Cycloisomerization of ω-Aryl-1-alkynes: $GaCl_3$ as a Highly Electrophilic Catalyst for Alkyne Activation

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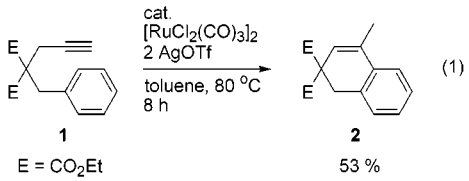
Abstract: Cycloisomerization of a variety of ω-aryl-1-alkynes, where ω = 5 or 6, in the presence of a catalytic amount of $GaCl_3$ provided dihydronaphthalene derivatives or dihydrobenzocycloheptenes, respectively, in high yields.

The Lewis acid-mediated and catalyzed addition of carbon nucleophiles to carbonyl compounds is one of the most efficient methods for the construction of C−C bonds and has found widespread use in organic synthesis.[1] Similarly, the Lewis acid-promoted addition of carbon nucleophiles to alkynes have also emerged as a promising method for C−C bond formation.[2−5] We recently reported that cycloisomerization of ω-aryl-1-alkynes leading to dihydronaphthalenes or dihydrobenzocycloheptenes is catalyzed by Ru(II) or Pt(II) complexes (eq 1).[6,7] However, the scope of this reaction was found to be limited to substrates that have an electron-rich benzene ring.



This limitation prompted us to investigate alternate, more reactive catalytic systems. Initially, it was our expectation that more strongly acidic Lewis acids might extend the scope of this process. On the basis of this expectation, a number of typical Lewis acids ($AlCl_3$, BF_3·Et_2O, and $TiCl_4$) were investigated; however, such Lewis acids failed to catalyze the cycloisomerization of (phenylmethyl)-2-propynylpropanedioic acid diethyl ester (**1**). We surmised that the tight coordination of these catalysts to the oxygen atom of the ester functionality in **1** might account for their lack of activity. Consequently, it appears that soft Lewis acids may be the reagent of choice for activation of alkynes even in the presence of oxygen atom for catalyzing the reaction of **1**.

A basic center such as an oxygen atom of a carbonyl group would be expected to bind more strongly to a hard acid rather than a soft acid. Similarly, a basic carbon center such as C−C double and triple bonds might show a preference for a soft acid. This is obvious from the hard and soft acid and base principle, but has not been clearly elucidated before to the best of our knowledge. On the basis of this rational, $GaCl_3$ might represent a Lewis acid of choice for the desired catalytic conversion of **1** into **2** for the following reasons. (1) Gallium is a soft element compared with boron and aluminum. As a result, a Lewis acid consisting of gallium would be expected to activate soft functional groups such as alkynes. In fact, Yamaguchi recently reported that the addition of a variety of carbon nucleophiles to alkynes in the presence of an excess amount of $GaCl_3$ proceeded smoothly.[3] Yamamoto also reported on an example of the $GaCl_3$-mediated regioselective hydrostannation and allylstanation of aldehydes that proceeds via the coordination of $GaCl_3$ to an alkyne π-bond.[8] (2) The softness of Ga compared to Al would decrease the Ga−O bond strength compared to that of Al−O one, thereby resulting in a more favor product decomplexation. Kobayashi recently reported that gallium nonafluorobutanesulfonate ($Ga(ONf)_3$) gave excellent results in *catalytic* Friedel−Crafts acylation reactions.[9] Maruoka has recently reported cases in which Me_3Ga has a remarkably higher catalytic activity for the alkylation of hetero-substituted epoxides with alkynyllithium compared with Me_3Al.[10] In this report, we wish to report some findings which show that $GaCl_3$ is highly active as a catalyst for the cycloisomerization of ω-aryl-1-alkynes.

We initially examined the reaction of **1**. When it was treated with 10 mol % $GaCl_3$ (1 M in methylcyclohexane)

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(2) For Al, Zr, and Hf, see: (a) Asao, N.; Yamamoto, Y. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 1071. (b) Asao, N.; Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3797. (c) Imamura, K.-I.; Yoshikawa, E.; Gevorgyan, V.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 4081. (d) Matsukawa, Y.; Asao, N.; Kitahara, H.; Yamamoto, Y. *Tetrahedron* **1999**, *55*, 3779. (e) Imamura, K.-I.; Yoshikawa, E.; Gevorgyan, V.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 5339. (f) Yoshikawa, E.; Gevorgyan, V.; Asao, N.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 6781. (g) Asao, N.; Matsukawa, Y.; Yamamoto, Y. *Chem. Commun.* **1996**, 1513. See also: Yeon, S. H.; Han, J. S.; Hong, E.; Do, Y.; Jung, I. N. *J. Organomet. Chem.* **1995**, *499*, 159.

(3) For Ga, see: (a) Arisawa, M.; Akamatsu, K.; Yamaguchi, M. *Org. Lett.* **2001**, *3*, 789. (b) Kido, Y.; Yonehara, F.; Yamaguchi, M. *Tetrahedron* **2001**, *57*, 827. (c) Kido, Y.; Arisawa, M.; Yamaguchi, M. *J. Synth. Org. Chem., Jpn.* **2000**, *58*, 1030. (d) Yonehara, F.; Kido, Y.; Yamaguchi, M. *Chem. Commun.* **2000**, 1189. (e) Yamaguchi, M.; Tsukagoshi, T.; Arisawa, M. *J. Am. Chem. Soc.* **1999**, *121*, 4074. (f) Kido, Y.; Yoshimura, S.; Yamaguchi, M.; Uchimaru, T. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1445. (g) Kido, Y.; Yamaguchi, M. *J. Org. Chem.* **1998**, *63*, 8086. (h) Yamaguchi, M.; Sotokawa, T.; Hirama, M. *Chem. Commun.* **1997**, 743. (i) Yamaguchi, M.; Kido, Y.; Hayashi, A.; Hirama, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1313.

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(5) For In and Sc, see: Tsuchimoto, T.; Maeda, T.; Shirakawa, E.; Kawakami, Y. *Chem. Commun.* **2000**, 1573.

(6) Chatani, N.; Inoue, H.; Ikeda, T.; Murai, S. *J. Org. Chem.* **2000**, *65*, 4913.

(7) It is assumed that the Ru(II)- and Pt(II)-catalyzed skeletal reorganization of enynes is initiated by the electrophilic addition of a transition-metal Lewis acid to alkynes. See: (a) Chatani, N.; Morimoto, T.; Muto, T.; Murai, S. *J. Am. Chem. Soc.* **1994**, *116*, 6049. (b) Chatani, N.; Furukawa, N.; Sakurai, H.; Murai, S. *Organometallics* **1996**, *15*, 901. (c) Chatani, N.; Kataoka, K.; Murai, S.; Furukawa, N.; Seki, Y. *J. Am. Chem. Soc.* **1998**, *120*, 9104. (d) Chatani, N.; Inoue, H.; Morimoto, T.; Muto, T.; Murai, S. *J. Org. Chem.* **2001**, *66*, 4433.

(8) Asao, N.; Asano, T.; Ohishi, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4817.

(9) (a) Kobayashi, S.; Komoto, I.; Matsuo, J.-I. *Adv. Synth. Catal.* **2001**, *343*, 71. (b) Kobayashi, S.; Komoto, I. *Tetrahedron* **2000**, *56*, 6463. (c) Matsuo, J.-I.; Odashima, K.; Kobayashi, S. *Synlett* **2000**, 403. See also: (d) Mukaiyama, T.; Ohno, T.; Nishimura, T.; Suda, S.; Kobayashi, S. *Chem. Lett.* **1991**, 1059. (e) Olah, G. A.; Farooq, O.; Farina, S. M. F.; Olah, J. A. *J. Am. Chem. Soc.* **1988**, *110*, 2560.

(10) Ooi, T.; Morikawa, J.; Ichikawa, H.; Maruoka, K. *Tetrahedron Lett.* **1999**, *40*, 5881.

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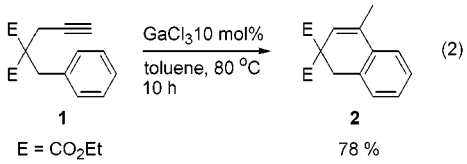
in toluene at 80 °C the dihydronaphthalene **2** was produced in 78% yield (eq 2). This yield exceeds the previously reported value (53%) in which $[RuCl_2(CO)_3]_2$/2 AgOTf was used as the catalyst.[6]

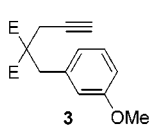
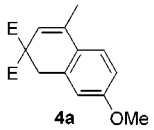
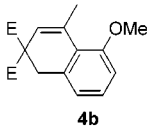
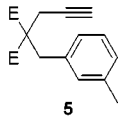
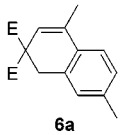
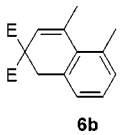
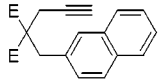
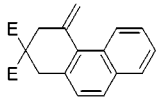
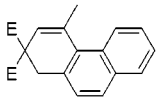
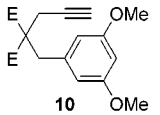
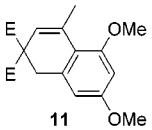
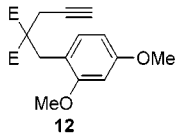
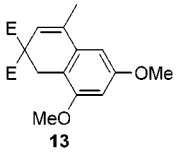
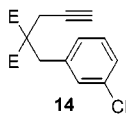
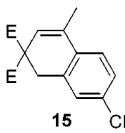


The next issue to be addressed was its performance relative to our previous catalyst systems in the cycloisomerization of *ω*-aryl-1-alkynes. In addition to **1**, a range of functionalized *ω*-aryl-1-alkynes was cycloisomerized in the presence of $GaCl_3$ to form the corresponding dihydronaphthalene derivatives in excellent yields and with high site selectivity (Table 1). In all cases, these reactions are faster or equal in rate to those using our previously reported catalyst systems, which contain Ru(II) or Pt(II).[6] The cycloisomerization of [(3-methoxyphenyl)methyl]-2-propynylpropanedioic acid diethyl ester (**3**) using 10 mol % $GaCl_3$ in toluene at 40 °C for 1 h gave cycloisomerization products **4** in 80% yield (**4a**:**4b** = 99:1). A significant improvement in site selectivity, which may, in part, be due to the milder conditions employed, was observed [80 °C with $GaCl_3$ 85% (94:6), 80 °C with $[RuCl_2(CO)_3]_2$/2 AgOTf 86% (78:22)]. As expected, the reaction of the methyl derivative **5** with the $GaCl_3$ catalyst afforded a mixture of similar products **6a**/**6b** in 85% yield (**6a**:**6b** = 94:6).

The cycloisomerization of the naphthyl derivative **7** occurred at the α-position of the naphthalene ring and no *β*-substituted product was observed, even though the latter is less sterically crowded. This indicates that the reaction proceeds via electrophilic substitution. The reaction afforded the endo product **9** as a major product along with the exo isomer **8** (77%, **8**/**9** = 34/66). This result strongly suggests that the exo product **8** underwent isomerization to the endo product **9**. The substrate **10** containing two methoxy substituents on the aryl moiety is readily cyclized to the corresponding product **11**. Substrate **12** which contains two methoxy substituents at the meta-position with respect to the reaction site, would be expected to be less reactive because methoxy substituents serve as electron-withdrawing groups in this case. In fact, the reaction of **12**, as catalyzed by $[RuCl_2(CO)_3]_2$/AgOTf, resulted in a lower yield (68 h, 4%). In sharp contrast, the $GaCl_3$ system converted **12** to **13** in good yield (58%). The reaction of substrate **14**, containing a chloro group on the aromatic ring, was also effectively converted to the corresponding dihydronaphthalene **15**, although an elevated temperature (reflux) was necessary to achieve a good conversion.

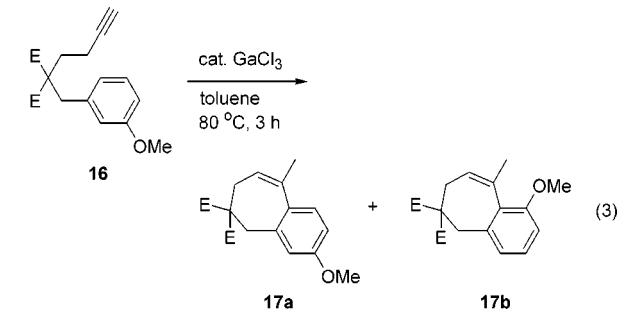
Given our success in the cycloisomerization of 5-aryl-1-alkynes, we turned our attention to 6-aryl-1-alkynes **16** (eq 3). Contrary to our previous study,[6] the reaction

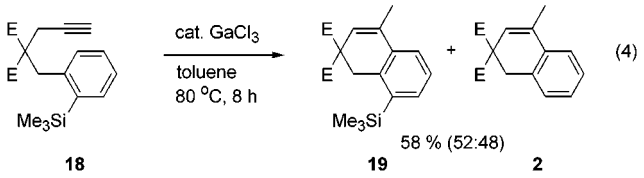
Table 1. $GaCl_3$-Catalyzed Cycloisomerization of 5-Aryl-1-pentynes[a]

substrate	conditions	products	yield
 **3**	40 °C, 1 h	 **4a**  **4b**	80 % (99:1)
 **5**	80 °C, 1 h	 **6a**  **6b**	85 % (94:6)
 **7**	40 °C, 2 h	 **8**  **9**	77 % (34:66)[b]
 **10**	40 °C, 0.5 h	 **11**	75 %
 **12**	80 °C, 30 h	 **13**	58 %
 **14**	reflux, 13 h	 **15**	69 %

[a] Reaction conditions: substrate (1 mmol), catalyst (0.1 mmol), and toluene (5 mL) under N_2. [b] The ratio of *exo* and *endo* isomers.

of **16** with 10 mol % $GaCl_3$ proceeds smoothly affording the expected products **17a** and **17b** in good yield in favor of **17a**.

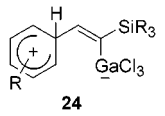




The reaction of **18** gave a nearly 1:1 mixture of normal cyclization product **19** and desilylation product **2** in 58% total yield (eq 4).[11] For the formation of **2** several possible pathways are possible: an *ipso* substitution pathway or a pathway involving protodesilylation before or after cycloisomerization. The mechanism which is operative is not clear.

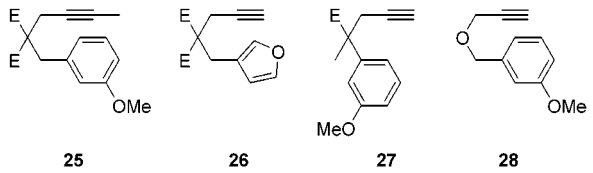
A reasonable mechanistic interpretation of the $GaCl_3$-catalyzed cycloisomerization is shown in Scheme 1. The $GaCl_3$ first coordinates to the alkyne to form a bridged-type cation complex **20a** or an open-type vinyl cation complex **20b**.[12,13] These complexes **20a** and **20b** would be expected to serve as a good electrophile. The electrophilic acetylenic carbon of the vinyl cation **20** is susceptible to intramolecular nucleophilic attack of the benzene moiety of **20** to afford an arenium intermediate **21**. On the basis of the observation of a rate dependence on the nucleophilicity of the aromatic ring of the substrates, we presume that this step is rate-limiting. The arenium complex **21** upon formal 1,3-proton shift of the *ipso* hydrogen forms **22** and the dissociation of the $GaCl_3$ from this intermediate **22** then provides the *exo* product **23**, which isomerizes to the *endo* product **4**. An alternative path involves a direct conversion of **21** to **23** via deprotonation with aromatization of **21** followed by protonation of the vinyl gallium moiety.

Yamaguchi has extensively studied a variety of the $GaCl_3$-mediated reactions of alkynes.[3] While the use of more than a stoichiometric amount of $GaCl_3$ is essential for the complete conversion of the substrate in his reaction systems, our reaction proceeds in the presence of catalytic amounts of $GaCl_3$. According to Yamaguchi's results, it appears that $GaCl_3$ does not detach from the arenium intermediate **24** at −78 °C, since ^1H NMR experiments show that **24** is sufficiently stable to be observed in CD_2Cl_2 at −78 °C.[3f] Thus, it can be seen that stoichiometric amount of $GaCl_3$ would be required in their reaction system. In contrast, in our systems, the reaction proceeds catalytically since the elimination of $GaCl_3$ from **21** occurs easily due to the higher reaction temperature (40 °C) used herein.



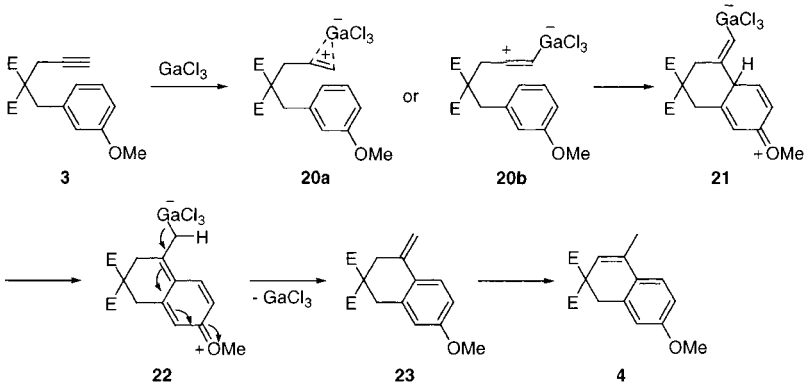
The substrates shown below were not viable substrates (Chart 1). The methyl-substituted alkyne **25** was not cycloisomerized with this catalyst system due to an unfavorable steric interaction between the methyl group and the aryl ring in the vinyl cation intermediate.[6] A complex mixture was obtained when the substrate **26**, containing a furan ring,[14] and the 4-aryl-1-alkyne **27** were used as the substrate in the cycloisomerization reaction. An ether-tethered substrate **28** proceeded with cleavage of carbon−oxygen bond.

Chart 1



In summary, the development of the $GaCl_3$- catalyzed cycloisomerization of ω-aryl-1-alkynes is described. The $GaCl_3$ catalyst has proven capable of cyclizing a variety of both 5-aryl-1-alkynes and 6-aryl-1-alkynes. Generally, the reactions were significantly improved with the $GaCl_3$ catalyst, compared with the previously reported catalytic system.[6] We are currently in the process of developing

Scheme 1. A Plausible Mechanism



reactions which are initiated by the electrophilic activation of C−C unsaturated bonds in the presence of a $GaCl_3$ catalyst.

Experimental Section

Materials. Toluene and methylcyclohexane were distilled over CaH_2. $GaCl_3$, purchased from Wako Pure Chemical Industries, Ltd, at a concentration of 1 M in methylcyclohexane was used as the catalyst.

Typical Procedure for $GaCl_3$-Catalyzed Cycloisomerization of ω-Aryl-1-Alkynes: 4-Methyl-2,2(1*H*)-Naphthalenedicarboxylic Acid Diethyl Ester (2). To a solution of (phenylmethyl)-2-propynylpropanedioic acid diethyl ester (**1**) (288.6 mg, 1.00 mmol) in toluene (5 mL) at 80 °C was added $GaCl_3$ (1.0 M in methylcyclohexane, 0.1 mL, 0.1 mmol) in one portion. After stirring at 80 °C for 10 h, sat. $NaHCO_3$ (5 mL) was added and the resulting mixture was extracted with Et_2O (10 mL × 3). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was subjected to flash column chromatography on silica gel (hexane/EtOAc = 5/1, R_f = 0.31) to afford 226 mg of 4-methyl-2,2(1*H*)-naphthalenedicarboxylic acid diethyl ester (**2**) (78%).

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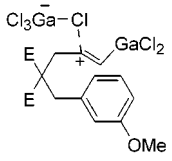
(11) Quite recently, Yamamoto Y. reported the $HfCl_4$-catalyzed cyclization of ω-(2-trimethylsilylaryl)-1-alkynes. Asao, N.; Shimada, T.; Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 10899.

(12) Shirakawa et al. suggested that a path involving the open-type vinyl cation species formed by alkynes with $In(OTf)_3$ exists in the intermolecular addition of alkynes to arenes in the presence of Lewis acid catalysts. See ref 5.

(13) An ion-paired cationic intermediate **20c** is also an alternative species. Yamaguchi et al. proposed that the vinyl cation species should be stabilized in the presence of $GaCl_3$. See: refs 3f and 3g.



20c

(14) For the $AuCl_3$-catalyzed cycloisomerization of ω-furyl-1-alkynes, see: Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553.