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Construction of dibenzo-fused seven- to nine-membered carbocycles via Brønsted acid-promoted intramolecular Friedel–Crafts-type alkenylation

Takashi Otani, a Kanako Ueki, b Kinryo Cho, b Kan Kanai, b Kotaro Tateno b and Takao Saito a,b

Brønsted acid-promoted intramolecular hydroarylation of alkynylbenzenes carrying an arylalkyl group at the ortho-position leads to alkylidenedibenzo[a,d]cycloheptenes, -octenes and -nonenes in up to quantitative yield with complete regioselectivity. The scope and limitation of this reaction and application to the synthesis of tricyclic antidepressants are described.

5-Alkylidene-10,11-dihydro-5H-dibenzo[a,d]cycloheptenes 1 are an important structural motif found in many biologically active compounds, as exemplified by tricyclic antidepressants (TCAs). For example, amitriptyline (1a),1,2 which has been prescribed since the 1950s, has been the most widely used TCA to treat a number of mental disorders. Structurally similar nortriptyline (1b)3 is also one of the often-prescribed TCAs.

Because of their medical importance, various synthetic methods for 1 have been developed to date.2,4 Widely reported syntheses of 1 exploit the corresponding ketone (dibenzosuberone (4)) backbone; treatment of dibenzosuberone with Grignard reagent (RCH2MgX) and the following elimination of water from the resulting carbino completes the synthesis of 1 (Fig. 1, eqn (1)).5 This protocol is quite practical to access the seven-membered ring system 1, but is unattractive to construct the homologous eight-6 and nine-membered7 ring systems 2 and 3 because the corresponding ketone precursors 5 and 6 are not commercially available nor easily prepared. Indeed, access to the nine-membered ring system is very difficult, and to our knowledge, synthesis of 13-alkylidene-6,7,8,13-tetrahydro-5H-dibenzo[a,d]cyclononene 3 has not been achieved to date.7

Palladium-catalysed alkenylation (i.e., reductive Heck reaction)6,9 and gold, platinum or gallium-catalysed Friedel–Crafts (F.C.)-type alkenylation10 of alkynylbenzenes carrying a heteroatom-tethered aryl group in the ortho-position have emerged as useful reactions for the synthesis of benzo- or dibenzo-fused seven- and eight-membered oxygen- and nitrogen-heterocycles. Curiously, however, these types of reactions have not been applied for the synthesis of all-carbon counterparts 1–3.11,12 Concerning F.C.-type alkenylations, other groups13 and we14 have demonstrated that strong Brønsted acids,15 such as trifluoromethanesulfonic (triflic) acid (TfOH), are more highly active promoters than Lewis acids in several reactions.16 This background prompted us to investigate intramolecular F.C.-type hydroarylation of alkyn-1-yl(arylalkyl)benzenes 7–9 leading to dibenzo-fused seven- to nine-membered carbocycles 1–3 (eqn (2)).

![Diagram of reaction](image-url)

**Fig. 1.**

1. R = Me; Ateben (Damilen)
2. R = H; Nortriptyline (Ateben)
3. R = Me; Ateben (Damilen)
4. n = 3
5. n = 2
6. n = 3
7. n = 1,2,3
8. R = Me; Ateben (Damilen)
9. R = H; Nortriptyline (Ateben)
10. R = Me; Ateben (Damilen)
11. R = H; Nortriptyline (Ateben)
12. R = Me; Ateben (Damilen)
13. R = H; Nortriptyline (Ateben)
14. R = Me; Ateben (Damilen)
15. R = H; Nortriptyline (Ateben)
16. R = Me; Ateben (Damilen)
17. R = H; Nortriptyline (Ateben)
18. R = Me; Ateben (Damilen)
19. R = H; Nortriptyline (Ateben)
20. R = Me; Ateben (Damilen)
21. R = H; Nortriptyline (Ateben)
22. R = Me; Ateben (Damilen)
23. R = H; Nortriptyline (Ateben)
24. R = Me; Ateben (Damilen)
25. R = H; Nortriptyline (Ateben)
26. R = Me; Ateben (Damilen)
27. R = H; Nortriptyline (Ateben)
28. R = Me; Ateben (Damilen)
29. R = H; Nortriptyline (Ateben)
30. R = Me; Ateben (Damilen)
We initially examined the feasibility of a Brønsted acid catalysed cyclisation of 1-(3,3-dimethyl-1-butyn-1-yl)-2-(3-phenylpropyl)benzene (8a) to dibenzocyclooctene derivative 2a in dichloromethane at 0 °C (Table 1). When 8a was treated with 10 mol% of triflic acid for 4 h, the reaction did not complete and formed 2a, albeit in a low yield of 21% (entry 1). The yield of 2a was improved by increasing the amount of triflic acid (entries 2 and 3), and the use of 100 mol% resulted in quantitative formation of 2a in the short reaction time of 10 min (entry 4). Other strong acids such as bis(trifluoromethane)sulfonimide (entry 5) and sulfuric acid (entry 6) also facilitated this reaction; however, trifluoroacetic acid and hydrogen chloride (ether solution) showed almost no activity (entries 7 and 8). We also examined a cationic gold(I) complex (5 mol%) prepared from AuCl(PPh₃)₂ with AgOTf; however, the reaction formed only a trace amount of 2a in spite of stirring at room temperature for 1 h followed by heating at reflux for 1 h in chloroform (entry 9).¹⁷

Table 1 Optimization of acids

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>mol%</th>
<th>Time (min)</th>
<th>2a (%)</th>
<th>8a (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>TIOH</td>
<td>10</td>
<td>240</td>
<td>21</td>
<td>62</td>
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<tr>
<td>2</td>
<td>TIOH</td>
<td>20</td>
<td>60</td>
<td>44</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>TIOH</td>
<td>50</td>
<td>20</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>TIOH</td>
<td>100</td>
<td>10</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>TfOH</td>
<td>100</td>
<td>10</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>H₂SO₄</td>
<td>100</td>
<td>45</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>HCl⁺</td>
<td>100</td>
<td>60</td>
<td>NDᵇ</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>CF₃CO₂H</td>
<td>100</td>
<td>1440</td>
<td>4</td>
<td>74</td>
</tr>
<tr>
<td>9</td>
<td>Au(OTf)(PPh₃)₄</td>
<td>5</td>
<td>120</td>
<td>NDᵇ</td>
<td>92</td>
</tr>
</tbody>
</table>

- Hydrogen chloride ether solution (1.0 M) was used. b Not detected. c In chloroform. d Prepared from AuCl(PPh₃)₂ with AgOTf. e 60 min at room temperature and 60 min at 50 °C.

With the effective reaction conditions in hand, we explored the compatibility of substrates on the alkyne terminus for the synthesis of dibenzocyclooctene and -heptene derivatives (Table 2). Secondary and primary alkyl groups, such as isopropyl and propyl groups, are more suitable groups for this reaction (entries 1 and 2). However, phenyl-substituted 8d produced a complex mixture without formation of the cyclized product 2d (entry 3), and the TMS-substituted 8e produced TMS-group eliminated exo-methylene compound 2e in 9% yield (entry 4). The conditions are applicable for construction of a seven-membered ring system 1 (n = 1), and 1c, 1d and 1e were synthesized from 7c-e in good to high yields (entries 5–7).

To demonstrate the utility of this protocol for the synthesis of medicines, amitriptyline (1a), nortriptyline (1b) and their derivatives were targeted. Although these reactions required 5 equiv of triflic acid, the cyclization of 7a and 7b produced 1a and 1b in 56% and 68% yields, respectively (entries 8 and 9).

Similarly, substrates 7f and 8f-h having hydroxyl or primary amino groups were also tolerant under the super acidic conditions and the corresponding alcohols and amines were obtained in acceptable yields (entries 10–13).

Next, we examined the effects of the substituents on the aromatic rings and stereoselectivity of the addition products (Table 3). The reaction of 8i, in which a methoxy group was installed in the phenylene moiety (R²), with triflic acid afforded the corresponding adduct 2i as a mixture of syn- and anti-addition products, along with dimer 10 (entry 1). In contrast, less acidic sulfuric acid produced syn-addition product (Z)-2i exclusively in moderate yield (entry 2). Similarly, the reaction of 8j, having a methoxy group at R³ on the pendant aryl group, with triflic acid produced a mixture of syn- and anti-adducts 2i, whereas sulfuric acid delivered syn-addition product (E)-2i with complete selectivity (entry 3 vs. 4). The separate formation of (E)-2i and (Z)-2i from 8i and 8j, respectively (entries 2 and 4), indicates that both syn-addition products are kinetic products. To prove further the above-mentioned product selectivity, we also examined the triflic and sulfuric acid-promoted reaction of methyl-substituted substrates 8k, 8l and 7g (entries 5–9). Consistent with the above, sulfuric acid delivered syn-addition products highly selectively (entries 6, 7, and 9), while triflic acid produced almost 1:1 mixtures of syn- and anti-addition products with high combined yields (entries 2, 5, and 8). The structures of (Z)-2j and (E)-1g were unambiguously confirmed by X-ray crystal analysis. The reaction of 7b bearing the electron-withdrawing trifluoromethyl group on the pendant aryl group (R³), with triflic acid formed a mixture of syn- and anti-adducts (Z₂Z and (E)-1h) along with a small amount of t-buty1-eliminated compound 1h' (entry 10); however, the reaction with sulfuric acid was completely suppressed (entry 11). The reaction of 7l, bearing an n-propyl group on the

Table 2 Synthesis of dibenzocycloheptenes and -octenes having various substituents on the alkyne terminus

<table>
<thead>
<tr>
<th>Entry</th>
<th>S.M.</th>
<th>n</th>
<th>R²</th>
<th>Time (min)</th>
<th>Product (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8b</td>
<td>2</td>
<td>iPr</td>
<td>10</td>
<td>2b (85)</td>
</tr>
<tr>
<td>2</td>
<td>8c</td>
<td>2</td>
<td>nPr</td>
<td>10</td>
<td>2e (75)</td>
</tr>
<tr>
<td>3</td>
<td>8d</td>
<td>2</td>
<td>Ph</td>
<td>40</td>
<td>2d (ND)</td>
</tr>
<tr>
<td>4</td>
<td>8e</td>
<td>2</td>
<td>TMS</td>
<td>30</td>
<td>2e' (9)</td>
</tr>
<tr>
<td>5</td>
<td>7c</td>
<td>1</td>
<td>iBu</td>
<td>10</td>
<td>1c (97)</td>
</tr>
<tr>
<td>6</td>
<td>7d</td>
<td>1</td>
<td>nPr</td>
<td>15</td>
<td>1d (96)</td>
</tr>
<tr>
<td>7</td>
<td>7e</td>
<td>1</td>
<td>TMS</td>
<td>20</td>
<td>1e' (50)</td>
</tr>
</tbody>
</table>

- Not detected. b 1 equiv of 8fOH was used.
alkyne terminus (R<sub>1</sub>), with triflic acid also proceeded efficiently (entry 12). However, the reaction of 7i with sulfuric acid is slower than that of the t-butyl counterpart 7g, and thus a longer reaction time and addition of another equivalent of sulfuric acid were required for full conversion of 7i, which resulted in the formation of syn- and anti-addition products 1i (60:40, entry 13). Finally, we found that quenching the reaction before complete consumption of 7i forms stereochemically pure syn-addition product (E)-1i, albeit in 9% yield (entry 14).

Based on the above results, we propose a possible reaction pathway (Scheme 1). By treatment with a Brønsted acid, regioselective protonation of the β-carbon atom of A forms a relatively stable benzyl vinyl cation B, after which the pendant aryl group attacked the α-carbon atom from the less hindered H-side in a F.C. manner to give the formal syn-addition product C. Under the super acidic conditions, however, olefin isomerization of the syn-addition product C occurs, which results in the formation of a mixture of syn- and anti-addition products C. Table 3 suggests that triflic acid rather than sulfuric acid and the smaller n-propyl group rather than the t-butyl group promote the rapid olefin isomerization.

To evaluate further the scope of this protocol, the construction of a nine-membered ring was explored (Table 4). Gratifyingly, triflic acid promoted the cyclization of 9 to 10, albeit in moderate yields (entries 1, 3–8), but the reaction of 9a with sulfuric acid formed only a complex mixture (entry 2). It is noteworthy that the flexible butylene chain-tethered aryl group participated in a formal 9-exo-dig cyclization. In addition, oxidative cleavage of the alkene double bond of 3b led to the corresponding ketone 6 in 61% yield (eqn (3)). Ketone 6 would serve as a practical building block for the synthesis of dibenzocyclononene derivatives.

In summary, we have developed a Brønsted acid-promoted intramolecular Friedel–Crafts-type alkenylation that produces dibeno-fused seven- to nine-membered carbocycles in up to quantitative yield with up to complete control of the olefin.

### Table 3  Effects of substituents on aromatic groups

<table>
<thead>
<tr>
<th>Entry</th>
<th>S.M.</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Acid</th>
<th>Time (min)</th>
<th>syn-addition product</th>
<th>anti-addition product</th>
<th>Yield</th>
<th>Ratio (syn-anti-addition product)&lt;sup&gt;5&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>1</td>
<td>8i</td>
<td>2</td>
<td>tBu</td>
<td>Me</td>
<td>TIOH</td>
<td>10</td>
<td>Z-2i</td>
<td>E-2i</td>
<td>72&lt;sup&gt;6&lt;/sup&gt;</td>
<td>79:21</td>
</tr>
<tr>
<td>2</td>
<td>8i</td>
<td>2</td>
<td>tBu</td>
<td>Me</td>
<td>H</td>
<td>10</td>
<td>Z-2i</td>
<td>E-2i</td>
<td>54&lt;sup&gt;6&lt;/sup&gt;</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>3</td>
<td>8j</td>
<td>2</td>
<td>tBu</td>
<td>Me</td>
<td>H</td>
<td>30</td>
<td>E-2i</td>
<td>Z-2i</td>
<td>92</td>
<td>79:21</td>
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<tr>
<td>4</td>
<td>8j</td>
<td>2</td>
<td>tBu</td>
<td>H</td>
<td>Me</td>
<td>10</td>
<td>E-2i</td>
<td>Z-2i</td>
<td>45</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>5</td>
<td>8k</td>
<td>2</td>
<td>tBu</td>
<td>Me</td>
<td>H</td>
<td>20</td>
<td>Z-2i</td>
<td>E-2i</td>
<td>quant.</td>
<td>45:55</td>
</tr>
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<td>6</td>
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<td>2</td>
<td>tBu</td>
<td>Me</td>
<td>H</td>
<td>20</td>
<td>Z-2i</td>
<td>E-2i</td>
<td>quant.</td>
<td>&gt;99:1</td>
</tr>
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<td>tBu</td>
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<td>Me</td>
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<td>Z-2i</td>
<td>86</td>
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</tr>
<tr>
<td>8</td>
<td>7g</td>
<td>1</td>
<td>tBu</td>
<td>H</td>
<td>Me</td>
<td>10</td>
<td>E-1g</td>
<td>Z-1g</td>
<td>94</td>
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<td>7g</td>
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<td>tBu</td>
<td>H</td>
<td>Me</td>
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<td>E-1g</td>
<td>Z-1g</td>
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<td>Me</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;</td>
<td>10</td>
<td>E-1h</td>
<td>Z-1h</td>
<td>35&lt;sup&gt;6&lt;/sup&gt;</td>
<td>55:45</td>
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<td>H</td>
<td>60</td>
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<td>Z-1i</td>
<td>91</td>
<td>50:50</td>
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<tr>
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<td>1</td>
<td>tBu</td>
<td>Me</td>
<td>H</td>
<td>20</td>
<td>E-1i</td>
<td>Z-1i</td>
<td>66</td>
<td>60:40</td>
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<tr>
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<td>7i</td>
<td>1</td>
<td>tBu</td>
<td>Me</td>
<td>H</td>
<td>20</td>
<td>E-1i</td>
<td>Z-1i</td>
<td>9</td>
<td>&gt;95:5</td>
</tr>
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</table>

* Combined yield of syn- and anti-addition product. *<sup>5</sup> Determined by <sup>1</sup>H NMR. “>99:1” denotes no anti-addition product was observed by <sup>1</sup>H-NMR. “Dimer”<sup>10</sup> was obtained in 13% yield. “Dimer”<sup>10</sup> was obtained in 1% yield. “1h’”<sup>6</sup> was also obtained in 10% yield. Additional 1 equiv of H<sub>2</sub>SO<sub>4</sub> was added after 15 min. “<sup>6</sup> Total time.

### Scheme 1 Possible reaction pathway

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geometry, and achieved construction of dibenzo-fused cyclononene derivatives 3 for the first time.

| Table 4 | Synthesis of dibenzo[cyclooctene-12(5H)]one (5) was prepared from 2-formylbenzoic acid, see: S. O. Winthrop, M. A. Davis, Herr, J. Stewart and R. Gaudry, J. Med. Chem., 1963, 6, 130. For the synthesis of 5,6,7,8-tetrahydro-13H-dibenzo[a,c]cycloocten-13-one (6), only one paper was found, see: P. Caubere, M. S. Mogerd, and G. Guillaumet, Tetrahedron, 1973, 29, 1851.


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<tbody>
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