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

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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.1 Another challenge in this area is to improve atom economy by minimizing waste product formation.2 C-H bond activation (including direct arylation), which avoids pre-activation of the substrate and thus minimizes the production of waste, is an important strategy for this purpose.3 As a result, considerable attention has been paid recently to catalytic cascade reactions including a C-H bond activation step.4 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.4,5 Reactions involving carbopalladation onto a carbon-carbon triple bond are especially useful for direct construction of fused aromatic ring systems6,7 such as oxindoles,6a,6b fluorenes6c indoles,6d phenanthrenes,6e biaryldienes,6f acenaphthylenes,6c and fused fulvenes.6d We recently found that palladium-catalyzed cascade cyclization of bromoenynes 1 provides direct access to benzoisoindole derivatives 2 (Scheme 1).8 This reaction proceeds through oxidative addition of a bromoenyne 1 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.
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.\textsuperscript{10} [cat. Pd(PPh\textsubscript{3})\textsubscript{4}, Cs\textsubscript{2}CO\textsubscript{3}, EtOH] for a cascade cyclization–cross-coupling reaction of 2-bromo-1,6-enynes with an aryloboronic acid promoted the desired bis-cyclization to give 12a, albeit in low yield (26\%, entry 1). Fortunately, use of Pd(OAc)\textsubscript{2} instead of Pd(PPh\textsubscript{3})\textsubscript{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 Pd\textsubscript{2}(dba)\textsubscript{3}·CHCl\textsubscript{3} as the catalyst (entry 5). Among several solvents examined, EtOH was the most effective (entries 3, 6, and 7). Other bases such as K\textsubscript{2}CO\textsubscript{3} and NaOAc proved ineffective for the reaction.\textsuperscript{11}

The reactions of various cinnamylamine-type enynes 11 using the optimized reaction conditions shown in Table 2. The influence of the substituent at the alkyne terminus was examined using N-rosylamides 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, benzylxymethyl 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 propargylic or nitrogen substitution formed elimination products 14 (Scheme 3).\textsuperscript{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(PPh\textsubscript{3})\textsubscript{4} (6)</td>
<td>EtOH</td>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)\textsubscript{2} (6)</td>
<td>EtOH</td>
<td>2.5</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)\textsubscript{2} (2)</td>
<td>EtOH</td>
<td>7</td>
<td>64</td>
</tr>
<tr>
<td>4</td>
<td>Pd(dppf)Cl\textsubscript{2} (2)</td>
<td>EtOH</td>
<td>3.5</td>
<td>38</td>
</tr>
<tr>
<td>5</td>
<td>Pd(dba)\textsubscript{2}·CHCl\textsubscript{3} (2)</td>
<td>EtOH</td>
<td>5</td>
<td>59</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)\textsubscript{2} (2)</td>
<td>DMF</td>
<td>21</td>
<td>35</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)\textsubscript{2} (2)</td>
<td>dioxane</td>
<td>21</td>
<td>27</td>
</tr>
</tbody>
</table>

\* Reactions were performed using Cs\textsubscript{2}CO\textsubscript{3} (2 equiv). \textsuperscript{b} Isolated yields. \textsuperscript{c} The reaction was performed at 100 °C.

### 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 = CMe\textsubscript{2}OH)</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 = CH\textsubscript{2}OBn)</td>
<td>1.5</td>
<td>12e (0%) \textsuperscript{a}</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</td>
<td>6</td>
<td>12g (46%)</td>
</tr>
<tr>
<td>7</td>
<td>11h (R = Ph)</td>
<td>1</td>
<td>12h (0%) \textsuperscript{a}</td>
</tr>
<tr>
<td>8</td>
<td>(±)-11j (R = n-Pent)</td>
<td>3</td>
<td>(±)-12j (65%)</td>
</tr>
<tr>
<td>9</td>
<td>(±)-11k (R = n-Pent)</td>
<td>1.5</td>
<td>(±)-12k (48%)</td>
</tr>
<tr>
<td>10</td>
<td>11i (R = i-Pr)</td>
<td>4</td>
<td>12i (24%)</td>
</tr>
<tr>
<td>11</td>
<td>11n</td>
<td>24</td>
<td>12n (39%)</td>
</tr>
<tr>
<td>12</td>
<td>11p (R\textsuperscript{1} = OMe, R\textsuperscript{2} = H)</td>
<td>5</td>
<td>12p (57%)</td>
</tr>
<tr>
<td>13</td>
<td>11q (R\textsuperscript{1} = H, R\textsuperscript{2} = OMe)</td>
<td>8</td>
<td>12q (37%)</td>
</tr>
</tbody>
</table>

\* Unless otherwise noted, reactions were carried out using Pd(OAc)\textsubscript{2} (2 mol\%) and Cs\textsubscript{2}CO\textsubscript{3} (2 equiv) in EtOH under reflux. \textsuperscript{b} Isolated yields. \textsuperscript{c} A complex mixture of unidentified products was formed. \textsuperscript{d} An increased amount of Pd(OAc)\textsubscript{2} (4 mol\%) was used.
The reaction of furan-substituted enyne heterocyclic substrates with the palladium catalyst (entries 2–9). For example, the bromoenyne bearing a pyrrole ring exhibited relatively low activity (entry 1). Bromoenyynes 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 Cs₂CO₃ in DMF did not reach completion within 72 h, giving the desired tetrahydropyrrolo[3,4-f]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).

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 furano[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 Cs₂CO₃ in DMF did not reach completion within 72 h, giving the desired tetrahydropyrrolo[3,4-f]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).

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>20 mol %, DMF, 2 h</td>
<td>16b (75%)</td>
</tr>
<tr>
<td>4</td>
<td>15c (R = Mts)</td>
<td>20 mol %, DMF, 2 h</td>
<td>16c (42%)</td>
</tr>
<tr>
<td>5</td>
<td>15c (R = Mts)</td>
<td>10 mol %, EtOH, 2 h</td>
<td>16c (81%)</td>
</tr>
<tr>
<td>6</td>
<td>15c (R = Mts)</td>
<td>10 mol %, EtOH, 12 h</td>
<td>16c (36%)</td>
</tr>
<tr>
<td>7</td>
<td>15d (R = SO₂NMe₂)</td>
<td>10 mol %, EtOH, 12 h</td>
<td>16d (52%)</td>
</tr>
<tr>
<td>8</td>
<td>15d (R = SO₂NMe₂)</td>
<td>10 mol %, DMF, 3 h</td>
<td>16d (33%)</td>
</tr>
<tr>
<td>9</td>
<td>15e</td>
<td>20 mol %, DMF, 4 h</td>
<td>16e (42%)</td>
</tr>
</tbody>
</table>

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 (S_{Ar}). The reaction of benzo[b]thiophen-3-yl- and benzofuran-2-yl enynes 17e and 17f produced the corresponding benzo[b]thiophene- and benzofuran-fused isoindoles 18e and 18f, respectively, in moderate yields (entries 6 and 7). 2,3-Dihydrobenzofuran[2,3-f]isoindole 18g was obtained in 43% yield by activation of the naphthalene C-H bond (entry 8).

Finally, construction of an indane skeleton using malonate as the electrophilic partner 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.

Melting points are uncorrected. Nominal (LRMS) and exact mass (HRMS) spectra were recorded on a JEOL JMS-700 or JMS-600 mass spectrometer. H 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 synthesis of bromoenynes (11) by condensation of propargyl amine derivatives (8) with 3-Aryl-2-bromoprop-2-en-1-ols (10)

To a stirred mixture of protected propargyl amine 8 (ca. 3 mmol), alcohol 10 (2.2 equiv), and PPh₃ (2.2 equiv) in THF (30 mL) was added dropwise diisopropyl azodicarboxylate (DIAD; 2.2 equiv) at 0 °C. The mixture was stirred for 4 h at room temperature and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel with an eluent of n-hexane–EtOAc to give 11.

General procedure for the palladium-catalyzed cascade cyclization of bromoenynes: Synthesis of (IR)-1-Cyclohexyl-9-(2-hydroxypropan-2-yl)-2-methylsulfonyl-2,3-dihydropyan-1H-benzof[f]isoindole (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, 0.00531 mmol; 2 mol %) in EtOH (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 (10:1) to give 12a (65.7 mg, 64% yield) along with an unidentified minor product (2.5 mg, 3% yield).

Compound 12a: colorless oil; [α]²⁸D +31.4 (c 0.62, CHCl₃).

IR (KBr): 3545 (OH), 1336 (NSO₂), 1153 cm⁻¹ (NSO₂).

H NMR (300 MHz, CDCl₃): δ = 0.90–1.28 (m, 5H), 1.58–1.85 (m, 6H), 1.96 (s, 3H, CMe), 2.03 (s, 3H, CMe), 2.55 (s, 3H, SO₂Me), 4.65 (dd, J = 16.8, 1.2 Hz, 3H).
1H, NCHH), 4.80 (dd, J = 16.8, 1.2 Hz, 1H, NCHH), 5.97 (d, J = 1.2 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 (67.5 MHz, CDCl3): δ = 26.2, 26.3, 26.7 (2C), 31.4, 32.6, 34.2 (2C), 47.0, 53.4, 71.9, 75.2, 120.8, 125.0, 125.1, 126.5, 129.0, 130.3, 134.6, 136.4, 137.3, 139.0.

MS (FAB): m/z (%) = 388 [MH+] (53), 154 (100).

HRMS–FAB: m/z [M + Na+] calcd for C28H33NO3S: 486.2074; found: 486.2079.

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

(3z)-9-Butyl-1-cyclohexyl-2-(4-methylphenylsulfonyl)-2,3-dihydro-1H-benzo[1]isoindole (12c)

Bromoxygen 11c (130 mg, 0.240 mmol) was converted to 12c (87.8 mg, 79% yield) by the reaction for 6 h.

Colorless oil; IR (KBr): 1346 (NSO2), 1161 cm–1.

1H NMR (300 MHz, CDCl3): δ = 0.90–2.16 (m, 18H), 2.38 (s, 3H, PhMe), 2.81–2.91 (m, 1H, 1'-CH3), 2.95–3.05 (m, 1H, 1'-CH2), 4.71 (d, J = 16.2 Hz, 1H, 3-CH3), 4.83 (d, J = 16.2 Hz, 1H, 3-CH3), 5.12 (s, 1H, 1-H), 6.99 (d, J = 8.1 Hz, 2H, Ph), 7.34–7.46 (m, 3H, Ar), 7.57 (d, J = 8.1 Hz, 2H, Ph), 7.70 (d, J = 7.5 Hz, 1H, Ar), 7.92 (d, J = 8.1 Hz, 1H, Ar).

13C NMR (75 MHz, CDCl3): δ = 12.3, 26.2, 26.3, 5.84 (s, 1H, C=CH), 7.13–7.27 (m, 5H, Ar).

Minor product: colorless crystals; Mp 152–154 °C (n-hexane–EtOAc); [α]23D +50.6 (c 0.60, CHCl3).

IR (KBr): 3519 (OH), 1338 (NSO2), 1159 cm–1.

HRMS–FAB: m/z (%) = 462 (60) [M + H]+, 378 (100).


(1R)-1-Cyclohexyl-9-(2-hydroxypropan-2-yl)-2-(4-methylphenylsulfonyl)-2,3-dihydro-1H-benzo[1]isoindole (12b)

Bromoxygen 11b (124 mg, 0.227 mmol) was converted to 12b (67.6 mg, 64% yield) and minor product (17.1 mg, 16% yield) by the reaction for 2.5 h.

12b: Colorless oil; [α]23D +144.3 (c 0.14, CHCl3).

IR (KBr): 3525 (OH), 1359 (naphthalene), 1340 (NHSO2), 1161 cm–1 (NHSO2).

1H NMR (300 MHz, CDCl3): δ = 1.10 (s, 3H, CMe), 1.15–1.96 (m, 12H), 1.31 (s, 3H, CMe), 2.79 (s, 3H, SO2Me), 4.47 (d, J = 1.2 Hz, 2H), 5.84 (s, 1H, C=CH), 7.13–7.27 (m, 5H, Ar).

13C NMR (67.8 MHz, CDCl 3): δ = 26.1, 26.2, 26.3, 26.7, 28.8, 29.1, 29.4, 34.5, 43.2, 49.7, 67.6, 70.8, 113.8, 127.4 (2C), 127.6, 128.7 (2C), 156.7, 138.6, 148.9, 149.3.

Minor product: colorless crystals; Mp 152–154 °C (n-hexane–EtOAc); [α]23D +280 (c 0.33, CHCl3).

IR (KBr): 3523 (OH), 1344 (NHSO2), 1166 cm–1 (NHSO2).

1H NMR (500 MHz, CDCl3): δ = 0.86–1.98 (m, 11H), 1.00 (s, 3H, CMe), 1.20 (s, 3H, CMe), 2.41–2.43 (m, 1H), 2.53 (s, 3H, PhMe), 4.36 (s, 1H), 4.41 (s, 1H), 5.93 (s, 1H, C=CH), 6.66 (d, 2H, J = 7.3 Hz, Ar), 7.13–7.35 (m, 5H, Ar), 7.66 (d, 2H, J = 8.5 Hz, Ph).

13C NMR (67.8 MHz, CDCl3): δ = 21.8, 26.2, 26.35, 26.42, 27.8, 29.0, 29.1, 29.2, 43.1, 49.4, 67.3, 70.6, 114.0, 127.2, 127.4 (2C), 128.0 (2C), 128.2 (2C), 129.4 (2C), 133.2, 137.1, 138.5, 143.3, 148.5, 149.1.

MS (FAB): m/z (%) = 464 (56) [M + Na+], 154 (100).

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).

HRMS – FAB: m/z [M + H]^+ cale d for C_{25}H_{28}NO_2S: 406.1841; found: 406.1823.

(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]^25_D = -46.5 (c 0.60, CHCl_3).

IR (KBr): 1344 (NSO_2), 1161 cm–1 (NSO_2).

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

HRMS – FAB: m/z [M + H]^+ cale d for C_{19}H_{24}NO_2S: 330.1528; found: 330.1514.

(±)-9-Butyl-2-(4-methylphenylsulfonyl)-1-pentyl-2,3-dihydro-1H-benzo/[f]isoindole (12i)

Bromoenyne 11i (72.0 mg, 0.136 mmol) was converted to 12i (39.9 mg, 65% yield) by the reaction for 3 h.

Colorless oil; IR (KBr): 1346 (NSO_2), 1161 cm–1 (NSO_2).

IR (KBr): 1344 (NSO_2), 1161 cm–1 (NSO_2).

13C NMR (75 MHz, CDCl_3): δ = 14.0, 14.1, 21.4, 22.5, 23.3, 24.1, 29.2, 31.8, 32.8, 36.4, 53.3, 65.4, 119.1, 123.9, 125.4, 125.5, 127.0 (2C), 128.5, 129.5 (2C), 131.5, 132.5, 133.7, 135.2, 135.6, 137.1, 143.2.

MS (FAB): m/z (%) = 450 (62) [M + H^+], 378 (100).

HRMS – FAB: m/z [M + H]^+ cale d for C_{28}H_{30}NO_2S: 450.2467; found: 450.2458.

(±)-2-(4-Methylphenylsulfonyl)-1-pentyl-2,3-dihydro-1H-benzo/[f]isoindole (12k)

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): 1346 (NSO_2), 1161 cm–1 (NSO_2).

IR (KBr): 1344 (NSO_2), 1161 cm–1 (NSO_2).

13C NMR (75 MHz, CDCl_3): 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, 129.5 (2C), 133.0, 133.2, 133.7, 135.2, 135.6, 137.1, 143.2.

MS (FAB): m/z (%) = 450 (62) [M + H^+], 378 (100).

HRMS – FAB: m/z [M + H]^+ cale d for C_{25}H_{28}NO_2S: 450.2467; found: 450.2458.

(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]^27_D = -20.8 (c 0.60, CHCl_3).

IR (KBr): 1344 (NSO_2), 1161 cm–1 (NSO_2).

IR (KBr): 1344 (NSO_2), 1161 cm–1 (NSO_2).

13C NMR (75 MHz, CDCl_3): 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, 133.4, 135.0, 139.3, 143.4.

IR (KBr): 1344 (NSO_2), 1161 cm–1 (NSO_2).

13C NMR (75 MHz, CDCl_3): 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, 133.4, 135.0, 139.3, 143.4.

(1R)-1-Isopropyl-2-(4-methylphenylsulfonyl)-2,3-dihydro-1H-benzo/[f]isoindole (12l)
Bromoenyne (11o) (57.3 mg, 0.0818 mmol) was converted to (12o) (29.4 mg, 57% yield) by the reaction using Pd(OAc)2 (0.8 mg, 0.00327 mmol) for 24 h.

IR (KBr): 1344 (NSO2), 1163 cm–1 (NSO2).

HRMS–FAB: \([M + H]^{+}\) calcd for C_{22}H_{24}NO_{2}S: 492.2572; found: 492.2581.

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

Bromoenyne (11q) (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 (NSO2), 1163 cm–1 (NSO2).

HRMS–FAB: \([M + H]^{+}\) calcd for C_{30}H_{38}NO_{3}SSi: 620.2665; found: 620.2663.
HRMS–FAB: $m/z$ [M + H]$^+$ calcd for C$_{27}$H$_{36}$NO$_2$S: 438.2467; found: 438.2481.

$N$-(But-2-ynyl)-$N$-(3-phenylprop-2-ynyl)-4-methylbenzenesulfonylamidine (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≡), 1352 (NSO$_2$), 1165 cm–1 (NSO$_2$).

Colorless oil; IR (KBr): 2362 (C≡).

Bromoenyne 11n (59.2 mg, 0.152 mmol) was converted to 14n (12.0 mg, 26% yield) by the reaction for 2.5 h.

Colorless oil; IR (KBr): 3317 (NH), 2237 cm–1 (C≡).

Bromoenyne 11n (59.2 mg, 0.152 mmol) was converted to 14n (21.3 mg, 43% yield) by the reaction for 2 h.

Colorless oil; IR (KBr): 3168 (NH), 2171 cm–1 (C≡).

HRMS–FAB: $m/z$ [M + H]$^+$ calcd for C$_{27}$H$_{34}$NO$_3$S: 452.2259; found: 452.2258.

(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; [α]$^D_{26}$ +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$_2$).

Bromoenyne 15a (58.2 mg, 0.109 mmol) was converted to 16a (21.3 mg, 43% yield) by the reaction for 2 h.

Colorless oil; [α]$^D_{26}$ −67.2 (c 1.02, CHCl$_3$).

IR (KBr): 1344 (NSO$_2$), 1163 cm–1 (NO$_2$).

HRMS–FAB: $m/z$ [M + H]$^+$ calcd for C$_{16}$H$_{17}$NO$_2$S$_2$: 405.26508; found: 405.2493.

(5R)-4-Butyl-5-cyclohexyl-1-(2,4,6-trimethylpyrrolyl)-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; [α]$^D_{26}$ +52.2 (c 1.645, CHCl$_3$).

IR (KBr): 1603 (NC=C), 1350 (NSO$_2$), 1161 cm–1 (NSO$_2$).

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

1H NMR (300 MHz, CDCl$_3$): δ = 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).

13C NMR (75 MHz, CDCl$_3$): δ = 3.46, 21.4, 37.0, 37.1, 71.6, 81.6, 81.9, 85.6, 122.2, 128.0 (2C), 128.1 (2C), 128.4, 129.4 (2C), 131.6 (2C), 135.4, 143.6.

(±)-N-(1-Cyclohexyleth-2-ynyl)-N-(3-phenylprop-2-ynyl)amine (14n)

Bromoenyne 11n (59.2 mg, 0.152 mmol) was converted to 14n (12.0 mg, 26% yield) by the reaction for 2.5 h.

Colorless oil; IR (KBr): 3317 (NH), 2237 cm–1 (C≡).

1H NMR (300 MHz, CDCl$_3$): δ = 0.92 (t, J = 7.5 Hz, 3H, CMe), 1.13–1.55 (m, 10H), 1.65–1.85 (m, 5H), 2.22 (td, J = 6.9, 1.8 Hz, 2H, CH$_2$C=C), 3.42 (dd, J = 5.1, 1.8 Hz, 1H, NCH), 3.68 (d, J = 16.8 Hz, 1H, NC/H), 3.84 (d, J = 16.8 Hz, 1H, NCH/H), 7.28–7.30 (m, 3H, Ph), 7.39–7.44 (m, 2H, Ph).

13C NMR (75 MHz, CDCl$_3$): δ = 13.6, 18.4, 22.0, 26.1, 26.2, 26.5, 28.4, 30.2, 31.1, 37.2, 42.5, 55.0, 79.2, 83.1, 85.1, 87.7, 123.3, 127.9, 128.2 (2C), 131.7 (2C).

(5R)-4-Butyl-5-cyclohexyl-6-(4-methylphenylsulfonyl)-6,7-dihydro-5H-furo[2,3-f]isoindole (16a)

Bromoenyne 15a (58.2 mg, 0.109 mmol) was converted to 16a (21.3 mg, 43% yield) by the reaction for 2 h.

Colorless oil; [α]$^D_{26}$ −67.2 (c 1.02, CHCl$_3$).

IR (KBr): 1344 (NSO$_2$), 1163 cm–1 (NO$_2$).

1H NMR (270 MHz, CDCl$_3$): δ = 0.94 (t, J = 7.3 Hz, 3H, CMe), 1.00–1.89 (m, 16H), 2.23 (s, 3H, PhMe), 2.71 (t, J = 6.8 Hz, 2H, 1′-CH$_2$), 4.63 (d, J = 15.9 Hz, 1H, 7-CH$^-$H), 4.72 (d, J = 15.9 Hz, 1H, 7-CH$^-$H), 5.02 (s, 1H, 8-H), 6.68 (d, J = 2.2 Hz, 1H, 2-H), 6.97 (s, 1H, 8-H), 7.03 (d, J = 8.4 Hz, 2H, Ph), 7.52 (d, J = 2.2 Hz, 1H, 3-H), 7.56 (d, J = 8.4 Hz, 2H, Ph).

13C NMR (68 MHz, CDCl$_3$): δ = 14.1, 21.4, 23.0, 26.3, 26.5, 26.6, 26.8, 30.5, 31.6, 32.7, 45.6, 55.1, 70.0, 102.4, 105.3, 126.7, 127.1 (2C), 129.2 (2C), 129.5, 132.7, 134.5, 135.1, 143.0, 144.5, 154.7.

HRMS–FAB: $m/z$ [M + H]$^+$ calcd for C$_{27}$H$_{34}$NO$_2$S: 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).

HRMS–FAB: \( m/z \) [M + H\(^+\)]\(^{\ddagger}\) calcd for C\(_{34}H\(_{41}\)N\(_2\)O\(_4\)S\(_2\): 655.2849; found: 655.2846.

HRMS–FAB: \( m/z \) [M + H\(^+\)]\(^{\ddagger}\) calcd for C\(_{38}H\(_{43}\)N\(_2\)O\(_4\)S\(_2\): 655.2846; found: 655.2843.

(5R)-4-Butyl-5-cyclohexyl-2,5-dimethylolethyl-6-(4-methylphenylsulfonyl)-6,7-dihydropyrrolo[3,4-\(\beta\)]indole-1(5H)-sulfonamide (16d)

Bromoeneynes 16d (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) for 12 h.

Pale orange oil; \([\alpha\]\(^{25}_D\) +37.8 (c 0.740, CHCl\(_3\)).

IR (KBr): 1599 (C\(=\)CN), 1387 (NSO\(_2\)), 1344 (NSO\(_2\)), 129.2 (3C), 129.3, 129.6, 132.3 (3C), 132.9, 134.6, 134.7, 135.1, 140.1, 143.0, 144.1.

HRMS–FAB: \( m/z \) [M + H\(^+\)]\(^{\ddagger}\) calcd for C\(_{34}H\(_{41}\)N\(_2\)O\(_4\)S\(_2\): 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)

Bromoeenyne 17a (74.0 mg, 0.101 mmol) was converted to 18a (33.8 mg, 51%) by the reaction using Pd(OAc)\(_2\) (2.3 mg, 0.0010 mmol) in DMF at 120 °C for 18 h.

Colorless oil; \([\alpha\]\(^{25}_D\) –122 (c 0.30, CHCl\(_3\)).

IR (KBr): 1579 (C\(=\)CN), 1367 (NSO\(_2\)), 1365 (NSO\(_2\)), 1173 (NSO\(_2\)), 1163 cm\(^{-1}\) (NSO\(_2\)).

HRMS–FAB: \( m/z \) [M + H\(^+\)]\(^{\ddagger}\) calcd for C\(_{38}H\(_{43}\)N\(_2\)O\(_4\)S\(_2\): 655.2849; found: 655.2846.

HRMS–FAB: \( m/z \) [M + H\(^+\)]\(^{\ddagger}\) calcd for C\(_{34}H\(_{41}\)N\(_2\)O\(_4\)S\(_2\): 655.2846; found: 655.2843.
2H, Ph), 7.15–7.20 (m, 2H, Ar), 7.35 (s, 1H, 10-H), 7.56–7.59 (m, 1H, Ar), 7.58 (d, J = 7.9 Hz, 2H, Ph), 7.66–7.67 (m, 1H, Ar).

$^1$C NMR (126 MHz, CDCl3): δ = 14.0, 20.9, 21.4, 22.5 (2C), 22.9, 26.2, 26.4, 26.6, 26.8, 31.1, 31.2, 31.4, 45.6, 55.3, 71.0, 110.4, 116.7, 119.4 (2C), 124.1, 126.5, 127.1, 127.2 (2C), 128.7, 129.1, 129.5 (2C), 131.8 (2C), 134.1, 134.6, 135.0, 139.9 (2C), 140.1, 141.1, 143.1, 143.3.

MS (FAB): m/z (%) = 683 (16) [M + H$^+$], 154 (100).

HRMS–FAB: m/z [M + H]$^+$ calced for C$_{36}$H$_{47}$N$_2$O$_4$S$_2$: 638.2977; found: 638.2974.

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

Bromoenyne 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 3 h.

Pale yellow oil; [α]$^D_{25}$ +10.2 (c 1.28, CHCl$_3$).

IR (KBr): 1346 (NSO$_2$), 1163 cm$^{-1}$ (NSO$_2$).

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

HRMS–FAB: m/z [M + H]$^+$ calced for C$_{31}$H$_{36}$NO$_3$S$_2$: 518.2187; found: 518.2188.

(3R)-4-Butyl-3-cyclohexyl-2-(4-methylphenylsulfonyl)-2,3-dihydro-1H-benzo[furo[2,3-j]isoindole (18f)

Bromoenyne 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]$^D_{26}$ = -119 (c 0.35, CHCl$_3$).

IR (KBr): 1344 (NSO$_2$), 1161 cm$^{-1}$ (NSO$_2$).

HRMS–FAB: m/z [M + H]$^+$ calced for C$_{31}$H$_{36}$NO$_3$S$_2$: 518.2187; found: 518.2188.

(3R)-4-Butyl-3-cyclohexyl-2-(4-methylphenylsulfonyl)-2,3-dihydro-1H-naphtho[2,3-j]isoindole (18g)

Bromoenyne 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]$^D_{26}$ = -165.5 (c 0.63, CHCl$_3$).

IR (KBr): 1344 (NSO$_2$), 1161 cm$^{-1}$ (NSO$_2$).

HRMS–FAB: m/z [M + H]$^+$ calced for C$_{31}$H$_{36}$NO$_3$S$_2$: 502.2416; found: 502.2409.
Diethyl 9-Butyl-1-pentyl-2,3-dihydro-1H-cyclopenta[b]naphthalene-2,2'-dicarboxylate (20a)

Diethyl 4-Butyl-1-(4-methylphenylsulfonyl)-5-pentyl-5,7-dihydrocyclooctatetraene-6,6'-difluoride (20b)

Supporting Information

Acknowledgment

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 K$_2$CO$_3$ (2 equiv) as the base stereoselectively gave the monocyclic product 13b in 94% yield.

![Chemical diagram](image)

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

![Chemical diagram](image)


Graphical Abstract

![Graphical Abstract Image]

Short Title: Palladium-Catalyzed Cascade Cyclization through Direct Arylation

R¹ = alkyl; R² = alkyl, phenyl, or H; X = NSO₂R or C(ÇO₂Et)₂