

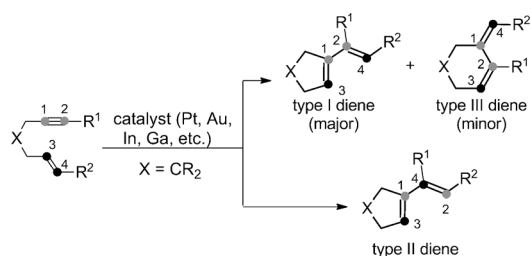
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Using the Type II Cycloisomerization Reaction of 1,6-Enynes as a Mechanistic Probe to Identify the Real Catalytic Species of GaX₃ and InX₃

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Abstract: Previously, we found that InCl₂⁺ is the real catalytic species in InCl₃-catalyzed type II cycloisomerization of 1,6-enynes for generating nonconjugated dienes. We further used this cycloisomerization reaction as a mechanistic probe to study whether GaCl₃, GaBr₃, InBr₃, InI₃ also have GaCl₂⁺, GaBr₂⁺, InBr₂⁺, and InI₂⁺ as the real catalytic species. Experimental and computational results from the mechanistic probe reaction here support that the real catalytic species are positively charged GaCl₂⁺, GaBr₂⁺, InBr₂⁺, and InI₂⁺.

The Lewis acids of group IIIA metals,^[1,2] including B(III),^[1] Al(III),^[2] Ga(III)^[2-4] and In(III),^[2,5] have been widely used as catalysts in synthesis. However, knowledge of the real catalytic species of these precatalysts is limited but is important for understanding and designing reactions. To date, several significant advances in the in-depth understanding of these group IIIA metals have been made. For example, it was found that Me₂AlCl has Me₂Al⁺ as the catalytic species in the Diels–Alder reaction and Petasis–Ferrier rearrangements.^[6] Transition-metal-catalyzed type I, II, and III cycloisomerizations of 1,6-enynes have been developed for the synthesis of dienes (Scheme 1).^[7] InCl₃ and

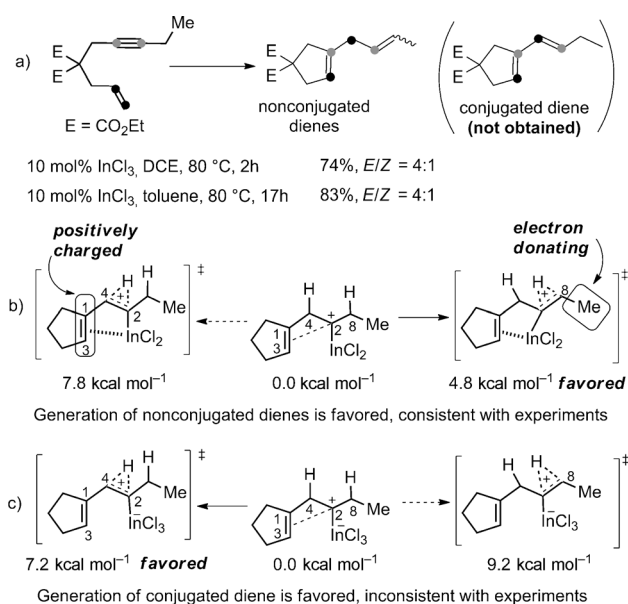


Scheme 1. Type I-III cycloisomerization of 1,6-enynes.

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GaCl₃ can also be used as catalysts for these cycloisomerizations. Recently, we found that InCl₂⁺ is the real catalytic species in InCl₃-catalyzed type II cycloisomerization of 1,6-enynes (Scheme 2a).^[8,9] Our DFT calculations found that,



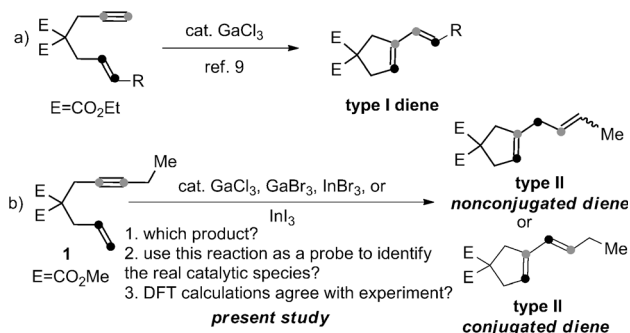
Scheme 2. Experimental and computational results of InCl₃-catalyzed type II cycloisomerization of 1,6-enynes.^[8] DCE = 1,2-dichloroethane.

using InCl₃ or its dimer as catalyst, the reaction would give conjugated type II dienes instead of the experimentally obtained nonconjugated diene (Scheme 2c).^[8] Based on experimental results that shown InCl₃ can dissociate into InCl₂⁺ and InCl₄⁻, we hypothesized that InCl₂⁺ was the real catalyst in the InCl₃-catalyzed cycloisomerization (Scheme 2b). This hypothesis was further supported by DFT calculations.

The main reason for generating the nonconjugated diene is the coordination of InCl₂⁺ to the alkene moiety in the transition states, which induces positive charge in the C1=C3 bond and makes the [1,2]-H shifts from the allylic position to generate conjugated diene disfavored. In contrast, the nonconjugated [1,2]-H shifts from the ordinary hydrogen atoms at the C8 position is further stabilized by the methyl group when InCl₂⁺ is the catalyst. If InCl₃ was the real catalyst, the C1=C3 bond would not coordinate to In, which is already saturated in terms of coordination. Consequently, [1,2]-H shifts from the allylic hydrogen atom

at the C4 position are favored over the [1,2]-H shifts from hydrogen atoms in the ordinary C8 position. This can be understood in terms of the weaker allylic C–H bond (in propene) compared with common sp^3 C–H bonds (in propane), 78.4 vs. 100.1 kcal mol⁻¹.^[10] The discovery of $InCl_2^+$ as the real catalyst is helpful for understanding the present cycloisomerization of 1,6-enynes and other $In(III)$,^[11a–c] $Al(III)$ ^[6d] and $Bi(III)$ ^[11d] catalyzed reactions as well.

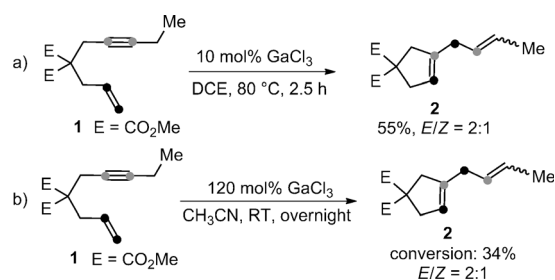
Herein, we propose that we can use the type II cycloisomerization of **1** as a reaction probe to identify whether the real catalytic species of other group IIIA metals are neutral or positively charged by checking the reaction products: formation of nonconjugated dienes implies that the catalysts could have their positively charged species as the real catalysts (Scheme 3). Chatani and co-workers found that



Scheme 3. $GaCl_3$ -catalyzed type I cycloisomerization from Miyahana and Chatani and the present investigation.

$GaCl_3$ can catalyze the type I cycloisomerization of 1,6-enynes (Scheme 3a).^[12] However, all substrates they studied did not contain a substituent in the alkyne moiety. We wondered if the $GaCl_3$ -catalyzed cycloisomerization of **1** would give either conjugated or nonconjugated type II dienes (Scheme 3b). If nonconjugated dienes are generated, this suggests that $GaCl_2^+$ could be the real catalyst. If conjugated dienes are generated, $GaCl_3$ or $(GaCl_3)_2$ could be the catalyst. Once we obtained experimental results, we used calculations to find whether the DFT results match experiments or not. With these studies together, we could then know the real catalytic species of $GaCl_3$ in the cycloisomerization reaction. We also studied whether other GaX_3 and InX_3 have their cationic species as the real catalysts by using this reaction as the mechanistic probe.

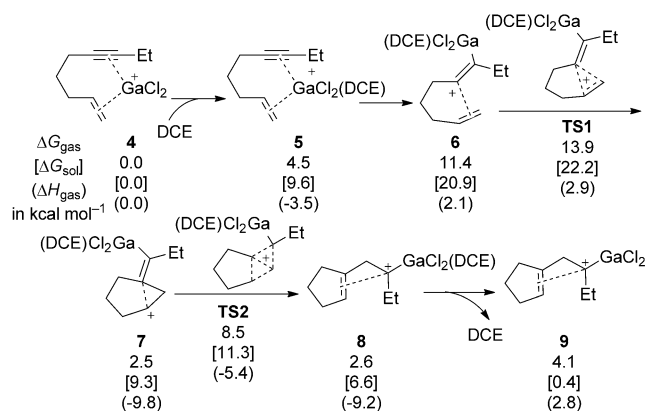
We carried out the $GaCl_3$ -catalyzed cycloisomerization of **1** in DCE (Scheme 4). We found that nonconjugated type II dienes **2** were generated with $E/Z=2:1$, similar to the result from the reaction catalyzed by $InCl_3$.^[8,9] This suggests that $GaCl_2^+$ could be the real catalyst. Cho found that $GaCl_3$ in CH_3CN dissociates into a mixture of the cation $(CH_3CN)_4GaCl_2^+$ together with some other cations with different coordinating ligands to Ga, and the anion $GaCl_4^-$.^[13] It was also found that ligands can facilitate $GaCl_3$ dissociation.^[14] To get further evidence of $GaCl_2^+$ as the catalytic species, a stoichiometric cycloisomerization re-



Scheme 4. $GaCl_3$ -catalyzed cycloisomerization of **1** in DCE and CH_3CN . The E/Z ratio and the conversion were determined by NMR spectroscopy and GC, respectively.

action of **1** catalyzed by $GaCl_3$ (120 mol %) was carried out in CH_3CN solution at room temperature. In this case, nonconjugated product **2** was detected by gas chromatography with $E/Z=2:1$ (Scheme 4).^[15] With these experimental results, we then wanted to test whether DFT calculations also support the hypothesis that $GaCl_2^+$ is the catalytic species.

DFT calculations using the B3LYP functional^[16,17] (for details, see Supporting Information) in the gas phase and DCE solution supported that $GaCl_2^+$ is the real catalyst but not $GaCl_3$ or its dimer. Similar to the type II cycloisomerization of enyne catalyzed by $InCl_2^+$,⁸ the present reaction also includes cyclopropanation, homoallylic rearrangement (Scheme 5), and [1,2]-H shifts (Figure 1). The cyclopropanation (via **TS1**, 13.9 kcal mol⁻¹) and homoallylic rearrangement (via **TS2**, 8.5 kcal mol⁻¹) shown in Scheme 5 are



Scheme 5. The cyclopropanation and homoallylic rearrangement processes leading to homoallylic cation **9**.

easy. These reactions transform the $GaCl_2^+$ -1,6-enyne complex **4** into a homoallylic cation, the intermediate **9**, which is the precursor for the following [1,2]-H-shift processes to give either conjugated or nonconjugated type II dienes.

The generation of **E-10** via **TS_{trans-c}**^[18] from **9** requires an activation free energy of 9.2 kcal mol⁻¹ whereas the generation of **Z-10** requires an activation free energy of 9.8 kcal mol⁻¹ (**TS_{cis-}**), which suggests that a mixture of *E* and *Z* products is produced and the *E* isomer is the major one (Figure 2). **TS_a** leading to the conjugated diene product is disfavored in terms of Gibbs free energy by 3.2 kcal mol⁻¹

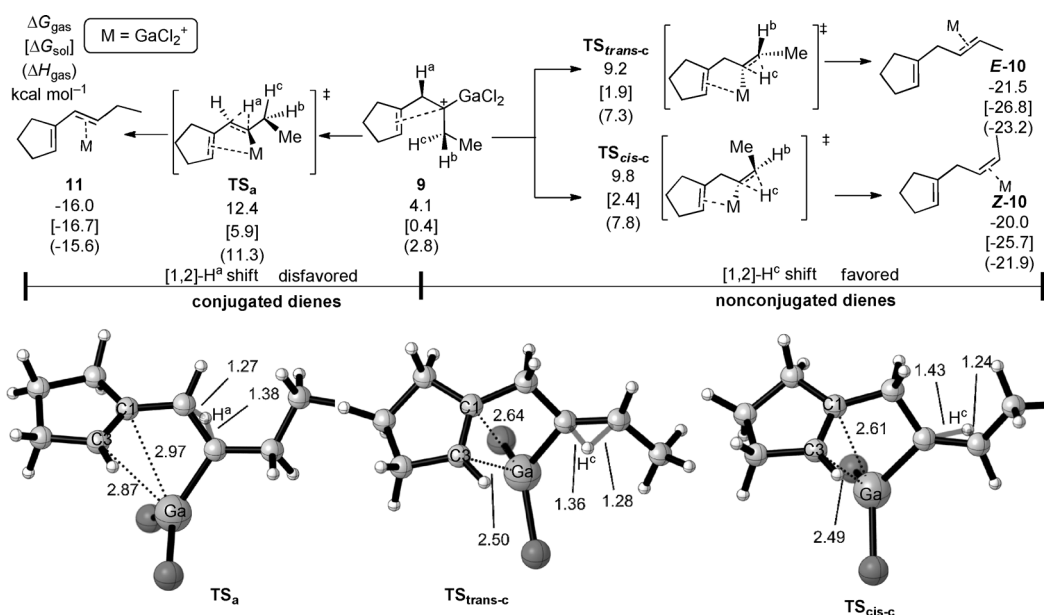


Figure 1. The competitive [1,2]-H shifts leading to nonconjugated dienes (favored) and nonconjugated dienes (distances in Å). The energies are relative to 4 shown in Scheme 5.

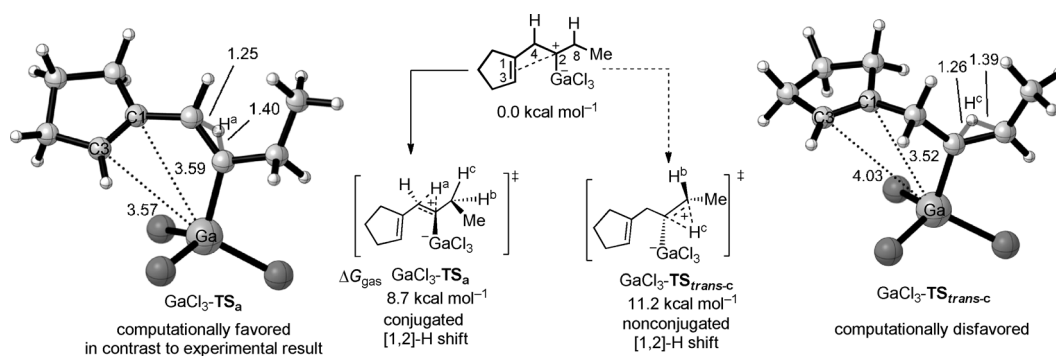


Figure 2. Relative energies and structures of [1,2]-H shifts using $GaCl_3$ as the possible catalytic species (distances in Å).

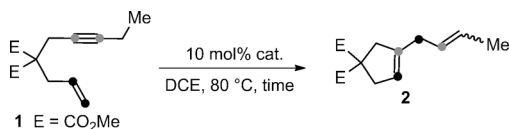
over $TS_{trans-c}$, which indicates that no conjugated diene can be formed. These results agree with the experiments in Scheme 4. The preference for nonconjugated over conjugated [1,2]-H shift can be understood in terms of $GaCl_2^+$ coordination to the alkene moiety (C1=C3) in the conjugated [1,2]-H shift transition state (TS_a), as suggested by the short distances of Ga-C1 (2.93 Å) and Ga-C3 (2.87 Å). This Ga coordination disfavors the [1,2]-H shift from the allylic hydrogen atom of the positively charged C1=C3 bond. In contrast, the methyl group as an electron-donating group can stabilize both $TS_{trans-c}$ and TS_{cis-c} . Also, the nonconjugated [1,2]-H shift is more exothermic than the conjugated [1,2]-H shift pathway, and this is another reason for the preference of the former over the latter.^[8a]

We calculated the regiochemistry with $GaCl_3$ as the possible catalyst (Figure 2) and found that the conjugated H-shift ($GaCl_3-TS_a$) is favored by 3.5 kcal mol⁻¹ over the *trans*-nonconjugated [1,2]-H shift transition state ($GaCl_3-TS_{trans-c}$). This is in contrast to the experimental results

given in Scheme 4, where only the nonconjugated dienes were obtained. Therefore, we can rule out the possibility that $GaCl_3$ acts as the real catalytic species (the dimer species ($GaCl_3$)₂ can also be ruled out, see the Supporting Information). The favored conjugated [1,2]-H shift in this case is that, in the transition state $GaCl_3-TS_a$, the Ga is saturatedly coordinated and there is no coordination of C1=C3 to the Ga atom. Consequently the more weakly bound allylic hydrogen atom is easier to migrate than the hydrogen atom connected to the sp³ carbon. This is similar to our previous understanding of type II cycloisomerizations catalyzed by $InCl_3$.^[8]

After establishing the use of type II cycloisomerization of 1 as the mechanistic probe for identifying the real catalytic species, we wanted to use this to identify whether $InBr_3$ and InI_3 have their cationic species as the real catalysts (Table 1). Previously, we found that InI_3 -catalyzed cycloisomerization of 1 gave 2 in 75% yield.^[8a] When $InBr_3$ or $GaBr_3$ were used as the catalyst, type II nonconjugated

Table 1. GaBr₃-, InBr₃-, and InI₃-catalyzed cycloisomerization of **1** in DCE.

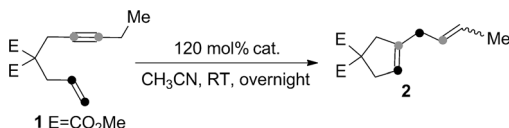


Catalyst	Time [h]	Yield [%]	<i>E/Z</i> ^[a]
InI ₃	2.0	75	3:1
InBr ₃	2.5	66	3:1
GaBr ₃	2.5	56	2:1

[a] Determined by NMR spectroscopy.

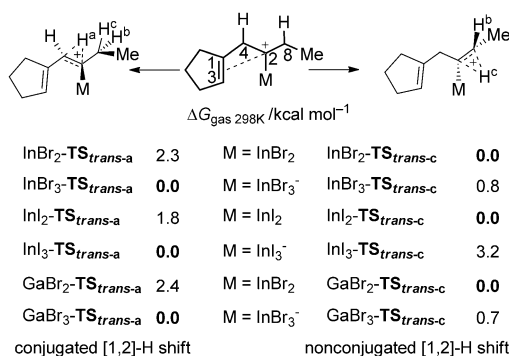
dienes **2** were also obtained, in 66 % and 56 % yield, respectively. The stoichiometric cycloisomerization reactions of **1** carried out in CH₃CN with InI₃, InBr₃, or GaBr₃ also gave the nonconjugated products (Table 2).^[15] The results of the DFT calculations in Scheme 6 show that InBr₂⁺, InI₂⁺, or GaBr₂⁺ as the real catalytic species give the correct regiochemistry as obtained experimentally, that is, all the nonconjugated H-shift transition states are more favored than the conjugated H-shift transition states. On the other hand, calculations using monomeric neutral catalysts InI₃, InBr₃, or GaBr₃ gave the wrong regiochemistry. Based on the experimental and DFT calculation results, we conclude that InBr₂⁺, InI₂⁺, and GaBr₂⁺ are the real catalytic species in InBr₃- and InI₃-catalyzed cycloisomerization of 1,6-enynes. This suggests that other InBr₃, InI₃, and GaBr₃

Table 2. GaBr₃-, InBr₃-, and InI₃-catalyzed cycloisomerization of **1** in CH₃CN.



Catalyst	Conversion [%] ^[a]	<i>E/Z</i> ^[a]
InI ₃	75	3:1
InBr ₃	66	3:1
GaBr ₃	56	2:1

[a] Determined by GC.



Scheme 6. The competitive [1,2]-H shifts leading to conjugated dienes and nonconjugated dienes using neutral or cationic catalytic species.

catalyzed reactions could also have their cationic species as the real catalysts.

In summary, by using the cycloisomerization of 1,6-enynes as a mechanistic probe, our experimental and computational results revealed that the catalytic species in GaCl₃-, GaBr₃-, InBr₃-, and InI₃-catalyzed cycloisomerization of 1,6-enynes **1** have the cationic species GaCl₂⁺, GaBr₂⁺, InBr₂⁺, and InI₂⁺, respectively, as the real catalysts. This finding is important for understanding many GaX₃- (X = Cl or Br) and InX₃-catalyzed (X = Cl, Br, or I) reactions.

Experimental Section

GaCl₃-Catalyzed 1,6-Enyne Cycloisomerizations of **1** in DCE.

1,6-Enyne **1** (0.50 mmol, 129 mg) was added to a mixture of anhydrous DCE (2.5 mL) and GaCl₃ (10 mol%, 8.6 mg) under argon. The resulting mixture was stirred at 80 °C for an additional 1.5 h. The reaction was cooled to room temperature and the reaction mixture was directly concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluted with petroleum ether/ethyl acetate = 30:1–20:1) to give a mixture of diene products **2**; 71 mg, 55% yield. The ratio of diene products was determined by NMR (*E/Z* = 2:1). InI₃- (75% yield of **2**, *E/Z* = 3:1), InBr₃- (66% yield of **2**, *E/Z* = 3:1), and GaBr₃-catalyzed (56% yield of **2**, *E/Z* = 2:1) 1,6-enyne cycloisomerization of **1** in DCE were performed by a similar procedure.

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Keywords: cycloisomerization • dienes • 1,6-enynes • gallium • indium

- [1] H. Yamamoto, *Lewis Acids in Organic Synthesis*, Wiley-VCH, Weinheim, **2000**.
- [2] Y. Hisashi, O. Koichiro, *Main Group Metals in Organic Synthesis*, Wiley-VCH, Weinheim, **2004**.
- [3] For reviews on gallium(III)-catalyzed reactions, see: a) R. Amemiya, M. Yamaguchi, *Eur. J. Org. Chem.* **2005**, 5145; b) M. K. Gupta, T. P. O'Sullivan, *RSC Adv.* **2013**, *3*, 25498; c) G. K. S. Prakash, T. Mathew, G. A. Olah, *Acc. Chem. Res.* **2012**, *45*, 565.
- [4] For selected recent examples of gallium(III)-catalyzed reactions, see: a) X. Han, H. Li, R. P. Hughes, J. Wu, *Angew. Chem. Int. Ed.* **2012**, *51*, 10390; *Angew. Chem.* **2012**, *124*, 10536; b) W. Jiang, J. D. Gordon, C. R. Goldsmith, *Inorg. Chem.* **2012**, *51*, 2725; c) L. Li, G. Huang, Z. Chen, W. Liu, X. Wang, Y. Chen, L. Yang, W. Li, Y. Li, *Eur. J. Org. Chem.* **2012**, 5564; d) B. V. S. Reddy, B. Bramha Reddy, K. V. Raghavendra Rao, J. S. Yadav, *Tetrahedron Lett.* **2012**, *53*, 2500; e) J.-J. Liu, B. Higgins, G. Ju, K. Kolinsky, K.-C. Luk, K. Packman, G. Pizzolatto, Y. Ren, K. Thakkar, C. Tovar, Z. Zhang, P. M. Wovkulich, *ACS Med. Chem. Lett.* **2013**, *4*, 259.
- [5] For reviews on indium(III)-catalyzed reactions, see: a) J. S. Yadav, A. Antony, J. George, B. V. Subba Reddy, *Eur. J. Org. Chem.* **2010**, 591; b) T. P. Loh, G. L. Chua, *Chem. Commun.* **2006**, 2739; c) J. Podlech, T. C. Maier, *Synthesis* **2003**, 0633.
- [6] The catalytic species in AlMe₂Cl-catalyzed Diels–Alder reactions and Petasis–Ferrier rearrangements is AlMe₂⁺. For Diels–Alder re-

- actions, see: a) D. A. Evans, K. T. Chapman, J. Bisaha, *J. Am. Chem. Soc.* **1988**, *110*, 1238; b) L. F. Tietze, A. Schuffenhauer, P. R. Schreiner, *J. Am. Chem. Soc.* **1998**, *120*, 7952; c) Y.-H. Lam, P. H.-Y. Cheong, J. M. Blasco Mata, S. J. Stanway, V. Gouverneur, K. N. Houk, *J. Am. Chem. Soc.* **2009**, *131*, 1947; d) R. K. Jangid, N. Sogani, N. Gupta, R. K. Bansal, M. von Hopffgarten, G. Frenking, *Beilstein J. Org. Chem.* **2013**, *9*, 392. For Petasis–Ferrier rearrangements, see: e) G.-J. Jiang, Y. Wang, Z.-X. Yu, *J. Org. Chem.* **2013**, *78*, 6947.
- [7] For recent reviews, see: a) S. I. Lee, N. Chatani, *Chem. Commun.* **2009**, 371; b) V. Michelet, P. Y. Toullec, J. P. Genét, *Angew. Chem. Int. Ed.* **2008**, *47*, 4268; *Angew. Chem.* **2008**, *120*, 4338.
- [8] a) L.-G. Zhuo, J.-J. Zhang, Z.-X. Yu, *J. Org. Chem.* **2012**, *77*, 8527. In this reference, we only discussed type II diene formation. For a discussion of type I, II, and III diene formations from InCl_3 -catalyzed cycloisomerization of 1,6-enynes, see: b) L.-G. Zhuo, J.-J. Zhang, Z.-X. Yu, *J. Org. Chem.* **2014**, *79*, 3809.
- [9] This reaction was discovered by the Chatani group, see: Y. Miyano-hana, N. Chatani, *Org. Lett.* **2006**, *8*, 2155.
- [10] J. A. Dean, *Lange's Handbook of Chemistry, 15th ed.* McGraw-Hill, Englewood Cliffs, NJ, **1998**.
- [11] a) Z.-G. Xi, L. Zhu, S. Luo, J.-P. Cheng, *J. Org. Chem.* **2013**, *78*, 606; b) P. Liu, Y.-M. Pan, K. Hu, X.-C. Huang, Y. Liang, H.-S. Wang, *Tetrahedron* **2013**, *69*, 7925; c) M. Veeranarayana Reddy, Y. T. Jeong, *Tetrahedron Lett.* **2013**, *54*, 3546; d) L. Zhang, Z.-M. Li, R. H. Fan, *Org. Lett.* **2013**, *15*, 2482.
- [12] H. Inoue, T. Kotsuma, S. Murai, N. Chatani, *J. Am. Chem. Soc.* **2002**, *124*, 10294.
- [13] H.-G. Cho, *Spectrochim. Acta Part A* **2003**, *59*, 1517.
- [14] For a review on ligand assisted GaCl_3 -dissociation, see: a) S. Dag-orne, D. A. Atwood, *Chem. Rev.* **2008**, *108*, 4037 and references therein. For recent examples, see: b) A. El-Hellani, J. Monot, R. Guillot, C. Bour, V. Gandon, *Inorg. Chem.* **2013**, *52*, 506; c) C. Bour, J. Monot, S. Tang, R. Guillot, J. Farjon, V. Gandon, *Organo-metallics* **2014**, *33*, 594.
- [15] The electrospray ionization high resolution mass spectrum (ESI-HRMS) of the mixture of GaCl_3 and **1** in CH_3CN demonstrated the existence of a $[\text{GaCl}_2+\mathbf{1}]^+$ complex ($m/z=376.98354$). The anion GaCl_4^- ($m/z=208.80101$) was detected in negative mode. Similarly, an $[\text{InI}_2+\mathbf{1}]^+$ complex ($m/z=606.83181$), an InI_4^- ($m/z=622.52030$), an $[\text{InBr}_2+\mathbf{1}]^+$ complex ($m/z=510.86104$), an InBr_4^- ($m/z=430.57681$) and GaBr_4^- ($m/z=384.59864$) were detected in ESI-HRMS. However, the $[\text{GaBr}_2+\mathbf{1}]^+$ complex was not detected in ESI-HRMS.
- [16] All calculations were performed with the Gaussian 09 program: Gaussian 09, revision A. 02, M. J. Frisch, et al., Gaussian, Inc, Wallingford CT, **2009**. All of the energies discussed in the this paper and the Supporting Information are Gibbs free energies in the gas phase at 298 K (ΔG_{gas}). Gibbs energies at 298 K in DCE solution (ΔG_{sol} , the entropies were approximated by using the calculated gas-phase entropies) and gas-phase enthalpies (ΔH_{gas}) are also provided for reference.
- [17] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648; b) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785.
- [18] H^b can also take part in the [1,2]-H shift to produce **E-10** or **Z-10**. The corresponding transition states are close in energy compared with the transition states involving [1,2]- H^a shifts (see the Supporting Information).

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