

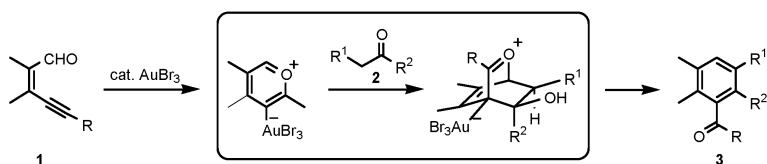
Communication

**AuBr-Catalyzed [4 + 2] Benzannulation between an Enynal Unit and Enol**

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## AuBr<sub>3</sub>-Catalyzed [4 + 2] Benzannulation between an Enynal Unit and Enol

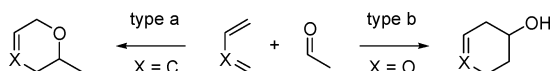
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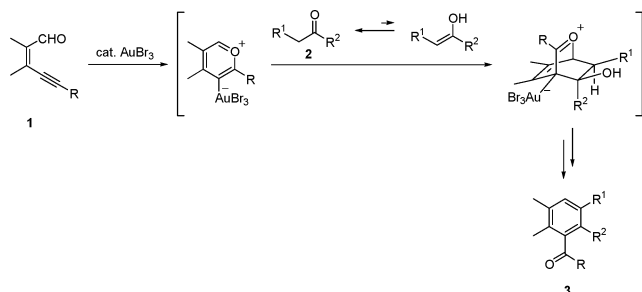
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The Diels–Alder reaction is one of the most powerful synthetic tools for the construction of various six-membered cyclic compounds.<sup>1</sup> Numerous studies on the normal electron demand-type reaction between diene systems and carbonyl compounds have been carried out. In such reactions, the carbon–oxygen double bond of carbonyl compounds acts as a 2π system in the hetero-Diels–Alder reaction with various 4π systems (type a in Scheme 1). However, to the best of our knowledge, there is no report on reverse electron demand-type cycloaddition between a 4π system and an enol derived from an aldehyde and ketone (type b).<sup>2</sup> In this paper, we report an unprecedented [4 + 2] benzannulation between the enynal unit **1**, including *o*-(alkynyl)benzaldehydes, and carbonyl compounds **2**, in which the hetero-Diels–Alder reaction (type b) becomes a key step; the AuBr<sub>3</sub>-catalyzed reaction of **1** with **2** gave **3**, through the pyrylium intermediate and hetero-Diels–Alder intermediate, in good to high yields (Scheme 2).

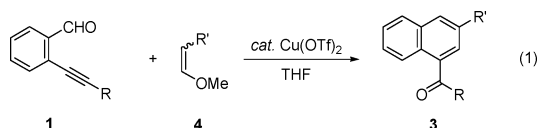
### Scheme 1



### Scheme 2



Recently, we reported a novel synthetic method of naphthalene derivatives via the Lewis acid-catalyzed benzannulation between *o*-(alkynyl)benzaldehydes **1** and enoethers **4** (eq 1).<sup>3,4</sup>The reaction



proceeded smoothly in THF in the presence of Cu(OTf)<sub>2</sub> catalyst to give the corresponding naphthalene products in high yields.<sup>5,6</sup> While optimizing the reaction of **1a** (R = Ph) with β-methoxystyrene **4a** (R' = Ph), we accidentally used (CICH<sub>2</sub>)<sub>2</sub> as a solvent instead of THF. Very interestingly, we observed that **4a** was consumed immediately at room temperature while **3a** (R, R' = Ph) was not produced at this stage. Then, **3a** was produced gradually by heating the reaction mixture at 50 °C. Accordingly, the reaction was monitored carefully by GC-mass and NMR spectroscopy, and we found that phenylacetaldehyde **2a** (R<sup>1</sup> = Ph, R<sup>2</sup> = H) was formed from **4a** in situ at a very early stage of the reaction.<sup>7</sup> This

**Table 1.** AuBr<sub>3</sub>-Catalyzed Benzannulation between *o*-Alkynylbenzaldehydes **1a–b** and Carbonyl Compounds **2a**

entry	1	R	2	R <sup>1</sup>	R <sup>2</sup>	ratio (3:5) <sup>b</sup>	yield (%) <sup>c</sup>
1	<b>1a</b>	Ph	<b>2a</b>	Ph	H	<b>3a:5a</b> 87:13	90
2 <sup>d,e</sup>	<b>1a</b>	Ph	<b>2b</b>	CH <sub>3</sub>	H	<b>3b:5b</b> 97:3	87
3	<b>1a</b>	Ph	<b>2c</b>	C <sub>3</sub> H <sub>11</sub>	H	<b>3c:5c</b> 99:<1	81
4 <sup>f</sup>	<b>1a</b>	Ph	<b>2d</b>	<sup>t</sup> Pr	H	<b>3d:5d</b> 80:20	81
5 <sup>g</sup>	<b>1a</b>	Ph	<b>2e</b>	–(CH <sub>2</sub> ) <sub>4</sub> –	H	<b>3e:5e</b> 82:18	56
6	<b>1a</b>	Ph	<b>2f</b>	BnO	H	<b>3f:5f</b> 99:<1	45
7 <sup>d</sup>	<b>1b</b>	C <sub>4</sub> H <sub>9</sub>	<b>2b</b>	CH <sub>3</sub>	H	<b>3g:5g</b> 99:<1	71

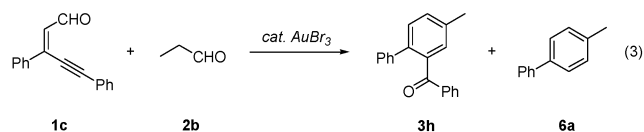
<sup>a</sup> Reaction was performed using **1a, b** (1 equiv) and **2a–f** (1.2 equiv) in the presence of AuBr<sub>3</sub> (10 mol %) in 1,4-dioxane at 100 °C within 3 h unless otherwise noted. <sup>b</sup> Determined by <sup>1</sup>H NMR. <sup>c</sup> Combined isolated yield. <sup>d</sup> Performed with 5 equiv of **2b**. <sup>e</sup> Reaction was carried out at 80 °C. <sup>f</sup> Reaction was carried out in the presence of 30 mol % AuBr<sub>3</sub>. <sup>g</sup> Reaction was carried out in the presence of 20 mol % AuBr<sub>3</sub>.

result suggested that the benzannulation in (CICH<sub>2</sub>)<sub>2</sub> would not proceed through the [4 + 2] cycloaddition between **1a** and **4a** but would proceed instead through **1a** and **2a**. Indeed, when the reaction of **1a** with **2a** was carried out under the same conditions mentioned above (Cu(OTf)<sub>2</sub>, (CICH<sub>2</sub>)<sub>2</sub>, 50 °C), **3a** was obtained in 43% yield together with **5a** in 37% yield (eq 2).

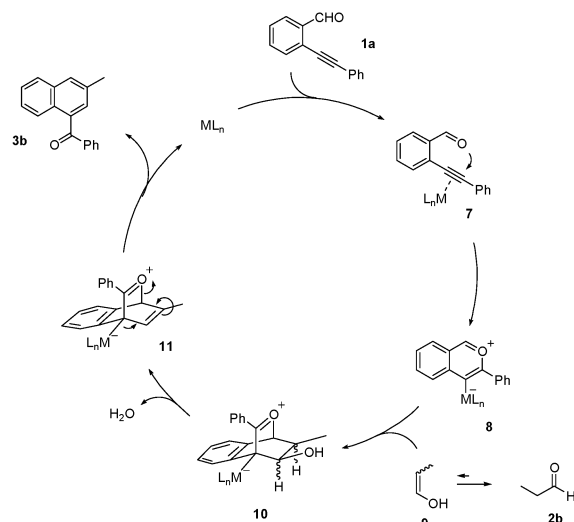
Optimization experiments revealed that the use of AuBr<sub>3</sub> catalyst (10 mol %) in 1,4-dioxane at 100 °C gave **3a** selectively in 78% yield accompanied by **5a** in 12% yield.<sup>8,9</sup> The results of the AuBr<sub>3</sub>-catalyzed benzannulation of **1** using various kinds of carbonyl compounds **2** are summarized in Table 1.

The reaction proceeded well even with sterically bulky aldehydes such as 3-methyl-butanal **2d**, although an increased amount of catalyst was needed (entry 4). Cyclohexanone **2e** was usable as a starting material, and the corresponding six-membered annulated naphthalene **3e** was obtained in a moderate yield (entry 5). Not only simple alkyl and aryl substituents but also an alkoxy group can be introduced into the naphthalene skeleton; the reaction of **1a** with benzyloxyacetaldehyde **2f** gave **3f** as the sole product (entry 6). The benzannulation of **1b**, having a butyl group at the terminal position of alkyne, with **2b** gave **3g** in 71% yield (entry 7). In every case, we did not detect the regioisomers of **3**; in all cases, R<sup>1</sup> was at the C-3 position and R<sup>2</sup> was at the C-2 position.

Not only the benzaldehyde derivatives but also an α,β-unsaturated aldehyde underwent the benzannulation.<sup>10</sup> The reaction of the enynal **1c** with propanal **2b** in the presence of Au catalyst proceeded smoothly, and the corresponding [4 + 2] adduct **3h** was obtained in 70% yield along with the formation of **6a** in 12% yield (eq 3).

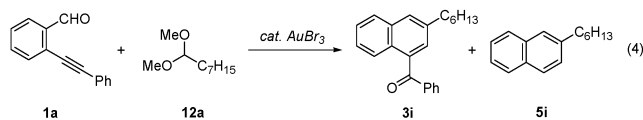


Scheme 3



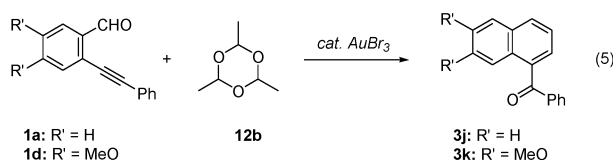
A plausible mechanism for the present benzannulation is shown in Scheme 3.<sup>3,4</sup> The coordination of the triple bond of **1a** to AuBr<sub>3</sub> enhances the electrophilicity of alkyne, and the subsequent nucleophilic attack (as shown in **7**) of the carbonyl oxygen to the electron-deficient alkyne would form the ate complex **8**.<sup>11</sup> The reverse electron demand-type Diels–Alder reaction of **8** with the enol **9**, derived from **2b**, followed by dehydration would generate the intermediate **11** through **10**. The subsequent bond rearrangement, as shown in **11** with arrows, would afford the naphthyl ketone derivative **3b** and regenerate AuBr<sub>3</sub>.<sup>12</sup> It is worth mentioning that when the reaction of **1a** with **2b** was carried out in the presence of 3 Å MS under conditions similar to those mentioned in Table 1, the chemical yield of **3b** was dramatically decreased and only trace amounts of **3b** were obtained. Trace amounts of water, which might exist in the reaction medium, would play an important role for the keto–enol tautomerization between **2b** and **9** in Scheme 3.<sup>13,14</sup> The reaction is not likely to proceed well without water due to the lack of the generation of enol form **9**.

Interestingly, the [4 + 2] benzannulation proceeded even with acetal compounds **12**. When **1a** was treated with 1,1-dimethyloctane **12a** in the presence of Au catalyst, the corresponding naphthalene derivative **3i** was obtained in 27% yield (eq 4). The



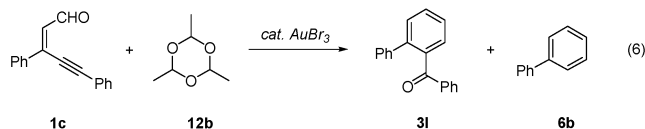
chemical yield was improved by addition of water (3 equiv), and **3i** was obtained in 68% yield together with **5i** in 5% yield.

We next examined the reaction of **1a** and **1d** with paraldehyde **12b**. Even without external addition of water, the corresponding products **3j** and **3k** were obtained in 61 and 52% yields, respectively (eq 5). This result clearly shows that **12b** can be used as a masked



acetaldehyde in the [4 + 2] benzannulation. Furthermore, the

reaction between **1c** and **12b** proceeded smoothly to give **3l** in 51% yield together with small amounts of **6b** (8%) (eq 6).



We are now in a position to synthesize functionalized aromatic compounds from enynals and carbonyl compounds in good to high yields. The reaction most probably proceeds through the reverse electron demand-type Diels–Alder reaction between the pyrylium 4π system **8** and enol 2π system **9**. Further studies to elucidate the precise mechanism of this reaction and to extend the scope of synthetic utility are in progress in our laboratory.

**Supporting Information Available:** Spectroscopic and analytical data for **3a–l** and the representative procedure for the synthesis of **3c** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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