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Cyclization of 1,6-Enynes with Allylic Chromate Species

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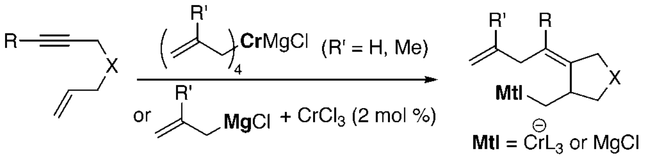
ABSTRACT

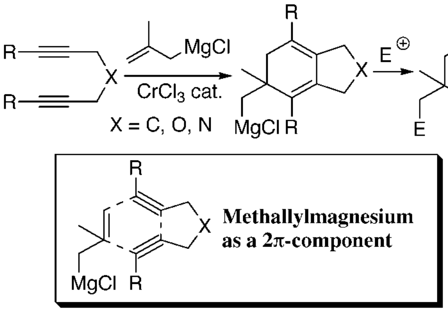


Treatment of 1,6-enynes with tetramethallylchromate induces a cyclization reaction with concurrent introduction of a methallyl group. A catalytic amount of $CrCl_3$ combined with methallylmagnesium chloride also achieves this cyclization process. The resultant cyclic organometallic species undergo further functionalization upon reaction with electrophiles.

The Nozaki−Hiyama−Kishi reaction, which exploits organochromium species, has been regarded as a key tool for the carbon−carbon bond-forming step in the field of total synthesis.[1] Organochromium reagents undergo facile addition reactions toward carbonyl compounds.[2] However, they do not usually react efficiently with a carbon−carbon multiple bond. Carbometalation with organochromium species has been scarcely investigated.[3] We have recently reported a $CrCl_3$-catalyzed [2 + 2 + 2] annulation reaction of 1,6-diynes with methallylmagnesium chloride, the reaction in which the methallyl group acts as a two-carbon component (Scheme 1).[4] Here we wish to describe an efficient cyclization of 1,6-enynes via sequential carbometalation, the cyclization for the synthesis of a variety of heterocyclic compounds. The resulting cyclic compound has a reactive carbon−metal bond that can be used for further elaboration.

Methallylchromate was easily prepared by mixing $CrCl_3$ and methallylmagnesium chloride[5] in a 1:4 molar ratio.[6] To the resulting dark-red solution was added allyl non-2-yn-1-yl ether (**1a**) in THF and the mixture was stirred for 6 h at 0 °C. Aqueous workup afforded alkylidenetetrahydrofuran **3a** in 90% yield (Scheme 2). An addition of DCl/D_2O before quenching the reaction mixture afforded the labeled product with 90% deuterium incorporation at the methyl group. This result clearly indicates the existence of organochromate species **2a** as an intermediate.[7] It proved to be crucial to employ the ate-type chromium reagent[8] for successful cyclization. Trimethallylchromium afforded the desired

Scheme 1



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[1] (a) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991. (b) Saccomano, N. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 1, Chapter 1.6, p 173. (c) Takai, K. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; p 1266.

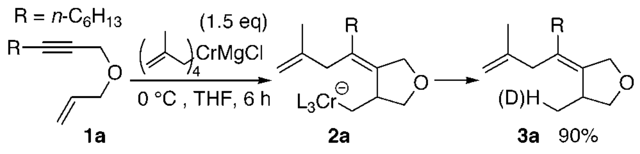
[2] (a) Kauffmann, T.; Hamsen, A.; Beirich, C. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 144. (b) Kauffmann, T.; Möller, T.; Rennefeld, H.; Welke, S.; Wieschollek, R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 348.

[3] Addition of diallylchromium phosphine complex toward alkynes was reported, see: Betz, P.; Jolly, P. W.; Krüger, C.; Zakrzewski, U. *Organometallics* **1991**, *10*, 3520.

[4] Nishikawa, T.; Kakiya, T.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 4629.

10.1021/ol026362o CCC: $22.00

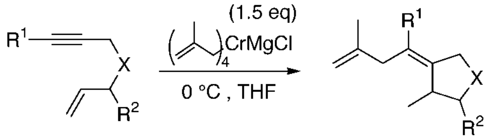
Scheme 2

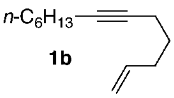
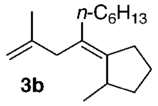
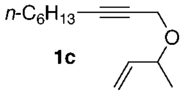
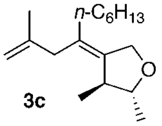
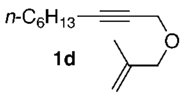
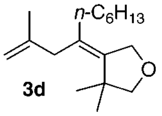
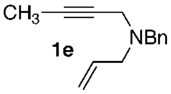
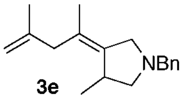
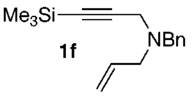
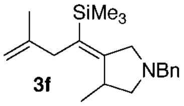
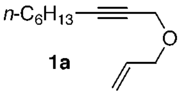
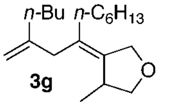


product **3a** in only 12% along with recovered starting enyne **1a** (72%).

The cyclization of various 1,6-enynes **1** with tetramethallylchromate is summarized in Table 1. The reaction of 1,6-enynes **1** with the chromate reagent provided the desired products **3** in good to excellent yields. Both oxygen- and nitrogen-tethered enynes **1c**−**f** were good substrates for this chromate-mediated reaction to furnish tetrahydrofurans and pyrrolidines easily (entry 2−5). The reaction of **1c** provided **3c** as a single diastereomer (entry 2). The use of 2-butylprop-2-en-1-ylchromate also afforded the expected cyclized product **3g** (entry 6).

Table 1. Methallylchromate-Induced Cyclization of Enynes[a]



entry	enyne	time (h)	product	yield (%)
1	 **1b**	4.5	 **3b**	75
2	 **1c**	4.5	 **3c**	81[b]
3	 **1d**	4.5	 **3d**	91
4	 **1e**	9	 **3e**	67
5[c]	 **1f**	5	 **3f**	73
6[d]	 **1a**	4.5	 **3g**	70

[a] Enyne (1.0 mmol), chromate (1.5 mmol), THF (5 mL), 0 °C. [b] The stereochemistry of **3c** was determined on the basis of NOE experiments. [c] Room temperature. [d] Tetra(2-butylprop-2-en-1-yl)chromate was employed.

We then devoted our effort to reduce the amount of chromium chloride. The catalytic reaction did not go to completion when **1a** was treated with a mixture of $CrCl_3$ (20 mol %) and methallylmagnesium chloride (4.0 equiv) at 0 °C. To our delight, however, the reaction proceeded smoothly at elevated temperature. An addition of **1a** to a solution of methallylmagnesium chloride (1.5 equiv) with 2.0 mol % of $CrCl_3$ in THF at 40 °C afforded **3a** in 80% yield (Table 2, entry 1). The results with a variety of 1,6-enynes are summarized in Table 2.

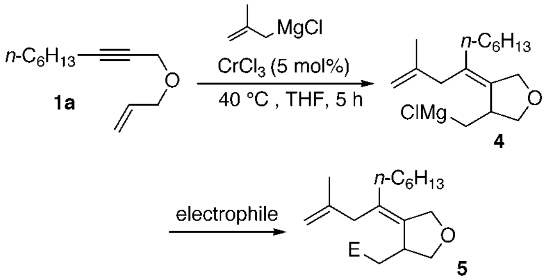
Table 2. $CrCl_3$-Catalyzed Cyclization of Enynes[a]

entry	enyne	product	$CrCl_3$ (mol %)	yield (%)
1	**1a**	**3a**	2.0	80
2[b]	**1c**	**3c**	10	78
3	**1d**	**3d**	2.0	60
4	**1e**	**3e**	2.0	71
5[b]	**1f**	**3f**	10	88

[a] Enyne (1.0 mmol), methallylmagnesium chloride (1.5 mmol), THF (5 mL), 40 °C, 6−6.5 h. [b] Methallylmagnesium chloride (3.0 mmol).

The cyclic magnesium species **4** undergoes further functionalization upon reaction with various electrophiles (Scheme 3). As for trapping with allyl bromide or acetyl chloride, the addition of CuCN·2LiCl (20 mol %) improved the yields of the coupling products **5c** and **5d**.[9]

Scheme 3



PhCHO	**5a**	84%
I_2	**5b**	82%
CH_3COCl	**5c**	87%*
CH_2=$CHCH_2Br$	**5d**	82%*

*cat. CuCN•2LiCl (20 mol%)

The use of allylmagnesium chloride instead of a methallyl Grignard reagent provided quite disappointing results. Although the starting material **1e** was consumed, none of the cyclization product was obtained under the same reaction conditions. After several trials, we found that an addition of pyridine as a cosolvent to the reaction system induced the ring formation to furnish **6** (Scheme 4).

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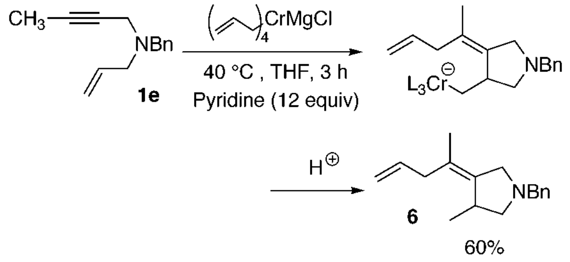
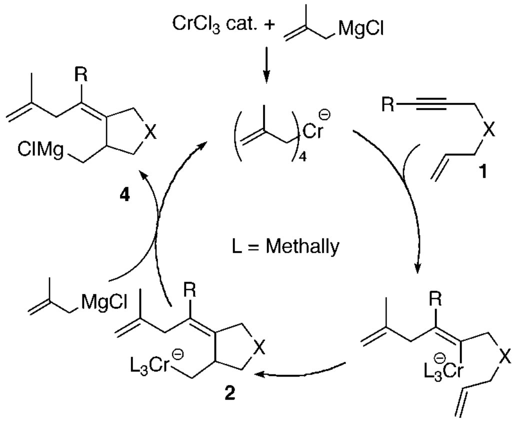
(5) Allylic Grignard reagents in THF are easily prepared according to the reported procedure. Lipshutz, B. H.; Hackmann, C. *J. Org. Chem.* **1994**, *59*, 7437.

Scheme 4



Scheme 5



We propose a plausible catalytic cycle involving a sequential carbometalation as depicted in Scheme 5. The allylchromation of the carbon−carbon triple bond triggers the cyclization to yield alkylchromate **2**. Ligand exchange of **2** from the cyclic alkyl to the methallyl ligand furnishes the cyclic magnesium compound **4** and regenerates tetramethallylchromate.

In conclusion, we have developed the chromate-induced cyclization of 1,6-enynes. Moreover, the cyclization is accomplished by the use of catalytic $CrCl_3$. The resultant cyclic magnesium compound can be utilized for the subsequent reaction. Further investigation on carbomatalation with chromium ate complex reagents is currently under way in our group.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research on Priority Area (No. 412: Exploitation of Multi-Element Cyclic Molecules) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Supporting Information Available: Experimental procedures and compound data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) The use of THF-soluble $CrCl_3(thf)_3$ afforded almost the same result as $CrCl_3$, although $CrCl_3$ is sparingly soluble in THF. $CrCl_3$ was dissolved in THF upon treatment with Grignard reagents.

(7) Protonation of alkylchromium species is normally inefficient. This fact suggests that **2a** is an ate complex type species.

(8) (a) Hojo, M.; Sakuragi, R.; Okabe, S.; Hosomi, A. *Chem. Commun.* **2001**, 357. (b) Hojo, M.; Sakata, K.; Ushioda, N.; Watanabe, T.; Hosomi, A. *Organometallics* **2001**, *20*, 5014. (c) Hojo, M.; Sakata, K.; Maimaiti, X.; Ueno, J.; Nishikori, H.; Hosomi, A. *Chem. Lett.* **2002**, 142.

(9) **General procedure**: The catalytic cyclization and trapping with allyl bromide is representative. A solution of methallylmagnesium chloride (2.25 mL, 0.89 M THF solution, 2.0 mmol) was added to a THF solution of $CrCl_3$ (4.0 mg, 0.025 mmol) at 0 °C. After the solution was stirred for 20 min, **1a** (90 mg, 0.5 mmol) was introduced and the mixture was stirred for 5 h at 40 °C. The reaction mixture was then cooled to 0 °C. To the mixture were added allyl bromide (2.25 mmol) and CuCN•2LiCl (0.1 mmol). After being stirred for another 45 min, the mixture was poured into 1 M HCl and extracted with ether. The organic layers were dried and concentrated. Purification by chromatography afforded **5d** (121 mg, 0.41 mmol) in 82% yield.