ORGANIC LETTERS

2005
Vol. 7, No. 2
331−334

$GaCl_3$-Catalyzed Skeletal Rearrangement of α,α,α-Trisubstituted Aldehydes

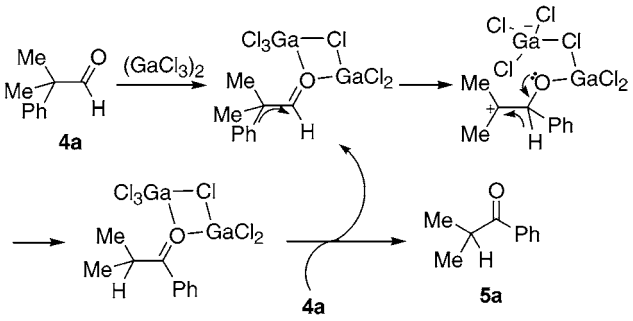
Masayuki Oshita,[†] Takao Okazaki,[‡] Kouichi Ohe,[‡] and Naoto Chatani*,[†]

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871, Japan, and Department of Energy and Hydrocarbon Chemistry, Graduate School of Engineering, Kyoto University, Nishikyo-ku, Kyoto 615-8510, Japan

chatani@chem.eng.osaka-u.ac.jp

Received November 16, 2004

ABSTRACT



$GaCl_3$ is found to be a superior catalyst for the skeletal rearrangement of α,α,α-trisubstituted aldehydes to ketones. The rearrangement can proceed smoothly in the presence of a catalytic amount of $GaCl_3$, and even substrates having no heteroatoms α to the carbonyl group or without steric strains can be used. Double activation of a carbonyl group by two molecules of $GaCl_3$ was supported on the basis of experimental data and a DFT study.

A skeletal rearrangement is a characteristic feature in carbocation chemistry.[1] Rearrangement can occur by the 1,2-shift of an alkyl group, an aryl group, or a hydrogen to an electrophilic carbocation center. A similar rearrangement can readily occur even on a less electrophilic carbon, such as is found in aldehydes, ketones, imines, or epoxides, provided the substrates contain a hydroxyl group or amino group adjacent to the electrophilic center. Such a system is frequently employed in organic synthesis.[2] In 1926, Danilov et al. reported on the rearrangement of pivalaldehyde to methyl isopropyl ketone in 70% H_2SO_4 at a temperature of 130 °C,[3] indicating that the presence of a heteroatom at the α position to the carbonyl group is not always necessary if the reaction conditions used are harsh. Hopff found that the rearrangement also proceeds in the presence of $AlCl_3$ and H_2SO_4.[4] Recently, Olah and Prakash reported that strong protic acids ($H_0 < -11$), such as TfOH, anhydrous HF, and trifluoroethanol/BF_3, mediate the rearrangement of pivalaldehyde to methyl isopropyl ketone, even at 0 °C.[5] They concluded that the reaction proceeds via a protosolvated carboxonium ion intermediate[6] on the basis that a large excess of the protic acids is required for the rearrangement to take place and based on a DFT study. A methyl group

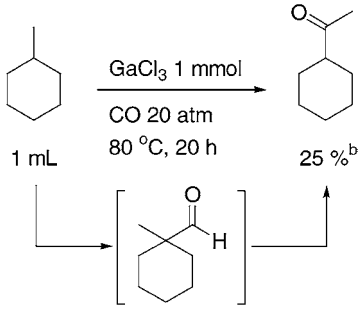
[†] Osaka University.
[‡] Kyoto University.

(1) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, Chapter 3.
(2) For a review, see: Paquette, L. A.; Hofferberth, J. E. *Org. React.* **2003**, *62*, 477−567. For recent papers, see: Ooi, T.; Saito, A.; Maruoka, K. *J. Am. Chem. Soc.* **2002**, *125*, 3220−3221. Suda, K.; Kikkawa, T.; Nakajima, S.; Takanami, T. *J. Am. Chem. Soc.* **2004**, *126*, 9554−9555.
(3) Danilov, S.; Venus-Danilova, E. *Ber. Dtsch. Chem. Ges.* **1926**, *59*, 377−387.
(4) Hopff, H.; Nenizescu, C. D.; Isacescu, D. A.; Cantuiari, I. P. *Chem. Ber.* **1936**, *69*, 2244−2251.
(5) Olah, G. A.; Mathew, T.; Marinez, E. R.; Esteves, P. M.; Etzkorn, M.; Rasul, G.; Prakash, G. K. S. *J. Am. Chem. Soc.* **2001**, *123*, 11556−11561.
(6) Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 767−922. Olah, G. A.; Klumpp, D. A. *Acc. Chem. Res.* **2004**, *37*, 211−220.

10.1021/ol047640h CCC: $30.25 © 2005 American Chemical Society
Published on Web 12/22/2004

moves to the aldehyde carbonyl carbon, which is activated by a strong protic acid to form a protosolvated carboxonium ion intermediate. A 1,2-hydride shift completes the rearrangement. Quite recently, Davies reported on a similar, ring-expansion rearrangement of *exo*-2-norbornanecarbaldehyde induced by $AlCl_3$.[7] As part of our interest in the unique catalytic or stoichiometric activity of $GaCl_3$,[8] we found the $GaCl_3$-mediated conversion of adamantane to 1-adamantanecarboxaldehyde under mild reaction conditions (1 atm of CO, at room temperature).[9] The use of methylcyclohexane as the substrate did not give the expected aldehyde, but cyclohexyl methyl ketone was formed instead (Scheme 1). Such a

Scheme 1. $GaCl_3$-Mediated Carbonylation of Methylcyclohexane[a]

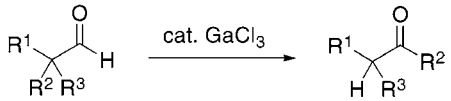


[a] Yield based on $GaCl_3$. [b]The product was isolated as a tosylhydrazone.

product would be formed by the formylation of methylcyclohexane followed by a skeletal rearrangement.[10]

This prompted us to examine the latter unique rearrangement. We wish to report here that a common Lewis acid, such as $GaCl_3$, catalyzes the rearrangement of α,α,α-trisubstituted aldehydes to ketones (Scheme 2). In addition,

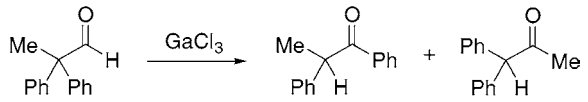
Scheme 2. $GaCl_3$-Catalyzed Rearrangement of Aldehydes



to develop a better understanding of the mechanism of the rearrangement, theoretical calculations were also done.

The treatment of 2,2-diphenylpropionaldehyde (**1**, 1 mmol) with 100 mol % of $GaCl_3$ in methylcyclohexane (3 mL) at room temperature for 1 h gave 1,2-diphenylpropan-1-one (**2**) in 92% isolated yield, and a trace amount of **3** was detected by GC (Table 1). It was found that the rearrangement proceeds in a catalytic manner (20 mol %) to give **2** in 73%

Table 1. Rearrangement of 2,2-Diphenylpropionaldehyde (**1**)[a]



1 (1 mmol) **2** **3**

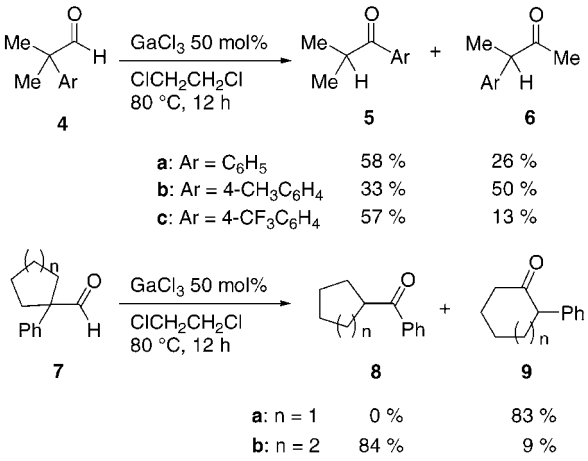
			yields (%)	
$GaCl_3$	solvent	conditions	**2**	**3**
100 mol %	methylcyclohexane	rt, 1 h	92	
20 mol %	methylcyclohexane	80 °C, 20 h	73	
20 mol %	$ClCH_2CH_2Cl$	80 °C, 1 h	87	9

[a] Isolated yield.

yield when the reaction is carried out at 80 °C. Among the solvents examined, 1,2-dichloroethane was found to be the solvent of choice (methylcyclohexane 12%, toluene 24%, THF 0%). Thus, the use of 1,2-dichloroethane gave **2** in 87% yield along with **3** in 9% at 80 °C for 1 h. We next examined the effect of Lewis acids other than $GaCl_3$. It was found that $GaCl_3$ is the most effective catalyst ($AlCl_3$ **2**/**3** = 66%/8%, $ZrCl_4$ 26%/2%, $Sc(OTf)_3$ 7%/0%, ineffective; $InCl_3$, $TiCl_4$, $HfCl_4$, $PtCl_2$, $ZnCl_2$, $SnCl_2$).

The relative preference for susceptibility to migration was next examined (Scheme 3). A phenyl group in **4a** migrates

Scheme 3. Relative Preference for Susceptibility to Migration



in preference to a methyl group, even though **4a** has two methyl groups. The product distribution remained unchanged during the reaction. The more electron-withdrawing a substituent on an aryl group is, the greater is the preference for the aryl group migrates compared with a methyl group, indicating that the migration directs the formation of a stable cation. The reaction of **7a** resulted in a selective ring expansion to give **9a** as a single product. On the other hand,

(7) Davies, H. M. L.; Dai, X. *J. Am. Chem. Soc.* **2004**, *126*, 2692−2693.

(8) Chatani, N.; Inoue, H.; Kotsuma, T.; Murai, S. *J. Am. Chem. Soc.* **2002**, *124*, 10294−10295. Chatani, N.; Oshita, M.; Tobisu, M.; Ishii, Y.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 7812−7813. Oshita, M.; Tobisu, M.; Yamashita, K.; Chatani, N. *J. Am. Chem. Soc.*, in press.

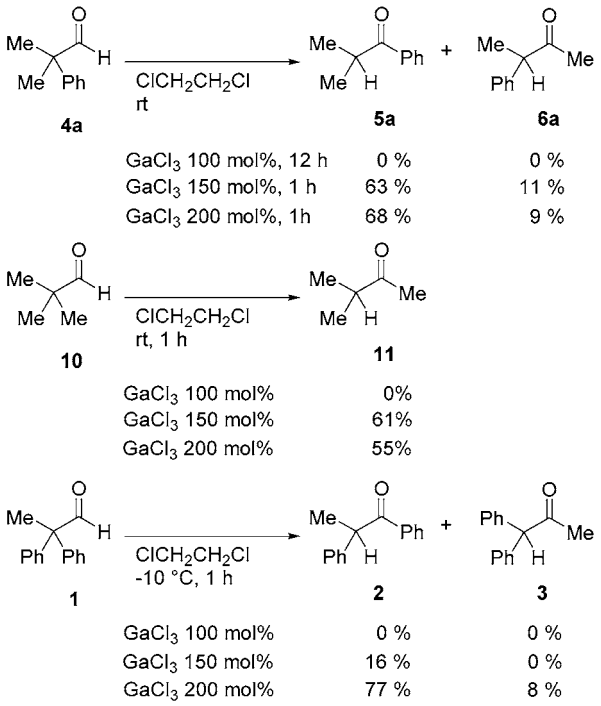
(9) Oshita, M.; Chatani, N. *Org. Lett.* **2004**, *6*, 4323−4325.

(10) Olah, G. A.; Prakash, G. K. S.; Marinez, E. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 2547−2548.

the reaction of **7b** resulted in the selective migration of a phenyl group to give **8b** in high yield and the ring-expansion product **9b** was obtained in 9% yield, although the latter product is derived from a more stable cation. This indicates that the nature of the reaction is also affected by the ring size.

Surprisingly, when a reaction using a stoichiometric amount of $GaCl_3$ and at lower reaction temperatures was employed, it was curiously found that the amount of $GaCl_3$ has a significant effect on the efficiency of the rearrangement (Scheme 4). No reaction took place when 100 mol % of

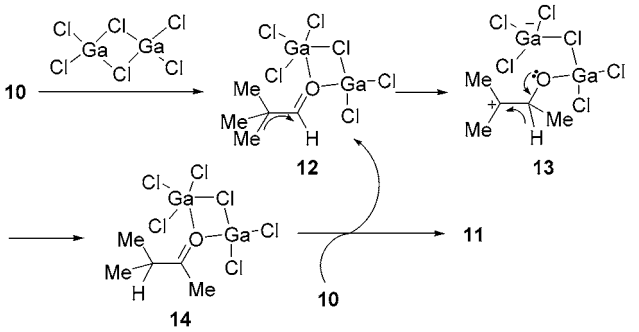
Scheme 4. Effect of the Amount of $GaCl_3$ on the Efficiency of the Rearrangement



$GaCl_3$ was used at room temperature in the reaction of **4a** for 12 h. However, the use of more than 150 mol % of $GaCl_3$ resulted in a smooth rearrangement to give **5a** and **6a** in good yields. A similar drastic effect was also observed for the reactions of **10** and **1**.[11] As mentioned above, Olah suggested that the rearrangement of pivalaldehyde in a large excess of the strong protic acids proceeds via a protosolvated carboxonium ion intermediate.[6] Therefore, the results described in Scheme 4 can possibly indicate that additional molecules of $GaCl_3$ are necessary for the reaction to proceed.

Scheme 5 shows the proposed mechanistic pathway for the reaction. We propose that two molecules of $GaCl_3$ are operative in the rearrangement based on the results shown in Scheme 4. The coordination of the carbonyl oxygen to a dimer of $GaCl_3$, as in **12**,[12] leads to a highly electrophilic carbonyl carbon, where a 1,2-methyl shift takes place to give a tertiary cation **13**. A 1,2-hydride shift leads to the formation of **14**, which then undergoes ligand exchange with **10** to give **11**.

Scheme 5. A Possible Mechanism



To rationalize the experimental results, density functional theory (DFT) calculations were performed at the B3LYP/6-31G(d) level.[13] Table S1 (see the Supporting Information) summarizes electronic energies for intermediates and transition states of the rearrangements.

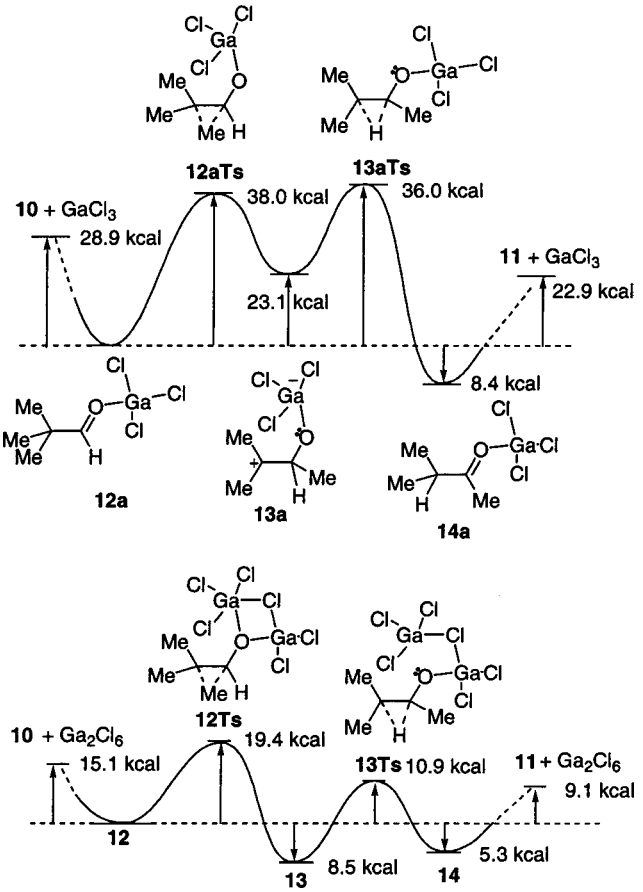


Figure 1. Energy Profile for the Rearrangement Computed by B3LYP/6-31G(d) Calculations

(11) In the reaction of **10**, the rearrangement product was isolated as a 4-tosylhydrazone because of the low boiling point of the product **11**.

Figure 1 shows a description of the potential energy surfaces of the isomerization for the di-$GaCl_3$-coordinated complex. The activation barriers are 19.4 kcal/mol for the methyl shift (**12** → **13**) and 19.4 kcal/mol for the hydrides shift (**13** → **14**). The activation energy from **12** to **13** is less than those in mono-$GaCl_3$-coordinated complex by 18.6 kcal/mol (Figure 1). This stabilization is caused by more efficient coordination of the $GaCl_3$ to a carbon center with developing positive charge in the transition state. The cationic intermediate **13** is thermodynamically stabilized with a similar effect, as shown in Scheme 5.

In conclusion, we demonstrate here that $GaCl_3$ is a superior catalyst for the skeletal rearrangement of α,α,α-trisubstituted aldehydes. The rearrangement can proceed smoothly in the presence of a catalytic amount of a weak Lewis acid, such as $GaCl_3$, and even substrates having no heteroatoms α to the carbonyl group or without steric strains can be used. Double activation of a carbonyl group by two molecules of $GaCl_3$ was supported by a DFT study. Such a unique characteristic feature of $GaCl_3$ may continue to have considerable impact on the development of new transformations.[8,9,14]

Acknowledgment. This work was supported, in part, by grants from Ministry of Education, Culture, Sports, Science and Technology, Japan. M.O. express his special thanks for the center of excellence (21COE) program "Creation of Integrated EcoChemistry of Osaka University".

Supporting Information Available: Experimental procedures, electronic energies (Table S1) and computed geometries (Figure S1, Tables S2−15) by DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

OL047640H

(12) For papers on a double activation of aldehydes by bidentate organoaluminum Lewis acids, see: Ooi, T.; Takahashi, M.; Yamada, M.; Tayama, E.; Omoto, K.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 1150−1160. For papers on diprotonated activation, see: Saito, S.; Sato, Y.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1994**, *116*, 2312−2317. Suzuki, T.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1997**, *119*, 6774−6780.

(13) Koch, W.; Holthausen, M. C. *A Chemist's Guide to Density Functional Theory*, 2nd ed.; Wiley-VCH: New York, 2000.

(14) Viswanathan, G. S.; Li, C.-J. *Synlett* **2002**, 1553−1555. Yonehara, F.; Kido, Y.; Sugimoto, H.; Morita, S.; Yamaguchi, M. *J. Org. Chem.* **2003**, *68*, 6752−6759. Bez, G.; Zhao, C.-G. *Org. Lett.* **2003**, *5*, 4991−4993. Usugi, S.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2004**, *6*, 601−603. Amemiya, R.; Nishimura, Y.; Yamaguchi, M. *Synthesis* **2004**, 1307−1314.