz, CDCl_3) δ 0.87 (t, $J = 7.4$ Hz, 3H, CH_2CH_3), 1.25–1.33 (m, 2H, CH_2), 1.40–1.46 (m, 2H, CH_2), 2.33 (s, 3H, ArCH_3), 2.57–2.60 (m, 2H, NCH_2), 3.38 (s, 2H, NCH_2), 4.05 (d, $J = 1.1$ Hz, 2H, NCH_2), 5.54 (s, 1H, $\text{C}=\text{CHH}$), 5.89 (d, $J = 1.1$ Hz, 1H, $\text{C}=\text{CHH}$), 6.81 (s, 1H, 3-H), 7.17–7.27 (m, 4H, Ar), 7.44–7.46 (m, 1H, Ar), 7.63–7.66 (m, 2H, Ar), 8.12–8.14 (m, 1H, Ar); ^{13}C NMR (125 MHz, CDCl_3) δ 14.1, 20.5, 21.5, 29.4, 52.2, 53.8, 62.6, 110.3, 114.5, 117.9, 120.5, 123.5, 124.0, 126.3 (2C), 129.69, 129.74 (2C), 131.9, 136.0, 137.4, 139.9, 144.7; MS (FAB) m/z (%): 475 [$\text{M}-\text{H}^+$ (^{81}Br), 100], 473 [$\text{M}-\text{H}^+$ (^{79}Br), 90]; HRMS (FAB) calcd for $\text{C}_{23}\text{H}_{26}\text{BrN}_2\text{O}_2\text{S}$ [$\text{M}-\text{H}^+$ (^{79}Br)]: 473.0898; found: 473.0900.

2.2.2.20 2-[[*N*-(2-Bromoprop-2-en-1-yl)-*N*-butylamino]methyl]-1-tosyl-5-trifluoromethylindole (7s)

By a procedure identical to that described for of indole **7r**, **1b** (125 mg, 0.37 mmol) was converted into **7s** (182.3 mg, 91%) as an yellow oil by the reaction at 80 °C for 3 h: ^1H NMR (500 MHz, CDCl_3) δ 0.88 (t, $J = 7.4$ Hz, 3H, CH_2CH_3), 1.26–1.33 (m, 2H, CH_2), 1.40–1.46 (m, 2H, CH_2), 2.36 (s, 3H, ArCH_3), 2.57–2.60 (m, 2H, NCH_2), 3.38 (s, 2H, NCH_2), 4.05 (d, $J = 1.1$ Hz, 2H, NCH_2), 5.55 (d, $J = 1.1$ Hz, 1H, $\text{C}=\text{CHH}$), 5.87 (d, $J = 1.1$ Hz, 1H, $\text{C}=\text{CHH}$), 6.91 (s, 1H, 3-H), 7.22 (d, $J = 8.6$ Hz, 2H, Ar), 7.50 (dd, $J = 8.6, 1.1$ Hz, 1H, Ar), 7.66 (d, $J = 8.6$ Hz, 2H, Ar), 7.76 (s, 1H, Ar), 8.23 (d, $J = 8.6$ Hz, 1H, Ar); ^{13}C NMR (125 MHz, CDCl_3) δ 14.1, 20.5, 21.6, 29.4, 52.2, 53.9, 62.6, 109.8, 114.6, 118.0 (q, $J = 3.6$ Hz), 118.2, 120.6 (q, $J = 3.6$ Hz), 124.6 (q, $J = 272.3$ Hz), 125.8 (q, $J = 32.4$ Hz), 126.4 (2C), 129.4, 130.0 (2C), 131.8, 135.7, 138.9, 142.0, 145.3; MS (FAB) m/z (%): 543 [$\text{M}-\text{H}^+$ (^{81}Br), 100], 541 [$\text{M}-\text{H}^+$ (^{79}Br), 90]; HRMS (FAB) calcd for $\text{C}_{24}\text{H}_{25}\text{BrF}_3\text{N}_2\text{O}_2\text{S}$ [$\text{M}-\text{H}^+$ (^{79}Br)]: 541.0772; found: 541.0775.

2.2.2.21 2-[[*N*-(2-Bromoprop-2-en-1-yl)-*N*-butylamino]methyl]-5-(methoxycarbonyl)-1-tosylindole (7t)

By a procedure identical to that described for indole **7r**, **1c** (121.3 mg, 0.37 mmol) was converted into **7t** (193.0 mg, 98%) as a colorless solid by the reaction at 80 °C for 3 h: mp 74 °C; ^1H NMR (500 MHz, CDCl_3) δ 0.88 (t, $J = 7.4$ Hz, 3H, CH_2CH_3), 1.26–1.33 (m, 2H, CH_2), 1.40–1.46 (m, 2H, CH_2), 2.35 (s, 3H, ArCH_3), 2.57–2.60 (m, 2H, NCH_2), 3.38 (s, 2H, NCH_2), 3.92 (s, 3H, OCH_3), 4.05 (d, $J = 1.1$ Hz, 2H, NCH_2), 5.55 (s, 1H, $\text{C}=\text{CHH}$), 5.88 (d, $J = 1.1$ Hz, 1H, $\text{C}=\text{CHH}$), 6.90 (s, 1H, 3-H), 7.20 (d, $J = 8.6$ Hz, 2H, Ar), 7.66 (d, $J = 8.6$ Hz, 2H, Ar), 7.95 (dd, $J = 8.6, 1.7$ Hz, 1H, Ar), 8.16–8.19 (m, 2H, Ar); ^{13}C NMR (125 MHz, CDCl_3) δ 14.1, 20.5, 21.6, 29.4, 52.1, 52.2, 53.9, 62.6, 110.3, 114.2, 118.2, 122.7, 125.2, 125.5, 126.4 (2C), 129.5, 129.9 (2C), 131.8, 135.8, 140.0, 141.5, 145.2, 167.3; MS (FAB) m/z (%): 533 [$\text{M}-\text{H}^+$ (^{81}Br), 100], 531 [$\text{M}-\text{H}^+$ (^{79}Br), 95]; HRMS (FAB) calcd for $\text{C}_{25}\text{H}_{28}\text{BrN}_2\text{O}_4\text{S}$ [$\text{M}-\text{H}^+$ (^{79}Br)]: 531.0953; found: 531.0957.

2.2.2.22 2-[[*N*-(2-Bromoprop-2-en-1-yl)-*N*-butylamino]methyl]-5-methyl-1-tosylindole (7u)

By a procedure identical to that described for indole **7r**, **1d** (105.1 mg, 0.37 mmol) was converted into **7u** (177 mg, 98%) as an yellow oil by the reaction at 80 °C for 3 h, then in the presence of Et_3N (205.5 μL , 1.47 mmol) under reflux for 1 h: ^1H NMR (500 MHz, CDCl_3) δ 0.87 (t, $J = 7.2$ Hz, 3H, CH_2CH_3), 1.25–1.32 (m, 2H, CH_2), 1.40–1.46 (m, 2H, CH_2), 2.32 (s, 3H, ArCH_3), 2.39 (s, 3H, ArCH_3), 2.56–2.59 (m, 2H, NCH_2), 3.37 (s, 2H, NCH_2), 4.03 (d, $J = 1.1$ Hz, 2H, NCH_2),

5.53 (d, $J = 1.1$ Hz, 1H, C=CHH), 5.88 (d, $J = 1.1$ Hz, 1H, C=CHH), 6.73 (s, 1H, 3-H), 7.07 (dd, $J = 8.6, 1.7$ Hz, 1H, Ar), 7.16 (d, $J = 8.6$ Hz, 2H, Ar), 7.24 (s, 1H, Ar), 7.62–7.64 (m, 2H, Ar), 8.00 (d, $J = 8.6$ Hz, 1H, Ar); ^{13}C NMR (125 MHz, CDCl_3) δ 14.1, 20.5, 21.2, 21.5, 29.4, 52.2, 53.8, 62.5, 110.2, 114.3, 117.9, 120.5, 125.3, 126.3 (2C), 129.7 (2C), 129.9, 132.0, 133.1, 135.6, 136.0, 139.9, 144.6; MS (FAB) m/z (%): 489 $[\text{M}-\text{H}^+ (^{81}\text{Br})]$, 100], 487 $[\text{M}-\text{H}^+ (^{79}\text{Br})]$, 90]; HRMS (FAB) calcd for $\text{C}_{24}\text{H}_{28}\text{BrN}_2\text{O}_2\text{S}$ $[\text{M}-\text{H}^+ (^{79}\text{Br})]$: 487.1055; found: 487.1051.

2.2.2.23 2- $\{[N-(2\text{-Bromoprop-2-en-1-yl})-N\text{-butylamino}]\text{methyl}\}$ -1-tosyl-6-(trifluoromethyl)indole (7v)

By a procedure identical to that described for of indole **7v**, **1e** (125 mg, 0.37 mmol) was converted into **7s** (188 mg, 94%) as an yellow oil by the reaction at 80 °C, for 3 h then under reflux for 1 h: ^1H NMR (500 MHz, CDCl_3) δ 0.87 (t, $J = 7.4$ Hz, 3H, CH_2CH_3), 1.26–1.33 (m, 2H, CH_2), 1.40–1.46 (m, 2H, CH_2), 2.36 (s, 3H, ArCH_3), 2.57–2.60 (m, 2H, NCH_2), 3.38 (s, 2H, NCH_2), 4.06 (s, 2H, NCH_2), 5.55 (s, 1H, C=CHH), 5.87 (s, 1H, C=CHH), 6.90 (s, 1H, 3-H), 7.22 (d, $J = 8.6$ Hz, 2H, Ar), 7.47 (d, $J = 8.0$ Hz, 1H, Ar), 7.55 (d, $J = 8.0$ Hz, 1H, Ar), 7.65 (d, $J = 8.6$ Hz, 2H, Ar), 8.44 (s, 1H, Ar); ^{13}C NMR (125 MHz, CDCl_3) δ 14.0, 20.5, 21.6, 29.4, 52.2, 53.9, 62.7, 109.6, 111.9 (q, $J = 4.8$ Hz), 118.3, 120.3 (m), 120.8, 124.7 (q, $J = 272.3$ Hz), 126.0 (q, $J = 32.4$ Hz), 126.4 (2C), 130.0 (2C), 131.8, 132.2, 135.7, 136.6, 143.0, 145.3; MS (FAB) m/z (%): 543 $[\text{M}-\text{H}^+ (^{81}\text{Br})]$, 100], 541 $[\text{M}-\text{H}^+ (^{79}\text{Br})]$, 90]; HRMS (FAB) calcd for $\text{C}_{24}\text{H}_{25}\text{BrF}_3\text{N}_2\text{O}_2\text{S}$ $[\text{M}-\text{H}^+ (^{79}\text{Br})]$: 541.0772; found: 541.0771.

2.2.2.24 2- $\{[N-(2\text{-Bromoprop-2-en-1-yl})-N\text{-butylamino}]\text{methyl}\}$ -6-(methoxycarbonyl)-1-tosylindole (7w)

By a procedure identical to that described for indole **7r**, **1c** (121 mg, 0.37 mmol) was converted into **7w** (194 mg, 99%) as an yellow oil by the reaction at 80 °C for 3 h, then under reflux for 1.5 h: ^1H NMR (500 MHz, CDCl_3) δ 0.88 (t, $J = 7.2$ Hz, 3H, CH_2CH_3), 1.26–1.33 (m, 2H, CH_2), 1.40–1.46 (m, 2H, CH_2), 2.34 (s, 3H, ArCH_3), 2.57–2.60 (m, 2H, NCH_2), 3.38 (s, 2H, NCH_2), 3.95 (s, 3H, OCH_3), 4.07 (d, $J = 1.1$ Hz, 2H, NCH_2), 5.55 (s, 1H, C=CHH), 5.88 (d, $J = 1.1$ Hz, 1H, C=CHH), 6.89 (s, 1H, 3-H), 7.21 (d, $J = 8.6$ Hz, 2H, Ar), 7.49 (d, $J = 8.0$ Hz, 1H, Ar), 7.68 (d, $J = 8.6$ Hz, 2H, Ar), 7.93 (dd, $J = 8.0, 1.1$ Hz, 1H, Ar), 8.85 (s, 1H, Ar); ^{13}C NMR (125 MHz, CDCl_3) δ 14.0, 20.4, 21.5, 29.4, 52.1, 52.3, 53.9, 62.7, 109.8, 116.1, 118.2, 120.2, 124.8, 125.7, 126.4 (2C), 129.9 (2C), 131.8, 133.4, 135.8, 136.9, 143.5, 145.1, 167.4; MS (FAB) m/z (%): 533 $[\text{M}-\text{H}^+ (^{81}\text{Br})]$, 100], 531 $[\text{M}-\text{H}^+ (^{79}\text{Br})]$, 90]; HRMS (FAB) calcd for $\text{C}_{25}\text{H}_{28}\text{BrN}_2\text{O}_4\text{S}$ $[\text{M}-\text{H}^+ (^{79}\text{Br})]$: 531.0953; found: 531.0947.

2.2.2.25 2-[[*N*-(2-Bromobenzyl)-*N*-butylamino]methyl]-1-tosylindole (7x)

By a procedure similar to that described for indole **7a**, **1a** (50.0 mg, 0.18 mmol) was converted into **7x** (77.8 mg, 80%) as a colorless solid by treatment with *N*-(2-bromobenzyl)butanamine **3h** (49.1 mg, 0.20 mmol) at 80 °C for 3 h, then under reflux for 1 h: mp 72 °C; ¹H NMR (400 MHz, CDCl₃) δ 0.87 (t, *J* = 7.3 Hz, 3H, CH₂CH₃), 1.25–1.34 (m, 2H, CH₂), 1.48–1.56 (m, 2H, CH₂), 2.31 (s, 3H, ArCH₃), 2.57–2.61 (m, 2H, NCH₂), 3.76 (s, 2H, NCH₂), 4.02 (d, *J* = 1.0 Hz, 2H, NCH₂), 6.77 (s, 1H, 3-H), 7.04–7.26 (m, 6H, Ar), 7.42–7.58 (m, 5H, Ar), 8.13 (d, *J* = 8.5 Hz, 1H, Ar); ¹³C NMR (100 MHz, CDCl₃) δ 14.1, 20.6, 21.5, 29.4, 52.7, 54.8, 58.5, 110.4, 114.6, 120.4, 123.5, 123.9, 124.0, 126.3 (2C), 127.2, 128.0, 129.7 (2C), 129.8, 129.9, 132.6, 136.0, 137.5, 138.8, 140.3, 144.6; MS (FAB) *m/z* (%): 525 [M–H⁺ (⁸¹Br), 100], 523 [M–H⁺ (⁷⁹Br), 95]; HRMS (FAB) calcd for C₂₇H₂₈BrN₂O₂S [M–H⁺ (⁷⁹Br)]: 523.1055; found: 523.1065.

2.2.3 General Procedure for Synthesis of Tetrahydropyridine-Fused Indole

2.2.3.1 Synthesis of 2-Butyl-4-methylene-9-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (9a)

The mixture of indole **7r** (50.0 mg, 0.11 mol), Pd(OAc)₂ (2.4 mg, 0.011 mmol), PPh₃ (5.5 mg, 0.021 mmol), and CsOAc (40.4 mg, 0.021 mmol) in DMA (2 mL) was stirred at 100 °C for 0.5 h under argon. Concentration under reduced pressure followed by column chromatography purification over silica gel with hexane–AcOEt (4:1) gave **9a** (26.8 mg, 65%) as a yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 0.94 (t, *J* = 7.4 Hz, 3H, CH₂CH₃), 1.30–1.38 (m, 2H, CH₂CH₃), 1.53–1.59 (m, 2H, NCH₂CH₂), 2.33 (s, 3H, ArCH₃), 2.53–2.56 (m, 2H, NCH₂CH₂), 3.38 (s, 2H, NCH₂), 4.16 (s, 2H, NCH₂), 5.10 (s, 1H, C=CHH), 5.59 (s, 1H, C=CHH), 7.20 (d, *J* = 8.6 Hz, 2H, Ar), 7.26–7.33 (m, 2H, Ar), 7.67 (d, *J* = 8.6 Hz, 2H, Ar), 7.76–7.78 (m, 1H, Ar), 8.18 (d, *J* = 8.1 Hz, 1H, Ar); ¹³C NMR (125 MHz, CDCl₃) δ 14.0, 20.6, 21.5, 29.6, 51.5, 55.8, 57.7, 108.6, 114.4, 116.5, 120.4, 124.0, 124.4, 126.4 (2C), 127.3, 130.0 (2C), 135.5, 135.7, 136.1, 136.6, 145.1; MS (FAB) *m/z* (%): 395 (MH⁺, 100); HRMS (FAB) calcd for C₂₃H₂₇N₂O₂S (MH⁺): 395.1793; found: 395.1804.

2.2.3.2 2-Butyl-4-methylene-9-tosyl-6-(trifluoromethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (9b)

By a procedure identical to that described for **9a**, **7s** (57.2 mg, 0.11 mmol) was converted into **9b** (31.3 mg, 64%) as a yellow solid: mp 133 °C; ¹H NMR (500 MHz, CDCl₃) δ 0.94 (t, *J* = 7.2 Hz, 3H, CH₂CH₃), 1.31–1.38 (m, 2H, CH₂), 1.52–1.58 (m, 2H, CH₂), 2.36 (s, 3H, ArCH₃), 2.53–2.56 (m, 2H, NCH₂), 3.39 (s,

2H, NCH₂), 4.16 (s, 2H, NCH₂), 5.15 (s, 1H, C=CHH), 5.59 (s, 1H, C=CHH), 7.24 (d, J = 8.6 Hz, 2H, Ar), 7.56 (dd, J = 8.6, 1.7 Hz, 1H, Ar), 7.68 (d, J = 8.6 Hz, 2H, Ar), 8.01–8.03 (m, 1H, Ar), 8.28 (d, J = 8.6 Hz, 1H, Ar); ¹³C NMR (125 MHz, CDCl₃) δ 14.0, 20.6, 21.6, 29.6, 51.4, 55.8, 57.5, 109.2, 114.5, 116.3, 117.6 (q, J = 3.6 Hz), 121.2 (q, J = 3.6 Hz), 124.5 (q, J = 271.1 Hz), 126.3 (q, J = 32.4 Hz), 126.5 (2C), 127.0, 130.2 (2C), 135.3, 135.4, 137.2, 138.1, 145.6; MS (FAB) m/z (%): 463 (MH⁺, 100); HRMS (FAB) calcd for C₂₄H₂₆F₃N₂O₂S (MH⁺): 463.1667; found: 463.1671.

2.2.3.3 2-Butyl-4-methylene-6-(methoxycarbonyl)-9-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-*b*]indole (9c)

By a procedure identical to that described for **9a**, **7t** (56.1 mg, 0.11 mmol) was converted into **9c** (25.5 mg, 54%) as an yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 0.94 (t, J = 7.4 Hz, 3H, CH₂CH₃), 1.31–1.38 (m, 2H, CH₂), 1.53–1.59 (m, 2H, CH₂), 2.35 (s, 3H, ArCH₃), 2.54–2.57 (m, 2H, NCH₂), 3.39 (s, 2H, NCH₂), 3.93 (s, 3H, OCH₃), 4.15 (s, 2H, NCH₂), 5.16 (s, 1H, C=CHH), 5.70 (s, 1H, C=CHH), 7.22 (d, J = 8.6 Hz, 2H, Ar), 7.68 (d, J = 8.6 Hz, 2H, Ar), 8.01 (dd, J = 8.6, 1.7 Hz, 1H, Ar), 8.22 (d, J = 8.6 Hz, 1H, Ar), 8.48 (d, J = 1.7 Hz, 1H, Ar); ¹³C NMR (125 MHz, CDCl₃) δ 14.0, 20.6, 21.6, 29.5, 51.4, 52.2, 55.8, 57.5, 109.4, 114.0, 116.7, 122.4, 125.7, 125.9, 126.4 (2C), 127.1, 130.1 (2C), 135.3 (2C), 136.7, 139.1, 145.5, 167.1; MS (FAB) m/z (%): 453 (MH⁺, 100); HRMS (FAB) calcd for C₂₅H₂₉N₂O₄S (MH⁺): 453.1848; found: 453.1854.

2.2.3.4 2-Butyl-6-methyl-4-methylene-9-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-*b*]indole (9d)

By a procedure identical to that described for **9a**, **7u** (51.5 mg, 0.11 mmol) was converted into **9d** (26.5 mg, 62%) as an yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 0.94 (t, J = 7.2 Hz, 3H, CH₂CH₃), 1.30–1.37 (m, 2H, CH₂), 1.52–1.58 (m, 2H, CH₂), 2.33 (s, 3H, ArCH₃), 2.43 (s, 3H, ArCH₃), 2.52–2.55 (m, 2H, NCH₂), 3.36 (s, 2H, NCH₂), 4.14 (s, 2H, NCH₂), 5.08 (s, 1H, C=CHH), 5.58 (s, 1H, C=CHH), 7.12 (dd, J = 8.6, 1.1 Hz, 1H, Ar), 7.19 (J = 8.0 Hz, 2H, Ar), 7.54–7.56 (m, 1H, Ar), 7.64–7.66 (m, 2H, Ar), 8.04 (d, J = 8.6 Hz, 1H, Ar); ¹³C NMR (125 MHz, CDCl₃) δ 14.0, 20.6, 21.46, 21.53, 29.6, 51.5, 55.8, 57.8, 108.5, 114.0, 116.4, 120.5, 125.6, 126.4 (2C), 127.5, 129.9 (2C), 133.6, 134.8, 135.6, 135.7, 136.2, 144.9; MS (FAB) m/z (%): 409 (MH⁺, 100); HRMS (FAB) calcd for C₂₄H₂₉N₂O₂S (MH⁺): 409.1950; found: 409.1953.

2.2.3.5 2-Butyl-4-methylene-9-tosyl-7-(trifluoromethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-*b*]indole (9e)

By a procedure identical to that described for **9a**, **7v** (57.2 mg, 0.11 mmol) was converted into **9e** (30.3 mg, 62%) as an yellow oil: ¹H NMR (500 MHz, CDCl₃)

δ 0.94 (t, $J = 7.4$ Hz, 3H, CH_2CH_3), 1.31–1.38 (m, 2H, CH_2), 1.52–1.58 (m, 2H, CH_2), 2.36 (s, 3H, ArCH_3), 2.53–2.56 (m, 2H, NCH_2), 3.38 (s, 2H, NCH_2), 4.17 (s, 2H, NCH_2), 5.14 (s, 1H, $\text{C}=\text{CHH}$), 5.59 (s, 1H, $\text{C}=\text{CHH}$), 7.24 (d, $J = 8.6$ Hz, 2H, Ar), 7.53–7.55 (m, 1H, Ar), 7.68 (d, $J = 8.6$ Hz, 2H, Ar), 7.86 (d, $J = 8.0$ Hz, 1H, Ar), 8.48 (s, 1H, Ar); ^{13}C NMR (125 MHz, CDCl_3) δ 14.0, 20.5, 21.6, 29.6, 51.4, 55.8, 57.5, 109.2, 111.7 (q, $J = 3.6$ Hz), 116.2, 120.6, 120.8 (q, $J = 3.6$ Hz), 124.5 (q, $J = 272.3$ Hz), 126.4 (q, $J = 32.4$ Hz), 126.5 (2C), 129.7, 130.2 (2C), 135.2, 135.5, 135.8, 138.1, 145.6; MS (FAB) m/z (%): 463 (MH^+ , 100); HRMS (FAB) calcd for $\text{C}_{24}\text{H}_{26}\text{F}_3\text{N}_2\text{O}_2\text{S}$ (MH^+): 463.1667; found: 463.1665.

2.2.3.6 2-Butyl-7-(methoxycarbonyl)-4-methylene-9-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-*b*]indole (9f)

By a procedure identical to that described for **9a**, **7w** (56.1 mg, 0.11 mmol) was converted into **9f** (36.8 mg, 77%) as a brown oil: ^1H NMR (500 MHz, CDCl_3) δ 0.94 (t, $J = 7.2$ Hz, 3H, CH_2CH_3), 1.31–1.38 (m, 2H, CH_2), 1.52–1.58 (m, 2H, CH_2), 2.35 (s, 3H, ArCH_3), 2.53–2.56 (m, 2H, NCH_2), 3.38 (s, 2H, NCH_2), 3.97 (s, 3H, OCH_3), 4.17 (s, 2H, NCH_2), 5.13 (s, 1H, $\text{C}=\text{CHH}$), 5.60 (s, 1H, $\text{C}=\text{CHH}$), 7.23 (d, $J = 8.6$ Hz, 2H, Ar), 7.70 (d, $J = 8.6$ Hz, 2H, Ar), 7.80 (d, $J = 8.6$ Hz, 1H, Ar), 7.99 (dd, $J = 8.6, 1.1$ Hz, 1H, Ar), 8.87 (s, 1H, Ar); ^{13}C NMR (125 MHz, CDCl_3) δ 14.0, 20.6, 21.6, 29.6, 51.6, 52.3, 55.8, 57.6, 109.1, 115.9, 116.4, 120.0, 125.2, 126.1, 126.5 (2C), 130.1 (2C), 130.8, 135.4, 135.6, 136.0, 138.6, 145.5, 167.1; MS (FAB) m/z (%): 453 (MH^+ , 100); HRMS (FAB) calcd for $\text{C}_{25}\text{H}_{29}\text{N}_2\text{O}_4\text{S}$ (MH^+): 453.1848; found: 453.1839.

2.2.3.7 6-Butyl-8-tosyl-5,6,7,8-tetrahydrobenzo[*e*]indolo[2,3-*c*]azepine (10)

The mixture of indole **7x** (50.0 mg, 0.095 mol), $\text{Pd}(\text{OAc})_2$ (4.3 mg, 0.019 mmol), PPh_3 (10.0 mg, 0.038 mmol), and CsOAc (36.5 mg, 0.19 mmol) in DMA (2 mL) was stirred at 140 °C for 1 h under argon. Concentration under reduced pressure followed by purification by column chromatography with hexane–AcOEt (4:1) gave **10** (42.3 mg, quant) as an yellow oil: ^1H NMR (400 MHz, CDCl_3) δ 0.98 (t, $J = 7.3$ Hz, 3H, CH_2CH_3), 1.39–1.49 (m, 2H, CH_2), 1.60–1.68 (m, 2H, CH_2), 2.30 (s, 3H, ArCH_3), 2.65–2.69 (m, 2H, NCH_2), 3.42 (s, 2H, NCH_2), 4.05 (s, 2H, NCH_2), 7.16 (d, $J = 8.3$ Hz, 2H, Ar), 7.25–7.44 (m, 5H, Ar), 7.66–7.69 (m, 1H, Ar), 7.72–7.74 (m, 1H, Ar), 7.83 (d, $J = 8.3$ Hz, 2H, Ar), 8.31 (d, $J = 8.3$ Hz, 1H, Ar); ^{13}C NMR (125 MHz, CDCl_3) δ 14.1, 20.6, 21.5, 30.2, 47.8, 55.8, 56.3, 115.6, 119.4, 123.8, 124.0, 124.8, 126.7 (2C), 127.2, 127.4, 127.6, 128.0, 129.7 (2C), 130.6, 134.4, 135.42, 135.43, 137.02, 137.04, 144.8; MS (FAB) m/z (%): 445 (MH^+ , 100); HRMS (FAB) calcd for $\text{C}_{27}\text{H}_{29}\text{N}_2\text{O}_2\text{S}$ (MH^+): 445.1950; found: 445.1952.

2.2.3.8 *N*-[1-(Naphthalen-1-yl)ethyl]prop-2-en-1-amine (11)

To a stirred solution of 1-(naphthalen-1-yl)ethanamine (1.1 g, 6.42 mmol) and DBU (0.98 mL, 6.55 mmol) in THF was added dropwise allyl bromide (0.56 mL, 6.42 mmol) at rt. The mixture was stirred for 7 h at this temperature, and the whole was extracted with CHCl_3 . The extract was washed with H_2O and dried over MgSO_4 . Usual workup followed by purification by column chromatography with hexane–AcOEt (1:1) afforded **11** as an yellow oil (779 mg, 57%): ^1H NMR (400 MHz, CDCl_3) δ 1.49 (d, J = 6.6 Hz, 3H, CHCH_3), 3.15–3.25 (m, 2H, NCH_2), 4.67 (q, J = 6.6 Hz, 1H, NCH), 5.06–5.16 (m, 2H, $\text{CH}=\text{CH}_2$), 5.89–5.98 (m, 1H, $\text{CH}=\text{CH}_2$), 7.44–7.51 (m, 3H, Ar), 7.66 (d, J = 7.1 Hz, 1H, Ar), 7.73 (d, J = 8.0 Hz, 1H, Ar), 7.84–7.87 (m, 1H, Ar), 8.17 (d, J = 8.0 Hz, 1H, Ar); ^{13}C NMR (100 MHz, CDCl_3) δ 23.6, 50.3, 52.7, 115.7, 122.6, 122.9, 125.2, 125.7 (2C), 127.1, 128.9, 131.3, 133.9, 137.0, 141.1; MS (FAB) m/z (%): 212 (MH^+ , 100), 196 (55); HRMS (FAB) calcd for $\text{C}_{15}\text{H}_{18}\text{N}$ (MH^+): 212.1439; found: 212.1443.

2.2.3.9 2-{*N*-(Prop-2-en-1-yl)-*N*-[1-(naphthalen-1-yl)ethyl]aminomethyl}-1-tosylindole (12)

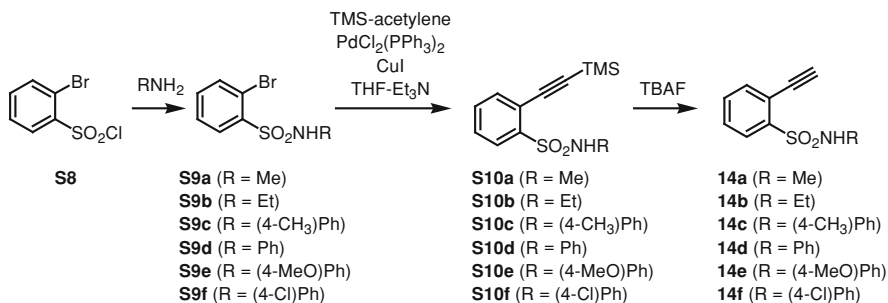
By a procedure similar to that described for indole **7a**, **1a** (250 mg, 0.92 mmol) was converted into **12** (539 mg, 85%) as an yellow oil using **11** (214 mg, 1.01 mmol): ^1H NMR (400 MHz, CDCl_3) δ 1.52 (d, J = 6.6 Hz, 3H, CHCH_3), 2.19 (s, 3H, ArCH_3), 3.33–3.44 (m, 2H, NCH_2), 3.99 (d, J = 17.8 Hz, 1H, NCHH), 4.20 (d, J = 17.8 Hz, 1H, NCHH), 4.84 (q, J = 6.6 Hz, 1H, NCH), 5.09–5.17 (m, 2H, $\text{CH}=\text{CH}_2$), 6.00–6.10 (m, 1H, $\text{CH}=\text{CH}_2$), 6.69 (s, 1H, 3-H), 6.92 (d, J = 8.3 Hz, 2H, Ar), 7.10–7.19 (m, 2H, Ar), 7.32–7.49 (m, 6H, Ar), 7.63 (d, J = 7.3 Hz, 1H, Ar), 7.68 (d, J = 8.3 Hz, 1H, Ar), 7.79 (d, J = 8.3 Hz, 1H, Ar), 8.07 (d, J = 8.0 Hz, 1H, Ar), 8.37 (d, J = 8.3 Hz, 1H, Ar); ^{13}C NMR (100 MHz, CDCl_3) δ 16.5, 21.4, 48.9, 54.9, 56.4, 110.2, 114.4, 117.7, 120.2, 123.3, 123.6, 124.18, 124.21, 125.1, 125.3, 125.5, 126.1 (2C), 127.4, 128.6, 129.5 (2C), 129.8, 131.8, 133.9, 135.4, 135.6, 137.2, 140.0, 141.2, 144.3; MS (FAB) m/z (%): 495 (MH^+ , 100), 479 (50), 339 (30), 284 (60); HRMS (FAB) calcd for $\text{C}_{31}\text{H}_{31}\text{N}_2\text{O}_2\text{S}$ (MH^+): 495.2106; found: 495.2108.

2.2.3.10 Calindol (13)

To a stirred mixture of $\text{Pd}(\text{PPh}_3)_4$ (8.9 mg, 0.0077 mmol) and 1,3-dimethylbarbituric acid (179.6 mg, 1.15 mmol) in CH_2Cl_2 (4 mL) was added a solution of **12** (190.0 mg, 0.38 mmol) in CH_2Cl_2 (1 mL) at rt under argon. The reaction mixture was stirred at 40 °C for 1 h, and the whole was extracted with CHCl_3 . The extract was washed successively with Na_2CO_3 and H_2O . Usual workup followed by purification by column chromatography with hexane–EtOAc (3:1) afforded *N*-tosylcalindole **13a** (156.9 mg, 90%) as a colorless solid: mp 104 °C; ^1H NMR

(400 MHz, CDCl_3) δ 1.48 (d, $J = 6.6$ Hz, 3H, CHCH_3), 2.26 (s, 3H, ArCH_3), 2.36 (br s, 1H, NH), 3.95 (d, $J = 15.4$ Hz, 1H, NCHH), 4.15 (d, $J = 15.4$ Hz, 1H, NCHH), 4.66 (q, $J = 6.6$ Hz, 1H, NCH), 6.36 (s, 1H, 3-H), 7.03 (d, $J = 8.3$ Hz, 2H, Ar), 7.20–7.31 (m, 2H, Ar), 7.38–7.51 (m, 4H, Ar), 7.56 (d, $J = 8.3$ Hz, 2H, Ar), 7.75–7.78 (m, 2H, Ar), 7.87–7.89 (m, 1H, Ar), 8.07 (d, $J = 8.0$ Hz, 1H, Ar), 8.17 (d, $J = 8.3$ Hz, 1H, Ar); ^{13}C NMR (100 MHz, CDCl_3) δ 21.5, 23.8, 44.9, 51.7, 111.2, 114.7, 120.6, 123.0, 123.1, 123.6, 124.4, 125.3, 125.7, 125.8, 126.2 (2C), 127.2, 128.9, 129.4, 129.7 (2C), 131.3, 134.0, 135.7, 137.4, 139.6, 140.6, 144.7; MS (FAB) m/z (%): 455 (MH^+ , 100), 479 (20), 284 (50); HRMS (FAB) calcd for $\text{C}_{28}\text{H}_{27}\text{N}_2\text{O}_2\text{S}$ (MH^+): 455.1793; found: 455.1787.

The mixture of *N*-tosylated indole **13a** (110 mg, 0.24 mmol) and TBAF (1 M in THF, 4.8 mL, 4.8 mmol) was stirred under reflux for 3 h. The whole was extracted with Et_2O , and the extract was washed with H_2O . Usual workup followed by purification by column chromatography with hexane– EtOAc (1:1) yielded calindol **13** as a brown oil (72.8 mg, quant): ^1H NMR (400 MHz, CDCl_3) δ 1.53 (d, $J = 6.6$ Hz, 3H, CHCH_3), 2.21 (br s, 1H, NH), 3.84 (d, $J = 14.1$ Hz, 1H, NCHH), 3.90 (d, $J = 14.1$ Hz, 1H, NCHH), 4.70 (q, $J = 6.6$ Hz, 1H, NCH), 6.27 (s, 1H, 3-H), 7.05–7.09 (m, 1H, Ar), 7.12–7.16 (m, 1H, Ar), 7.30 (d, $J = 7.8$ Hz, 1H, Ar), 7.46–7.54 (m, 4H, Ar), 7.68 (d, $J = 7.1$ Hz, 1H, Ar), 7.77 (d, $J = 8.3$ Hz, 1H, Ar), 7.86–7.96 (m, 1H, Ar), 8.10–8.13 (m, 1H, Ar), 8.44 (br s, 1H, 1-H); ^{13}C NMR (100 MHz, CDCl_3) δ 23.4, 44.8, 53.0, 100.1, 110.7, 119.6, 120.1, 121.4, 122.6, 122.9, 125.5, 125.7, 125.9, 127.5, 128.5, 129.0, 131.3, 134.0, 135.8, 137.8, 140.5; MS (FAB) m/z (%): 401 (MH^+ , 100); HRMS (FAB) calcd for $\text{C}_{21}\text{H}_{21}\text{N}_2$ (MH^+): 301.1715; found: 301.1716.



2.2.3.11 2-Ethynyl-*N*-methylbenzenesulfonamide (**14a**)

To a solution of 2-bromobenzenesulfonylchloride **S8** (3.00 g, 11.8 mmol) in CHCl_3 (100 mL) was added dropwise methanamine (40% in MeOH, 3.47 mL, 33.5 mmol) at 0 °C and the reaction mixture was stirred at rt for 5 min. After concentration under reduced pressure, the residue was dissolved in Et_2O . The solution was washed successively with 1 N HCl and brine, and dried over MgSO_4 . The filtrate was concentrated under reduced pressure and the residue was purified

by column chromatography over silica gel with hexane–EtOAc (3:1) to give the known sulfonamide **S9a** (2.70 g, 92%).

To a stirred mixture of **S9a** (2.65 g, 10.7 mmol), PdCl₂(PPh₃)₂ (0.38 g, 0.53 mmol) and CuI (0.10 g, 0.53 mmol) in a mixed solvent of THF (25 mL) and Et₃N (25 mL) was added TMS-acetylene (1.75 mL, 12.8 mmol) at rt under argon, and the reaction mixture was stirred at 100 °C for 2 h. The mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography over silica gel with hexane–EtOAc (5:1) to give **S10a** as an yellow oil (2.63 g, 92%). To a solution of **S10a** (54.0 mg, 0.20 mmol) in THF (1 mL) was added TBAF (1 M in THF, 0.21 mL, 0.21 mmol) at –78 °C and the reaction mixture was stirred for 1 min at this temperature. After quenching with aqueous saturated citric acid, the whole was extracted with Et₂O. The extract was washed with water, NaHCO₃, and brine, and dried over MgSO₄. Usual workup followed by purification by column chromatography over silica gel with hexane–EtOAc (3:1) gave **14a** (33.6 mg, 86%) as a pale yellow solid, which was recrystallized from hexane–CHCl₃ to give pure **14a** as pale yellow crystals: mp 94 °C; IR (neat) cm^{–1} 3268 (NH), 2110 (C≡C); ¹H NMR (500 MHz, CDCl₃) δ 2.63 (d, *J* = 5.2 Hz, 3H, CH₃), 3.65 (s, 1H, C≡CH), 5.15–5.18 (m, 1H, NH), 7.51–7.57 (m, 2H, Ar), 7.70 (d, *J* = 7.4 Hz, 1H, Ar), 8.05–8.07 (m, 1H, Ar); ¹³C NMR (125 MHz, CDCl₃) δ 29.4, 80.1, 85.7, 119.3, 129.2, 129.7, 132.3, 135.2, 140.3. Anal. Calcd for C₉H₉NO₂S: C, 55.37; H, 4.65; N, 7.17. Found: C, 55.41; H, 4.65; N, 7.16.

2.2.3.12 *N*-Ethyl-2-ethynylbenzenesulfonamide (14b)

By a procedure similar to that described for **S9a**, **S8** (2.00 g, 7.83 mmol) was converted into the known sulfonamide **S9b** (1.90 g, 92%) using ethylamine (70% in H₂O, 1.82 mL, 22.3 mmol).

By a procedure identical to that described for **S10a**, **S9b** (820 mg, 3.12 mmol) was converted into **S10b** as a brown oil (568 mg, 65%). By a procedure identical to that described for **14a**, **S10b** (360 mg, 1.28 mmol) was converted into **14b** (210 mg, 79%): brown crystals; mp 98 °C; IR (neat) cm^{–1} 3293 (NH), 2109 (C≡C); ¹H NMR (500 MHz, CDCl₃) δ 1.10 (t, *J* = 7.4 Hz, 3H, CH₃), 2.95–3.01 (m, 2H, CH₂), 3.69 (s, 1H, C≡CH), 5.23 (t, *J* = 5.4 Hz, 1H, NH), 7.49–7.56 (m, 2H, Ar), 7.69 (dd, *J* = 7.4, 1.1 Hz, 1H, Ar), 8.05 (m, *J* = 7.4, 1.1 Hz, 1H, Ar); ¹³C NMR (125 MHz, CDCl₃) δ 15.0, 38.4, 80.3, 85.9, 119.3, 129.18, 129.22, 132.1, 135.2, 141.6. Anal. Calcd for C₁₀H₁₁NO₂S: C, 57.39; H, 5.30; N, 6.69. Found: C, 57.31; H, 5.37; N, 6.64.

2.2.3.13 2-Ethynyl-*N*-*p*-tolylbenzenesulfonamide (14c)

To a solution of 2-bromobenzenesulfonyl chloride **S8** (1.00 g, 3.92 mmol) in DMF (50 mL) was added *p*-toluidine (1.68 g, 15.7 mmol) at 0 °C and the

reaction mixture was stirred at rt for 10 min. The whole was extracted with Et₂O. The extract was washed successively with 1 N HCl and brine, and dried over MgSO₄. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography over silica gel with hexane–EtOAc (5:1) to give **S9c** (1.03 g, 81%) as a colorless solid, which was recrystallized from hexane–CHCl₃ to give pure **S9c** as colorless crystals: mp 151–152 °C; IR (neat) cm⁻¹ 3284 (NH); ¹H NMR (500 MHz, CDCl₃) δ 2.23 (s, 3H, ArCH₃), 6.99–7.02 (m, 4H, Ar), 7.07 (br s, 1H, NH), 7.33–7.37 (m, 2H, Ar), 7.69–7.72 (m, 1H, Ar), 7.97–8.01 (m, 1H, Ar); ¹³C NMR (125 MHz, CDCl₃) δ 20.8, 119.6, 122.2 (2C), 127.7, 129.8 (2C), 132.2, 132.9, 133.9, 134.9, 135.7, 137.8. Anal. Calcd for C₁₃H₁₂BrNO₂S: C, 47.86; H, 3.71; N, 4.29. Found: C, 47.79; H, 3.78; N, 4.25.

By a procedure identical to that described for **S10a**, **S9c** (944 mg, 2.90 mmol) was converted into **S10c** (722 mg, 73%) as an yellow oil. By a procedure identical to that described for **14a**, **S10c** (671 mg, 1.96 mmol) was converted into **14c** as a white solid (283 mg, 53%), which was recrystallized from hexane–CHCl₃ to give pure **14c** as colorless crystals: mp 158 °C; IR (neat) cm⁻¹ 3290 (NH), 2110 (C≡C); ¹H NMR (500 MHz, CDCl₃) δ 2.22 (s, 3H, ArCH₃), 3.77 (s, 1H, C≡CH), 6.98–7.03 (m, 4H, Ar), 7.19 (br s, 1H, NH), 7.36–7.39 (m, 1H, Ar), 7.45–7.48 (m, 1H, Ar), 7.66 (d, *J* = 8.0 Hz, 1H, Ar), 7.89 (d, *J* = 8.0 Hz, 1H, Ar); ¹³C NMR (125 MHz, CDCl₃) δ 20.8, 80.7, 86.0, 119.4, 122.5 (2C), 129.1, 129.8 (3C), 132.4, 133.2, 135.1, 135.7, 140.6. Anal. Calcd for C₁₅H₁₃NO₂S: C, 66.40; H, 4.83; N, 5.16. Found: C, 66.27; H, 4.86; N, 5.27.

2.2.3.14 2-Ethynyl-*N*-phenylbenzenesulfonamide (14d)

By a procedure identical to that described for **S9c**, **S8** (3.00 g, 11.8 mmol) was converted into the known compound **S9d** (2.87 g, 79%) using aniline (3.05 mL, 33.5 mmol).

By a procedure identical to that described for **S10a**, **S9d** (2.50 g, 8.04 mmol) was converted into **S10d** as an yellow oil (2.43 g, 97%). By a procedure identical to that described for **14a**, **S10d** (55.0 mg, 0.18 mmol) was converted into **14d** (33.0 mg, 71%): brown crystals; mp 107 °C; IR (neat) cm⁻¹ 3283 cm⁻¹ (NH), 2111 (C≡C); ¹H NMR (500 MHz, CDCl₃) δ 3.78 (s, 1H, C≡CH), 7.05–7.08 (m, 1H, Ar), 7.13–7.15 (m, 2H, Ar), 7.18–7.21 (m, 2H, Ar), 7.33 (br s, 1H, NH), 7.37–7.40 (m, 1H, Ar), 7.45–7.48 (m, 1H, Ar), 7.65 (dd, *J* = 7.4, 1.1 Hz, 1H, Ar), 7.93 (dd, *J* = 8.0, 1.1 Hz, 1H, Ar); ¹³C NMR (125 MHz, CDCl₃) δ 80.5, 86.1, 119.5, 121.8 (2C), 125.6, 129.1, 129.2 (2C), 129.8, 132.5, 135.1, 136.0, 140.5. Anal. Calcd for C₁₄H₁₁NO₂S: C, 65.35; H, 4.31; N, 5.44. Found: C, 65.43; H, 4.46; N, 5.53.

2.2.3.15 2-Ethynyl-*N*-(4-methoxyphenyl)benzenesulfonamide (14e)

By a procedure identical to that described for **S9c**, **S8** (1.00 g, 3.92 mmol) was converted into **S9e** (1.13 g, 84%) using *p*-anisidine (1.45 g, 11.7 mmol): colorless crystals; mp 127–128 °C; IR (neat) cm^{-1} 3285 (NH); ^1H NMR (500 MHz, CDCl_3) δ 3.71 (s, 3H, OCH_3), 6.72 (d, $J = 8.6$ Hz, 2H, Ar), 7.05 (d, $J = 8.6$ Hz, 2H, Ar), 7.09 (br s, 1H, Ar), 7.31–7.37 (m, 2H, Ar), 7.72 (dd, $J = 7.4$, 1.1 Hz, 1H, Ar), 7.92 (dd, $J = 7.4$, 2.3 Hz, 1H, Ar); ^{13}C NMR (125 MHz, CDCl_3) δ 55.3, 114.4 (2C), 119.6, 125.3 (2C), 127.8, 128.0, 132.2, 133.9, 134.9, 137.7, 158.1. Anal. Calcd for $\text{C}_{13}\text{H}_{12}\text{BrNO}_3\text{S}$: C, 45.63; H, 3.53; N, 4.09. Found: C, 45.78; H, 3.49; N, 4.15.

By a procedure identical to that described for **S10a**, **S9e** (1.03 g, 3.02 mmol) was converted into **S10e** as a yellow oil (778 mg, 72%). By a procedure identical to that described for **14a**, **S10e** (685 mg, 1.91 mmol) was converted into **14e** (364 mg, 66%): pale yellow crystals; mp 122 °C; IR (neat) cm^{-1} 3291 (NH), 2254 cm^{-1} ($\text{C}\equiv\text{C}$); ^1H NMR (500 MHz, CDCl_3) δ 3.71 (s, 3H, OCH_3), 3.78 (s, 1H, $\text{C}\equiv\text{CH}$), 6.71 (d, $J = 8.6$ Hz, 2H, Ar), 7.06 (d, $J = 8.6$ Hz, 2H, Ar), 7.14 (br s, 1H, NH), 7.35–7.38 (m, 1H, Ar), 7.46–7.49 (m, 1H, Ar), 7.68 (d, $J = 8.0$ Hz, 1H, Ar), 7.84 (d, $J = 8.0$ Hz, 1H, Ar); ^{13}C NMR (125 MHz, CDCl_3) δ 55.3, 80.6, 86.2, 114.3 (2C), 119.4, 125.3 (2C), 128.3, 129.1, 129.8, 132.3, 135.0, 140.6, 158.0. Anal. Calcd for $\text{C}_{15}\text{H}_{13}\text{NO}_3\text{S}$: C, 62.70; H, 4.56; N, 4.87. Found: C, 62.77; H, 4.53; N, 4.96.

2.2.3.16 *N*-(4-Chlorophenyl)-2-ethynylbenzenesulfonamide (14f)

By a procedure identical to that described for **S9c**, **S8** (1.00 g, 3.92 mmol) was converted into **S9f** (1.06 g, 78%) using 4-chloroaniline (1.99 g, 15.7 mmol): colorless crystals; mp 133–134 °C; IR (neat) cm^{-1} 3276 (NH); ^1H NMR (500 MHz, CDCl_3) δ 7.08–7.10 (m, 2H, Ar), 7.14–7.17 (m, 2H, Ar), 7.35–7.40 (m, 2H, Ar), 7.49 (br s, 1H, NH), 7.67–7.70 (m, 1H, Ar), 8.01–8.05 (m, 1H, Ar); ^{13}C NMR (125 MHz, CDCl_3) δ 119.6, 122.8 (2C), 127.8, 129.4 (2C), 131.1, 132.3, 134.2, 134.3, 135.1, 137.3. Anal. Calcd for $\text{C}_{12}\text{H}_9\text{BrClNO}_2\text{S}$: C, 41.58; H, 2.62; N, 4.04. Found: C, 41.54; H, 2.62; N, 4.04.

By a procedure identical to that described for **S10a**, **S9f** (0.93 g, 2.71 mmol) was converted into **S10f** (546 mg, 55%) as a yellow oil. By a procedure identical to that described for **14a**, **S10f** (491 mg, 1.35 mmol) was converted into **14f** (238 mg, 61%): yellow crystals; mp 123–124 °C; IR (neat) cm^{-1} 3286 (NH), 2112 ($\text{C}\equiv\text{C}$); ^1H NMR (500 MHz, CDCl_3) δ 3.79 (s, 1H, $\text{C}\equiv\text{CH}$), 7.07–7.10 (m, 2H, Ar), 7.15–7.18 (m, 2H, Ar), 7.37 (br s, 1H, NH), 7.40–7.43 (m, 1H, Ar), 7.48–7.51 (m, 1H, Ar), 7.66 (d, $J = 8.0$ Hz, 1H, Ar), 7.92 (d, $J = 8.0$ Hz, 1H, Ar); ^{13}C NMR (125 MHz, CDCl_3) δ 80.4, 86.3, 119.4, 123.2 (2C), 129.2, 129.4 (2C), 129.8, 131.2, 132.7, 134.5, 135.2, 140.1. Anal. Calcd for $\text{C}_{14}\text{H}_{10}\text{ClNO}_2\text{S}$: C, 57.63; H, 3.45; N, 4.80. Found: C, 57.79; H, 3.64; N, 4.80.

2.2.4 General Procedure for Synthesis of Benzo[e][1,2]thiazine-1,1-dioxide

2.2.4.1 3-[(*N,N*-Diisopropylamino)methyl]-2-methyl-2*H*-benzo[e][1,2]thiazine-1,1-dioxide (15a)

To a stirred mixture of **14a** (50.0 mg, 0.26 mmol), (HCHO)_n (15.4 mg, 0.51 mmol), and CuBr (1.8 mg, 0.013 mmol) in dioxane (3 mL) was added diisopropylamine (43.1 μ L, 0.31 mmol) at rt under argon. The reaction mixture was stirred at 100 °C for 16 h. Concentration under reduced pressure followed by column chromatography purification over silica gel with hexane–EtOAc (8:1) gave **15a** as a pale yellow solid (27.2 mg, 34%): mp 94.5–98.5 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.06 (d, *J* = 6.9 Hz, 12H, 4 $\times$ CHCH₃), 3.11–3.19 (m, 2H, 2 $\times$ CH), 3.40 (s, 3H, NCH₃), 3.50 (s, 2H, NCH₂), 6.51 (s, 1H, 4-H), 7.32 (d, *J* = 8.0 Hz, 1H, Ar), 7.39–7.42 (m, 1H, Ar), 7.52–7.55 (m, 1H, Ar), 7.84 (d, *J* = 8.0 Hz, 1H Ar); ¹³C NMR (125 MHz, CDCl₃) δ 20.4 (4C), 30.9, 47.5 (2C), 48.4, 109.0, 121.5, 126.3, 126.8, 130.5, 131.7, 132.9, 143.5. Anal. Calcd for C₁₆H₂₄N₂O₂S: C, 62.30; H, 7.84; N, 9.08. Found: C, 62.09; H, 7.57; N, 8.88.

2.2.4.2 3-[(*N,N*-Diisopropylamino)methyl]-2-ethyl-2*H*-benzo[e][1,2]thiazine-1,1-dioxide (15b)

By a procedure identical to that described for **15a**, **14b** (25.0 mg, 0.12 mmol) was converted into **15b** as an yellow oil (14.3 mg, 37%): ¹H NMR (500 MHz, CDCl₃) δ 1.06 (d, *J* = 6.3 Hz, 12H, 4 $\times$ CHCH₃), 1.09 (t, *J* = 7.2 Hz, 3H, CH₂CH₃), 3.11–3.18 (m, 2H, 2 $\times$ NCH), 3.49 (s, 2H, NCH₂), 3.95 (q, *J* = 7.2 Hz, 2H, CH₂CH₃), 6.66 (s, 1H, 4-H), 7.33 (d, *J* = 8.0 Hz, 1H, Ar), 7.40–7.43 (m, 1H, Ar), 7.51–7.54 (m, 1H, Ar), 7.83 (d, *J* = 8.0 Hz, 1H, Ar); ¹³C NMR (125 MHz, CDCl₃) δ 15.3, 20.4 (4C), 40.4, 47.7 (2C), 47.9, 110.9, 121.3, 126.5, 127.0, 131.6 (2C), 132.8, 142.9; MS (FAB) *m/z* (%): 323 (MH⁺, 100); HRMS (FAB) calcd for C₁₇H₂₇N₂O₂S (MH⁺): 323.1793; found, 323.1765.

2.2.4.3 3-[(*N,N*-Diisopropylamino)methyl]-2-(*p*-tolyl)-2*H*-benzo[e][1,2]thiazine-1,1-dioxide (15c)

By a procedure identical to that described for **15a** from **14a**, **14c** (25.0 mg, 0.09 mmol) was converted into **15c** (31.9 mg, 90%): colorless crystals; mp 100–101 °C; ¹H NMR (500 MHz, CDCl₃) δ 0.90 (d, *J* = 6.3 Hz, 12H, 4 $\times$ CH₃), 2.34 (s, 3H, ArCH₃), 3.01–3.08 (m, 2H, 2 $\times$ NCH), 3.21 (d, *J* = 1.1 Hz, 2H, NCH₂), 6.92 (s, 1H, 4-H), 7.06 (d, *J* = 8.6 Hz, 2H, Ar), 7.14 (d, *J* = 8.6 Hz, 2H, Ar), 7.40–7.44 (m, 2H, Ar), 7.56–7.59 (m, 1H, Ar), 7.78 (d, *J* = 8.0 Hz, 1H, Ar); ¹³C NMR (125 MHz, CDCl₃) δ 20.5 (4C), 21.3, 47.8, 48.2 (2C), 111.6, 122.4, 127.0, 127.4, 128.1 (2C), 129.6 (2C), 131.4, 132.0, 133.1, 133.2, 138.5, 145.0.

Anal. Calcd for $C_{22}H_{28}N_2O_2S$: C, 68.72; H, 7.34; N, 7.29. Found: C, 68.45; H, 7.46; N, 7.13.

2.2.4.4 3-[(*N,N*-Diisopropylamino)methyl]-2-phenyl-2*H*-benzo[*e*][1,2]thiazine-1,1-dioxide (15d)

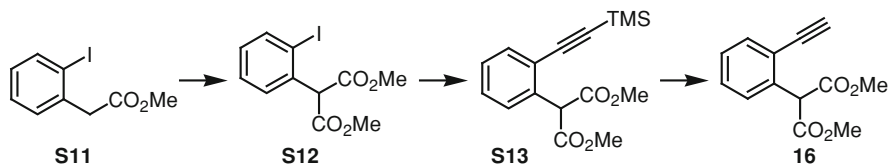
By a procedure identical to that described for **15a** from **14a**, **14d** (25.0 mg, 0.10 mmol) was converted into **15d** (33.0 mg, 92%): colorless crystals; mp 73.5–74.0 °C; 1H NMR (500 MHz, $CDCl_3$) δ 0.88 (d, J = 6.3 Hz, 12H, 4 $\times$ CH_3), 3.00–3.08 (m, 2H, 2 $\times$ NCH), 3.23 (s, 2H, NCH₂), 6.92 (s, 1H, 4-H), 7.18–7.20 (m, 2H, Ar), 7.30–7.36 (m, 3H, Ar), 7.41–7.45 (m, 2H, Ar), 7.57–7.60 (m, 1H, Ar), 7.79 (d, J = 7.4 Hz, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.4 (4C), 47.8, 47.9 (2C), 112.0, 122.4, 127.1, 127.5, 128.28 (2C), 128.31, 128.9 (2C), 131.6, 132.1, 133.0, 135.9, 144.8. Anal. Calcd for $C_{21}H_{26}N_2O_2S$: C, 68.08; H, 7.07; N, 7.56. Found: C, 67.96; H, 7.22; N, 7.26.

2.2.4.5 3-[(*N,N*-Diisopropylamino)methyl]-2-(4-methoxyphenyl)-2*H*-benzo[*e*][1,2]thiazine-1,1-dioxide (15e)

By a procedure identical to that described for **15a** from **14a**, **14e** (25.0 mg, 0.09 mmol) was converted into **15e** as a yellow oil (31.1 mg, 89%): 1H NMR (500 MHz, $CDCl_3$) δ 0.91 (d, J = 6.9 Hz, 12H, 4 $\times$ $CHCH_3$), 3.00–3.08 (m, 2H, 2 $\times$ NCH), 3.20 (s, 2H, NCH₂), 3.79 (s, 3H, OCH₃), 6.85 (d, J = 9.2 Hz, 2H, Ar), 6.88 (s, 1H, 4-H), 7.10 (d, J = 9.2 Hz, 2H, Ar), 7.41–7.44 (m, 2H, Ar), 7.56–7.59 (m, 1H, Ar), 7.79 (d, J = 7.4 Hz, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.5 (4C), 47.8, 48.1 (2C), 55.5, 112.2, 114.2 (2C), 122.4, 127.0, 127.3, 128.5, 129.6 (2C), 131.3, 132.0, 133.1, 145.1, 159.6; MS (FAB) m/z (%): 401 (MH^+ , 65); HRMS (FAB) calcd for $C_{22}H_{29}N_2O_3S$ (MH^+): 401.1899; found, 401.1893.

2.2.4.6 2-(4-Chlorophenyl)-3-[(*N,N*-diisopropylamino)methyl]-2*H*-benzo[*e*][1,2]thiazine-1,1-dioxide (15f)

By a procedure identical to that described for **15a** from **14a**, **14f** (25.0 mg, 0.09 mmol) was converted into **15f** (33.1 mg, 95%): colorless crystals; mp 113–114 °C; 1H NMR (500 MHz, $CDCl_3$) δ 0.89 (d, J = 6.9 Hz, 12H, 4 $\times$ CH_3), 3.01–3.09 (m, 2H, 2 $\times$ NCH), 3.22 (d, J = 1.1 Hz, 2H, NCH₂), 6.91 (s, 1H, 4-H), 7.10–7.13 (m, 2H, Ar), 7.30–7.33 (m, 2H, Ar), 7.43–7.46 (m, 2H, Ar), 7.58–7.61 (m, 1H, Ar), 7.78 (d, J = 7.4 Hz, 1H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.4 (4C), 47.8, 47.9 (2C), 112.7, 122.5, 127.2, 127.7, 129.1 (2C), 129.4 (2C), 131.5, 132.3, 132.8, 134.2, 134.5, 144.3; MS (FAB) m/z (%): 405 (MH^+ , 72). Anal. Calcd for $C_{21}H_{25}ClN_2O_2S$: C, 62.28; H, 6.22; N, 6.92. Found: C, 62.15; H, 6.31; N, 6.87.



2.2.4.7 Dimethyl 2-(2-Iodophenyl)malonate (S12)

To a solution of NaH (0.80 g, 20.1 mmol) in $C(O)(OMe)_2$ (15 mL) was added **S11** (1.38 g, 5.01 mmol) at 0 °C. The reaction mixture was stirred at rt for 1.5 h and additional 0.5 h under reflux. To a mixture was added saturated aqueous NH_4Cl at 0 °C, and the mixture was stirred for 10 min. Then water was added and the mixture was extracted with CH_2Cl_2 three times. The organic layer was dried over $MgSO_4$. Usual workup followed by purification by column chromatography over silica gel with hexane–EtOAc (5:1) gave the known compound **S12** (1.38 g, 83%).

2.2.4.8 Dimethyl 2-(2-Ethynylphenyl)malonate (16)

To a stirred solution of **S12** (1.26 g, 3.77 mmol), $PdCl_2(PPh_3)_2$ (66.6 mg, 0.094 mmol) and CuI (17.9 mg, 0.094 mmol) in a mixed solvent of THF (2 mL) and Et_3N (25 mL) was added TMS-acetylene (0.62 mL, 4.52 mmol) at rt under argon, and the reaction mixture was stirred at 55 °C for 20 min. The mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography over silica gel with hexane–EtOAc (5:1) to give **S13** as a brown oil (1.13 g, 99%). To a solution of **S13** (0.89 g, 2.90 mmol) in THF (10 mL) was added TBAF (1 mol/L in THF, 3.05 mL, 3.05 mmol) at –78 °C and the reaction mixture was stirred for 25 min at this temperature. After the reaction mixture was quenched with aqueous saturated citric acid, the whole was extracted with Et_2O . The extract was washed successively with water, aqueous saturated $NaHCO_3$, and brine, and dried over $MgSO_4$. Usual workup followed by purification by column chromatography over silica gel with hexane–EtOAc (8:1) gave **16** (509.2 mg, 76%) as a red solid which was recrystallized from hexane– $CHCl_3$ to give pure **16** as pink crystals: mp 41–42 °C; IR (neat) cm^{-1} 2106 ($C\equiv C$), 1733 cm^{-1} ($C=O$); 1H NMR (500 MHz, $CDCl_3$) δ 3.32 (s, 1H, $C\equiv CH$), 3.76, (s, 6H, 2 $\times$ OMe), 5.37 (s, 1H, ArCH), 7.28–7.31 (m, 1H, Ar), 7.36–7.40 (m, 1H, Ar), 7.50–7.54 (m, 2H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.3 (2C), 55.0, 81.0, 82.3, 122.6, 128.0, 128.8, 129.2, 132.8, 134.9, 168.3 (2C). Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.14; H, 5.24.

2.2.4.9 Dimethyl 2-[(*N,N*-Diisopropylamino)methyl]indene-1,1-dicarboxylate (17)

To a stirred mixture of **16** (51.0 mg, 0.22 mmol), (HCHO)_n **2a** (13.2 mg, 0.44 mmol), and CuBr (1.58 mg, 0.011 mmol) in DMF (2 mL) was added **3a** diisopropylamine (34.0 μ L, 0.24 mmol) at rt under argon. After the reaction mixture was stirred at 110 °C for 30 min, diisopropylethylamine (77.0 μ L, 0.44 mmol) was added to the mixture. The mixture was additionally stirred at 110 °C for 9.5 h. Concentration under reduced pressure followed by purification by column chromatography over alumina with hexane–EtOAc (20:1) gave **17** (52.8 mg, 70%) as a brown oil: IR (neat) 1732 (C=O) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.02 (d, J = 14.0 Hz, 12H, 4 $\times$ CCH₃), 3.06–3.11 (m, 2H, 2 $\times$ NCH), 3.50 (d, J = 1.1 Hz, 2H, NCH₂), 3.73 (s, 6H, 2 $\times$ OCH₃), 7.00 (s, 1H, 3-H), 7.15–7.18 (m, 1H, Ar), 7.24–7.31 (m, 2H, Ar), 7.57 (d, J = 7.4 Hz, 1H, Ar); ^{13}C NMR (125 MHz, CDCl_3) δ 20.7 (4C), 43.8, 48.7, 53.0 (2C), 70.3, 120.8, 124.8, 125.1, 128.7, 131.6, 141.0, 144.3, 149.4, 168.9 (2C); MS (FAB) m/z : 346 (MH^+ , 100), 286 (35), 245 (60); HRMS (FAB) calcd for $\text{C}_{20}\text{H}_{28}\text{NO}_4$ (MH^+), 346.2018; found, 346.2008.

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