Palladium-Catalyzed Construction of Polycyclic Heterocycles by an Alkyne Insertion and Direct Arylation Cascade

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Received: The date will be inserted once the manuscript is accepted.

Abstract: Cascade cyclization of bromoenynes bearing an aryl group with catalytic Pd(OAc)₂ and Cs₂CO₃ led to direct construction of tri- or tetracyclic heterocycles. Direct arylation of a pyrrole, furan or thiophene ring in the cascade reaction affords the corresponding fused heteroarenes in moderate to good yields.

Key words: tandem reaction, palladium, polycycles, fused-ring systems, ring closure

The development of cascade reactions that realize step-economical synthesis of complex compounds by multiple bond formation represents one of the most attractive subjects in modern organic chemistry. Another challenge in this area is to improve atom economy by minimizing waste product formation. As a result, considerable attention has been paid recently to catalytic cascade reactions including a C-H bond activation step.

Palladium catalysts are well known to promote a variety of transformations including C-H bond activation. Several palladium-catalyzed cascade reactions have been reported recently, including carbopalladation onto a carbon-carbon multiple bond followed by C-H bond activation to form cyclic products. Reactions involving carbopalladation onto a carbon-carbon triple bond are especially useful for direct construction of fused aromatic ring systems such as oxindoles, fluorenes, indoles, phenanthrenes, biarylidenes, acenaphthenes, and fused fulvenes. We recently found that palladium-catalyzed cascade cyclization of bromoenynes provides direct access to benzoisoindole derivatives (Scheme 1). This reaction proceeds through oxidative addition of a bromoenyne to palladium(0), carbopalladation, and aromatic C-H bond activation. Herein, our detailed studies on this cascade cyclization including aromatic C-H bond activation for the synthesis of various tri- and tetracyclic heterocycles are reported. A reaction involving direct arylation with heteroarenes is also described.

The cinnamylamine-type bromoenynes required for the cascade reaction were prepared according to the general route shown in Scheme 2. Carreira asymmetric alkynylation of aldehydes with alkynes gave propargylic alcohols, which were converted to the corresponding protected propargylic amines by Mitsunobu reaction with Boc-amides followed by acid treatment. In some cases, racemic propargylamines, which were readily prepared by reaction of lithium acetylide with aldehydes followed by amination, were used. A second Mitsunobu condensation with 2-bromocinnamyl alcohols, which were obtained by Wittig reaction of aldehydes followed by reduction with DIBAL-H, afforded the desired bromoenynes in good yields. Other substrates were also prepared using a similar protocol (see the Supporting Information).
First, the reaction conditions were optimized using bromoenyne 11a (Table 1). After considerable experimentation, it was found that the conditions used by Oh et al.10 [cat. Pd(PPh₃)₄, Cs₂CO₃, EtOH] for a cascade cyclization–cross-coupling reaction of 2-bromo-1,6-enynes with an arylboronic acid promoted the desired bis-cyclization to give 12a, albeit in low yield (26%, entry 1). Fortunately, use of Pd(OAc)₂ instead of Pd(PPh₃)₄ produced 12a in 74% yield (entry 2). Decreasing the catalyst loading to 2 mol % slightly decreased the yield (64%, entry 3). A similar result was obtained using Pd₂(dba)₃·CHCl₃ as the catalyst (entry 5). Among several solvents examined, EtOH was the most effective (entries 3, 6, and 7). Other bases such as K₂CO₃ and NaOAc proved ineffective for the reaction.11

The reactions of various cinnamylamine-type enynes 11 using the optimized reaction conditions shown in Table 1 were investigated. The results of these reactions are summarized in Table 2. The influence of the substituent at the alkyn terminus was examined using N-tosylamides 11b–f. 2-Hydroxypropan-2-yl, n-butyl, and unsubstituted derivatives 11b–d gave the corresponding bis-cyclization products 12b–d in 56–79% yield (entries 1–3). On the other hand, benzoxymethyl derivative 11e gave a complex mixture of unidentified products (entry 4). For an unclear reason, phenyl substitution also had a negative effect on the reaction, giving 12f in just 27% yield (entry 5). Using different sulfonamide moieties (Ts vs. Ms) was relatively unimportant (Table 2, entry 3 vs. 6, and Table 2, entry 1 vs. Table 1, entry 3). In contrast, the reaction is sensitive to the substituent at the propargylic position (entries 7–11); unfortunately, substitution with a phenyl group was not tolerated (entry 7). The presence of a relatively bulky substituent such as an isopropyl or 1-siloxyethyl group at this position decreased the reaction yield (entries 10 and 11). When tert-butyl derivative 11j was used (Scheme 3), only the monocyclization product 13j was obtained in 7% yield; the desired bis-cyclization product did not form. These bulky substituents might hamper the access of the palladium(II) intermediate of type 3 (Scheme 1) to the alkyne moiety. It should be noted that enynes 11m and 11n without propargyl or nitrogen substitution formed elimination products 14 (Scheme 3).12 From these observations, the presence of both a substituent with appropriate bulkiness at the propargylic position and at the nitrogen atom are important for the cascade cyclization to proceed. Methoxy substitution at the para-position of the benzene ring decreased the reaction yield (37%, entry 13), while meta-methoxy substitution was tolerated (57%, entry 12).

**Table 1** Optimization of Reaction Conditions Using Bromoenyne 11a

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst (mol %)</th>
<th>solvent</th>
<th>time (h)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh₃)₄ (6)</td>
<td>EtOH</td>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)₂ (6)</td>
<td>EtOH</td>
<td>2.5</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)₂ (2)</td>
<td>EtOH</td>
<td>7</td>
<td>64</td>
</tr>
<tr>
<td>4</td>
<td>Pd(dppf)C₁₂ (2)</td>
<td>EtOH</td>
<td>3.5</td>
<td>38</td>
</tr>
<tr>
<td>5</td>
<td>Pd₂(dba)₃·CHCl₃ (2)</td>
<td>EtOH</td>
<td>5</td>
<td>59</td>
</tr>
<tr>
<td>6*</td>
<td>Pd(OAc)₂ (2)</td>
<td>DMF</td>
<td>21</td>
<td>35</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)₂ (2)</td>
<td>dioxane</td>
<td>21</td>
<td>27</td>
</tr>
</tbody>
</table>

*Reactions were performed using Cs₂CO₃ (2 equiv). Isolated yields.

The reactions of various cinnamylamine-type enynes 11 using the optimized reaction conditions shown in entry 3 (Table 1) were investigated. The results of these reactions are summarized in Table 2. The influence of the substituent at the alkyn terminus was examined using N-tosylamides 11b–f. 2-Hydroxypropan-2-yl, n-butyl, and unsubstituted derivatives 11b–d gave the corresponding bis-cyclization products 12b–d in 56–79% yield (entries 1–3). On the other hand, benzoxymethyl derivative 11e gave a complex mixture of unidentified products (entry 4). For an unclear reason, phenyl substitution also had a negative effect on the reaction, giving 12f in just 27% yield (entry 5). Using different sulfonamide moieties (Ts vs. Ms) was relatively unimportant (Table 2, entry 3 vs. 6, and Table 2, entry 1 vs. Table 1, entry 3). In contrast, the reaction is sensitive to the substituent at the propargylic position (entries 7–11); unfortunately, substitution with a phenyl group was not tolerated (entry 7). The presence of a relatively bulky substituent such as an isopropyl or 1-siloxyethyl group at this position decreased the reaction yield (entries 10 and 11). When tert-butyl derivative 11j was used (Scheme 3), only the monocyclization product 13j was obtained in 7% yield; the desired bis-cyclization product did not form. These bulky substituents might hamper the access of the palladium(II) intermediate of type 3 (Scheme 1) to the alkyne moiety. It should be noted that enynes 11m and 11n without propargyl or nitrogen substitution formed elimination products 14 (Scheme 3).12 From these observations, the presence of both a substituent with appropriate bulkiness at the propargylic position and at the nitrogen atom are important for the cascade cyclization to proceed. Methoxy substitution at the para-position of the benzene ring decreased the reaction yield (37%, entry 13), while meta-methoxy substitution was tolerated (57%, entry 12).

**Table 2** Synthesis of Benzoisoindole Derivatives

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>time (h)</th>
<th>product (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11b (R = CMe₂OH)</td>
<td>2.5</td>
<td>12b (64%)</td>
</tr>
<tr>
<td>2</td>
<td>11c (R = n-Bu)</td>
<td>6</td>
<td>(±)-12c (79%)</td>
</tr>
<tr>
<td>3</td>
<td>11d (R = H)</td>
<td>2</td>
<td>(±)-12d (56%)</td>
</tr>
<tr>
<td>4</td>
<td>11e (R = CH₂OBn)</td>
<td>1.5</td>
<td>12e (0%)</td>
</tr>
<tr>
<td>5</td>
<td>11f (R = Ph)</td>
<td>6</td>
<td>12f (27%)</td>
</tr>
<tr>
<td>6</td>
<td>11g (R = n-Bu)</td>
<td>6</td>
<td>12g (46%)</td>
</tr>
<tr>
<td>7</td>
<td>11h (R = Ph)</td>
<td>1</td>
<td>12h (0%)</td>
</tr>
<tr>
<td>8</td>
<td>11i (R = n-Pent)</td>
<td>3</td>
<td>(±)-12i (65%)</td>
</tr>
<tr>
<td>9</td>
<td>11j (R = n-Pent)</td>
<td>1.5</td>
<td>(±)-12j (48%)</td>
</tr>
<tr>
<td>10</td>
<td>11k (R = i-Pr)</td>
<td>4</td>
<td>12k (24%)</td>
</tr>
<tr>
<td>11</td>
<td>11l (R = Ph)</td>
<td>24</td>
<td>12l (39%)</td>
</tr>
</tbody>
</table>

*Unless otherwise noted, reactions were carried out using Pd(OAc)₂ (2 mol %) and Cs₂CO₃ (2 equiv) in EtOH under reflux. Isolated yields. *A complex mixture of unidentified products was formed. An increased amount of Pd(OAc)₂ (4 mol %) was used.
To expand the reaction to construct various heterocyclic ring systems, the direct arylation of heterocyclic substrates 15a–e was investigated (Table 3). The reaction of furan-substituted enyne 15a was complete within 2 h to afford furyl[2,3-f]isoindole 16a in moderate yield (43%, entry 1). Bromoenynes 15b–e bearing a pyrrole ring exhibited relatively low reactivity and thus required an increased loading of the palladium catalyst (entries 2–9). For example, the reaction of tosylamide 15b with 10 mol % Pd(OAc)$_2$ and Cs$_2$CO$_3$ in DMF did not reach completion within 72 h, giving the desired tetrahydropyrrolo[3,4-b]indole 16b in 27% yield along with the recovered starting material (entry 2). In contrast, the yield of 16b was improved to 75% when 20 mol % of the catalyst was used (entry 3). Similar results were obtained using N-Mts derivative 15c (Mts = 2,4,6-trimethylbenzenesulfonyl, entries 4 and 5). It is worth noting that DMF was the solvent of choice for the reaction of protected pyrroles 15b and 15c because the reaction in EtOH was relatively inefficient and caused decomposition of the starting material (entry 6). When using electron-rich sulfonamide 15d, the decomposition of the substrate in EtOH was suppressed to some extent, and the desired fused indole 16d was produced in 52% yield (entry 7). The 2-position of the pyrrole was less reactive toward direct arylation than the 3-position in this cascade reaction (entry 3 vs. entry 9).

![Scheme 3](image)

### Table 3 Synthesis of Tricyclic Heterocycles

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>conditions</th>
<th>product (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15a</td>
<td>2 mol %, EtOH, 2 h</td>
<td>16a (43%)</td>
</tr>
<tr>
<td>2</td>
<td>15b (R = Ts)</td>
<td>10 mol %, DMF, 72 h</td>
<td>16b (27%)</td>
</tr>
<tr>
<td>3</td>
<td>15b (R = Mts)</td>
<td>10 mol %, DMF, 2 h</td>
<td>16b (75%)</td>
</tr>
<tr>
<td>4</td>
<td>15c (R = Mts)</td>
<td>10 mol %, DMF, 2 h</td>
<td>16b (81%)</td>
</tr>
<tr>
<td>5</td>
<td>15c (R = Mts)</td>
<td>20 mol %, DMF, 2 h</td>
<td>16c (36%)</td>
</tr>
<tr>
<td>6</td>
<td>15d (R = S$_2$NMe$_2$)</td>
<td>10 mol %, EtOH, 12 h</td>
<td>16d (52%)</td>
</tr>
<tr>
<td>7</td>
<td>15d (R = S$_2$NMe$_2$)</td>
<td>10 mol %, DMF, 3 h</td>
<td>16d (33%)</td>
</tr>
<tr>
<td>8</td>
<td>15e</td>
<td>20 mol %, DMF, 3 h</td>
<td>16e (42%)</td>
</tr>
</tbody>
</table>

* The reactions were carried out using Pd(OAc)$_2$ and Cs$_2$CO$_3$ (2 equiv) in EtOH (under reflux) or DMF (at 120 °C). Catalyst loading, reaction solvent, and reaction time are shown. Isolated yields. The starting material was recovered (27%). Abbreviation: Mts = 2,4,6-trimethylbenzenesulfonyl.

The synthesis of tetracyclic fused ring systems was investigated next (Table 4). Among the protected indole-derived bromoenynes 17a–c (entries 1–4), tosylate 17a proved the most efficient substrate for the cascade reaction, giving the desired tetrahydropyrrolo[3,4-b]carbazole 18a upon reaction in DMF (entry 1). The reaction of carbamate 17c in EtOH only promoted demethoxycarbonylation of the substrate (entry 4). Interestingly, the electron-rich N-
methylindole-derived enyne 17d was less reactive, affording 18d in 43% yield using an increased loading of the palladium catalyst (10 mol %, entry 5). These results suggest that the direct arylation of indole derivatives 17 proceeds through a concerted metalation-deprotonation (CMD) pathway rather than electrophilic aromatic substitution (Sₛₛ₆₆₆₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆₁₆� heterocycles to be produced from readily prepared enynes.

Melting points are uncorrected. Nominal (LRMS) and exact mass (HRMS) spectra were recorded on a JEOL JMS-700 or JMS-600 mass spectrometer. ¹H NMR spectra were recorded in CDCl₃. Chemical shifts are reported in parts per million downfield from internal Me₄Si (s = singlet, d = doublet, dd = double doublet, ddd = doublet of double doublet, t = triplet, dt = double triplet, tt = triple triplet, q = quartet, m = multiplet). Optical rotations were measured in CHCl₃ with a JASCO DIP-360 digital polarimeter. For flash chromatography, silica gel 60 H (silica gel for thin-layer chromatography, Merck) or silica gel 60 (finer than 230 mesh, Merck) was employed.

General procedure for the Palladium-Catalyzed Cascade Cyclization of Bromoenynes: Synthesis of (1R)-1-Cyclohexyl-9-(2-hydroxypropan-2-yl)-2-methylsulfonyl-2,3-dihydro-1H-benzof[λ]soindole (12a) (Table 1, Entry 3)

A mixture of 11a (124 mg, 0.265 mmol), Cs₂CO₃ (173 mg, 0.531 mmol), and Pd(OAc)₂ (1.2 mg, 0.0531 mmol; 2 mol %) in THF (1.5 mL) was heated under reflux for 7 h. After cooling the mixture, saturated NH₄Cl was added. The mixture was then extracted with EtOAc and dried over MgSO₄. Concentration under reduced pressure gave an oily residue, which was purified by column chromatography over silica gel with n-hexane–EtOAc to give 12a (65.7 mg, 64% yield) along with an unidentified minor product (2.5 mg, 3% yield).

In conclusion, we have developed a palladium-catalyzed cascade cyclization of bromoenynes. The reaction proceeds through carboxypalladation onto a carbon-carbon triple bond and C-H bond activation of a benzene ring, leading to the direct construction of isoindole derivatives. The presence of a propargylic substituent is quite important for the progress of the reaction. Direct arylation of heteroarenes such as pyrrole, furan, thiophene and their benzene-fused rings allows various types of tri- and tetracyclic heterocycles to be produced from readily prepared enynes.
1H, NCH(H)), 4.80 (dd, J = 16.8, 1.2 Hz, 1H, NCH(H)), 5.97 (d, J = 1.12 Hz, 1H, 1-H), 7.42–7.50 (m, 2H, Ar), 7.61 (s, 1H, Ar), 7.79–7.82 (m, 1H, Ar), 8.25 (dd, J = 9.9, 2.7 Hz, 1H, Ar).

13C NMR (75.4 MHz, CDCl3): δ = 13.9–14.5, 14.6 (2C), 27.9 (s, 3H, CMe), 44.7 (d, J = 1.12 Hz, 2H), 5.84 (s, 1H, C=CH), 7.13–7.27 (m, 5H, Ar).


Anal. Calcd for C28H33NO3S: C, 72.54; H, 7.17; N, 3.02. Found: C, 72.50; H, 7.19; N, 2.99.

(1R)-1-Cyclohexyl-9-(2-hydroxypropan-2-yl)-2-(4-methylphenylsulfonyl)-2,3-dihydro-1H-benzofuroisindole (12f)

Bromoeyene 11f (124 mg, 0.227 mmol) was converted to 12f (67.6 mg, 64% yield) and minor product (17.1 mg, 16% yield) by the reaction for 2 h.

IR (KBr): 3525 (OH), 1599 (naphthalene), 1340 (NHSO2), 1161 cm–1 (NHSO2).

1H NMR (500 MHz, CDCl3): δ = 0.86–1.94 (m, 11H), 1.76 (s, 3H, CMe), 1.96 (s, 3H, CMe), 2.12 (s, 3H, PhMe), 4.62 (d, J = 16.5 Hz, 1H, NCH(H)), 4.75 (d, J = 16.5 Hz, 1H, NCH(H)), 6.08 (d, J = 1.15 Hz, 1H, 1-H), 7.00 (d, J = 7.9 Hz, 2H, Ph), 7.35–7.40 (m, 3H, Ar), 7.64–7.70 (m, 3H, Ar), 8.14 (d, J = 8.5 Hz, 1H, Ar).

13C NMR (75 MHz, CDCl3): δ = 13.9–14.5, 14.6 (2C), 27.9 (s, 3H, CMe), 44.7 (d, J = 1.12 Hz, 2H), 5.84 (s, 1H, C=CH), 7.13–7.27 (m, 5H, Ar).

HRMS–FAB: m/z [M + Na] + calcd for C28H33NO3S: 456.2074; found: 462.2467; 

Anal. Calcd for C28H33NO3S: C, 72.54; H, 7.17; N, 3.02. Found: C, 72.50; H, 7.19; N, 2.99.
127.0 (2C), 127.5, 127.9, 129.4 (2C), 132.6, 132.8, 135.2, 135.8, 137.9, 143.1.

MS (FAB): m/z (%) = 406 (70) [M + H]+, 322 (100).


(1R)-1-Cyclohexyl-2-(4-methylphenylsulfonyl)-9-phenyl-2,3-dihydro-1H-benzo[f]isoindole (12f)

Bromoenyne 11f (64.0 mg, 0.114 mmol) was converted to 12f (15.0 mg, 27% yield) by the reaction for 6 h.

Colorless oil; [α]25D = 46.5 (c 0.60, CHCl3).

IR (KBr): 1394 cm–1 (C=O), 3466 cm–1 (OH), 1442 cm–1 (CH3).

1H NMR (300 MHz, CDCl3): δ = 8.28 (1H, Ar), 7.42 (m, 2H, Ar), 7.31 (m, 2H, Ar), 7.18 (m, 2H, Ar), 7.04 (m, 5H), 1.34–1.50 (m, 5H), 1.65–1.75 (m, 1H), 1.84–1.92 (m, 1H), 2.04 (s, 3H, PhMe), 2.87 (dt, 2H, Ph), 2.72–2.78 (m, 4H, Ph, Ar), 4.06 (d, J = 2.4 Hz, 1H, 1-H), 6.96–7.01 (m, 2H, Ar), 7.13 (d, J = 8.4 Hz, 1H, Ph), 7.28–7.38 (m, 2H, Ph, Ar), 7.41 (dd, J = 8.1, 8.1 Hz, 1H, Ar), 7.48–7.51 (m, 5H, Ar), 7.66 (d, J = 8.4 Hz, 2H, Ph), 7.76 (d, J = 8.1 Hz, 1H, Ar).

13C NMR (75 MHz, CDCl3): δ = 214.4, 261, 262, 265 (2C), 31.2, 43.7, 55.0, 70.6, 78.9, 119.5, 125.6, 125.7, 125.9, 127.3 (2C), 127.8 (2C), 128.2, 128.6, 129.1, 129.5 (2C), 130.5, 132.0, 133.3, 134.1, 134.5, 135.8, 137.3, 137.6, 134.4.

HRMS–FAB: m/z (%) = 482 (6.8) [M + H]+, 154 (100).

(±)-1-Cyclohexyl-2-methylsulfonyl-2,3-dihydro-1H-benzo[f]isoindole (12g)

Bromoenyne 11g (36.8 mg, 0.0897 mmol) was converted to 12g (13.7 mg, 46% yield) by the reaction for 6 h.

Colorless oil; IR (KBr): 1394 cm–1 (C=O), 3466 cm–1 (OH), 1442 cm–1 (CH3).

1H NMR (300 MHz, CDCl3): δ = 8.09–8.10 (m, 1H, 1-H), 6.60–6.61 (m, 2H, Ar), 5.36 (d, J = 16.2 Hz, 1H, 3-CH/H), 4.86 (d, J = 16.2 Hz, 1H, 3-CH/H), 4.92 (d, J = 4.5 Hz, 1H, 1-H), 7.48–7.51 (m, 2H, Ar), 7.77 (s, 2H, 4-H and 9-H), 7.82–7.87 (m, 2H, Ar).

13C NMR (75 MHz, CDCl3): δ = 214.4, 261, 262, 265 (2C), 31.2, 43.7, 55.0, 70.6, 78.9, 119.5, 125.6, 125.7, 125.9, 127.3 (2C), 127.8 (2C), 128.2, 128.6, 129.1, 129.5 (2C), 130.5, 132.0, 133.3, 134.1, 134.5, 135.8, 137.3, 137.6, 134.4.

HRMS–FAB: m/z (%) = 330 (34) [M + H]+, 246 (100).

Bromoenyne 11k (94.2 mg, 0.199 mmol) was converted to 12k (37.8 mg, 48% yield) by the reaction for 1.5 h.

Colorless oil; IR (KBr): 1394 cm–1 (C=O), 3466 cm–1 (OH), 1442 cm–1 (CH3).

1H NMR (300 MHz, CDCl3): δ = 0.81 (t, J = 6.9 Hz, 3H, CMe), 1.02–1.05 (m, 4H), 1.13–1.16 (m, 4H), 1.38–1.41 (m, 4H), 1.39–1.47 (m, 1H), 1.85–2.00 (m, 1H), 2.13–2.25 (m, 1H), 2.31 (s, 3H, PhMe), 4.77 (d, J = 14.7 Hz, 1H, 3-CH/H), 4.83 (d, J = 14.7 Hz, 1H, 3-CH/H), 5.16 (t, J = 4.5 Hz, 1H, 1-H), 7.20 (d, J = 8.1 Hz, 2H, Ph), 7.40–7.46 (m, 2H, Ar), 7.53 (s, 1H, Ar), 7.57 (s, 1H, Ar), 7.72 (d, J = 8.1 Hz, 2H, Ph), 7.75–7.79 (m, 2H, Ar).

13C NMR (75 MHz, CDCl3): δ = 14.0, 21.4, 22.5, 23.2, 31.8, 37.0, 53.4, 65.5, 120.8, 120.9, 125.88, 125.93, 127.3 (2C), 127.67, 127.68, 127.8, 129.7 (2C), 133.0, 134.9, 135.6, 139.3, 143.4.

(1R)-1-Isopropyl-2-(4-methylphenylsulfonyl)-2,3-dihydro-1H-benzo[f]isoindole (12l)

Bromoenyne 11l (52.8 mg, 0.118 mmol) was converted to 12l (10.5 mg, 24% yield) by the reaction for 4 h.

Colorless oil; [α]25D = 20.8 (c 0.60, CHCl3).

IR (KBr): 1394 cm–1 (C=O), 3466 cm–1 (OH), 1442 cm–1 (CH3).

1H NMR (500 MHz, CDCl3): δ = 0.80 (d, J = 6.7 Hz, 3H, CMe), 0.99 (d, J = 7.3 Hz, 3H, CMe), 2.19 (s, 3H, PhMe), 2.32–2.36 (m, 1H, MeCH), 4.71 (s, 1H, J = 15.5 Hz, 3-CH/H), 4.74 (d, J = 15.5 Hz, 1H, 3-CH/H), 4.99 (d, J = 4.3 Hz, 1H, 1-H), 7.06 (d, J = 7.9 Hz, 2H,
Ph), 7.357 (d, J = 6.1 Hz, 1H, Ar), 7.365 (d, J = 6.1 Hz, 1H, Ar), 7.47 (s, 1H, Ar), 7.50 (s, 1H, Ar), 7.59 (d, J = 7.9 Hz, 2H, Ph), 7.66–7.71 (m, 2H, Ar).

13C NMR (75 MHz, CDCl3): δ = 17.3, 18.4, 21.4, 35.8, 53.8, 70.9, 120.6, 121.9, 125.8, 125.9, 127.1 (2C), 127.6, 128.0, 129.6 (2C), 132.8, 133.0, 135.3, 135.9, 137.6, 143.3.

MS (FAB): m/z (%) = 366 (22) [M + H]+, 154 (100).

HRMS–FAB: m/z [M + H]+ calcd for C30H36NO3SSi: 492.2572; found: 492.2581.

(1R)-9-Butyl-1-cyclohexyl-6-methoxy-2-(4-methylphenylsulfonyl)-2,3-dihydro-1H-benzo/[f]isoindole (12p)

Bromoeneone 11p (60.2 mg, 0.105 mmol) was converted to 12p (29.4 mg, 57% yield) by the reaction for 7 h.

Colorless oil; IR (KBr): 1344 (NSO), 1163 cm–1 (NH).

HRMS–FAB: m/z [M + H]+ calcd for C30H36NO3SSi: 492.2572; found: 492.2581.

(P)-4-[(Z)-Benzylidene]-2-tert-butyl-1-(4-methylphenylsulfonyl)-3-[(Z)-pentylidene]-1H-pyrrole (13j)

Bromoeneone 11j (61.3 mg, 0.119 mmol) was converted to 13j (3.6 mg, 7% yield) by the reaction for 7 h.

Colorless oil; IR (KBr): 1348 (NSO), 1163 cm–1 (NSO).

HRMS–FAB: m/z [M + H]+ calcd for C38H36NO3SSi: 512.2737; found: 512.2737.
$N$-(But-2-ynyl)-$N$-(3-phenylprop-2-ynyl)-4-methylbenzenesulphonamide (14m)
Bromoenyne $11m$ (43.7 mg, 0.105 mmol) was converted to $14m$ (19.2 mg, 54% yield) by the reaction for 0.5 h.

Colorless oil; IR (KBr): 2362 (C≡C), 1603 (NC=C), 1350 (NSO$_2$), 1165 cm$^{-1}$ (NSO$_2$).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta = 1.69$ (t, $J = 2.4$ Hz, 3H, CMe), 2.35 (s, 3H, PhMe), 4.13 (q, $J = 2.4$ Hz, 2H, NCH$_2$), 4.38 (s, 2H, NCH$_2$), 7.16 (dd, $J = 6.6$, 1.8 Hz, 2H, Ph), 7.23–7.30 (m, 5H, Ph), 7.75 (dd, $J = 6.6$, 1.8 Hz, 2H, Ph).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 26.2, 26.5, 26.7, 30.1, 31.5, 32.7, 45.3, 55.2, 69.9, 103.7, 105.2$ (2C), 125.9, 126.8 (2C), 127.2 (2C), 131.7 (2C).

HRMS–FAB: $m/z$ [M + H$^+$] calcd for C$_{27}$H$_{36}$NO$_2$S: 438.2467; found: 438.2481.

(5R)-4-Butyl-5-cyclohexyl-1,6-bis(4-methylphenylsulfonyl)-1,5,6,7-tetrahydropyrrolo[3,4-f]indole (16b)

Bromoenyne $15b$ (111 mg, 0.162 mmol) was converted to $16b$ (73.3 mg, 75%) by the reaction using Pd(OAc)$_2$ (7.7 mg, 0.0346 mmol) in DMF at 120 °C for 2 h.

Colorless oil; $[\alpha]_{D}^{26}$ +79.7 (c 0.98, CHCl$_3$).

IR (KBr): 1597 (NC=C), 1360 (NSO$_2$), 1346 (NSO$_2$), 1178 (NSO$_2$), 1161 cm$^{-1}$ (NSO$_2$).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta = 0.92$ (t, $J = 7.1$ Hz, 3H, CMe), 1.01–1.37 (m, 8H), 1.61–1.85 (m, 7H), 2.20 (s, 3H, PhMe), 2.38 (s, 3H, PhMe), 2.61–2.67 (m, 2H, 1'-CH$_2$), 4.63 (d, $J = 15.9$ Hz, 1H, 7-CHF), 4.76 (dd, $J = 15.9$, 1H, 7-CHF), 4.97 (s, 1H, 5-H), 6.57 (dd, $J = 3.8$, 0.7 Hz, 1H, 3-H), 6.97 (d, $J = 7.9$ Hz, 2H, Ph), 7.25 (d, $J = 7.9$ Hz, 2H, Ph), 7.46 (d, $J = 3.8$ Hz, 1H, 2-H), 7.48 (s, 1H, 8-H), 7.53 (dd, $J = 7.9$, 1.8 Hz, 2H, Ph), 7.73 (dd, $J = 7.9$, 1.8 Hz, 2H, Ph).

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta = 14.0, 21.3, 21.6, 22.9, 26.2, 26.4, 26.5, 26.7, 30.1, 31.5, 32.6, 45.4, 55.2, 69.9, 104.5, 107.2, 125.8, 126.8 (2C), 127.2 (2C), 129.3 (3C), 129.6, 129.9, 130.0, 133.5, 143.7, 131.5, 135.2, 143.0, 145.0.

MS (FAB): $m/z$ (%) = 605 (5.2) [M + H$^+$], 521 (100).

HRMS–FAB: $m/z$ [M + H$^+$] calcd for C$_{34}$H$_{41}$N$_2$O$_5$S$_2$: 605.2508; found: 605.2493.

(5R)-4-Butyl-5-cyclohexyl-1-(2,4,6-trimethylphenylsulfonyl)-6-(4-methylphenylsulfonyl)-1,5,6,7-tetrahydropyrrolo[3,4-f]indole (16c)

Bromoenyne $15c$ (72.0 mg, 0.101 mmol) was converted to $16c$ (51.4 mg, 81%) by the reaction using Pd(OAc)$_2$ (4.5 mg, 0.0202 mmol) in DMF at 120 °C for 2 h.

Colorless oil; $[\alpha]_{D}^{26}$ +52.2 (c 1.645, CHCl$_3$).

IR (KBr): 1603 (NC=C), 1350 (NSO$_2$), 1161 cm$^{-1}$ (NSO$_2$).

$^1$H NMR (270 MHz, CDCl$_3$): $\delta = 0.86$ (t, $J = 6.9$ Hz, 3H, CMe), 0.91–1.34 (m, 8H), 1.40–1.86 (m, 7H), 2.23 (s, 3H, PhMe), 2.32 (s, 3H, PhMe), 2.46 (s, 6H, PhMe), 2.68 (t, $J = 6.6$ Hz, 2H, 1'-CH$_2$), 4.54 (d, $J = 16.0$ Hz, 1H, 7-CHF), 4.66 (dd, $J = 16.0$, 1H, 7-CHF), 4.96 (s, 1H, 5-H), 6.53 (dd, $J = 3.7$, 1H, 3-H), 6.94–6.99 (m, 5H, Ar), 7.39 (d, $J = 3.7$ Hz, 1H, 2-H), 7.50 (d, $J = 8.1$ Hz, 2H, Ph).

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta = 14.0, 21.0, 21.3, 22.5 (2C), 22.9, 26.2, 26.5, 26.7, 30.1, 31.5, 32.7, 45.3, 55.2, 69.9, 103.7, 105.2 (2C), 125.9, 127.2 (2C), 132.7, 134.5, 135.1, 143.0, 144.5, 154.7.

MS (FAB): $m/z$ (%) = 452 (45) [M + H$^+$], 368 (100).

HRMS–FAB: $m/z$ [M + H$^+$] calcd for C$_{27}$H$_{34}$NO$_2$: 452.2259; found: 452.2258.
129.2 (3C), 129.3, 129.6, 132.3 (3C), 132.9, 134.6, 134.7, 135.1, 140.1, 143.0, 144.1.

MS (FAB): m/z (%) = 633 (28) [M + H⁺], 549 (100).


(5R)-4-Butyl-5-cyclohexyl-N,N-dimethyl-6-(4-methylphenylsulfonyl)-6,7-dihydropyrrolo[3,4-\(f\)]indole-1(5H)-sulfonamide (16d)

Bromoenyne 15d (49.7 mg, 0.0778 mmol) was converted to 16d (22.7 mg, 52%) by the reaction using Pd(OAc)₂ (1.8 mg, 0.00802 mmol) in DMF at 120 °C for 12 h.

Pale orange oil; [α]²⁶ –37.8 (c 0.740, CHCl₃).

IR (KBr): 1599 (NC=C), 1387 (NSO₂), 1344 (NSO₂), 1174 (NSO₂), 1163 cm –1 (NSO₂).

HRMS–FAB: [M + H⁺]_calcd for C₃₄H₄₁N₂O₄S₂: 605.2508; found: 605.2531.

(3R)-4-Butyl-3-cyclohexyl-2,5-bis(4-methylphenylsulfonyl)-1,2,3,5-tetrahydropyrrolo[3,4-b]carbazole (18a)

Bromoenyne 17a (74.0 mg, 0.101 mmol) was converted to 18a (33.8 mg, 51% yield) by the reaction using Pd(OAc)₂ (2.3 mg, 0.00101 mmol) in DMF at 120 °C for 18 h.

Colorless oil; [α]²⁶ –122 (c 0.30, CHCl₃).

IR (KBr): 1597 (C=CN), 1367 (NSO₂), 1346 (NSO₂), 1173 (NSO₂), 1163 cm –1 (NSO₂).

(3R)-4-Butyl-3-cyclohexyl-5-methyl-2-(4-methylphenylsulfonyl)-1,2,3,5-tetrahydropyrrolo[3,4-b]carbazole (18d)

Bromoeneyne 17d (118 mg, 0.20 mmol) was converted to 18d (43.7 mg, 43%) by the reaction using Pd(OAc)2 (4.5 mg, 0.0198 mmol) for 36 h.

Pale yellow oil; [α]25D +10.2 (c 1.28, CHCl3).

IR (KBr): 1344 (NSO2), 1161 cm–1 (NSO2).

HRMS–FAB: m/z (%) = 518 (23) [M + H+], 154 (100).

HRMS–FAB: m/z [M + H]+ calcd for C31H36NO3S2: 518.2187; found: 518.2186.

Bromoeneyne 17f (62.0 mg, 0.106 mmol) was converted to 18f (31.4 mg, 59% yield) by the reaction for 1 h.

Colorless oil; [α]26D –119 (c 0.35, CHCl3).

IR (KBr): 1346 (NSO2), 1163 cm–1 (NSO2).


Bromoeneyne 17g (132 mg, 0.22 mmol) was converted to 18g (48.7 mg, 43%) by the reaction using Pd(OAc)2 (1.0 mg, 0.0044 mmol) in DMF at 120 °C for 2 h and a further 3 h with additional Pd(OAc)2 (1.5 mg, 0.0066 mmol).

Colorless oil; [α]25D –165.5 (c 0.63, CHCl3).

IR (KBr): 1344 (NSO2), 1161 cm–1 (NSO2).

1H, Ar), 7.54–7.64 (m, 6H, Ar), 7.86 (dd, J = 6.8, 2.2 Hz, 1H, Ar), 8.74 (d, J = 7.8 Hz, 1H, Ar).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 13.9, 21.3, 23.1, 26.2, 26.5, 26.7$ (2C), 31.1, 31.5, 33.9, 45.6, 55.3, 71.4, 120.1, 125.8, 125.9, 126.7, 127.2 (3C), 128.0, 128.9, 129.0, 129.4 (2C), 131.1, 133.3, 134.1, 134.6, 135.1, 135.9, 139.8, 143.2.

MS (FAB): m/z (%) = 512 (49) [M + H$^+$], 428 (100).

HRMS–FAB: m/z [M + Na$^+$] calced for C$_{33}$H$_{37}$NNaO$_6$: 604.2709; found: 604.2724.

Supporting Information

This work was supported in part by a Grant-in-Aid for Scientific Research on Innovative Areas "Integrated Organic Synthesis" (H.O.) and for Scientific Research (B) (T.T.) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

References


(8) A portion of this study (Table 1; Table 2: entries 2, 3, 6, 11, 12; Table 4: entries 1 and 7) has already been reported in a preliminary communication: Ohno, H.; Yamamoto, M.; Iuchi, M.; Tanaka, T. Angew. Chem., Int. Ed. 2005, 44, 5103–5106.


(11) For example, the reaction of 11b with Pd(OAc)2 (2 mol %) using K2CO3 (2 equiv) as the base stereoselectively gave the monocyclic product 13b in 94% yield.

(12) A similar result was obtained with malonate congener 19e, which produced diyne 21 in 69% yield.


Graphical Abstract

Short Title: Palladium-Catalyzed Cascade Cyclization through Direct Arylation