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 C7 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.3 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-isoproxy-2-methoxybenzyl bromide (6a), which was prepared from 3-isoproxy-2-methoxybenzaldehyde7 in 54% yield via reduction with NaBH4 and bromination with Br2, and N-methyl-6,7-methylenedioxy-1-naphthyl-

Scheme 2 Palladacycles of benzylamine 1 and naphthylamine 2
amine (7a) in the presence of K₂CO₃ and Bu₄NI 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 Ag₂CO₃ 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. Using K₂CO₃, KHCO₃, or Cs₂CO₃ 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 Cy₃P as a ligand gave 8a in a good yield as well as that using (o-tol)₃P (Table 2, entry 13). We decided to use (o-tol)₃P 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 ¹H NMR data, in which 8a showed only one singlet signal (d = 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 via etherification with isopropyl bromide, followed by reductive alkylation with 6,7-methylenedioxy-1-naphthalamin and NaBH₄. 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 K₂CO₃ 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 and 7-isopropoxy-6-methoxy-1-naphthylamine 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 and N-

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substituent</th>
<th>Method</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R¹ = OMe, R² = O-i-Pr, R³ + R⁴ = OCH₂O</td>
<td>A</td>
<td>5a</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>R¹ = R² = R³ = R⁴ = H</td>
<td>A</td>
<td>5b</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>R¹ = R² = H, R³ + R⁴ = OCH₂O</td>
<td>A</td>
<td>5c</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>R³ = R² = OMe, R¹ = R⁴ = H</td>
<td>A</td>
<td>5d</td>
<td>63</td>
</tr>
<tr>
<td>5</td>
<td>R¹ = R² = OMe, R³ + R⁴ = OCH₂O</td>
<td>A</td>
<td>5e</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>R¹ = R² = H, R³ = R⁴ = OMe</td>
<td>B</td>
<td>5f</td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>R¹ = R² = R³ = R⁴ = OMe</td>
<td>B</td>
<td>5g</td>
<td>74</td>
</tr>
<tr>
<td>8</td>
<td>R¹ = R² = H, R³ = OMe, R⁴ = O-i-Pr</td>
<td>B</td>
<td>5h</td>
<td>quant.</td>
</tr>
<tr>
<td>9</td>
<td>R¹ = R² = R³ = OMe, R⁴ = O-i-Pr</td>
<td>B</td>
<td>5i</td>
<td>96</td>
</tr>
</tbody>
</table>

*Method A: K₂CO₃, Bu₄NI, DMF, 100 °C, 1–2 h; Method B: i-Pr₂NEt, DMF, 100 °C, 1 h.*
methyl-1-naphthylamines 7a<sup>2e–d</sup> 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 C7 on the naphthalene ring produced benzonaphthazepines 8f and 8g) and benzo[c]phenanthridines 14f and 14g<sup>12</sup> (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 C7 on the naphthalene ring might hinder the coupling reaction at the peri position (C8 position) relative to the amino group on the naphthalene ring.<sup>13</sup> Subsequently, the reaction of N-bromobenzyl-naphthylamines 5h and 5i) possessing a bulky isopropoxy group relative to a methoxy group at C7 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 <sup>1</sup>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<sup>14</sup> in 78% total yield via trifluoracetylation, 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.

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**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<sup>a</sup>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand (L/Pd)</th>
<th>Base</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>P(o-tol)&lt;sub&gt;3&lt;/sub&gt; (2)</td>
<td>Ag&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>12</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>P(o-tol)&lt;sub&gt;3&lt;/sub&gt; (2)</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;N</td>
<td>6</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>P(o-tol)&lt;sub&gt;3&lt;/sub&gt; (2)</td>
<td>pyridine</td>
<td>6</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>P(o-tol)&lt;sub&gt;3&lt;/sub&gt; (2)</td>
<td>DBU</td>
<td>4</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>P(o-tol)&lt;sub&gt;3&lt;/sub&gt; (2)</td>
<td>KOH</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>6</td>
<td>P(o-tol)&lt;sub&gt;3&lt;/sub&gt; (2)</td>
<td>t-BuOK</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>7</td>
<td>P(o-tol)&lt;sub&gt;3&lt;/sub&gt; (2)</td>
<td>Li&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>4</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>P(o-tol)&lt;sub&gt;3&lt;/sub&gt; (2)</td>
<td>Na&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>9</td>
<td>P(o-tol)&lt;sub&gt;3&lt;/sub&gt; (2)</td>
<td>CaCO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>4</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td>P(o-tol)&lt;sub&gt;3&lt;/sub&gt; (2)</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>2</td>
<td>76</td>
</tr>
<tr>
<td>11</td>
<td>P(o-tol)&lt;sub&gt;3&lt;/sub&gt; (2)</td>
<td>KHCO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>2</td>
<td>66</td>
</tr>
<tr>
<td>12</td>
<td>P(o-tol)&lt;sub&gt;3&lt;/sub&gt; (2)</td>
<td>Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>3</td>
<td>75</td>
</tr>
<tr>
<td>13</td>
<td>Cy&lt;sub&gt;2&lt;/sub&gt;P (2)</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>2</td>
<td>75</td>
</tr>
<tr>
<td>14&lt;sup&gt;b&lt;/sup&gt;</td>
<td>DPPP (1)</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>2</td>
<td>48</td>
</tr>
<tr>
<td>15&lt;sup&gt;c&lt;/sup&gt; &amp;&lt;sup&gt;d&lt;/sup&gt;</td>
<td>–</td>
<td>KOAc</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>16&lt;sup&gt;d&lt;/sup&gt;</td>
<td>–</td>
<td>KOAc</td>
<td>2</td>
<td>–</td>
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<tr>
<td>17</td>
<td>–</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>18</td>
<td>P(o-tol)&lt;sub&gt;3&lt;/sub&gt; (2)</td>
<td>–</td>
<td>6</td>
<td>–</td>
</tr>
</tbody>
</table>

<sup>a</sup> All reactions were carried out using Pd(OAc)<sub>2</sub> (0.2 equiv), P(o-tol)<sub>3</sub> (0.4 equiv), and base (2 equiv) under Ar atmosphere.

<sup>b</sup> One equiv of Bu<sub>3</sub>P was added.

<sup>c</sup> Reaction was carried out using KOAc (5.5 equiv) at 130 °C.

<sup>d</sup> Reaction was carried out using KOAc (5.5 equiv) and N-methyl-6,7-methylenedioxy-1-naphthylamine (7a) was obtained in 20 % yield.
The coupling reaction of 16 using Pd(OAc)$_2$, P(o-tol)$_3$, and K$_2$CO$_3$ 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.
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 ($\delta = 0.0$) 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$_2$CO$_3$, and filtered, and the filtrate was concentrated to dryness un-

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Yield (%)</th>
<th>8</th>
<th>14</th>
<th>9</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5a b</td>
<td>R$^1$ = OMe, R$^2 = $ O-i-Pr, R$^3 + R^4 = $ OCH$_2$O</td>
<td>76</td>
<td>–</td>
<td>trace</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>5b</td>
<td>R$^1 = R^2 = R^3 = R^4 = $ H</td>
<td>81</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>5c</td>
<td>R$^1 = R^2 = $ H, R$^3 + R^4 = $ OCH$_2$O</td>
<td>86</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>5d</td>
<td>R$^1 = R^2 = $ OMe, R$^3 = R^4 = $ H</td>
<td>44</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>5e</td>
<td>R$^1 = R^2 = $ OMe, R$^3 + R^4 = $ OCH$_2$O</td>
<td>60</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>5f</td>
<td>R$^1 = R^2 = $ H, R$^3 = R^4 = $ OMe</td>
<td>22</td>
<td>33</td>
<td>12</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>5g</td>
<td>R$^1 = R^2 = R^3 = R^4 = $ OMe</td>
<td>18</td>
<td>34</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>5h</td>
<td>R$^1 = R^2 = $ H, R$^3 = $ OMe, R$^4 = $ O-i-Pr</td>
<td>–</td>
<td>44</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>5i</td>
<td>R$^1 = R^2 = R^3 = $ OMe, R$^4 = $ O-i-Pr</td>
<td>–</td>
<td>53</td>
<td>11</td>
<td>26</td>
</tr>
</tbody>
</table>

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**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
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 (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 (1.5 g, 76%); colorless needles; mp 73.35; H, 7.60; N, 5.51.

3-Isopropoxy-2-methoxybenzylalcohol
IR (CHCl$_3$): 3011 cm$^{-1}$.

1H NMR (500 MHz, CDCl$_3$): $\delta$ = 1.34 (d, $J$ = 6.2 Hz, 2 H), 2.71 (s, 6 H), 3.01 (s, 3 H), 3.92 (s, 3 H), 4.69 (septet, $J$ = 6.2 Hz, 1 H), 7.11–7.29 (m, 4 H). 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$_4$NI (148 mg, 0.40 mmol), and K$_2$CO$_3$ (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.

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$_3$): $\delta$ = 1.34 (d, $J$ = 6.2 Hz, 2 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), 6.60 (s, 2 H), 6.73–7.79 (m, 7 H). 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$_3$): $\delta$ = 2.88 (s, 3 H), 4.37 (s, 2 H), 7.10–8.25 (m, 11 H).
Coupling Reaction of N-(6-Bromo-3-isopropoxy-2-methoxy- benzyl)-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 CHCl₃ 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-methoxy-benzyl)-N-methyl-6,7-methylenedioxy-1-naphthylamine (59a) and then 7,8-dihydro-10-isopropoxy-9-methoxy-7-methyl-1,2-methylenedioxybenzen[e]naphthalene [1,8-bc]jazepine (8a).

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

IR (KBr): 1250, 1042 cm⁻¹.

1H NMR (200 MHz, CDCl₃): δ = 1.18 (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 C₂₃H₂₂NO₄: 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, CDCl₃): 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 (d, 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 C₂₃H₂₁N₃O₉: C, 72.80; H, 6.64; N, 3.69. Found: C, 73.01; H, 6.70; N, 3.66.
N-(6-Bromo-3-isopropoxy-2-methoxybenzyl)-6,7-methylene-dioxo-1-naphthylamine (10); Typical Procedure
To a mixture of 6-bromo-3-hydroxy-2-methoxybenzaldehyde\(^2\) (100 mg, 0.43 mmol) and K\(_2\)CO\(_3\) (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\(_2\)O. The residue was dissolved in CHCl\(_3\) and subjected to chromatography on silica gel. Elution with EtOAc–hexane (1:20) gave 9 (569 mg, 70%) as colorless prisms; mp 86–88 °C (Et\(_2\)O).
IR (KBr): 1635 cm\(^{-1}\).
FAB–MS: \([M]^{+}\) calcd for C\(_{24}\)H\(_{23}\)NO\(_5\): 406.1654; found: 406.1637.

1H NMR (200 MHz, CDCl\(_3\)): \(\delta = 1.39\) (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, 79.05; H, 5.47; N, 4.74.

To a solution of compound 9 (190 mg, 0.427 mmol) in anhyd pyridine (2 mL) was added Na\(_2\)CO\(_3\) (210 mg, 1.52 mmol) and K\(_2\)CO\(_3\) (55.2 mg, 0.4 mmol), and the reaction mixture was stirred at r.t. overnight and poured into 10% HCl and then extracted with CHCl\(_3\). The residue was dissolved in CHCl\(_3\) and subjected to chromatography on silica gel. Elution with EtOAc–hexane (1:20) gave 10 (509 mg, 70%) as colorless prisms; mp 80–83 °C (Et\(_2\)O).
IR (KBr): 1684 cm\(^{-1}\).
H NMR (200 MHz, CDCl\(_3\)): \(\delta = 1.38\) (d, \(J = 6.1\) Hz, 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: \([M]^{+}\) calcd for C\(_{18}\)H\(_{15}\)N: 245.1204; found: 245.1161.

N-(6-Bromo-3-isopropoxy-2-methoxybenzyl)-6,7-methylene-dioxo-1-naphthylamine (11); Typical Procedure
To a solution of 10 (569 mg, 0.43 mmol) in anhyd pyridine (2 mL) was added Na\(_2\)CO\(_3\) (210 mg, 1.52 mmol) and K\(_2\)CO\(_3\) (55.2 mg, 0.4 mmol), and the reaction mixture was stirred at r.t. overnight and poured into 10% HCl and then extracted with CHCl\(_3\). The residue was dissolved in CHCl\(_3\) and subjected to chromatography on silica gel. Elution with EtOAc–hexane (1:20) gave 11 (161 mg, 77%) as colorless prisms; mp 134–135 °C (Et\(_2\)O).
IR (KBr): 1654 cm\(^{-1}\).
H NMR (200 MHz, CDCl\(_3\)): \(\delta = 1.22\) (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), 6.04 (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\(_{23}\)NO\(_5\): C, 71.10; H, 5.72; N, 3.45. Found: C, 79.05; H, 5.47; N, 4.74.

5-Acetyl-5,6-dihydro-8-isopropoxy-7-methoxy-2,3-methylene-dioxo[\(e\)]-phenanthridine (12) and 7-Acetyl-5,7-dihydro-10-isopropoxy-9-methoxy-1,2-methylene-dioxo[\(e\)]-phenanthridine (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-tol),\(_2\) (12.2 mg, 0.040 mmol), and K\(_2\)CO\(_3\) (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\(_2\)O).
IR (KBr): 1660 cm\(^{-1}\).
H NMR (200 MHz, CDCl\(_3\)): \(\delta = 1.39\) (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).

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Isolation of Products from Coupling Reaction of N-(2-Bromobenzyl)-6,7-dimethoxy-1,2-naphtho[1,8-bc]azeapine (5f)

Elution with EtOAc–hexane (1:30) gave 7,8-dihydro-1,2-dimethoxy-6,7-dimethoxy-naphtho[1,8-bc]azeapine (8e) (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-6,5-dihydrobenzo[e]phenanthridine (14f) (33%).

8f
Colorless amorphous solid.
IR (CHCl3): 1214, 1020 cm⁻¹.

1H NMR (500 MHz, CDCl3): δ = 2.98 (s, 3 H), 3.36 (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 C₂₀H₁₉NO₂: 305.1215; found: 305.1264.

9f
Colorless needles; mp 91–92.5 °C (MeOH).
IR (KBr): 1260, 1045 cm⁻¹.

1H NMR (200 MHz, CDCl3): δ = 2.82 (s, 3 H), 3.38 (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 C₂₁H₂₃NO₄: C, 71.37; H, 6.86; N, 3.96. Found: C, 71.68; H, 6.94; N, 3.65.

14f
Colorless prisms; 144–146 °C (MeOH).
IR (KBr): 1255, 1030 cm⁻¹.

1H NMR (200 MHz, CDCl3): 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 (dd, 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 C₂₀H₁₉NO₂: C, 78.66; H, 6.56; 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]naphth[1,8-bc]azeapine (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[e]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 (CHCl3): 1230, 1020 cm⁻¹.

1H NMR (500 MHz, CDCl3): 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).

1H NMR (200 MHz, CDCl3): 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 C23H27NO4: C, 73.26; H, 6.92; N, 3.56. Found: C, 73.10; H, 6.52; N, 3.42.

15i Colorless needles; mp 125–127 °C (MeOH).
IR (KBr): 3420, 1505, 1405, 1340, 1241, 1041 cm–1.

1H NMR (200 MHz, CDCl3): 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 C23H27NO4: C, 73.79; H, 6.92; N, 3.56. Found: C, 73.26; H, 6.18; N, 3.36.

14i Colorless needles; mp 127–131 °C.

1H NMR (200 MHz, CDCl3): 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 C23H27NO4: 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.

1H NMR (200 MHz, CDCl3): 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 C23H27NO4: C, 73.42; 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-naphthylamine14 (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 Et2O–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 Mel (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 EtOAc. The residue was recrystallized from EtOAc 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.

1H NMR (200 MHz, CDCl3): δ = 6.09 (s, 2 H), 7.02 (s, 1 H), 7.25 (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 C23H27BrNO4: 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.

1H NMR (200 MHz, CDCl3): 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).


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), Br2/NI (148 mg, 0.40 mmol), and K2CO3 (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 EtOAc. The residue was dissolved in CHCl3 and subjected to column chromatography on silica gel. Elution with EtOAc–hexane (1:30) gave 16 (724 mg, 98%) as a colorless oil.

IR (CHCl3): 1411, 1041 cm–1.

1H NMR (200 MHz, CDCl3): 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).


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), (35.2 mg, 0.116 mmol), and K2CO3 (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 CHCl3 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 (13.3 mg, 29%).

17 Colorless prisms; mp 146–147 °C (EtOH).
IR (KBr): 3393, 1242, 1044 cm–1.

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1H NMR (200 MHz, CDCl3): 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 C18H15NO2: C, 77.96; H, 5.45; N, 5.05. Found: C, 78.19; H, 5.60; N, 5.05.

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References


(8) The coupling reaction of 5a using Pd2(dba)3 (0.2 equiv) in degassed DMF gave no product and this was accompanied by decomposition of the starting material.


