Novel Synthesis of a New Skeletal Compound Benzonaphthazepine by Regioselective C-H Activation Utilizing the Intramolecular Coordination of an Amine to Pd

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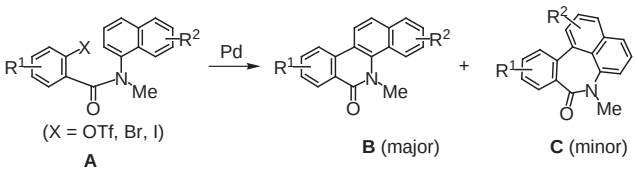
Abstract: The novel synthesis of a new skeletal compound, benzonaphthazepine, from *N*-bromobenzylnaphthylamine using a Pd reagent is described. In the biaryl coupling reaction of *N*-bromobenzylnaphthylamine using a Pd reagent, the intramolecular coordination of the benzylamino group to Pd causes regioselective C-H activation at the *peri* position relative to the amine group on the naphthalene ring, producing benzonaphthazepine in good to excellent yield. The bulkiness of the substituent at C_7 on the naphthalene ring affects the regioselectivity of the biaryl coupling reaction.

Key Words: C-H activation, heterocycles, palladium, regioselectivity, coordination

Palladium-assisted biaryl coupling reactions have been used to synthesize many polycyclic aromatic compounds.[1] Recently, we reported that intramolecular biaryl coupling reactions of 2-halo-*N*-arylbenzamides using palladium reagents were very useful methods to synthesize polycyclic aromatic lactams, some of which can be transformed into several condensed heteroaromatic alkaloids.[2] Moreover, we succeeded in synthesizing pyrroloquinazoline alkaloids, luotonine A and B, and pyrrolophenanthridine alkaloids using this method.[3] In the biaryl coupling reaction of 2-halo-*N*-naphthylbenzamide **A** using a Pd reagent, a small amount of benzonaphthazepinone **C**, which is a new skeletal compound, was always obtained along with the expected benzo[*c*]phenanthridone **B**, as shown in Scheme 1.[2b,c,2e–g] Since benzonaphthazepine, which is the parent skeleton of **C**, is a new skeletal compound, we planned to develop a general synthetic method for benzonaphthazepine utilizing a Pd-assisted biaryl coupling reaction. The results are the subject of this paper.[4]

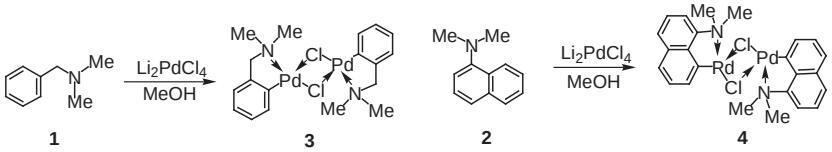
In 1967, Cope et al. reported that cyclopalladation reactions of benzylamine **1** and naphthylamine **2** with palladium (II) chlorides selectively gave palladacycles **3** and **4**, respectively, indicating that regioselective C-H bond activation occurs at the *ortho* position relative to the methylene group of **1** and the *peri* position relative to the amino group of **2**, respectively (see Scheme 2).[5] Therefore, we envisioned that the intramolecular biaryl coupling reaction of *N*-(2-bromobenzyl)naphthylamine **D** using Pd reagent would afford a new skeletal compound, benzonaphthazepine **E**, directly, via oxidative addition to Pd(0) and coordination of the amine to Pd(II), followed by the regioselective electrophilic substitution of Pd(II) at the *peri* position and reductive elimination of Pd(0), as shown in Scheme 3 (phosphine ligands are omitted for clarity).[1c,6]

To verify the coordination effect of the amine on the intramolecular biaryl coupling reaction, the coupling reaction of *N*-(2-bromobenzyl)naphthylamine (**5a**) was first examined in relation to synthetic studies of fagaridine and decarine,[2f] because 2-bromo-*N*-naphthylbenzamide (**A**) gave **B** as a major product and **C** as a minor product.[2b,c,2e–g]



Scheme 1 Pd-assisted biaryl coupling reaction of *N*-naphthylbenzamide **A**

Compound **5a** was synthesized from 6-bromo-3-isopropoxy-2-methoxybenzyl bromide (**6a**), which was prepared from 3-isopropoxy-2-methoxybenzaldehyde[7] in 54% yield via reduction with $NaBH_4$ and bromination with Br_2, and *N*-methyl-6,7-methylenedioxy-1-naphthyl-



Scheme 2 Palladacycles of benzylamine **1** and naphthylamine **2**

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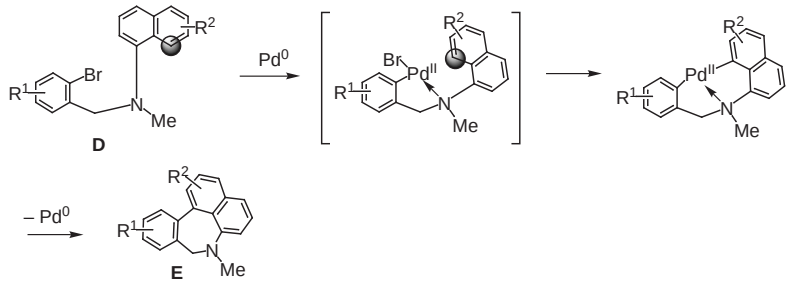


Scheme 3 Synthetic strategy of naphthylbenzazepine **E** from *N*-benzylnaphthylamine **D** using regioselective C-H activation by Pd

amine (**7a**)[2e] in the presence of K_2CO_3 and Bu_4NI in DMF at 100 °C (Table 1, entry 1). Then, we investigated the coupling reaction using a system combining $Pd(OAc)_2$, P(*o*-tol)$_3$, and Ag_2CO_3 in degassed DMF under reflux, because the coupling reaction of bromo-naphthobenzamide **A** under the same reaction conditions produced **B** and **C** in good to excellent yields. However, no coupling reaction occurred (Table 2, entry 1). Subsequently, coupling reactions under various conditions were examined and the results are summarized in Table 2.[8] Using K_2CO_3, $KHCO_3$, or Cs_2CO_3 as the base, the biaryl coupling reaction proceeded smoothly to provide only benzonaphthazepine **8a**, a new skeletal compound, in good yields (Table 2, entries 10–13), while organic bases were not effective (Table 2, entries 2–4). The reaction using Cy_3P as a ligand gave **8a** in a good yield as well as that using (*o*-tol)$_3$P (Table 2, entry 13). We decided to use (*o*-tol)$_3$P as the ligand, because it was easier to separate each product from the extracts. The structures of the products (**8a** and **9a**) were elucidated using elemental analyses and ^{1}H NMR data, in which **8a** showed only one singlet signal (δ = 7.02) due to the aromatic proton in addition to the signals due to other aromatic protons. This indicates that the coordination of the amine group to Pd is very important for the production of **8a** via the intramolecular biaryl coupling reaction.

Moreover, in order to prove the contribution of the amine group, the biaryl coupling reaction of *N*-acetate **11** was examined. Compound **11** was prepared by the acetylation of *N*-benzylnaphthylamine **10**, which was synthesized from 6-bromo-3-hydroxy-2-methoxybenzaldehyde[9] via etherification with isopropyl bromide, followed by reductive alkylation with 6,7-methylenedioxy-1-naphthylamine and $NaBH_4$. The reaction of **11** using Pd afforded *N*-acetyl benzo[*c*]phenanthridine **12** and *N*-acetyl benzonaphthazepine **13** in 45% and 55% yields, respectively (see Scheme 4). This strongly supports the contribution of the benzylamino group to the production of **8a**, as shown in Scheme 3.

Next, in order to examine the generality of this method, we examined the coupling reaction of *N*-(6′-bromobenzyl)-1-naphthylamines **5b–i** using a system combining $Pd(OAc)_2$, P(*o*-tol)$_3$, and K_2CO_3 in degassed DMF. For this, 6,7-dimethoxy-*N*-methyl-1-naphthylamine (**7c**) and 7-isopropoxy-6-methoxy-*N*-methyl-1-naphthylamine (**7d**) were first prepared from 6,7-dimethoxy-1-naphthylamine[10] and 7-isopropoxy-6-methoxy-1-naphthylamine[10] in 86% and 76% yields, respectively, via trifluoroacetylation, methylation with MeI, and alkaline hydrolysis. Then, the starting materials (**5b–i**) for the coupling reaction were synthesized from dibromides **6a–c**[11] and *N*-

Table 1 Synthesis of *N*-(6′-Bromobenzyl)-1-naphthylamine **5** from Benzyl Bromide **6** and Naphthylamine **7**

Entry	Substituent	Method[a]	Product	Yield (%)
1	R^1 = OMe, R^2 = O*i*-Pr, $R^3 + R^4 = OCH_2O$	A	**5a**	71
2	$R^1 = R^2 = R^3 = R^4$ = H	A	**5b**	98
3	$R^1 = R^2$ = H, $R^3 + R^4 = OCH_2O$	A	**5c**	70
4	$R^1 = R^2$ = OMe, $R^3 = R^4$ = H	A	**5d**	63
5	$R^1 = R^2$ = OMe, $R^3 + R^4 = OCH_2O$	A	**5e**	98
6	$R^1 = R^2$ = H, $R^3 = R^4$ = OMe	B	**5f**	95
7	$R^1 = R^2 = R^3 = R^4$ = OMe	B	**5g**	74
8	$R^1 = R^2$ = H, R^3 = OMe, R^4 = O*i*-Pr	B	**5h**	quant.
9	$R^1 = R^2 = R^3$ = OMe, R^4 = O*i*-Pr	B	**5i**	96

[a] Method A: K_2CO_3, Bu_4NI, DMF, 100 °C, 1–2 h; Method B: *i*-Pr_2NEt, DMF, 100 °C, 1 h.

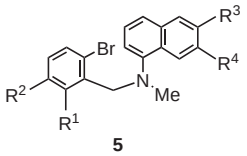
Table 2 Results of the Coupling Reaction of *N*-(6-Bromo-3-isopropoxy-2-methoxybenzyl)-*N*-methyl-6,7-methylenedioxy-1-naphthylamine (**5a**) in DMF under Reflux[a]

Entry	Ligand (L/Pd)	Base	Time (h)	Yield (%)		
				8a	**9a**	**5a**
1	P(*o*-tol)$_3$ (2)	Ag_2CO_3	12	–	18	55
2	P(*o*-tol)$_3$ (2)	Et_3N	6	–	18	69
3	P(*o*-tol)$_3$ (2)	pyridine	6	–	–	63
4	P(*o*-tol)$_3$ (2)	DBU	4	–	trace	65
5	P(*o*-tol)$_3$ (2)	KOH	4	13	56	–
6	P(*o*-tol)$_3$ (2)	*t*-BuOK	8	13	41	–
7	P(*o*-tol)$_3$ (2)	Li_2CO_3	4	–	–	99
8	P(*o*-tol)$_3$ (2)	Na_2CO_3	6	13	13	61
9	P(*o*-tol)$_3$ (2)	$CaCO_3$	4	–	–	93
10	P(*o*-tol)$_3$ (2)	K_2CO_3	2	76	trace	18
11	P(*o*-tol)$_3$ (2)	KHCO3	2	66	–	7
12	P(*o*-tol)$_3$ (2)	Cs_2CO_3	3	75	12	10
13	Cy_3P (2)	K_2CO_3	2	75	8	–
14[b]	DPPP (1)	K_2CO_3	2	48	9	–
15[c]	–	KOAc	2	–	–	96
16[d]	–	KOAc	2	–	–	39
17	–	K_2CO_3	2	–	–	74
18	P(*o*-tol)$_3$ (2)	–	6	–	12	79

[a] All reactions were carried out using $Pd(OAc)_2$ (0.2 equiv), P(*o*-tol)$_3$ (0.4 equiv), and base (2 equiv) under Ar atmosphere.
[b] One equiv of Bu_3P was added.
[c] Reaction was carried out using KOAc (5.5 equiv) at 130 °C.
[d] Reaction was carried out using KOAc (5.5 equiv) and *N*-methyl-6,7-methylenedioxy-1-naphthylamine (**7a**) was obtained in 20 % yield.

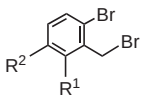
methyl-1-naphthylamines **7a**[2e]–**d** using Method A or B (see the experimental section) in high yields, as shown in Table 1. Subsequently, the coupling reaction of **5** using a Pd reagent was examined, and the results are summarized in Table 3. *N*-Bromobenzylnaphthylamines **5b**–**e** that possess a methylenedioxy group or no substituent group on the naphthalene ring produced only benzonaphthazepines **8b**–**e** in moderate to high yields (Table 3, entries 2–5). Interestingly, *N*-bromobenzylnaphthylamines **5f** and **5g** that possess a methoxy group at C_7 on the naphthalene ring produced benzonaphthazepines **8f** and **8g**) and benzo[*c*]phenanthridines **14f** and **14g**[12] (Figure 1) along with debromo-products **9f** and **9g** (Table 3, entries 6 and 7). The proposed mechanism is illustrated in Scheme 5. The methoxy group at C_7 on the naphthalene ring might hinder the coupling reaction at the *peri* position (C_8 position) relative to the amino group on the naphthalene ring.[13] Subsequently, the reaction of *N*-bromobenzylnaphthylamines **5h** and **5i**) possessing a bulky isopropoxy group relative to a methoxy group at C_7 on the naphthalene ring was examined and they produced benzo[*c*]phenanthridines (**14h** and **14i**) along with debromo- and demethylated products (**9** and **15**) (Table 3, entries 8 and 9). These results strongly support the proposed mechanism shown in Scheme 5. The structures of the products were elucidated using ^{1}H NMR data, elementary analysis, and MS data. The δ values of the *N*-methyl signals were especially useful for structure elucidation. *N*-Methyl signals appeared at δ = 2.97–3.08 for the benzonaphthazepines **5**, δ = 2.62–2.65 for the benzo[*c*]phenanthridines **14**, and δ = 2.75–2.84 for the dibromo amines **9**.

To examine the effect of the location of the leaving group on the coupling reaction using Pd, *N*-benzylbromonaphthylamine **16**, which possesses a bromo group on the naphthalene ring as the leaving group, was synthesized. Bromonaphthylamine **7e** was prepared from 2-bromo-6,7-methylenedioxy-1-naphthylamine[14] in 78% total yield via trifluoroacetylation, *N*-methylation with MeI, and hydrolysis with alkaline. *N*-Benzylation of **7e** with benzyl bromide using Method A in Table 1 gave **16** in 98% yield.



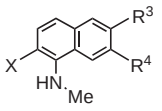
5

5a : R^1=OMe, R^2=O^{i}Pr, R^3+R^4=OCH_2O
5b : R^1=R^2=R^3=R^4=H
5c : R^1=R^2=H, R^3+R^4=OCH_2O
5d : R^1=R^2=OMe, R^3=R^4=H
5e : R^1=R^2=OMe, R^3+R^4=OCH_2O
5f : R^1=R^2=H, R^3=R^4=OMe
5g : R^1=R^2=R^3=R^4=OMe
5h : R^1=R^2=H, R^3=OMe, R^4=O^{i}Pr
5i : R^1=R^2=R^3=OMe, R^4=O^{i}Pr

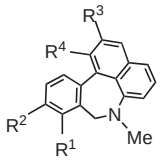


6

6a : R^1=OMe, R^2=O^{i}Pr,
6b : R^1=R^2=H,
6c : R^1=R^2=OMe,

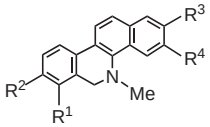


7a : R^3+R^4=OCH_2O, X=H
7b : R^3=R^4=H, X=H
7c : R^3=R^4=OMe, X=H
7d : R^3=OMe, R^4=O^{i}Pr, X=H
7e : R^3+R^4=OCH_2O, X=Br

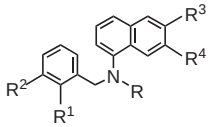


8

8a : R^1=OMe, R^2=O^{i}Pr, R^3+R^4=OCH_2O
8b : R^1=R^2=R^3=R^4=H
8c : R^1=R^2=H, R^3+R^4=OCH_2O
8d : R^1=R^2=OMe, R^3=R^4=H
8e : R^1=R^2=OMe, R^3+R^4=OCH_2O
8f : R^1=R^2=H, R^3=R^4=OMe
8g : R^1=R^2=R^3=R^4=OMe

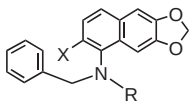


14



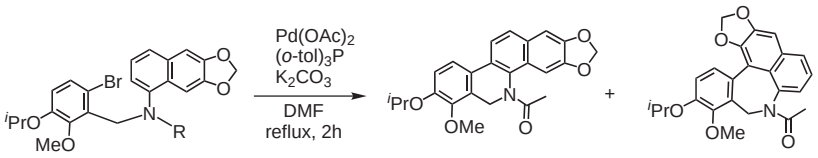
9 : R = Me
15 : R = H

f : R^1=R^2=H, R^3=R^4=OMe
g : R^1=R^2=R^3=R^4=OMe
h : R^1=R^2=H, R^3=OMe, R^4=O^{i}Pr
i : R^1=R^2=R^3=OMe, R^4=O^{i}Pr



16 : R=Me, X=Br
17 : R=X=H

Figure 1



10 R=H
11 R=Ac

12
(45%)

13
(55%)

Scheme 4 Biaryl coupling reaction of amide **11**

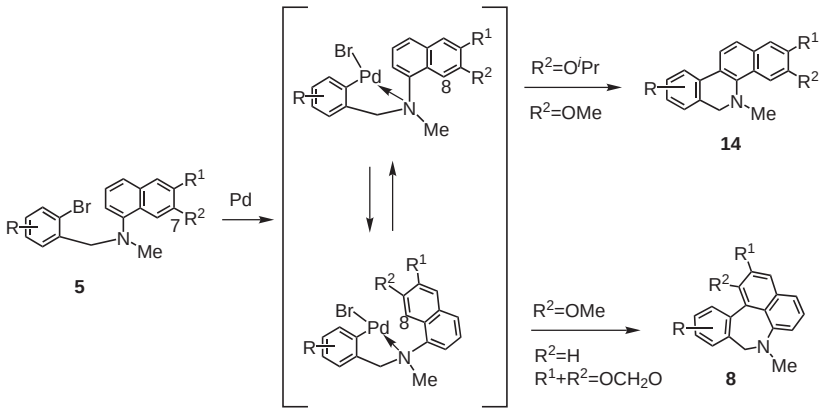
The coupling reaction of **16** using $Pd(OAc)_2$, P(*o*-tol)$_3$, and K_2CO_3 in degassed DMF gave a debromo-demethyl compound **17** and *N*-methyl-6,7-methylenedioxy-1-naphthylamine (**7a**)[2e] in 59% and 29% yields, respectively, and no coupling product. The proposed mechanism is shown in Scheme 6. The elimination of a proton from the coordinated intermediate (**F**) may help to relieve the strain on the four-membered ring.

Consequently, in a biaryl coupling reaction of *N*-bromobenzylnaphthylamine **5** using a Pd reagent, the intramolecular coordination of the benzylamino group to Pd causes regioselective C-H activation to produce a new skeletal compound, benzonaphthazepine **8**, and the bulkiness of the substituent at C_7 on the naphthalene ring affects the regioselectivity of the biaryl coupling reaction.

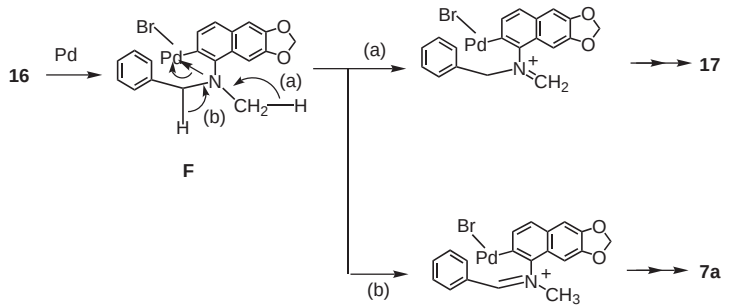
Table 3 Results of the Coupling Reaction of Substituted *N*-(6-Bromobenzyl)-*N*-methyl-1-naphthylamines **5** in DMF under Reflux[a]

Entry		Substrate	Yield (%)			
			8	**14**	**9**	**15**
1	**5a**[b]	R^1 = OMe, R^2 = O*i*-Pr, $R^3 + R^4 = OCH_2O$	76	–	trace	–
2	**5b**	$R^1 = R^2 = R^3 = R^4$ = H	81	–	–	–
3	**5c**	$R^1 = R^2$ = H, $R^3 + R^4 = OCH_2O$	86	–	–	–
4	**5d**	$R^1 = R^2$ = OMe, $R^3 = R^4$ = H	44	–	–	–
5	**5e**	$R^1 = R^2$ = OMe, $R^3 + R^4 = OCH_2O$	60	–	–	–
6	**5f**	$R^1 = R^2$ = H, $R^3 = R^4$ = OMe	22	33	12	–
7	**5g**	$R^1 = R^2 = R^3 = R^4$ = OMe	18	34	10	10
8	**5h**	$R^1 = R^2$ = H, R^3 = OMe, R^4 = O*i*-Pr	–	44	11	20
9	**5i**	$R^1 = R^2 = R^3$ = OMe, R^4 = O*i*-Pr	–	53	11	26

[a] All reactions were carried out using $Pd(OAc)_2$ (0.2 equiv), P(*o*-Tol)$_3$ (0.4 equiv), and K_2CO_3 (2 equiv) under Ar atmosphere for 2 h.
[b] See entry 10 in Table 2.



Scheme 5 Proposed mechanism for the biaryl coupling reaction of *N*-(bromobenzyl)naphthylamine **5** with Pd



Scheme 6 Proposed mechanism for the reaction of *N*-benzyl-1-naphthylamine **16** with Pd

Melting points were measured on a micro-melting point hot-stage apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded on JASCO A-102 or FT/IR 350 spectrophotometers, and ^{1}H NMR spectra in $CDCl_3$ were recorded on JNM-MY60FT (60 MHz), Varian VXR-200 (200 MHz), or VXR-500 (500 MHz) spectrometers. NMR spectral data are reported in ppm downfield from the internal standard TMS (δ = 0.0) and the coupling constants are given in Hz. MS spectra were obtained on a VG-70SE spectrometer. Column chromatography was carried out with Merck silica gel (230–400 mesh) and Wako activated alumina (300 mesh). All the experiments were carried out in an argon atmosphere, unless otherwise noted, and the extract was washed with brine, dried over anhyd K_2CO_3, and filtered, and the filtrate was concentrated to dryness un-

der reduced pressure. $Pd(OAc)_2$ was treated with boiling benzene and the mixture was filtered while hot. The hot filtrate was then concentrated to dryness to give purified $Pd(OAc)_2$.

6-Bromo-3-isopropoxy-2-methoxybenzyl Bromide (6a); Typical Procedure

To a suspension of $NaBH_4$ (195 mg, 5.15 mmol) in anhyd MeOH (40 mL) was added 3-isopropoxy-2-methoxybenzaldehyde[6] (2.0 g, 1.03 mmol) and the mixture was stirred for 30 min at r.t. The reaction mixture was poured into water and extracted with EtOAc. The residue dissolved in $CHCl_3$ was subjected to column chromatography on silica gel. Elution with EtOAc–hexane (1:5) gave 3-isopropoxy-2-methoxybenzylalcohol (1.86 g, 92%) as a colorless oil. To the solution of 3-isopropoxy-2-methoxybenzylalcohol (1.5 g, 7.64 mmol) in $CHCl_3$ (80 mL) was then added dropwise a solution of bromine (0.47 mL, 9.17 mmol) in $CHCl_3$ (10 mL) under ice-cooling. The mixture was stirred for 3 h at r.t. and the solvent was evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ and subjected to column chromatography on silica gel. Elution with EtOAc–hexane (1:20) gave **6a** (1.52 g, 59%); colorless needles; mp 61–62 °C (Et_2O).

3-Isopropoxy-2-methoxybenzylalcohol

IR ($CHCl_3$): 3463 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.37 (d, *J* = 6.5 Hz, 6 H), 3.90 (s, 3 H), 4.56 (septet, *J* = 6.0 Hz, 1 H), 4.68 (s,2 H), 6.87–7.02 (m, 3 H).

FAB–MS: *m*/*z* calcd for $C_{11}H_{16}O_3$: 196.1099; found: 196.1134.

6-Bromo-3-isopropoxy-2-methoxybenzyl Bromide (6a)

^1H NMR (200 MHz, $CDCl_3$): δ = 1.36 (d, *J* = 6.0 Hz, 6 H), 3.98 (s, 3 H), 4.52 (septet, *J* = 6.0 Hz, 1 H), 4.70 (s, 2 H), 6.77 (d, *J* = 9.0 Hz, 1 H), 7.23 (d, *J* = 9.0 Hz, 1 H).

FAB–MS: *m*/*z* = 336 $[M]^+$, 338 $[M + 2]^+$, 340 $[M + 4]^+$.

Anal. Calcd for $C_{11}H_{14}Br_2O_2$: C, 39.08; H, 4.17. Found: C, 39.32; H, 4.23.

6,7-Dimethoxy-*N*-methyl-1-naphthylamine (7c); Typical Procedure

To a solution of 6,7-dimethoxy-1-naphthylamine[8] (3.12 g, 15.35 mmol) in anhyd pyridine (40 mL) was added TFAA (3.30 mL, 23.03 mmol). The reaction mixture was stirred at r.t. for 30 min and poured into ice water. The mixture was made acidic with 10% HCl and extracted with EtOAc. The residue was recrystallized from EtOAc–hexane to give *N*-(6,7-dimethoxy-1-naphthyl)trifluoroacetamide (4.00 g, 87%) as colorless needles; mp 146–147 °C. To the solution of *N*-(6,7-dimethoxy-1-naphthyl)trifluoroacetamide (4.26 g, 14.24 mmol) and MeI (3.54 mL, 56.94 mmol) in anhyd acetone (120 mL) was added solid KOH (3.20 g, 56.94 mmol). The reaction mixture was refluxed for 45 min and the solvent removed under reduced pressure. The residue was dissolved in EtOH (80 mL) and aq 5% NaOH solution (80 mL), and refluxed for 15 min. The reaction mixture was diluted with water and extracted with Et_2O. The residue dissolved in $CHCl_3$ was subjected to column chromatography on Al_2O_3. Elution with hexane–EtOAc (10:1) gave **7c** (2.54 g, 82%) as colorless needles; mp 168–170 °C (MeOH).

***N*-(6,7-Dimethoxy-1-naphthyl)trifluoroacetamide**

IR (KBr): 3256, 1705 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.99 (s, 3 H), 4.01 (s, 3 H), 6.92 (s, 1 H), 7.16 (s, 1 H), 7.36 (dt, *J* = 8.0, 7.9 Hz, 1 H), 7.57 (br d, *J* = 7.9 Hz, 1 H), 7.68 (br d, *J* = 8.0 Hz, 1 H), 8.07 (br s, 1 H).

Anal. Calcd for $C_{14}H_{12}F_3NO_3$: C, 56.19; H, 4.04; N, 4.68. Found: C, 56.38; H, 4.02; N, 4.66.

6,7-Dimethoxy-*N*-methyl-1-naphthylamine (7c)

IR (KBr): 3400 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.02 (s, 3 H), 3.99 (s, 3 H), 4.01 (s, 3 H), 6.57 (dd, *J* = 7.4, 1.2 Hz, 1 H), 7.03 (s, 1 H), 7.10 (s, 1 H), 7.14 (dd, *J* = 8.4, 1.2 Hz, 1 H), 7.26 (dd, *J* = 8.4, 7.2 Hz, 1 H).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.85; H, 6.66; N, 6.36.

7-Isopropoxy-6-methoxy-*N*-methyl-1-naphthylamine (7d); Typical Procedure

To a solution of 7-isopropoxy-6-methoxy-1-naphthylamine[9] (578 mg, 2.50 mmol) in anhyd pyridine (7 mL) was added TFAA (494 μL, 3.50 mmol). The reaction mixture was stirred at r.t. for 30 min and poured into ice water. The mixture was made to acidic with 10% HCl and extracted with EtOAc. To a solution of the residue in anhyd acetone (5 mL) were added MeI (331 μL, 5.00 mmol) and solid NaOH (100 mg, 2.50 mmol). The reaction mixture was refluxed for 30 min and the solvent was removed under reduced pressure. The residue was dissolved in EtOH (15 mL) and aq 5% NaOH solution (8 mL), and refluxed for 1.5 h. The reaction mixture was diluted with water and the precipitates were collected by filtration. The crystalline mass was recrystallized from EtOAc to give **7d** (463 mg, 76%) as colorless needles; mp 168–170 °C.

IR (KBr): 3390, 1255, 1030 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.44 (d, *J* = 6.2 Hz, 2 × 3 H), 3.01 (s, 3 H), 3.96 (s, 3 H), 4.69 (septet, *J* = 6.2 Hz, 1 H), 6.53 (d, *J* = 7.4 Hz, 1 H), 7.11–7.29 (m, 4 H).

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.35; H, 7.60; N, 5.51.

Preparation of *N*-Benzyl-*N*-methyl-1-naphthylamines 5 (Table 1); Typical Procedure

Method A: To a suspension of *N*-methyl-1-naphthylamines **7a**–**c** (4.00 mmol), Bu_4NI (148 mg, 0.40 mmol), and K_2CO_3 (1.10 g, 8.00 mmol) in anhyd DMF (20 mL) were added bromobenzyl bromides **6a**–**c** (4.00 mmol), and the reaction mixture was stirred for 1–2 h at 100 °C. The mixture was poured into water and extracted with EtOAc. The residue was dissolved in $CHCl_3$ and subjected to column chromatography on silica gel.

Method B: To a solution of *N*-methyl-1-naphthylamines (**7c** and **7d**) (1.00 mmol) and *i*-Pr_2NEt (348 μL, 2.00 mmol) in anhyd DMF (4 mL) were added bromobenzyl bromides **6b** and **6c** (1.10 mmol) and the reaction mixture was stirred for 1 h at 100 °C. The mixture was diluted with EtOAc and the entire organic layer was washed with brine. The residue was dissolved in $CHCl_3$ and subjected to column chromatography on silica gel.

***N*-(6-Bromo-3-isopropoxy-2-methoxybenzyl)-*N*-methyl-6,7-methylenedioxy-1-naphthylamine (5a)**

Elution with EtOAc–hexane (1:20) gave **5a** (71%) as colorless prisms; mp 110–111 °C (EtOH).

IR (KBr): 1248, 1034 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.34 (d, *J* = 6.2 Hz, 6 H), 2.71 (s, 3 H), 3.85 (s, 3 H), 4.36 (s, 2 H), 4.52 (septet, *J* = 6.0 Hz, 1 H), 6.00 (s, 2 H), 6.73–7.79 (m, 7 H).

Anal. Calcd for $C_{23}H_{24}BrNO_4$: C, 60.27; H, 5.28; N, 3.06. Found: C, 60.17; H, 5.26; N, 2.87.

***N*-(2-Bromobenzyl)-*N*-methyl-1-naphthylamine (5b)**

Elution with EtOAc–hexane (1:30) gave **5b** (98%) as a colorless oil.

IR ($CHCl_3$): 3011 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.88 (s, 3 H), 4.37 (s, 2 H), 7.10–8.25 (m, 11 H).

Anal. Calcd for $C_{18}H_{16}BrN$: C, 66.27; H, 4.94; N, 4.29. Found: C, 65.96; H, 5.15; N, 4.26.

***N*-(6-Bromobenzyl)-*N*-methyl-6,7-methylenedioxy-1-naphthylamine (5c)**
Elution with EtOAc–hexane (1:30) gave **5c** (70%) as colorless prisms; mp 91–92 °C (EtOH).

IR (KBr): 1239, 1036 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.80 (s, 3 H), 4.30 (s, 2 H), 6.02 (s, 2 H), 7.09–7.70 (m, 9 H).

Anal. Calcd for $C_{19}H_{16}BrNO_2$: C, 61.64; H, 4.36; N, 3.78. Found: C, 61.35; H, 4.65; N, 3.70.

***N*-(6-Bromo-2,3-dimethoxybenzyl)-*N*-methyl-1-naphthylamine (5d)**
Elution with EtOAc–hexane (1:15) gave **5d** (63%) as a colorless oil.

IR ($CHCl_3$): 3014 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.82 (s, 3 H), 3.80 (s, 3 H), 3.88 (s, 3 H), 4.34 (s, 2 H), 6.84–8.34 (m, 9 H).

FAB–MS: *m*/*z* = 385 $[M]^+$, 387 $[M + 2]^+$.

FAB–MS: *m*/*z* calcd for $C_{20}H_{20}BrNO_2$: 385.0677; found: 385.0736.

***N*-(6-Bromo-2,3-dimethoxybenzyl)-*N*-methyl-6,7-methylenedioxy-1-naphthylamine (5e)**
Elution with EtOAc–hexane (1:10) gave **5e** (98%) as colorless prisms; mp 97–98 °C (EtOH).

IR (KBr): 1247, 1072 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.70 (s, 3 H), 3.83 (s, 3 H), 3.85 (s, 3 H), 4.37 (s, 2 H), 6.00 (s, 2 H), 6.74 (d, *J* = 8.8 Hz, 1 H), 7.09 (s, 1 H), 7.18–7.42 (m, 4 H), 7.77 (s, 1 H).

Anal. Calcd for $C_{21}H_{20}BrNO_4$: C, 58.62; H, 4.68; N, 3.26. Found: C, 58.35; H, 4.73; N, 3.25.

***N*-(2-Bromobenzyl)-6,7-dimethoxy-*N*-methyl-1-naphthylamine (5f)**
Elution with EtOAc–hexane (1:10) gave **5f** (95%) as colorless needles; mp 120–123 °C (Et_2O).

IR (KBr): 1260, 1020 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.90 (s, 3 H), 3.65 (s, 3 H), 3.98 (s, 3 H), 4.29 (s, 2 H), 7.11 (s, 1 H), 7.08–7.19 (m, 2 H), 7.29 (dd, *J* = 8.0, 7.6 Hz, 1 H), 7.33 (dd, *J* = 7.4, 1.4 Hz, 1 H), 7.39–7.42 (m, 2 H), 7.58 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.80 (dd, *J* = 7.4, 1.4 Hz, 1 H).

Anal. Calcd for $C_{20}H_{20}BrNO_2$: C, 62.19; H, 5.22; N, 3.63. Found: C, 62.11; H, 5.28; N, 3.56.

***N*-(6-Bromo-2,3-dimethoxybenzyl)-*N*-methyl-6,7-dimethoxy-1-naphthylamine (5g)**
Elution with EtOAc–hexane (1:10) gave **5g** (74%) as colorless prisms; mp 111–112 °C (EtOH).

IR (KBr): 1252, 1012 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.76 (s, 3 H), 3.73 (s, 3 H), 3.83 (s, 3 H), 3.98 (s, 3 H), 3.99 (s, 3 H), 4.39 (s, 2 H), 6.72 (d, *J* = 8.8 Hz, 1 H), 7.09 (s, 1 H), 7.24–7.36 (m, 3 H), 7.44 (dd, *J* = 7.5, 1.6 Hz, 1 H), 7.74 (s, 1 H).

Anal. Calcd for $C_{22}H_{24}BrNO_4$: C, 59.20; H, 5.42; N, 3.14. Found: C, 59.12; H, 5.18; N, 3.14.

***N*-(2-Bromobenzyl)-7-isopropoxy-6-methoxy-*N*-methyl-1-naphthylamine (5h)**
Elution with EtOAc–hexane (1:30) gave **5h** (quantitative) as colorless needles; mp 102–103 °C (MeOH).

IR (KBr): 1260, 1025 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.18 (s, 3 H), 1.21 (s, 3 H), 2.90 (s, 3 H), 3.96 (s, 3 H), 4.25 (septet, *J* = 6.0 Hz, 1 H), 4.28 (s, 2 H), 7.12 (s, 1 H), 7.07–7.21 (m, 2 H), 7.27 (dd, *J* = 8.0, 7.4 Hz, 1 H), 7.35–7.42 (m, 3 H), 7.58 (d, *J* = 7.8 Hz, 1 H), 7.86 (d, *J* = 7.4 Hz, 1 H).

Anal. Calcd for $C_{22}H_{24}BrNO_2$: C, 63.77; H, 5.84; N, 3.38. Found: C, 63.81; H, 5.69; N, 3.30.

***N*-(6-Bromo-2,3-dimethoxybenzyl)-7-isopropoxy-6-methoxy-*N*-methyl-1-naphthylamine (5i)**
Elution with EtOAc–hexane (1:10) gave **5i** (96%) as colorless needles; mp 116.5–118 °C (*i*-PrOH).

IR (KBr): 1250, 1010 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.42 (d, *J* = 6.0 Hz, 2 × 3 H), 2.74 (s, 3 H), 3.76 (s, 3 H), 3.84 (s, 3 H), 3.96 (s, 3 H), 4.41 (s, 2 H), 4.71 (septet, *J* = 6.0 Hz, 1 H), 6.73 (d, *J* = 8.8 Hz, 1 H), 7.10 (s, 1 H), 7.20–7.33 (m, 3 H), 7.42 (d, *J* = 7.2 Hz, 1 H), 7.72 (s, 1 H).

Anal. Calcd for $C_{24}H_{28}BrNO_4$: C, 60.76; H, 5.95; N, 2.95. Found: C, 60.94; H, 6.20; N, 2.65.

Coupling Reaction of *N*-(6-Bromo-3-isopropoxy-2-methoxybenzyl)-*N*-methyl-6,7-methylenedioxy-1-naphthylamine (5a) under Various Conditions (Table 2); General Procedure
Compound **5a** (0.3 mmol) was reacted with $Pd(OAc)_2$ (0.2 equiv), a phosphine ligand, and a base in degassed DMF (8 mL) using $Pd(OAc)_2$ and the phosphine ligand in the ratios indicated in Table 2, and base (2 equiv) for the times and at the temperatures indicated in the Table 2. Then, the reaction mixture was diluted with EtOAc and the precipitate was removed by filtration. The residue dissolved in $CHCl_3$ was subjected to column chromatography on silica gel. Elution with EtOAc–hexane (1:30) gave **5a**. Successive elution with the same solvent gave *N*-(3-isopropoxy-2-methoxybenzyl)-*N*-methyl-6,7-methylenedioxy-1-naphthylamine (**9a**) and then 7,8-dihydro-10-isopropoxy-9-methoxy-7-methyl-1,2-methylenedioxybenzo[*e*]naphth[1,8-*bc*]azepine (**8a**).

8a
Colorless prisms; mp 128–129 °C (EtOAc).

IR (KBr): 1250, 1042 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.42 (d, *J* = 6.0 Hz, 2 × 3 H), 3.01 (s, 3 H), 3.92 (s, 3 H), 4.38 (s, 2 H), 4.64 (septet, *J* = 6.0 Hz, 1 H), 5.98 (s, 2 H), 6.57 (d, *J* = 7.5 Hz, 1 H), 6.86 (d, *J* = 7.5 Hz, 1 H), 7.02 (s, 1 H), 7.08 (d, *J* = 7.0 Hz, 1 H), 7.14 (t, *J* = 7.5 Hz, 1 H), 7.41 (d, *J* = 8.5 Hz, 1 H).

Anal. Calcd for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71. Found: C, 73.10; H, 6.10; N, 3.64.

9a
Colorless prisms; mp 93–94 °C (EtOH).

IR (KBr): 1250, 1039 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 6.1 Hz, 6 H), 2.75 (s, 3 H), 3.83 (s, 3 H), 4.23 (s, 2 H), 4.57 (septet, *J* = 6.1 Hz, 1 H), 6.02 (s, 2 H), 6.84 (dd, *J* = 7.8, 1.6 Hz, 1 H), 7.01 (dd, *J* = 7.8, 7.8 Hz, 1 H), 7.09 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.11 (s, 1 H), 7.13 (dd, *J* = 7.8, 1.6 Hz, 1 H), 7.26 (dd, *J* = 7.8, 7.8 Hz, 1 H), 7.38 (br d, *J* = 7.8 Hz, 1 H), 7.75 (s, 1 H).

Anal. Calcd for $C_{23}H_{25}NO_4$: C, 72.80; H, 6.64; N, 3.69. Found: C, 73.07; H, 6.70; N, 3.66.

***N*-(6-Bromo-3-isopropoxy-2-methoxybenzyl)-6,7-methylenedioxy-1-naphthylamine (10); Typical Procedure**

To a mixture of 6-bromo-3-hydroxy-2-methoxybenzaldehyde[7] (100 mg, 0.43 mmol) and K_2CO_3 (210 mg, 1.52 mmol) in anhyd DMF (15 mL) was added *i*-PrBr (50 μL, 0.52 mmol), and the reaction mixture was stirred at 100 °C for 2 h. The mixture was poured into water and extracted with Et_2O. The residue was dissolved in $CHCl_3$ and subjected to chromatography on silica gel. Elution with EtOAc–hexane (1:19) gave 6-bromo-3-isopropoxy-2-methoxybenzaldehyde (105 mg, 89%) as pale yellow needles, mp 32–35 °C (Et_2O). A solution of 6-bromo-3-isopropoxy-2-methoxybenzylaldehyde (500 mg, 1.83 mmol) and 6,7-methylenedioxy-1-naphthylamine (343 mg, 1.83 mmol) in EtOH (3 mL) was refluxed for 2 h. After evaporating the solvent, the residue was dissolved in EtOH (5 mL), $NaBH_4$ (1.39 g, 36.6 mmol) was added to the solution, and the mixture was refluxed for 1 h. The solvent was evaporated under reduced pressure and the residue was diluted with water, and then extracted with $CHCl_3$. The residue was dissolved in $CHCl_3$ and subjected to chromatography on alumina. Elution with EtOAc–hexane (1:20) gave **10** (569 mg, 70%) as colorless prisms; mp 80–83 °C (EtOH).

6-Bromo-3-isopropoxy-2-methoxybenzaldehyde

IR (KBr): 1684 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 6.1 Hz, 2 × 3 H), 3.94 (s, 3 H), 4.55 (septet, *J* = 6.1 Hz, 1 H), 6.96 (d, *J* = 8.8 Hz, 1 H), 7.31 (d, *J* = 8.8 Hz, 1 H), 10.34 (s, 1 H).

FAB-MS: *m*/*z* calcd for $C_{11}H_{13}BrO_3$: 272.0048; found: 272.0001.

***N*-(6-Bromo-3-isopropoxy-2-methoxybenzyl)-6,7-methylenedioxy-1-naphthylamine (10)**

IR (KBr): 1247, 1042 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.37 (d, *J* = 6.0 Hz, 2 × 3 H), 3.86 (s, 3 H), 4.54 (septet, *J* = 6.0 Hz, 1 H), 4.43 (br s, 1 H), 4.55 (s, 2 H), 5.99 (s, 2 H), 6.75–7.30 (m, 7 H).

Anal. Calcd for $C_{22}H_{22}BrNO_4$: C, 59.47; H, 4.99; N, 3.15. Found: C, 59.21; H, 5.13; N, 3.14.

***N*-(6-Bromo-3-isopropoxy-2-methoxybenzyl)-*N*-(6,7-methylenedioxy-1-naphthyl)acetamide (11); Typical Procedure**

To a solution of **10** (190 mg, 0.427 mmol) in anhyd pyridine (2 mL) was added Ac_2O (81 μL, 0.853 mmol). The reaction mixture was stirred at r.t. overnight and poured into 10% HCl and then extracted with EtOAc. The residue was dissolved in $CHCl_3$ and subjected to chromatography through silica gel. Elution with EtOAc–hexane (1:20) gave **11** (161 mg, 77%) as colorless prisms; mp 134–135 °C (Et_2O).

IR (KBr): 1654 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.22 (d, *J* = 6.1 Hz, 3 H), 1.24 (d, *J* = 6.1 Hz, 3 H), 1.76 (s, 3 H), 3.25 (s, 3 H), 4.35 (septet, *J* = 6.1 Hz, 1 H), 4.82 (d, *J* = 13.6 Hz, 1 H), 5.69 (d, *J* = 13.6 Hz, 1 H), 6.06 (s, 2 H), 6.64 (d, *J* = 8.8 Hz, 1 H), 7.26 (dd, *J* = 7.4, 1.2 Hz, 1 H), 7.02–7.56 (m, 5 H).

Anal. Calcd for $C_{24}H_{24}BrNO_5$: C, 59.27; H, 4.97; N, 2.88. Found: C, 59.10; H, 4.78; N, 2.87.

5-Acetyl-5,6-dihydro-8-isopropoxy-7-methoxy-2,3-methylenedioxybenzo[*c*]-phenanthridine (12) and 7-Acetyl-7,8-dihydro-10-isopropoxy-9-methoxy-1,2-methylenedioxybenzo[*e*]naphth[1,8-*bc*]azepine (13); Typical Procedure

To a solution of compound **11** (48.6 mg, 0.100 mmol) in DMF (2 mL) were added $Pd(OAc)_2$ (4.5 mg, 0.020 mmol), $P(o\text{-tol})_3$ (12.2 mg, 0.040 mmol), and K_2CO_3 (27.6 mg, 0.200 mmol). The reaction mixture was refluxed for 1 h and diluted with EtOAc. The precipitate was removed by filtration. The residue was dissolved in $CHCl_3$ and subjected to chromatography through silica gel. Elution with EtOAc–hexane (1:2) gave **12** (18.1 mg, 45%) and successive elution with the same solvent gave **13** (22.4 mg, 55%).

12

Colorless prisms; mp 176–177 °C (Et_2O).

IR (KBr): 1660 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.39 (d, *J* = 6.0 Hz, 3 H), 1.41 (d, *J* = 6.0 Hz, 3 H), 1.79 (s, 3 H), 3.80 (d, *J* = 15.4 Hz, 1 H), 3.97 (s, 3 H), 4.62 (septet, *J* = 6.0 Hz, 1 H), 6.08 (br d, *J* = 2.4 Hz, 2 H), 6.25 (d, *J* = 15.4 Hz, 1 H), 6.93 (d, *J* = 8.6 Hz, 1 H), 7.15 (s, 1 H), 7.28 (s, 1 H), 7.52 (d, *J* = 8.6 Hz, 1 H), 7.62 (d, *J* = 8.6 Hz, 1 H), 7.69 (d, *J* = 8.6 Hz, 1 H).

Anal. Calcd for $C_{24}H_{23}NO_5$: C, 71.10; H, 5.72; N, 3.45. Found: C, 69.81; H, 5.77; N, 3.24.

13

Colorless prisms; mp 86–88 °C (Et_2O).

IR (KBr): 1635 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.42 (d, *J* = 6.0 Hz, 2 × 3 H), 2.00 (s, 3 H), 3.93 (d, *J* = 15.8 Hz, 1 H), 4.16 (s, 3 H), 4.62 (septet, *J* = 6.0 Hz, 1 H), 5.89 (br s, 1 H), 5.97 (d, *J* = 15.8 Hz, 1 H), 6.17 (br s, 1 H), 6.84 (d, *J* = 8.8 Hz, 1 H), 7.10 (dd, *J* = 7.6, 1.4 Hz, 1 H), 7.17 (s, 1 H), 7.29 (dt, *J* = 7.8, 7.6 Hz, 1 H), 7.59 (d, *J* = 8.8 Hz, 1 H), 7.61 (dd, *J* = 7.8, 1.4 Hz, 1 H).

FAB–MS: *m*/*z* calcd for $C_{24}H_{24}NO_5$: 406.1654; found: 406.1637.

Coupling Reaction of *N*-Bromobenzyl-*N*-methyl-1-naphthylamines (5b–i) Using Palladium Reagent (Table 3); General Procedure

To a solution of **5b–i** (0.2 mmol) in degassed DMF (3 mL) were added $Pd(OAc)_2$ (8.8 mg, 0.04 mmol), $P(o\text{-tol})_3$ (24.4 mg, 0.08 mmol), and K_2CO_3 (55.2 mg, 0.4 mmol), and the reaction mixture was stirred for 2 h under reflux. Then, the mixture was diluted with EtOAc and the precipitate was removed by filtration. The filtrate was washed with brine. The residue was dissolved in $CHCl_3$ and subjected to column chromatography on silica gel.

7,8-Dihydro-7-methylbenzo[*e*]naphth[1,8-*b*,*c*]azepine (8b)

Elution with EtOAc–hexane (1:50) gave **8b** (81%) as a pale yellow oil.

IR ($CHCl_3$): 3022 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.05 (s, 3 H), 4.26 (s, 2 H), 6.67 (dd, *J* = 5.0, 4.0 Hz, 1 H), 7.05–7.95 (m, 9 H).

FAB-MS: *m*/*z* $[M]^+$ calcd for $C_{18}H_{15}N$: 245.1204; found: 245.1161.

7,8-Dihydro-7-methyl-1,2-methylenedioxybenzo[*e*]naphth[1,8-*b*,*c*]azepine (8c)

Elution with EtOAc–hexane (1:30) gave **8c** (86%) as colorless prisms; mp 125–126 °C (EtOAc).

IR (KBr): 1278, 1051 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.97 (s, 3 H), 4.24 (br s, 2 H), 5.99 (s, 2 H), 6.48 (dd, *J* = 6.8, 2.2 Hz, 1 H), 7.06 (s, 1 H), 7.09–7.40 (m, 5 H), 7.73 (br d, *J* = 7.2 Hz, 1 H).

Anal. Calcd for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84. Found: C, 79.05; H, 5.47; N, 4.74.

7,8-Dihydro-9,10-dimethoxy-7-methylbenzo[*e*]naphth[1,8-*b*,*c*]azepine (8d)

Elution with EtOAc–hexane (1:30) gave **8d** (44%) as pale yellow prisms; mp 119–121 °C (EtOAc).

IR (KBr): 1231, 1036 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.08 (s, 3 H), 3.93 (s, 2 × 3 H), 4.43 (br s, 2 H), 6.63 (dd, *J* = 6.2, 2.8 Hz, 1 H), 6.92 (d, *J* = 8.6 Hz, 1 H), 7.14 (d, *J* = 8.6 Hz, 1 H), 7.23–7.46 (m, 4 H), 7.71 (dd, *J* = 8.0, 1.6 Hz, 1 H).

FAB–MS: *m*/*z* $[M]^+$ calcd for $C_{20}H_{19}NO_2$: 305.1215; found: 305.1264.

7,8-Dihydro-9,10-dimethoxy-7-methyl-1,2-methylenedioxybenzo[*e*]naphtha-[1,8-*bc*]-azepine (8e)

Elution with EtOAc–hexane (1:50) gave **8e** (60%) as pale yellow prisms; mp 128–129 °C (EtOAc).

IR (KBr): 1276, 1065 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.00 (s, 3 H), 3.91 (s, 3 H),3.92 (s, 3 H), 4.39 (br s, 2 H), 5.98 (s, 2 H), 6.58 (dd, *J* = 7.2, 1.8 Hz, 1 H), 6.88 (d, *J* = 8.6 Hz, 1 H), 7.03 (s, 1 H), 7.08 (dd, *J* = 7.8, 1.8 Hz, 1 H), 7.15 (t, *J* = 7.8, 7.2 Hz, 1 H), 7.45 (d, *J* = 8.6 Hz, 1 H).

FAB–MS: *m*/*z* $[M + 1]^+$ calcd for $C_{21}H_{20}NO_4$: 350.1392; found: 350.1422.

Isolation of Products from Coupling Reaction of *N*-(2-Bromobenzyl)-6,7-dimethoxy-*N*-methyl-1-naphthylamine (5f)

Elution with EtOAc–hexane (1:30) gave 7,8-dihydro-1,2-dimethoxy-7-methyl-benzo[*e*]naphth[1,8-*b*,*c*]azepine (**8f**) (22%) and successive elution with the same solvent gave *N*-benzyl-6,7-dimethoxy-*N*-methyl-1-naphthylamine (**9f**) (12%). Elution with EtOAc–hexane (1:10) gave 2,3-dimethoxy-5-methyl-5,6-dihydrobenzo[*c*]phenanthridine (**14f**) (33%).

8f

Colorless amorphous solid.

IR ($CHCl_3$): 1240, 1020 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.98 (s, 3 H), 3.46 (s, 3 H), 3.81 (br s, 1 H), 4.00 (s, 3 H), 4.75 (br s, 1 H), 6.52 (br s, 1 H), 7.07 (s, 1 H), 7.09 (d, *J* = 8.0 Hz, 1 H), 7.19 (dd, *J* = 8.0, 8.0 Hz, 1 H), 7.25–7.31 (m, 3 H), 7.58 (d, *J* = 8.5 Hz, 1 H).

FAB–MS: *m*/*z* $[M]^+$ calcd for $C_{20}H_{19}NO_2$: 305.1416; found: 305.1415.

9f

Colorless needles; mp 91–92.5 °C (MeOH).

IR (KBr): 1260, 1030 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.82 (s, 3 H), 3.83 (s, 3 H), 4.00 (s, 3 H), 4.25 (s, 2 H), 7.04 (dd, *J* = 7.4, 1.2 Hz, 1 H), 7.13 (s, 1 H), 7.24–7.49 (m, 7 H), 7.63 (s, 1 H).

Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 77.96; H, 6.74; N, 4.47.

14f

Colorless prisms; 144–146 °C (MeOH).

IR (KBr): 1255, 1030 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.65 (s, 3 H), 4.02 (s, 3 H), 4.08 (s, 3 H), 4.22 (s, 2 H), 7.14 (s, 1 H), 7.28–7.32 (m, 2 H), 7.40 (ddd, *J* = 7.2, 6.6, 2.4 Hz, 1 H), 7.54 (d, *J* = 8.6 Hz, 1 H), 7.66 (s, 1 H), 7.79 (d, *J* = 8.6 Hz, 1 H), 7.80 (d, *J* = 7.2 Hz, 1 H).

Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found : C, 79.06; H, 6.32; N, 4.66.

Isolation of Products from Coupling Reaction of *N*-(6-Bromo-2,3-dimethoxybenzyl)-6,7-dimethoxy-*N*-methyl-1-naphthylamine (5g)

Elution with EtOAc–hexane (1:10) gave 7,8-dihydro-1,2,9,10-tetramethoxy-7-methyl-benz[*e*]naphtha[1,8-*b*,*c*]azepine (**8g**) (18%) and successive elution with the same solvent gave 6,7-dimethoxy-*N*-(2,3-dimethoxybenzyl)-*N*-methyl-1-naphthylamine (**9g**) (10%). Elution with EtOAc–hexane (1:6) gave 2,3,7,8-tetramethoxy-5-methyl-5,6-dihydrobenzo[*c*]phenanthridine (**14g**) (34%) and elution with EtOAc–hexane (1:4) gave 6,7-dimethoxy-*N*-(2,3-methoxybenzyl)-1-naphthylamine (**15g**) (10%).

8g

Colorless amorphous solid.

IR ($CHCl_3$): 1230, 1020 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.03 (s, 3 H), 3.45 (s, 3 H), 3.93 (s, 3 H), 3.95 (s, 3 H), 3.99 (s, 3 H), 4.43 (br s, 2 H), 6.46 (d, *J* = 7.5 Hz, 1 H), 6.85 (d, *J* = 8.8 Hz, 1 H), 7.03 (s, 1 H), 7.07 (d, *J* = 7.5 Hz, 1 H), 7.18 (dd, *J* = 8.0, 7.5 Hz, 1 H), 7.27 (d, *J* = 8.8 Hz, 1 H).

FAB–MS: *m*/*z* $[M]^+$ calcd for $C_{22}H_{23}NO_4$: 365.1627; found: 365.1641.

9g

Colorless needles; mp 102–104 °C (MeOH).

IR (KBr): 1260, 1045 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.84 (s, 3 H), 3.77 (s, 3 H), 3.78 (s, 3 H), 3.88 (s, 3 H), 3.99 (s, 3 H), 4.29 (s, 2 H), 6.86 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.05–7.12 (m, 3 H), 7.28 (dd, *J* = 8.0, 7.6 Hz, 1 H), 7.30 (d, *J* = 7.6 Hz, 1 H), 7.40 (d, *J* = 7.8 Hz, 1 H), 7.59 (s, 1 H).

Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.68; H, 6.94; N, 3.65.

14g

Colorless prisms; 180–183 °C ($CHCl_3$–MeOH) (lit.[10] 186–188 °C)

15g

Colorless needles; mp 140–142 °C ($CHCl_3$–MeOH).

IR (KBr): 3380, 1255, 1030 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.89 (s, 2 × 3 H), 3.99 (s, 2 × 3 H), 4.52 (s, 2 H), 6.56 (d, *J* = 7.2 Hz, 1 H), 6.87–7.26 (m, 7 H).

FAB–MS: *m*/*z* = 353 $[M]^+$

Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.86; N, 3.96. Found: C, 70.91; H, 6.56; N, 3.62.

Isolation of Products from Coupling Reaction of *N*-(2-Bromobenzyl)-6,7-dimethoxy-*N*-methyl-1-naphthylamine (5h)

Elution with EtOAc–hexane (1:50) gave 7-isopropoxy-6-methoxy-*N*-(2,3-dimethoxybenzyl)-*N*-methyl-1-naphthylamine (**9h**) (11%) and elution with EtOAc–hexane (1:30) gave 3-isopropoxy-2-methoxy-5-methyl-5,6-dihydrobenzo[*c*]phenanthridine (**14h**) (44%). Elution with EtOAc–hexane (1:6) gave *N*-benzyl-7-isopropoxy-6-methoxy-1-naphthylamine (**15h**) (20%).

9h

Colorless oil.

IR ($CHCl_3$): 1255, 1010 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.31 (s, 3 H), 1.34 (s, 3 H), 2.81 (s, 3 H), 3.97 (s, 3 H), 4.25 (s, 2 H), 4.49 (septet, *J* = 6.0 Hz, 1 H), 7.02 (dd, *J* = 7.6, 1.2 Hz, 1 H), 7.13 (s, 1 H), 7.22–7.45 (m, 7 H), 7.62 (s, 1 H).

FAB–MS: *m*/*z* $[M]^+$ calcd for $C_{22}H_{25}NO_2$: 335.1885; found: 335.1862.

14h

Colorless prisms; 159–161 °C (MeOH).

IR (KBr): 1255, 1045 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.49 (s, 3 H), 1.52 (s, 3 H), 2.63 (s, 3 H), 3.99 (s, 3 H), 4.21 (s, 2 H), 4.85 (septet, *J* = 6.0 Hz, 1 H), 7.14 (s, 1 H), 7.28–7.32 (m, 2 H), 7.39 (ddd, *J* = 7.2, 6.6, 2.4 Hz, 1 H), 7.53 (d, *J* = 8.6 Hz, 1 H), 7.69 (s, 1 H), 7.78 (d, *J* = 8.6 Hz, 1 H), 7.80 (d, *J* = 7.0 Hz, 1 H).

Anal. Calcd for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20. Found: C, 79.39; H, 6.83; N, 4.08.

15h

Colorless needles; mp 125–127 °C (MeOH).

IR (KBr): 3410, 1250, 1035 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.40 (s, 3 H), 1.43 (s, 3 H), 3.96 (s, 3 H), 4.49 (s, 2 H), 4.68 (septet, *J* = 6.0 Hz, 1 H), 6.55 (dd, *J* = 7.0, 1.4 Hz, 1 H), 7.12 (s, 1 H), 7.16–7.49 (m, 8 H).

Anal. Calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.74; H, 7.46; N, 3.89.

Isolation of Products from Coupling Reaction of *N*-(2-Bromobenzyl)-6,7-dimethoxy-*N*-methyl-1-naphthylamine (5i)

Elution with EtOAc–hexane (1:50) gave 7-isopropoxy-6-methoxy-*N*-(2,3-dimethoxybenzyl)-*N*-methyl-1-naphthylamine (**9i**) (11%) and elution with EtOAc–hexane (1:50) gave 3-isopropoxy-2,7,8-trimethoxy-5-methyl-5,6-dihydrobenzo[*c*]phenanthridine (**14i**) (53%). Elution with EtOAc–hexane (1:10) gave 7-isopropoxy-*N*-(2,3-methoxybenzyl)-6-methoxy-1-naphthylamine (**15i**) (26%).

9i

Colorless needles; mp 102–104 °C (MeOH).

IR (KBr): 1260, 1030 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.25 (s, 3 H), 1.28 (s, 3 H), 2.84 (s, 3 H), 3.76 (s, 3 H), 3.88 (s, 3 H), 3.96 (s, 3 H), 4.29 (s, 2 H), 4.40 (septet, *J* = 6.0 Hz, 1 H), 6.87 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.04–7.41 (m, 6 H), 7.56 (s, 1 H).

Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54. Found: C, 72.69; H, 7.18; N, 3.36.

14i

Colorless needles; mp 127–131 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.48 (s, 3 H), 1.52 (s, 3 H), 2.62 (s, 3 H), 3.88 (s, 3 H), 3.93 (s, 3 H), 3.98 (s, 3 H), 4.31 (s, 2 H), 4.85 (septet, *J* = 6.0 Hz, 1 H), 6.94 (d, *J* = 8.4 Hz, 1 H), 7.13 (s, 1 H), 7.50 (d, *J* = 8.4 Hz, 1 H), 7.51 (d, *J* = 8.6 Hz, 1 H), 7.69 (s, 1 H), 7.71 (d, *J* = 8.6 Hz, 1 H).

Anal. Calcd for $C_{24}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56. Found: C, 73.10; H, 6.52; N, 3.42.

15i

Colorless needles; mp 117–118 °C (MeOH).

IR (KBr): 3380, 1250, 1035 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.40 (s, 3 H), 1.43 (s, 3 H), 3.90 (s, 3 H), 3.96 (s, 3 H), 4.51 (s, 2 H), 4.68 (septet, *J* = 6.0 Hz, 1 H), 6.60 (dd, *J* = 7.4, 1.2 Hz, 1 H), 6.86–7.25 (m, 7 H).

Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.08; H, 6.97; N, 3.57.

2-Bromo-*N*-methyl-6,7-methylenedioxy-1-naphthylamine (7e); Typical Procedure

To a solution of 2-bromo-6,7-methylenedioxy-1-naphthylamine[14] (533 mg, 2.00 mmol) in anhyd pyridine (4 mL) was added TFAA (0.42 mL, 3.00 mmol). The reaction mixture was stirred at r.t. for 30 min and poured into ice water. The mixture was made acidic with 10% HCl and extracted with EtOAc. The residue was recrystallized from Et_2O–hexane to give *N*-(2-bromo-6,7-methylenedioxy-1-naphthyl)trifluoroacetamide (632 mg, 88%) as colorless needles, mp 182–183 °C. To the solution of *N*-(2-bromo-6,7-methylenedioxy-1-naphthyl)trifluoroacetamide (2.50 g, 6.90 mmol) and MeI (1.72 mL, 27.62 mmol) in anhyd acetone (200 mL) was added solid KOH (1.60 g, 27.62 mmol). The reaction mixture was refluxed for 50 min and the solvent was removed under reduced pressure. The residue was dissolved in EtOH (80 mL) and aq 5% NaOH solution (80 mL), and refluxed for 30 min. The reaction mixture was diluted with water and extracted with Et_2O. The residue was recrystallized from EtOH to give **7e** (1.71 g, 89%) as colorless needles; mp 83–84 °C.

***N*-(2-Bromo-6,7-methylenedioxy-1-naphthyl)trifluoroacetamide**

IR (KBr): 3320, 1714 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.09 (s, 2 H), 7.02 (s, 1 H), 7.13 (s, 1 H), 7.53 (d, *J* = 8.8 Hz, 1 H), 7.58 (d, *J* = 8.8 Hz, 1 H), 7.90 (br s, 1 H).

Anal. Calcd for $C_{13}H_7BrF_3NO_3$: C, 43.12; H, 1.95; N, 3.87. Found: C, 42.89; H, 2.27; N, 3.75.

2-Bromo-*N*-methyl-6,7-methylenedioxy-1-naphthylamine (7e)

IR (KBr): 3347, 1244, 1037 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.89 (s, 3 H), 3.78 (br s, 1 H), 6.06 (s, 2 H), 7.06 (s, 1 H), 7.20 (d, *J* = 8.7 Hz, 1 H), 7.40 (d, *J* = 8.7 Hz, 1 H), 7.49 (s, 1 H).

Anal. Calcd for $C_{12}H_{10}BrNO_2$: C, 51.45; H, 3.60; N, 5.00. Found: C, 51.25; H, 3.78; N, 4.91.

***N*-Benzyl-*N*-methyl-2-bromo-6,7-methylenedioxy-1-naphthylamine (16); Typical Procedure**

To a suspension of *N*-methyl-1-naphthylamine **7e** (560 mg, 2.00 mmol), Bu_4NI (148 mg, 0.40 mmol), and K_2CO_3 (553 mg, 4.00 mmol) in anhyd DMF (4 mL) was added benzyl bromide (0.48 mL, 4.00 mmol), and the reaction mixture was stirred for 2 h at 100 °C. The mixture was poured into water and extracted with Et_2O. The residue was dissolved in $CHCl_3$ and subjected to column chromatography on silica gel. Elution with EtOAc–hexane (1:30) gave **16** (724 mg, 98%) as a colorless oil.

IR ($CHCl_3$): 1241, 1041 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.82 (s, 3 H), 4.28 (d, *J* = 13.8 Hz, 2 H), 4.52 (d, *J* = 13.8 Hz, 2 H), 6.05 (d, *J* = 1.8 Hz, 1 H), 7.07 (s, 1 H), 7.29–7.48 (m, 6 H), 7.75 (s, 1 H).

FAB–MS: *m*/*z* = 369 $[M]^+$, 371 $[M + 2]^+$.

FAB–MS: *m*/*z* $[M]^+$ calcd for $C_{19}H_{16}BrNO_2$: 369.0364; found: 369.0364.

Coupling Reaction of *N*-Benzyl-*N*-methyl-2-bromo-6,7-methylenedioxy-1-naphthylamine (16) Using Pd Reagent

To a solution of compound **16** (107 mg, 0.289 mmol) in degassed DMF (6 mL) were added $Pd(OAc)_2$ (13.0 mg, 0.058 mmol), P(*o*-tol)$_3$ (35.2 mg, 0.116 mmol), and K_2CO_3 (79.9 mg, 0.578 mmol). The reaction mixture was refluxed for 4 h and diluted with EtOAc. The precipitate was removed by filtration. The residue was dissolved in $CHCl_3$ and subjected to column chromatography on silica gel. Elution with EtOAc–hexane (1:10) gave *N*-benzyl-6,7-methylenedioxy-1-naphthylamine (**17**) (47.0 mg, 59%), and successive elution with the same solvent gave **7a**[2e] (13.3 mg, 29%).

17

Colorless prisms; mp 146–147 °C (EtOH).

IR (KBr): 3393, 1242, 1044 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.31 (br s, 1 H), 4.46 (s, 2 H), 6.02 (s, 2 H), 6.58 (dd, *J* = 7.4, 1.4 Hz, 1 H), 7.10–7.48 (m, 9 H).

Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 78.19; H, 5.60; N, 5.05.

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