

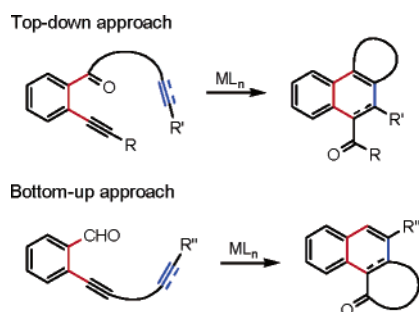
AuBr₃- and Cu(OTf)₂-Catalyzed Intramolecular [4 + 2] Cycloaddition of Tethered Alkynyl and Alkenyl Enynones and Enynals: A New Synthetic Method for Functionalized Polycyclic Hydrocarbons

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Treatment of tethered alkynyl enynones **8**, in which a carbon chain is attached to the carbonyl group, with a catalytic amount of AuBr₃ in (ClCH₂)₂ gave the naphthyl ketones **9** in good to high yields (top-down approach). Analogously, the AuBr₃-catalyzed benzannulations of **10**, in which a carbon tether is extended from the alkynyl terminus, also proceeded smoothly, and the cyclized naphthyl ketones **11** were obtained in high yields (bottom-up approach). Similarly, when two kinds of tethered alkenyl enynones **12** and **14** were treated with Cu(OTf)₂ catalyst, the corresponding dihydronaphthyl ketone products **13** and **15** were obtained in high yields, respectively. The present formal [4 + 2] intramolecular cycloaddition proceeds most probably through the coordination of the triple bond at the ortho position of substrates to Lewis acids, the formation of benzopyrylium ate complex **16** via the nucleophilic addition of the carbonyl oxygen atom, the reverse electron demand type Diels–Alder addition of the tethered alkynes or alkenes to the ate complex, and subsequent bond rearrangement.

Introduction

Lewis acid-catalyzed cyclization reaction is one of the most fundamental and important methods for the preparation of functionalized polycyclic hydrocarbons.¹ Among them, the intramolecular cyclization based on the Friedel–Crafts reaction has been widely used as one of the most effective preparative methods for functionalized polycyclic

hydrocarbons. However, such a reaction often provides products as a mixture of regioisomers due to the lack of regioselective control on the Friedel–Crafts reaction. Accordingly, an alternative method for regioselective construction of functionalized polycyclic structures has been highly desirable. Recently, we reported that the AuX₃-catalyzed intermolecular [4 + 2] benzannulation between enynal units **1** and alkynes gave the naphthyl ketones **2** in high yields.^{2–4} We also found that a similar [4 + 2] cycloaddition between **1** and alkenes took place in the presence of Cu(OTf)₂ catalyst to give the 1,2-

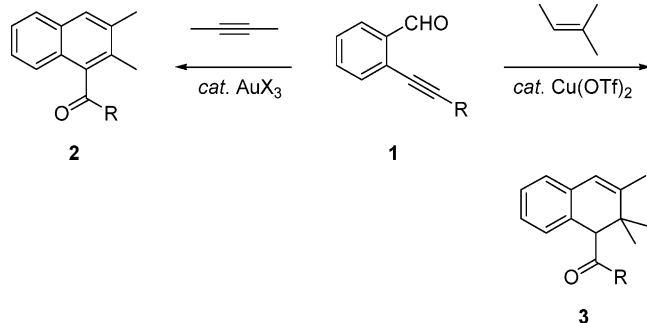
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(1) (a) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 2000; Vols. 1–2. (b) *Lewis Acid Reagents*; Yamamoto, H., Ed.; Oxford University Press: New York, 1999. (c) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095–1120. (d) Santelli, M.; Pons, J. M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC Press: Boca Raton, FL, 1996. (e) Shambayati, S.; Schreiber, S. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 283–324. (f) Yamaguchi, M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 325–353.

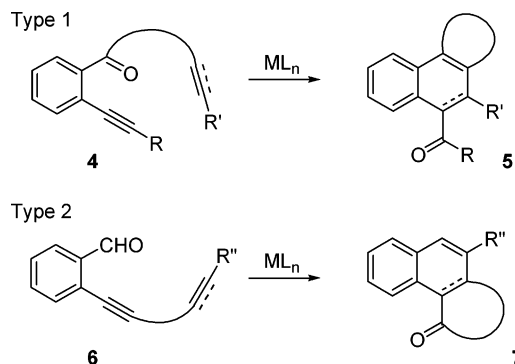
(2) (a) Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12650–12651. (b) Asao, N.; Nogami, T.; Lee, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 10921–10925.

(3) For reviews on the synthesis of naphthalenes, see: (a) de Koning, C. B.; Rousseau, A. L.; van Otterlo, W. A. L. *Tetrahedron* **2003**, *59*, 7–36. (b) Katritzky, A. R.; Li, J.; Xie, L. *Tetrahedron* **1999**, *55*, 8263–8293.

SCHEME 1. Lewis Acid-Catalyzed Intermolecular [4 + 2] Benzannulation and Cycloaddition



SCHEME 2. Lewis Acid-Catalyzed Intramolecular [4 + 2] Benzannulation and Cycloaddition



dihydronaphthalene derivatives **3** in good to high yields (Scheme 1).^{5–7} It occurred to us that the intramolecular version of the [4 + 2] benzannulation and [4 + 2] cycloaddition would produce a variety of polycyclic naphthalene and dihydronaphthalene derivatives and the scope of the [4 + 2] benzannulation and cycloaddition would be expanded very much because such products are quite useful building blocks for the synthesis of natural products such as tanshinones.⁸ In this paper, we wish to report two different kinds of the intramolecular [4 + 2] cycloaddition reactions; one is the top-down approach using **4** (type 1), in which a carbon chain is attached to the carbonyl group, and another is the bottom-up approach using **6** (type 2), in which a carbon tether is extended from the alkyne terminus (Scheme 2). Both

(4) For recent examples for naphthalene syntheses, see: (a) Iwasawa, N.; Shido, M.; Maeyama, K.; Kusama, H. *J. Am. Chem. Soc.* **2000**, *122*, 10226–10227. (b) Wakasugi, K.; Nishi, Y.; Tanabe, Y. *Tetrahedron Lett.* **2000**, *41*, 5937–5942. (c) Miura, T.; Iwasawa, N. *J. Am. Chem. Soc.* **2002**, *124*, 518–519. (d) Huang, Q.; Larock, R. C. *Org. Lett.* **2002**, *4*, 2505–2508. (e) Viswanathan, G. S.; Wang, M.; Li, C.-J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2138–2141. (f) Yasukawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 12680–12681. (g) Viswanathan, G. S.; Li, C.-J. *Synlett* **2002**, 1553–1555. (h) Ramakrishna, T. V. V.; Sharp, P. R. *Org. Lett.* **2003**, *5*, 877–879. (i) Barluenga, J.; Vazquez-Villa, H.; Ballesteros, A.; Gonzalez, J. M. *Org. Lett.* **2003**, *5*, 4121–4123. (j) Shen, H.-C.; Pal, S.; Lian, J.-J.; Liu, R.-S. *J. Am. Chem. Soc.* **2003**, *125*, 15762–15763. (k) Kusama, H.; Funami, H.; Takaya, J.; Iwasawa, N. *Org. Lett.* **2004**, *6*, 605–608.

(5) Asao, N.; Kasahara, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 3504–3506.

(6) For reviews, see: Pape, A. R.; Kaliappan, K. P.; Kundig, E. P. *Chem. Rev.* **2000**, *100*, 2917–2940.

(7) For recent examples for 1,2-dihydronaphthalene syntheses, see: (a) Ahmed, A.; Clayden, J.; Rowley, M. *Synlett* **1999**, 1954–1956. (b) Shindo, M.; Koga, K.; Asano, Y.; Tomioka, K. *Tetrahedron* **1999**, *55*, 4955–4968. (c) Chatani, N.; Inoue, H.; Ikeda, T.; Murai, S. *J. Org. Chem.* **2000**, *65*, 4913–4918. (d) Inoue, H.; Chatani, N.; Murai, S. *J. Org. Chem.* **2002**, *67*, 1414–1417.

TABLE 1. Lewis Acid-Catalyzed Intramolecular Cyclization of **8**^a

entry	8	R	n	Lewis acid	conditions	9	yield (%) ^b
1	8a	Ph	3	AuCl ₃	rt, 3 h	9a	89 ^c
2	8a	Ph	3	AuBr ₃	rt, 3 h	9a	92
3 ^d	8a	Ph	3	AuBr ₃	rt, 3 h	9a	91
4	8a	Ph	3	Cu(OTf) ₂	rt, 2 h	9a	84 ^c
5	8b	Bu	3	AuBr ₃	rt, 5 h	9b	57
6	8c	H	3	AuBr ₃	rt, 4.5 h	9c	41
7	8d	TMS	3	AuBr ₃	rt, 36 h	9d	40
8	8e	Ph	4	AuBr ₃	80 °C, 5 h	9e	72

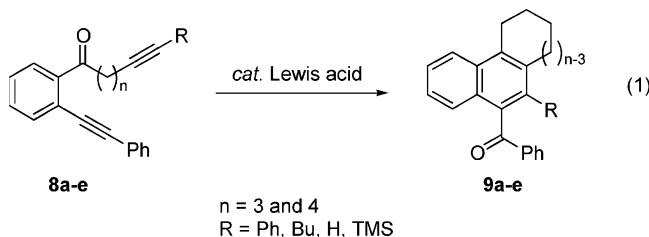
^a Reaction was carried out using **8** (0.5 mmol) in the presence of 5 mol % Lewis acid in (CH₂Cl)₂ unless otherwise noted.

^b Isolated yields. ^c Yield was determined by ¹H NMR using dibromomethane as an internal standard. ^d Reaction was conducted using 1 g of **8a** (2.9 mmol).

reactions produced the corresponding polycyclic naphthalene derivatives **5** and **7** in good to high yields.⁹

Results and Discussion

First, we examined the reaction of **8** (type 1) under several conditions (eq 1), and the results are summarized in Table 1. When **8a** (R = Ph, n = 3) was treated with 5 mol % AuCl₃ in (CH₂Cl)₂ at rt for 3 h, the naphthyl ketone **9a** was obtained in 89% yield (entry 1).^{10–11}



The chemical yield of **9a** was increased up to 92% yield by using AuBr₃ catalyst instead of AuCl₃ (entry 2). The present benzannulation proceeded smoothly even when 1 g of **8a** (2.9 mmol) was used and the corresponding product **9a** was obtained in 91% (entry 3). When we used Cu(OTf)₂ as a catalyst, **9a** was obtained in 84% yield together with 4-phenyl-2,3-dihydro-1H-cyclopenta[a]-naphthalene (13% yield), which was produced by the cleavage of benzoyl group (entry 4).^{2b} The reaction proceeded at high temperatures even in the absence of Lewis acid catalyst; however, it was very sluggish at 80 °C, and the chemical yield of **9a** was 34% even after 10 days. The AuBr₃-catalyzed reaction of the other starting materials **8b–d** also proceeded smoothly, and the corresponding products **9b–d** were obtained in good to high yields (entries 5–7). While the reaction of **8e**, having a tether chain consisting of four methylene groups (n = 4), did not proceed at rt, it proceeded at 80 °C and the corresponding tetrahydrophenanthrene product **9e** was obtained in 72% yield (entry 8).

We next examined the type 2 reaction by using the substrates **10** (eq 2), and the results are summarized in

(8) For examples, see: (a) Yagi, A.; Takeo, S. *Yakugaku Zasshi* **2003**, *123*, 517–532. (b) Takatsuki, A.; Sekino, Y.; Kadono, T.; Wakayama, S. *Jpn. Kokai Tokkyo Koho* 11171765 A2 19990629, 1999.

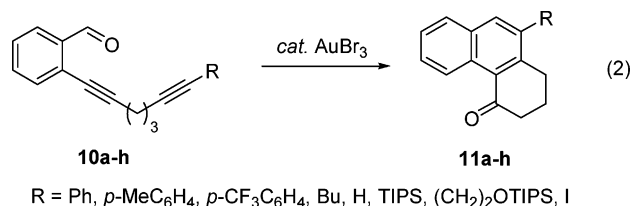
(9) Dyker reported one example of the intramolecular acylnaphthalene synthesis using bialkynylbenzil as the starting material; see: Dyker, G.; Stirner, W.; Henkel, G.; Kockerling, M. *Tetrahedron Lett.* **1999**, *40*, 7457–7458.

TABLE 2. AuBr₃-Catalyzed Intramolecular Cyclization of **10**^a

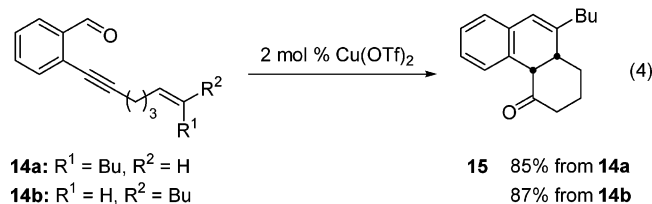
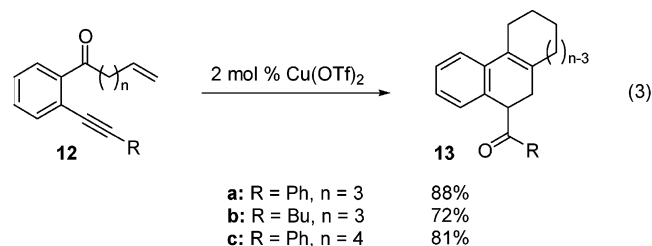
entry	10	R	conditions	11	yield (%) ^b
1	10a	Ph	80 °C, 4 h	11a	66
2	10b	<i>p</i> -MeC ₆ H ₄	80 °C, 3 h	11b	47
3	10c	<i>p</i> -CF ₃ C ₆ H ₄	80 °C, 8 h	11c	67
4	10d	Bu	80 °C, 2 h	11d	89
5	10e	H	50 °C, 1.5 h	11e	91
6	10f	TIPS	80 °C, 3 h	11f	88
7	10g	(CH ₂) ₂ OTIPS	80 °C, 1 h	11g	82
8	10h	I	80 °C, 1 h	11h	89

^a Reaction was carried out using **10** in the presence of 2 mol % AuBr₃ in (CH₂Cl)₂. ^b Isolated yields.

Table 2. When the reaction of **10a** (R = Ph) was carried out in the presence of 2 mol % AuBr₃ at 80 °C for 4 h, the desired product **11a** was obtained in 66% yield (entry 1). When a tolyl group was substituted at the terminus of alkyne (**10b**), the chemical yield was decreased to 47% yield (entry 2). On the other hand, the reaction of **10c**, bearing a *p*-CF₃C₆H₄ group at the terminus, gave **11c** in 67% yield, while 8 h was needed for the completion of the reaction (entry 3). Other arylaldehydes such as **10d–h** were also suitable as the starting materials for the present reaction, and the corresponding 10-substituted-2,3-dihydrophenanthrenones **11d–h** were obtained in high yields (entries 4–8).

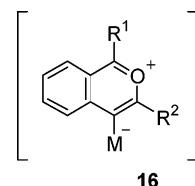
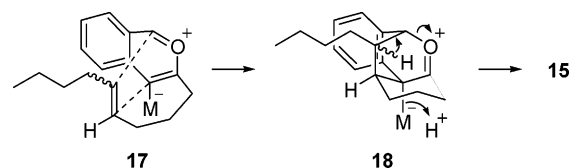


Since the intramolecular benzannulation of enynones with tethers having an alkynyl group proceeded unexpectedly easily, we next turned our attention to the cycloaddition reactions of the *o*-alkynyl-arylalkenyl ketones. The requisite substrates **12a–c** were easily prepared and were treated with 2 mol % Cu(OTf)₂ (eq 3), because the intermolecular reaction of *o*-alkynyl-arylaldehydes and alkenes with Cu(OTf)₂ catalyst, rather than with AuX₃, proceeded smoothly to give the corresponding cycloaddition products in higher yields. The reactions of **12a** and **12b**, bearing three methylene groups as a tether,



proceeded smoothly, and the corresponding cyclization products **13a** and **13b** were obtained in 88 and 72% yields, respectively. Analogously, the phenanthrene derivative **13c** was produced from **12c** in 81% yield. Furthermore, the reactions of **14a** and **14b**, in which the geometry of the olefin was *Z* and *E*, respectively, gave **15** as the sole product in 85 and 87% yields, respectively (eq 4).

The present reaction most probably proceeds through the formation of benzopyrylium-type intermediate **16**, followed by the intramolecular [4 + 2]-type cycloaddition with alkynes or alkenes.^{2,5,12} In particular, the stereoselective formation of **15** is able to be explained as follows: The pyrylium intermediate **17** gives the intramolecular [4 + 2] adduct **18**. The carbon–metal bond of the ate complex **18** is displaced by carbon–hydrogen bond by trapping the proton with retention of configuration to give the *cis* product (**15**) as shown in Scheme 3.

**SCHEME 3.** Proposed Pathway for the Cu(OTf)₂-Catalyzed Reaction of **14**

Conclusion

We are now in a position to synthesize functionalized polycyclic hydrocarbons from carbon-tethered alkynyl and alkenyl enynons and enynals in good to high yields. By choosing the reaction mode (type 1 and 2), a variety of functionalized polycyclic hydrocarbons can be obtained, which could potentially become an essential structural framework for polycyclic natural products. Further studies to extend the scope of the reaction and to apply the present methodology for the synthesis of natural products are in progress in our laboratory.

Experimental Section

Lewis Acid-Catalyzed [4 + 2] Cycloaddition. The preparation of **9a** is representative. To AuBr₃ (11 mg, 5 mol %) was added a solution of **8a** (0.17 g, 0.5 mmol) in (ClCH₂)₂ (1.5 mL) at rt under an Ar atmosphere. After the reaction mixture was stirred for 3 h at rt, the resulting solution was filtered through

(10) For reviews on the gold catalyst, see: (a) Dyker, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 4237–4239. (b) Hashmi, A. S. K. *Gold Bull.* **2003**, *36*, 3–9.

(11) Gold-catalyzed benzannulation, see: (a) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553–11554. (b) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *Org. Lett.* **2001**, *3*, 3769–3771. (c) Dankwardt, J. W. *Tetrahedron Lett.* **2001**, *42*, 5809–5812. (d) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *Catal. Today* **2002**, *72*, 19–27.

(12) [3 + 2] cycloaddition of **16** with alkyne was proposed as another possible mechanism for the intermolecular benzannulation; see: Straub, B. F. *Chem. Commun.* **2004**, 1726–1728.

a short silica gel column. The solvent was removed under reduced pressure to give the crude product. ¹H NMR analysis of the crude product, using CH₂Br₂ as an internal standard, showed that **9a** was produced in 98% yield. The product was isolated as a white solid (0.16 g, 0.46 mmol) in 92% yield by silica gel column chromatography using ether as an eluent.

Supporting Information Available: Preparation methods of **8a**, **10a**, **12a**, and **14a**, and spectroscopic and analytical data for **8a–e**, **9a–e**, **10a–h**, **11a–h**, **12a–c**, **13a–c**, **14a,b**, and **15**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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