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$AuCl_3$-Catalyzed Benzannulation: Synthesis of Naphthyl Ketone Derivatives from *o*-Alkynylbenzaldehydes with Alkynes

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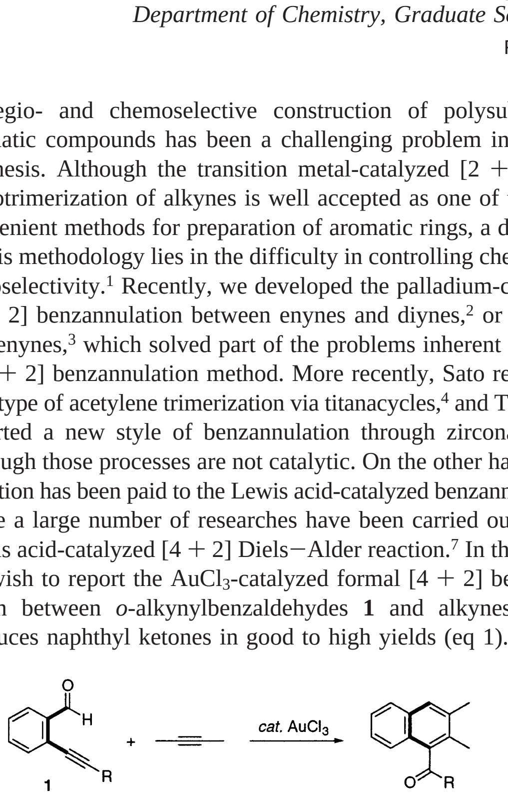
Regio- and chemoselective construction of polysubstituted aromatic compounds has been a challenging problem in organic synthesis. Although the transition metal-catalyzed [2 + 2 + 2] cyclotrimerization of alkynes is well accepted as one of the most convenient methods for preparation of aromatic rings, a drawback of this methodology lies in the difficulty in controlling chemo- and regioselectivity.[1] Recently, we developed the palladium-catalyzed [4 + 2] benzannulation between enynes and diynes,[2] or between two enynes,[3] which solved part of the problems inherent in the [2 + 2 + 2] benzannulation method. More recently, Sato reported a new type of acetylene trimerization via titanacycles,[4] and Takahashi reported a new style of benzannulation through zirconacycles,[5] although those processes are not catalytic. On the other hand, little attention has been paid to the Lewis acid-catalyzed benzannulation,[6] while a large number of researches have been carried out for the Lewis acid-catalyzed [4 + 2] Diels−Alder reaction.[7] In this paper, we wish to report the $AuCl_3$-catalyzed formal [4 + 2] benzannulation between *o*-alkynylbenzaldehydes **1** and alkynes, which produces naphthyl ketones in good to high yields (eq 1).[8,9]



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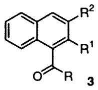
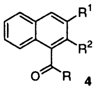
(1)

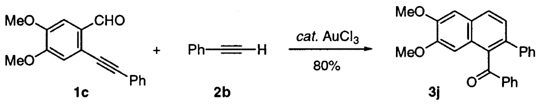
Table 1. The $AuCl_3$-Catalyzed Reaction of *o*-Alkynylbenzaldehydes **1** with Alkynes **2**[a]

entry	**1**	R	**2**	$R^1{-}{\equiv}{-}R^2$		time	ratio[b]	yield[c]
				R^1	R^2		 **3**  **4**	%
1[d]	**1a**	Ph	**2a**	C_3H_7	H	1 d	**3a**:**4a** = 95:5	57
2	**1a**	Ph	**2a**	C_3H_7	H	1.5 h	**3a**:**4a** = 92:8	91
3[e]	**1a**	Ph	**2a**	C_3H_7	H	3 h	**3a**:**4a** = 89:11	72
4[f]	**1a**	Ph	**2b**	Ph	H	2.5 h	**3b**:**4b** = 99:<1	96
5	**1a**	Ph	**2c**	Me_3Si	H	6 h	**3c**:**4c** = 16:84	82
6	**1a**	Ph	**2d**	CO_2Et	H	3 h	**3d**:**4d** = 18:82	72
7	**1a**	Ph	**2e**	$COCH_3$	H	3.5 h	**3e**:**4e** = <1:99	75
8	**1a**	Ph	**2f**	C_3H_7	C_3H_7	13 h	**3f(=4f)**	52
9	**1a**	Ph	**2g**	Ph	Me_3Si	2 h	**3g**:**4g** = 99:<1	92
10	**1a**	Ph	**2h**	Ph	CH_3	3 h	**3h**:**4h** = 99:<1	89
11	**1b**	C_6H_{13}	**2b**	Ph	H	1.5 h	**3i**:**4i** = 92:8	91

[a] The reaction was performed using *o*-alkynylbenzaldehydes **1** (1 equiv) and alkynes **2** (3 equiv) in the presence of $AuCl_3$ (3 mol %) in $(ClCH_2)_2$ at 80 °C unless otherwise noted. [b] Determined by ^1H NMR. [c] Combined isolated yield. [d] The reaction was carried out at 30 °C in CH_2Cl_2. [e] The reaction was carried out in the presence of 1 mol % $AuCl_3$. [f] The reaction was carried out using 1.2 equiv of **2b**.

The reaction of *o*-(phenylethynyl)benzaldehyde **1a** (R = Ph) with 3 equiv of pentyne **2a** ($R^1 = C_3H_7$, $R^2 = H$) in the presence of 5 mol % $AuCl_3$ in CH_2Cl_2 at 30 °C for 1 day gave 1-benzoyl-2-propyl-naphthalene **3a** in 53% yield along with its regioisomer **4a** in 4% yield (entry 1). The reaction speed was accelerated dramatically at higher temperatures, and the chemical yield was increased. For example, the combined yield of **3a** and **4a** was increased up to 91% when the reaction was carried out in 1,2-dichloroethane at 80 °C for 1.5 h (entry 2). The reaction proceeded even in the presence of 1 mol % $AuCl_3$, affording the 1-benzoyl-naphthalenes in 72% yield (entry 3). Besides $(ClCH_2)_2$, other solvents such as CH_3CN, AcOEt, and 1,4-dioxane were usable for the present reaction. In the absence of $AuCl_3$ catalyst, no reaction took place. When phenylacetylene was used as an alkyne, the reaction proceeded very well even by the use of 1.2 equiv of the acetylene, and **3b** was obtained as a sole product in 96% yield (entry 4). In entries 1−4, the sterically bulky group (R^1) was oriented either exclusively or predominantly at the position neighboring the benzoyl group. However, in the case of trimethylsilylacetylene **2c**, the reversal of the regioselectivity was observed, and **4c** was obtained predominantly (entry 5). The alkynes **2d** and **2e** bearing electron-withdrawing groups also produced the regioisomeric benzoylnaphthalenes **4d** and **4e**, respectively, in good yields with predominant or exclusive regioselectivity (entries 6 and 7). The reaction using the internal alkyne **2f** gave **3f** in a moderate yield (entry 8). The reaction using the internal nonsymmetrical phenyl-substituted alkynes **2g** and **2h** afforded **3g** and **3h** exclusively in high yields (entries 9−10). The reaction of the benzaldehyde **1b**, bearing an octynyl group at the *ortho*-position, with phenylacetylene **2b** also proceeded well, and naphthyl hexyl ketone **3i** was formed regioselectively in high yield along with a small amount of **4i** (entry 11).

Furthermore, the reaction of the *o*-alkynylbenzaldehyde **1c**, bearing dimethoxy groups on the benzene ring, with phenylacetylene gave the naphthyl ketone **3j** in high yield, and the regioisomer **4j** was not obtained at all (eq 2).



1c **2b** **3j**

(2)

The preparation of **3b** is representative. To $AuCl_3$ (4.5 mg, 3 mol %) was added a mixture of **1a** (103 mg, 0.5 mmol) and **2b** (0.066 mL, 0.6 mmol) in $(ClCH_2)_2$ (1.5 mL) at room temperature under Ar atmosphere. The resulting homogeneous solution was stirred at 80 °C for 1.5 h and then cooled to room temperature. The reaction mixture was transferred to a silica gel column, and the product was isolated using ether as eluent; **3b** was obtained as a yellow solid (148 mg, 0.48 mmol) in 96% yield. For assignment of the ^1H NMR spectrum of **3b**, the deuterated product (*d*-**3b**) was prepared using deuterated phenylacetylene under the same reaction conditions mentioned above. When deuterated phenylacetylene was used, one of the two doublet peaks of **3b** at 8.00 and 7.55 ppm

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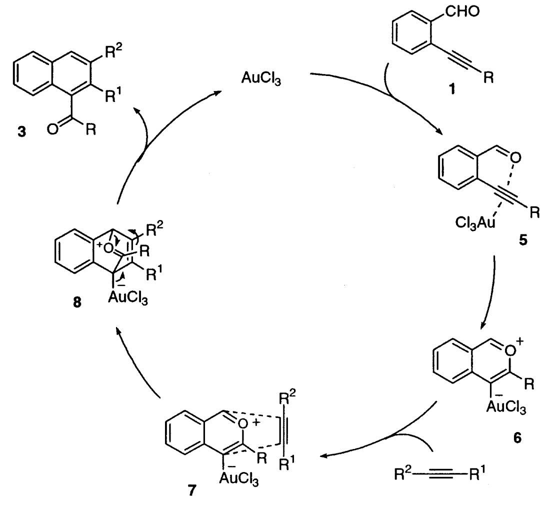
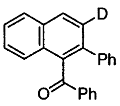
Scheme 1

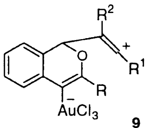


disappeared in the spectrum of *d*-**3b**, and the remaining peak at 8.00 ppm was changed to a singlet peak. These results clearly showed the product obtained in the reaction of **1a** with **2b** was **3b** but not **4b**. The regiochemistries of the other products were determined in a similar way by ^{1}H NMR or NOE experiments (see the Supporting Information).



***d*-3b**

A plausible mechanism for the AuCl$_3$-catalyzed formal [4 + 2] benzannulation is shown in Scheme 1. The coordination of the triple bond of **1** to AuCl$_3$ enhances the electrophilicity of alkyne,[9] and the subsequent nucleophilic attack of the carbonyl oxygen to the electron-deficient alkyne would form the intermediate auric ate complex **6**.[10] The Diels–Alder type [4 + 2] cycloaddition of **6** with an alkyne would occur as shown in **7** to form the intermediate **8**. The subsequent bond rearrangement, as shown in **8** with arrows, would afford the naphthalene derivatives **3** and regenerate AuCl$_3$.[11] If the [4 + 2] cycloaddition proceeds in a stepwise manner, the putative zwitterionic intermediates **9** are involved. The regioselectivities observed in Table 1 are accounted for by intervention of **9**. In the reaction of 1-pentyne **2a**, **3a** is produced very predominantly because the vinyl cation having a propyl group at R^1 of **9** is much more stabilized in comparison with that having H at R^1. A similar argument can be made for the reactions of phenylacetylenes **2b**, **g**, and **h**, because the resonance effect of the phenyl group at the R^1 position stabilizes very much the corresponding vinyl cation. On the other hand, the preferred formation of **4c** in the reaction of trimethylsilylacetylene **2c** is ascribed to the well-known β-silyl effect: a carbocation β to trimethylsilyl group is stabilized significantly.[12] Either predominant or exclusive formation of **4d**,**e** in the reaction of the alkynes bearing an electron-withdrawing group at R^1 is due to the fact that a carbocation is destabilized by a neighboring EWG group, and therefore an opposite orientation of the acetylenes takes place.



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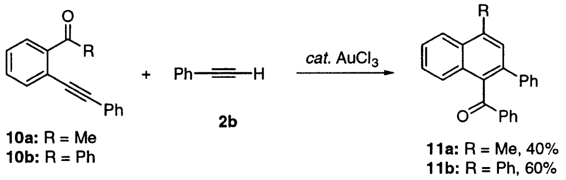
Because substituted acyl and benzoylnaphthalenes were produced unexpectedly easily from the aldehydes **1**, we next examined the reaction of the ketones **10a** and **b** with **2b** (eq 3). As expected, the



(3)

corresponding 1-benzoylnaphthalenes **11a** and **11b** were obtained regioselectively, although the chemical yields were slightly lower than those of the reactions using the aldehydes **1**.

A novel and efficient synthetic method for substituted polyaromatics has been developed. We are now at a position to synthesize regioselectively substituted naphthalenes and related polyaromatics. The AuCl$_3$-catalyzed formal [4 + 2] benzannulation between **1** and alkynes involves an interesting mechanistic aspect through Lewis acid-catalyzed processes. Further studies to elucidate the 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**,**b**, *d*-**3b**, **3f**–**j**, **4a**, **4c**–**e**, and **11a**,**b** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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