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$GaCl_3$-Catalyzed Formation of Eight-Membered Rings from Enynes Bearing a Cyclic Olefin

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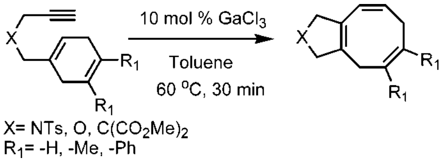
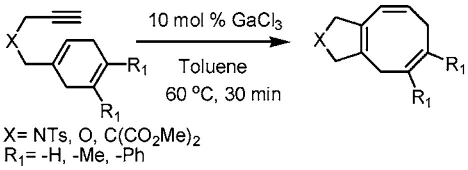
ABSTRACT



$GaCl_3$-catalyzed cycloisomerization of enynes having a cyclic olefin led to isolation of eight-membered ring compounds.

The development of organometallic transformations[1] offers exciting opportunities for the rapid access to structurally complex targets. Ring synthesis through modular, complexity-building reactions in a catalytic manner is a tremendous challenge.[2] Recently, many research groups have demonstrated that treatment of enynes bearing an olefinic cycle with a catalytic amount of Pd,[3] Pt,[4] Ga,[5] and Fe[6] complexes leads to a cycloisomerized reaction product. In some cases,[3−5] a highly strained cyclobutene was proposed as a key intermediate in the process. Depending upon the circumstances, liberation of metal from the butene intermediate will lead to the formation of bicyclic compounds. For example, six-, seven-, and ten-membered bicyclic compounds have been generated. We are not aware, however, of any precedent of cyclobutene intermediates generating eight-membered ring compounds from the reaction. Many strategies toward cyclooctanoids have been developed in the context of specific targets, but their generality, operational simplicity, and regio- and stereocontrol elements still remain to be fully delineated.[7] In this Communication, we establish that gallium chloride ($GaCl_3$) catalyzes a novel cycloisomerization of enynes having an olefinic cycle to generate eight-membered ring compounds (eq 1). Our recent investigation on the gold(I)-catalyzed cycloisomerization of enynes showed that the introduction of an olefinic group to the enyne substrates dramatically increased the yield.[8]



(eq 1)

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(1) For selected reviews, see: (a) Dyker, G., Ed. *Handbook of C−H Transformations*; Wiley-VCH: Weinheim, 2005. (b) Evans, P. A., Ed. *Modern Rhodium-Catalyzed Organic Reactions*; Wiley-VCH: Weinheim, 2005. (c) Tamaru, Y., Ed. *Modern Organonickel Chemistry*; Wiley-VCH: Weinheim, 2005. (d) Shibasaki, M.; Yamamoto, Y., Ed. *Multimetallic Catalysts in Organic Synthesis*; Wiley-VCH: Weinheim, 2004.

(2) For selective reviews, see: (a) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001−1020. (b) McManus, H. A.; Guiry, P. J. *Chem. Rev.* **2004**, *104*, 4151−4202. (c) Skda-Foldes, R.; Kollar, L. *Chem. Rev.* **2003**, *103*, 4095−4130. (d) Widenhoefer, R. A. *Acc. Chem. Res.* **2002**, *35*, 905−913. (e) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813−834. (f) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29. (g) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467−473. (h) Malacria, M. *Chem. Rev.* **1996**, *96*, 289−306. (i) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49−92.

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(4) (a) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2001**, *123*, 6785−6786. (b) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863−11869.

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(7) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881−930.

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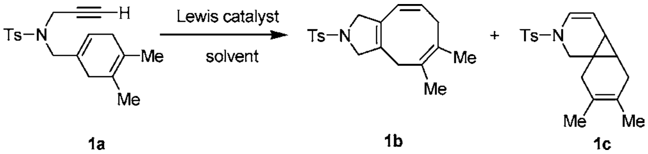
Thus, we chose enynes bearing a cyclic olefin as substrates for our study and screened Lewis acids such as [Au(PPh$_3$)]-OTf, PtCl$_2$,[4] FeCl$_3$,[6] and GaCl$_3$[5] (Table 1).

Table 1. Various Lewis Acid Catalyzed Metatheses[a]

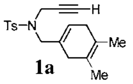
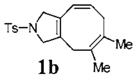
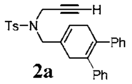
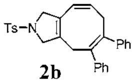
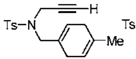
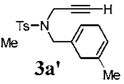
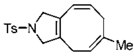
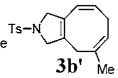
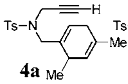
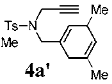
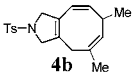
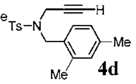
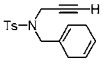
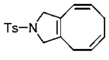
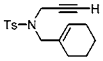
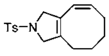
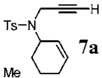
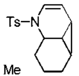
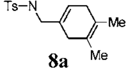
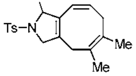
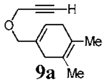
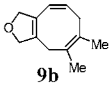
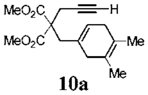
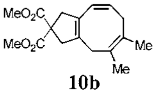
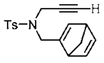
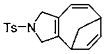
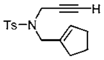
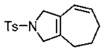


1a **1b** **1c**

entry	catalyst	solvent	temp (°C)	time	yield (%)[b] 1b	1c
1	5 mol % of AuCl(PPh$_3$)/AgOTf	CH$_2$Cl$_2$	15~20	1 h	–	30
2	5 mol % of PtCl$_2$	toluene	80	6 h	–	39
3	5 mol % of FeCl$_3$	toluene	90	24 h	12	10
4	10 mol % of GaCl$_3$	toluene	60	30 min	91	–

[a] 0.5 mmol of **1a** (0.165 g) in 3 mL of toluene was used. [b] Isolated yield. [c] 5 mL of Et$_2$NH was used.

Table 2. GaCl$_3$-Catalyzed Ring-Opening Metathesis of Cyclic Enyne to an Eight-Membered Ring[a]

entry	reactant	product	yield (%)[b]
1	 **1a**	 **1b**	91
2	 **2a**	 **2b**	63
3	 **3a**  **3a'**	 **3b**  **3b'**	69(46/23)
4[c]	 **4a**  **4a'**	 **4b**  **4d**	93(79/14)
5	 **5a**	 **5b**	75
6	 **6a**	 **6b**	39[c]
7	 **7a**	 **7b**	12[d]
8	 **8a**	 **8b**	16
9	 **9a**	 **9b**	88
10	 **10a**	 **10b**	33[e]
11	 **11a**	 **11b**	19
12	 **12a**	 **12b**	76

[a] 0.5 mmol of enyne in 3 mL of toluene was used. [b] Isolated yield. [c] 14% of reactant was recovered. [d] 72% of reactant was recovered. [e] The reaction was run at 0 °C.

When the gold compound was used as a catalyst, a cyclopropanated compound was obtained in 30% yield with the concomitant formation of polymerized compounds. When PtCl$_2$ was used as a catalyst, a cyclopropanated compound (39%) with an unidentifiable compound was obtained. Use of FeCl$_3$ as a catalyst gave a mixture of a cyclopropanated and an eight-membered compound in 10% and 13% yields, respectively, with 57% recovery of the reactant. However, fortunately, treatment of enyne with GaCl$_3$ afforded an eight-membered ring compound in 91% yield. Formation of eight-membered ring compounds was confirmed by an X-ray diffraction study of one of the reaction products.[9] The reaction provides a simple and rapid synthesis of eight-membered rings.

Encouraged by this result, we investigated the GaCl$_3$-catalyzed cycloisomerization of various enynes bearing a cyclic olefin (Table 2). Enynes bearing a cyclic diene with an NTs tether group (entries 1−5) were quite viable substrates for the cycloisomerization. In entry 3, a mixture of two isomers in a ratio of 2:1 was used as a substrate and the same ratio of two isomeric products was obtained. However, in the case of entry 4, one of the isomers was completely aromatized. Compared to the substrates with a cyclic diene, an enyne with a cyclic monoene with an NTs tether group (entry 6) is inferior. Interestingly, an enyne with no spacer between an N atom and cyclohexene (entry 7) did not give the expected product.

Instead, a cyclopropanated compound was obtained in 12% yield with 72% recovery of the reactant. When an alkyl group was introduced at the carbon atom between an alkyne and a nitrogen atom (entry 8), the yield was poor presumably due to the steric congestion. An enyne having oxygen in a tether (entry 9) was found to serve as a good substrate. When the tether atom was carbon (entry 10), the reaction at 0 °C went to completion within 10 min. However, the yield was poor (33%). Interestingly, the lowering of the reaction temperature or the lengthening of the reaction time did not improve the reaction yield. When the reaction was conducted at −15 °C, 29% of the reaction product was obtained with recovery of the same amount (29%) of the reactant. Interestingly, no reaction was observed at 80 °C for an enyne having a nobornadienyl group (entry 11). However, when the reaction temperature increased to 100 °C, a seven-membered compound was obtained in 19% yield. Furthermore, a substrate with a cyclopentene moiety gave a seven-membered compound in 76% yield (entry 12). Thus, the methodology

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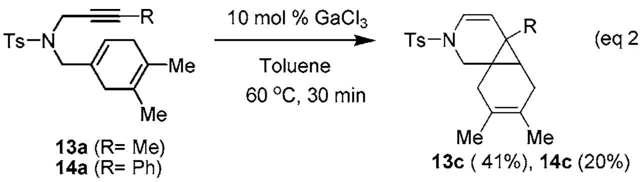
(8) Lee, S. I.; Kim, S. M.; Choi, M. R.; Kim, S. Y.; Chung, Y. K.; Han, W.-S.; Kang, S. O. *J. Org. Chem.* **2006**, in press.

(9) See the Supporting Information: Crystal data for **1b**: $C_{19}H_{23}S_1O_2N_1$, MW = 329.46, triclinic, space group *P*-1, $a = 5.0300(4)$ Å, $b = 12.3658(9)$ Å, $c = 14.0720(10)$ Å, $\alpha = 102.516(1)°$, $\beta = 95.968(1)°$, $\gamma = 95.375(1)°$, $V = 843.74(3)$ Å^3, $Z = 2$, final R indices [$I > 2\sigma(I)$], $R_1 = 0.0236$, w$R_2 = 0.0339$. CCDC reference number: 614687.

developed in this study can be extended to a synthesis of seven-membered ring compounds. We also investigated the cycloisomerization of enynes with an internal alkyne (eq 2).



(eq 2)

However, the well-known cyclopropanated compound was isolated in low yields.

To gain some insight on the reaction mechanism, the following substrates were tested (Figure 1).

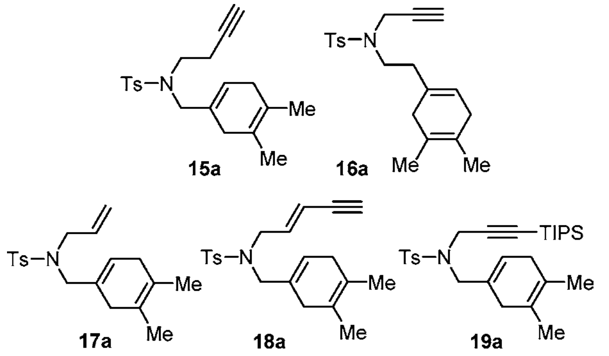


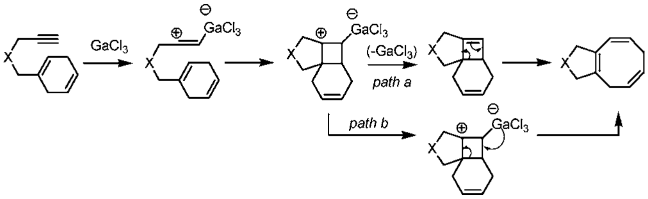
Figure 1. Different types of cyclic enynes tested for $GaCl_3$-catalyzed ring-opening metathesis.

When a substrate (**15a**, **16a**) expecting a 6.6.4-tricyclic intermediate was reacted, a ring-opened product was not obtained. Moreover, the increase of the reaction time led to decomposition. Other cyclic enynes such as **17a**, **18a**, and **19a** were also reacted. However, in those cases, no reaction proceeded.

Many research groups reported[10] the formation of 8.6.4- and/or 6.6.4-tricycles and their attempts to open the cyclobutene ring. However, their endeavor was unsuccessful. On the contrary, a transformation of an 8.5.4-tricyclic intermediate to a 10.5-bicyclic compound was reported by Fürstner and Szillat[4b] and a transformation of a 6.5.4-tricyclic compound to an 8.5-bicyclic compound were reported by Paquette and Wang.[11] Thus, the ring opening seemed to be highly dependent upon the fused rings and there should be substantial ring strain for a ring to be opened during the reaction. In our study, the substrates in Table 2 were designed to give a 6.5.4-tricyclic intermediate, eventually resulting in an eight-membered ring compound.

As already mentioned, the $GaCl_3$-catalyzed cycloisomerization of enynes has been reported by Chatani's group.[5] They also proposed a plausible reaction mechanism. We expected that the formation of an eight-membered ring would follow a mechanism similar to that suggested by Chatani's group except in the ring opening (Scheme 1).

Scheme 1



In conclusion, we have demonstrated that the $GaCl_3$-catalyzed reactions of enynes bearing an olefinic cycle represent a versatile new catalytic method for the synthesis of bicyclic eight-membered ring compounds. The reaction is highly sensitive to the distance between a tether atom and an olefinic cycle and between a tether atom and an alkyne moiety, and an olefinic cycle with a diene is more favorable than that with a monoene. This method compares favorably with other approaches to the construction of this important family of compounds. Additional synthetic investigations of this ring-forming process are underway.

Acknowledgment. This work was supported by the Korea Research Foundation Grant funded by the Korean Government (MOEHRD) (R02-2004-000−10005-0) and the Korea Science and Engineering Foundation (KOSEF) through the SRC/ERC Program of MOST/KOSEF (R11-2005-065).

Supporting Information Available: Procedures, spectral data for new compounds, and details for the crystal structure of **1b**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061801V

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(10) (a) Trost, B. M.; Yani, M.; Hoogsteen, K. *J. Am. Chem. Soc.* **1993**, *115*, 5294−5295. (b) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6146−6148.

(11) Wang, T.-Z.; Paquette, L. A. *J. Org. Chem.* **1986**, *51*, 5232−5234.