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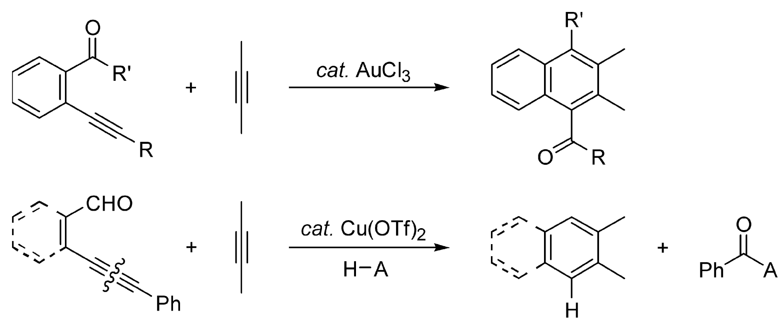

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Lewis Acid-Catalyzed Benzannulation via Unprecedented [4+2] Cycloaddition of *o*-Alkynyl(oxo)benzenes and Enynals with Alkynes

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Abstract: The reaction of *o*-alkynyl(oxo)benzenes **1** with alkynes **2** in the presence of a catalytic amount of $AuCl_3$ in $(CH_2Cl)_2$ at 80 °C gave the [4+2] benzannulation products, naphthyl ketone derivatives **3** and **4**, in high yields. When the reaction was carried out using $AuBr_3$ instead of $AuCl_3$, the reaction speed was enhanced and the chemical yield was increased. On the other hand, when the reaction was carried out in the presence of a catalytic amount of $Cu(OTf)_2$ and 1 equiv of a Brønsted acid, such as CF_2HCO_2H, in $(CH_2Cl)_2$ at 100 °C, the decarbonylated naphthalene products **5** were obtained in high yields. Similarly, the $Cu(OTf)_2-H_2O$-promoted reaction of the enynals **7** with an alkyne **2** afforded the corresponding [4+2] benzannulation products, decarbonylated benzene derivatives **8**, in good yields. Both AuX_3- and $Cu(OTf)_2$-catalyzed benzannulations proceed most probably through the formation of the benzo[*c*]pyrylium ate complex **10**, the Diels−Alder addition of alkynes **2** to the ate complex, and the resulting bicyclic pyrylium ion intermediate **12**. The mechanistic difference between the AuX_3 and $Cu(OTf)_2$−HA system is discussed.

Introduction

Regio- and chemoselective construction of polysubstituted aromatic compounds has been a challenging problem in organic synthesis.[1] Although the transition metal-catalyzed [2+2+2] cyclotrimerization of alkynes is well accepted as one of the most convenient methods for the preparation of aromatic rings, a drawback of this methodology lies in the difficulty in controlling chemo- and regioselectivity.[2] Recently, Sato reported a new type of acetylene trimerization via titanacycles[3] and Takahashi reported a new style of benzannulation through zirconacycles,[4] although those processes are not catalytic. On the other hand, we developed the palladium-catalyzed [4+2] benzannulation between enynes and diynes,[5] or between two enynes,[6] which solved a part of the problems inherent in the [2+2+2] benzannulation method. Among the methods for the preparation of arene compounds, there has been a lot of effort in the synthesis of naphthalene derivatives, which are important as bioactive agents and in structural and synthetic chemistry.[7] Many modern methods for the synthesis of naphthalene frameworks using several transition metal catalysts, such as Pd,[8] W,[9] Rh,[10] Ru,[11] and Ir,[12] have been reported. However, little attention has

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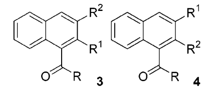
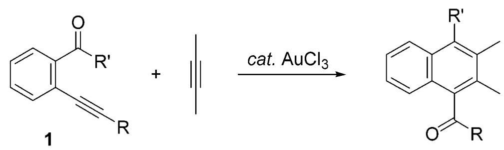
Table 1. The AuX_3-Catalyzed Reaction of *o*-Alkynylbenzaldehydes **1** with Alkynes **2**[a]



entry	1	R	2	R^1—≡—R^2: R^1	R^2	catalyst	time	ratio[b]	yield (%)[c]
1[d]	**1a**	Ph	**2a**	C_3H_7	H	$AuCl_3$	1 d	**3a**:**4a** = 95:5	57
2	**1a**	Ph	**2a**	C_3H_7	H	$AuCl_3$	1.5 h	**3a**:**4a** = 92:8	91
3[e]	**1a**	Ph	**2a**	C_3H_7	H	$AuCl_3$	3 h	**3a**:**4a** = 89:11	72
4	**1a**	Ph	**2a**	C_3H_7	H	$AuBr_3$	1.5 h	**3a**:**4a** = 93:7	100
5[f]	**1a**	Ph	**2b**	Ph	H	$AuCl_3$	2.5 h	**3b**:**4b** = 99:<1	96
6[f]	**1a**	Ph	**2b**	Ph	H	$AuBr_3$	0.7 h	**3b**:**4b** = 99:<1	100
7	**1a**	Ph	**2c**	Me_3Si	H	$AuCl_3$	6 h	**3c**:**4c** = 16:84	82
8	**1a**	Ph	**2d**	CO_2Et	H	$AuCl_3$	3 h	**3d**:**4d** = 18:82	72
9	**1a**	Ph	**2e**	$COCH_3$	H	$AuCl_3$	3.5 h	**3e**:**4e** = <1:99	75
10	**1a**	Ph	**2f**	C_3H_7	C_3H_7	$AuCl_3$	2.5 h	**3f**(=**4f**)	52
11	**1a**	Ph	**2f**	C_3H_7	C_3H_7	$AuBr_3$	2.5 h	**3f**(=**4f**)	70
12	**1a**	Ph	**2g**	Ph	Me_3Si	$AuCl_3$	2 h	**3g**:**4g** = 99:<1	92
13	**1a**	Ph	**2h**	Ph	Me	$AuCl_3$	3 h	**3h**:**4h** = 99:<1	89
14	**1b**	C_6H_{13}	**2b**	Ph	H	$AuCl_3$	1.5 h	**3i**:**4i** = 92:8	91

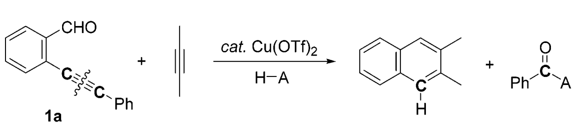
[a] The reaction was performed using *o*-alkynylbenzaldehydes **1** (1 equiv) and alkynes **2** (3 equiv) in the presence of AuX_3 (3 mol %) in $(ClCH_2)_2$ at 80 °C unless otherwise noted. [b] Determined by ^1H NMR. [c] Combined isolated yield. [d] The reaction was carried out at 30 °C in CH_2Cl_2. [e] The reaction was carried out in the presence of 1 mol % of $AuCl_3$. [f] The reaction was carried out using 1.2 equiv of **2b**.

been paid to the Lewis acid-catalyzed benzannulation,[7,13] while a large amount of research has been carried out for the Lewis acid-catalyzed [4+2] Diels−Alder reaction.[14] Recently, we have communicated the $AuCl_3$-catalyzed formal [4+2] benzannulation between *o*-alkynyl(oxo)benzenes **1** and alkynes, which produces naphthyl ketones in good to high yields (eq 1).[15]

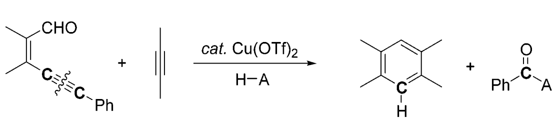


(1)

Now, we report the detailed study on the gold-catalyzed benzannulation reaction together with an unprecedented [4+2] benzannulation between *o*-(alkynyl)benzaldehyde **1a** (or enynals) and alkynes, which produces the debenzoylated naphthalenes (or benzenes, respectively) in good to high yields (eqs 2 and 3). The combined use of a catalytic amount of Lewis acidic $Cu(OTf)_2$ and a stoichiometric amount of a Brønsted acid (HA) is a key for this novel transformation.



(2)



(3)

Results and Discussion

(A) AuX_3-Catalyzed Benzannulation. As we previously communicated, the reaction of *o*-alkynyl(oxo)benzenes **1** with alkynes **2** proceeded smoothly in the presence of a catalytic amount of $AuCl_3$ to afford naphthyl ketone derivatives **3** and **4** in good to high yields (Table 1).[15−17] As shown in entries 1−3, the $AuCl_3$ (3 mol %)-catalyzed reaction of **1a** with **2a** gave a 92−95:5−8 mixture of **3a** and **4a** in good to high yields. The reaction progress depended on the reaction temperature and on the amount of the catalyst. We searched for a more efficient catalyst than $AuCl_3$ and found that $AuBr_3$ exhibited higher catalytic activity. The reaction of **1a** with **2a** in the presence of 3 mol % of $AuBr_3$ in 1,2-dichloroethane at 80 °C for 2.5 h gave a 93:7 mixture of **3a** and **4a** in essentially quantitative yield (entry 4). The $AuBr_3$-catalyzed reaction of **1a** with **2b** also proceeded smoothly to give **3b** exclusively in a quantitative yield (entry 6). The reaction with $AuBr_3$ was much quicker than that with $AuCl_3$ (entry 6 vs 5). The regioisomers **4c**−**e** became major products in entries 7−9, in which the R^1 substituent is either an electron-withdrawing group or an Me_3Si group: the reason for this change of the regioselectivity was mentioned previously.[15] Even with the symmetrically substituted internal alkyne **2f**, the chemical yield of **3f** was increased up to 70% yield when the reaction was catalyzed by $AuBr_3$ (entry 11 vs 10). The reaction of the unsymmetrically substituted internal alkynes **2g** and **2h** proceeded in high yields with exclusive regioselectivity (entries 12 and 13). Not only the *ortho*-phenylalkyne derivative **1a** but also the *ortho*-*n*-hexyl substituted alkyne derivative **1b** underwent the [4+2] benzannulation (entry 14).

(B) $Cu(OTf)_2$-Catalyzed Benzannulation. During the research on the $AuCl_3$-catalyzed [4+2] benzannulation between

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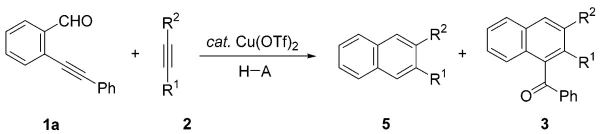
Table 2. The $Cu(OTf)_2$-Catalyzed Reaction of *o*-(Phenylethynyl)benzaldehyde **1a** with Alkynes **2**[a]

entry	2	R^1	R^2	additive	conditions	yield (%)[b] 5		3	
1	**2h**	Ph	Me	none	80 °C, 0.5 h	**5a**	56	**3h**	22
2	**2h**	Ph	Me	H_2O	80 °C, 19 h	**5a**	52	**3h**	12
3	**2h**	Ph	Me	MeOH	80 °C, 1 h	**5a**	44	**3h**	13
4	**2h**	Ph	Me	HCO_2H	80 °C, 0.5 h	**5a**	79	**3h**	8
5	**2h**	Ph	Me	CH_3CO_2H	80 °C, 0.5 h	**5a**	67	**3h**	17
6	**2h**	Ph	Me	CF_2HCO_2H	80 °C, 0.5 h	**5a**	82	**3h**	trace
7	**2h**	Ph	Me	CF_3CO_2H	80 °C, 0.5 h	**5a**	78	**3h**	trace
8[c]	**2h**	Ph	Me	CF_2HCO_2H	80 °C, 15 h	**5a**	6	**3h**	0
9	**2h**	Ph	Me	CF_2HCO_2H	100 °C, 0.25 h	**5a**	86	**3h**	0
10	**2b**	Ph	H	CF_2HCO_2H	100 °C, 0.25 h	**5b**	90	**3b**	0
11	**2i**	C_4H_9	H	CF_3CO_2H	100 °C, 0.25 h	**5c**	72	**3j**	8
12	**2j**	Ph	Ph	CF_2HCO_2H	100 °C, 0.25 h	**5d**	85	**3k**	0
13	**2f**	C_3H_7	C_3H_7	CF_2HCO_2H	100 °C, 0.25 h	**5e**	74	**3f**	0
14	**2k**	Ph	Br	CF_2HCO_2H	100 °C, 0.25 h	**5f**	73	**3l**	0
15	**2l**	Ph	PhS	CF_2HCO_2H	100 °C, 0.25 h	**5g**	60	**3m**	0
16	**2d**	CO_2Et	H	CF_3CO_2H	100 °C, 0.25 h	**5h**	60	**3d**	0[d]

[a] The reaction was carried out using **1a** (1 equiv) and **2** (1.2 equiv) in the presence of $Cu(OTf)_2$ (5 mol %) and additives (1 equiv) in $(ClCH_2)_2$ unless otherwise noted. [b] Isolated yield. [c] The reaction was performed in the presence of 10 mol % of TfOH instead of $Cu(OTf)_2$. [d] **4d** was obtained in 14% yield.

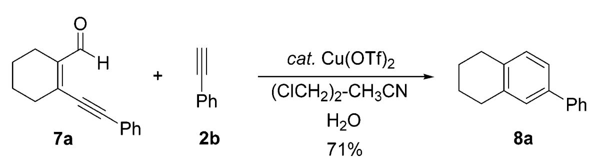
1a and **2**, when we utilized some metal triflates instead of $AuCl_3$, the yield of the desired [4+2] benzannulation products **3** and **4** decreased, and trace to very small amounts of benzoic acid were detected. To clarify the origin of benzoic acid, a systematic investigation of the reaction between *o*-(phenylethynyl)benzaldehyde **1a** and **2** was carried out (eq 4, Table 2). The reaction



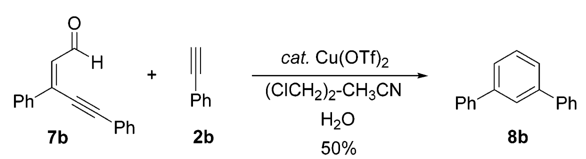
(4)

of **1a** with 1.2 equiv of **2h** (R^1 = Ph, R^2 = Me) in the presence of 5 mol % of $Cu(OTf)_2$ in 1,2-dichloroethane at 80 °C for 30 min gave 2-methyl-3-phenyl-naphthalene **5a** in 56% yield along with 1-benzoyl-3-methyl-2-phenyl-naphthalene **3h** in 22% yield (entry 1). Besides the naphthalene products, benzoic acid (14%) and benzoic anhydride (12%) were also produced. This result was in marked contrast to the finding that the AuX_3-catalyzed reaction of **1** with **2** produced **3** and **4** exclusively and did not produce benzoic acid and benzoic anhydride at all. No reaction took place with other Lewis acidic copper salts, such as CuF_2, $CuCl_2$, $CuBr_2$, and $Cu(OAc)_2$, and the starting materials were recovered. We thought that trace amounts of water, which might exist in the reaction medium, would play an important role for the formation of benzoic acid. Accordingly, we investigated the effect of water and other protic additives. Addition of water or MeOH did not exert a dramatic influence upon the product distribution (entries 2 and 3). Interestingly, the addition of formic acid increased the chemical yield of **5a** up to 79% yield and decreased the yield of **3h** (entry 4). After several trials using other Brønsted acids, we found that the reaction using CF_2HCO_2H gave **5a** in 82% yield and suppressed dramatically the formation of **3h** (entries 5−7). The reaction of **1a** with **2h** using 10 mol % of TfOH in the absence of $Cu(OTf)_2$ catalyst gave only 6% of **5a** even after 15 h (entry 8). This blank test clearly showed the combination between $Cu(OTf)_2$ catalyst and CF_2HCO_2H was essential for the present benzannulation. The best result was obtained when the reaction was carried out at 100 °C; **5a** was obtained in 86% yield (entry 9). To clarify whether **5a** was formed from **3h** by the cleavage of benzoyl group under the reaction conditions, **3h** was treated with 10 mol % of $Cu(OTf)_2$ in the presence of 1 equiv of CF_2HCO_2H at 100 °C for 15 min. However, no reaction took place, and **3h** was recovered. Even when the reaction was carried out for 1 day, **5a** was not formed at all. It is clear that **5a** is not produced through the C−C bond cleavage of **3h**. We next examined the reaction of **1a** with the other alkynes **2b**, **2i**, **2j**, **2f**, **2k**, **2l**, and **2d**. The reaction proceeded smoothly irrespective of internal or terminal alkynes and of aromatic or aliphatic alkynes to give the corresponding benzannulation products **5b−e** in good to high yields (entries 10−13). Even bromo-, phenylthio-, and ethoxycarbonyl-substituted alkynes were able to be used as alkynes to lead the corresponding functionalized naphthalenes **5f−h** in good yields (entries 14−16).

Because the naphthalene derivatives **5** were produced unexpectedly easily from **1a**, we were interested in the possibility of whether the present [4+2] benzannulation methodology would be applicable to the synthesis of polysubstituted benzenes or not. The reaction of the enynal **7a** with phenylacetylene **2b** under similar reaction conditions as shown in Table 2 (cat $Cu(OTf)_2$ and HA) gave **8a** in a low yield; the use of Brønsted acids (HA) as an additive was not so effective. After many attempts, we found that the treatment of **7a** with **2b** (5 equiv) in the presence of 10 mol % of $Cu(OTf)_2$ and 1 equiv of H_2O in a mixture of 1,2-dichloroethane and CH_3CN (3:1) gave the corresponding benzene derivative **8a** in 71% yield as a sole product (eq 5). Similarly, the reaction of **7b** with **2b** under the same reaction conditions afforded **8b** in 50% yield (eq 6).



(5)



(6)

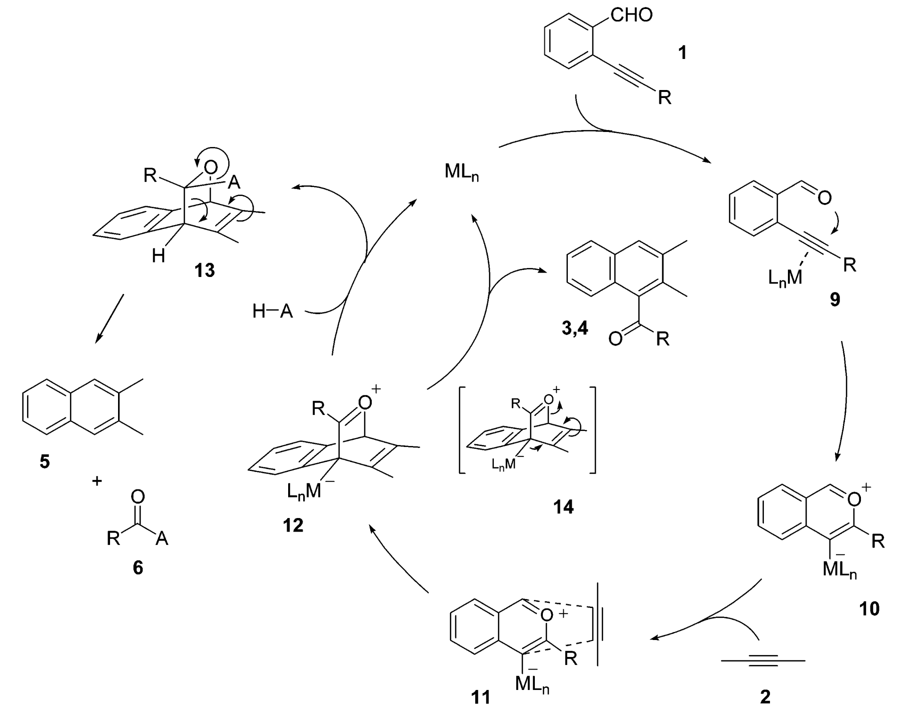
(C) Reaction Mechanism. A plausible mechanism for the present benzannulation is shown in Scheme 1. The coordination of the triple bond of **1** to Lewis acid (ML_n: AuX_3 or $Cu(OTf)_2$) enhances the electrophilicity of alkyne, and the subsequent nucleophilic attack (as shown in **9**) of the carbonyl oxygen to the electron-deficient alkyne would form the ate complex **10**.[18,19] The Diels−Alder reaction of **10** with an alkyne **2** would form the intermediate **12** through **11**.[20] When the reaction is catalyzed by AuX_3, the subsequent bond rearrangement, as shown in **14**

(18) (a) Asao, N.; Shimada, T.; Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 10899−10902. (b) Asao, N.; Yamamoto, Y. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 1071−1087 and references therein.

(19) Iwasawa has proposed the similar intermediate in the reaction of *o*-ethynylphenyl ketones with alkenes in the presence of $W(CO)_5$·THF, see: Iwasawa, N.; Shido, M.; Kusama, H. *J. Am. Chem. Soc.* **2001**, *123*, 5814−5815.

(20) Benzo[*c*]pyrylium salts are known to play a dien part in the Diels−Alder reaction with ethyl vinyl ether, see: Kuznetsov, E.; Shcherbakova, I. V.; Balaban, A. T. *Adv. Heterocycl. Chem.* **1990**, *50*, 157−254.

Scheme 1



with arrows, would afford the naphthyl ketone derivatives **3** and **4** and regenerate AuX_3. On the other hand, in the $Cu(OTf)_2$−HA system, protonolysis of the C−Cu bond of **12** by a Brønsted acid (HA) such as CF_2HCO_2H, followed by the attack of A^- to the carbon of RCO, would produce **13**, which would undergo the retro Diels−Alder reaction shown in **13** to lead the formation of **5** and **6**.[21] Even in the absence of HA, the protonolysis would occur partially by trace amounts of water that exist in the media, and subsequent addition of OH to RCO would give benzoic acid **6a** (R = Ph, A = OH) (eq 2). As we mentioned above, benzoic anhydride **6b** (R = Ph, A = $PhCO_2$) was also obtained in the reaction of **1a** with **2h**. A blank test indicated that benzoic anhydride was not formed from benzoic acid under the reaction conditions. This result indicates that benzoic acid **6a** generated in situ may behave also as a HA to give **5** and **6b**. If the protonolysis of the C−Cu bond does not proceed efficiently, the naphthyl ketone derivatives **3** and **4** are produced directly from **12** through the bond rearrangement similar to that in the case of the AuX_3-catalyzed reaction. To clarify whether the debenzoylated naphthalene products **5** are obtained also in the AuX_3−HA system, we examined the reaction of **1a** with **2h** in the presence of 5 mol % of $AuBr_3$ and 1 equiv of CF_2HCO_2H. As we expected, **5a** was obtained in 32% yield along with 21% of **3h**. During the reaction, the mirror of Au was observed in the reaction vessel due to the decomposition of $AuBr_3$, and the starting material **1a** was recovered in 14% yield. Accordingly, the protonolysis of the C−M bond of **12** would be more efficient in the case of the Cu-catalyzed reaction, as compared to the Au-catalyzed reaction.

Another intriguing point of the $Cu(OTf)_2$-benzannulation is seemingly facile C−C bond cleavage of the triple bond of **1a**. Although several reactions are known for single and double bond cleavage,[22] only a few transformations for triple bond are known, including alkyne−ligand scission on metal complexes,[23] oxidative cleavage,[24] and the transition metal-catalyzed alkyne methathesis.[25] Recently, Jun and co-workers developed the Rh-catalyzed hydroiminoacylation, which resulted in the cleavage of the triple bond, although the chelation-assistance was required.[26] We also recently reported the triple bond cleavage of diynes through the hydroamination with transition metal catalysts.[27] On the other hand, to the best of our knowledge,

(21) The tandem Diels−Alder/retro-Diels−Alder reactions using 6-aminopyrimidin-4(*3H*)-one derivatives with dimethyl acetylenedicarboxylate were reported, see: (a) Cobo, J.; Melguizo, M.; Sánchez, A.; Nogueras, M. *Synlett* **1993**, 297−299. (b) Cobo, J.; García, C.; Melguizo, M.; Sánchez, A.; Nogueras, M. *Tetrahedron* **1994**, *50*, 10345−10358. (c) Cobo, J.; Melguizo, M.; Sánchez, A.; Nogueras, M.; Clercq, E. D. *Tetrahedron* **1996**, *52*, 5845−5856. (d) Cobo, J.; Melguizo, M.; Nogueras, M.; Sánchez, A.; Dobado, J. A.; Nonella, M. *Tetrahedron* **1996**, *52*, 13721−13732.

(22) For reviews, see: (a) Rybtchinski, B.; Milstein, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 870−883. (b) Jennings, P. W.; Johnson, L. L. *Chem. Rev.* **1994**, *94*, 2241−2290. (c) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245−269. (d) Murakami, M.; Ito, Y. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: Berlin, 1999; pp 97−129.

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the present reaction is the first example of the Lewis acid-catalyzed cleavage of a triple bond.

Conclusion

We are now in a position to synthesize functionalized multisubstituted naphthalene derivatives in good to high yields through the Lewis acid-catalyzed [4+2] benzannulation between *o*-alkynyl(oxo)benzenes and alkynes. Just by changing the catalyst system, we obtained either the naphthyl ketone derivatives **3** and **4** or the decarbonylated naphthalenes **5**. The Lewis acid-catalyzed [4+2] benzannulation can be extended to enynals, which provides a new method for the synthesis of substituted benzenes.

Experimental Section

$AuBr_3$-Catalyzed Benzannulation. The preparation of **3b** is representative. To $AuBr_3$ (6.5 mg, 3 mol %) was added a mixture of **1a** (103 mg, 0.5 mmol) and **2b** (66 μL, 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 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 (154 mg, 0.5 mmol) in 100% yield.

$Cu(OTf)_2$-Catalyzed Benzannulation. The preparation of **5a** is representative. To a mixture of **1a** (103 mg, 0.5 mmol) and $Cu(OTf)_2$ (9.0 mg, 5 mol %) in 1,2-dichloroethane (2 mL) were added **2h** (75 μL, 0.6 mmol) and CF_2HCO_2H (31 μL, 0.5 mmol) successively at room temperature under Ar atmosphere. The resulting mixture was stirred at 100 °C for 15 min and then cooled to room temperature. A saturated aqueous solution of $NaHCO_3$ was added, and the mixture was extracted with ether three times. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated to leave the crude product, which was purified by silica gel column chromatography using hexane as an eluent to give **5a** (93.7 mg, 0.43 mmol) in 86% yield.

Supporting Information Available: Spectroscopic and analytical data for **5a−h** and **8a−b** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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