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Triethylborane-Induced Radical Reactions with Gallium Hydride Reagent $HGaCl_2$

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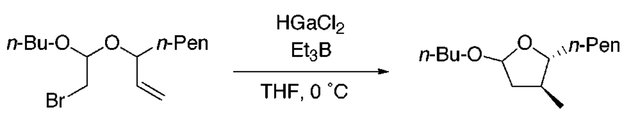
ABSTRACT



A gallium hydride reagent, $HGaCl_2$, was found to act as a radical mediator, like tributyltin hydride. Treatment of alkyl halides with the gallium hydride reagent, generated from gallium trichloride and sodium bis(2-methoxyethoxy)aluminum hydride, provided the corresponding reduced products in excellent yields. Radical cyclization of halo acetals was also successful with not only the stoichiometric gallium reagent but also a catalytic amount of gallium trichloride combined with stoichiometric aluminum hydride as a hydride source.

Organotin hydrides have played an extraordinarily important role in synthetic radical chemistry because of their excellent reactivity.[1] However, organotin compounds are usually toxic[2] and difficult to remove completely from the desired reaction products. Therefore, many efforts have been made to overcome these difficulties.[3,4] Silanes[5] and germanes,[6] group 14 metal hydrides, are good alternatives to tributyltin hydride and are used in organic synthesis. The phosphorus−hydrogen bond in phosphites, phosphines, and hypophosphorous acid is also weak, allowing these reagents to act as hydrogen atom transfer agents and radical chain carriers.[7] Very recently, we reported the $Cp_2Zr(H)Cl$-mediated radical reaction involving homolytic cleavage of the zirconium−hydrogen bond.[8] Here we wish to introduce the gallium hydride reagent $HGaCl_2$, a group 13 metal hydride, as an efficient radical mediator.[9,10]

Gallium trichloride (2.0 mmol) was treated with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al, 1.0 mmol)

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(2) Boyer, I. J. *Toxicology* **1989**, *55*, 253−298.

(3) Studies on removal of tin residues or on tin hydride-catalyzed reaction in conjunction with a stoichiometric reductant: (a) Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 7200−7201. (b) Clive, D. L. J.; Yang, W. *J. Org. Chem.* **1995**, *60*, 2607−2609. (c) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140−3157. (d) Curran, D. P.; Hadida, S. *J. Am. Chem. Soc.* **1996**, *118*, 2531−2533. (e) Gerlach, M.; Jördens, F.; Kuhn, H.; Neumann, W. P.; Peterseim, M. *J. Org. Chem.* **1991**, *56*, 5971−5972. (f) Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 4−5. (g) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1975**, *40*, 2554−2555. (h) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303−304.

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in THF at 0 °C for 30 min to prepare dichlorogallane.[11,12] 1-Iodododecane (1.0 mmol) and triethylborane (0.20 mmol) as an initiator[13] were sequentially added, and the whole mixture was stirred for 4 h. Dodecane was obtained in 92% yield after usual workup and purification. Various halides were examined (Table 1).

Table 1. Radical Reduction of Various Halides with Gallium Hydride[a]

entry	R−X	time/h	yield/%
1	1-iodododecane	4	92
2	1-bromododecane	5	88[b]
3	1-bromododecane	5	81[b,c]
4	2-bromododecane	5	81[b,c]
5	1-bromoadamantane	5	78[b]
6	c-$C_{12}H_{23}OC(=S)SMe$	6	84
7	3-bromopropyl benzoate	5	88[b]
8	4-iodobutyrophenone	9	80

[a] Halide (1.0 mmol), $GaCl_3$ (2.0 mmol), Red-Al (1.0 mmol), triethylborane (0.20 mmol), and THF (3 mL) were used. [b] 1.0 mmol of Et_3B was employed. [c] Diisobutylaluminum hydride (2.0 mmol) was used instead of Red-Al (1.0 mmol).

Alkyl bromides were also reduced to the corresponding hydrocarbons in excellent yields, although a larger amount of triethylborane (1.0 mmol) was necessary. Without Red-Al and gallium trichloride, reduction of 1-bromododecane in the presence of triethylborane in THF resulted in recovery of the starting material. A combination of gallium trichloride and an equimolar amount of diisobutylaluminum hydride was also effective, forming the gallium hydride reagent (entries 3 and 4). Unfortunately, alkyl chloride and aryl iodide remained almost unchanged. Radical deoxygenation via dithiocarbonate was successful (entry 6). Interestingly, reduction of the ketone did not take place at all under the reaction conditions (entry 8). However, reduction of a benzylic bromide, 4-bromobenzyl bromide, resulted in recovery of the starting material (89%).

(9) Baba's group orally presented the reduction of halide with indium hydride species, derived from indium trichloride and tributyltin hydride: Inoue, K.; Sawada, A.; Shibata, I.; Baba, A. The 78th Annual Meeting of the Chemical Society of Japan, March, 28−31, 2000, 4F230.

(10) The reaction of dichlorogallane with ethyl halides has been reported, although the reaction was concluded to proceed via σ-bond metathesis: (a) Csákvári, B.; Jenei, S.; Knausz, D.; Meszticzky, A. *Acta Chim. Acad. Sci. Hung.* **1969**, *59*, 225−227. (b) Meszticzky, A.; Knausz, D.; Csákvári, B.; Emmer, J. *Acta Chim. Acad. Sci. Hung.* **1976**, *89*, 203−208.

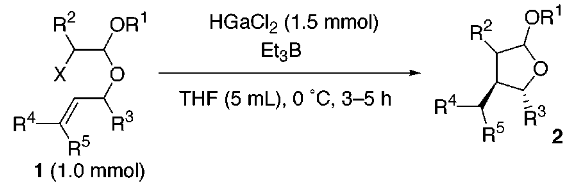
(11) Examples of gallium hydride reagents, especially $LiGaH_4$, used for reduction of various functional groups such as carbonyl groups and halides: (a) Schmidba, H.; Findeiss, W.; Gast, E. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 152. (b) Choi, J. H.; Yun, J. H.; Hwang, B. K.; Baek, D. J. *Bull. Korean Chem. Soc.* **1997**, *18*, 541−542. (c) Kim, J. S.; Choi, J. H.; Kim, H. D.; Yun, J. H.; Joo, C. Y.; Baek, D. J. *Bull. Korean Chem. Soc.* **1999**, *20*, 237−240. Review on gallium hydrides: (d) Barron, A. R.; MacInnes, A. N. In *Encyclopedia of Inorganic Chemistry*; King, R. B., Ed.; John Wiley & Sons: Chichester, 1994; Vol. 3, p 1249.

(12) The gallium species, described as a monomeric form in the present text, would exist as a certain dimeric or polymeric form: Duke, B. J.; Hamilton, T. P.; Schaefer, H. F, III. *Inorg. Chem*. **1991**, *30*, 4225−4229 and references therein.

(13) (a) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547−2548. (b) Oshima, K.; Utimoto, K. *J. Synth. Org. Chem. Jpn.* **1989**, *47*, 40−52. (c) Yorimitsu, H.; Oshima, K. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, Chapter 1.2.

We then turned our attention to the radical cyclization of halo acetals.[14] Substrates shown in Table 2 underwent 5-exo

Table 2. Radical Cyclization of Halo Acetals



1	X	R[1]	R[2]	R[3]	R[4]	R[5]	2	yield/%[a]
1a	I	$(CH_2)_3$		H	Me	Me	**2a**	87 (70/30)[b]
1b	Br	$(CH_2)_3$		H	Me	Me	**2a**	82 (71/29)[c]
1c	I	$(CH_2)_3$		H	*n*-Pr	H	**2c**	85 (84/16)[b]
1d	Br	$(CH_2)_3$		H	*n*-Pr	H	**2c**	80 (84/16)[c]
1e	I	$(CH_2)_3$		*n*-Pen	H	H	**2e**	85 (57/43)[b]
1f	Br	$(CH_2)_3$		*n*-Pen	H	H	**2e**	80 (56/44)[c]
1g	I	*n*-Bu	H	H	*n*-Pr	H	**2g**	97 (84/16)[b]
1h	Br	*n*-Bu	H	H	*n*-Pr	H	**2g**	79 (84/16)[c]
1i	I	*n*-Bu	H	*n*-Pen	H	H	**2i**	99 (50/50)[b]
1j	Br	*n*-Bu	H	*n*-Pen	H	H	**2i**	94 (52/48)[c]

[a] Isolated yield. Diastereomer ratios are in parentheses. [b] 0.20 mmol of Et_3B was used. [c] 1.0 mmol of Et_3B was used.

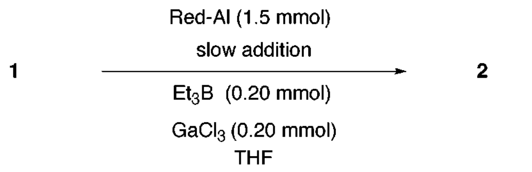
reductive cyclization smoothly by the action of the gallium hydride reagent in the presence of triethylborane.

The reaction of **1a** did not proceed in the absence of triethylborane. 2,2,6,6-Tetramethylpiperidine-*N*-oxyl completely inhibited the reaction. The reaction of halo acetals **1a**, **1c**, and **1e** with tributyltin hydride, a representative method for radical cyclization, under similar reaction conditions provided the corresponding products **2a**, **2c**, and **2e**, respectively, in moderate yields with the same diastereoselctivities as in the reaction with $HGaCl_2$ (**2a**, 60% (69/31), **2c**, 63% (86/14), **2e**, 46% (52/48)). These results support a radical mechanism for the present reaction. It is worth noting that the reaction proceeded less efficiently when monochlorogallane (H_2GaCl), which can be prepared by mixing $GaCl_3$ and Red-Al in 1:1 ratio, was used. For example, the reaction of **1g** provided **2g** in 74% yield. Furthermore, treatment of **1f** with H_2GaCl (1.5 mmol) yielded a complex mixture. Red-Al itself worked far less efficiently compared with $HGaCl_2$. Treatment of **1c** and **1e** with Red-Al in the presence of triethylborane provided **2c** and **2e** in 23% and <1% yields, respectively. The starting materials **1c** (57%) and **1e** (74%) were recovered.

Gallium trichloride is not cheap. It is of importance to reduce the amount of $GaCl_3$ employed for the reaction. Thus, the catalytic reaction was examined. The cyclization of **1a** was performed by slow addition (2 h) of Red-Al (1.5 mmol) to a solution of **1a** (1.0 mmol), $GaCl_3$ (0.20 mmol), and Et_3B (1.0 mmol) in THF (Table 3). The mixture was stirred for

(14) (a) Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564−5566. (b) Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741−3742.

Table 3. Radical Cyclization with a Catalytic Amount of Gallium Trichloride



substrate	time/h[a]	product	yield/%[b]
1a	2 + 1	**2a**	79 (70/30)
1c	2 + 8	**2c**	64 (88/12)
1e	2 + 4	**2e**	95 (59/41)

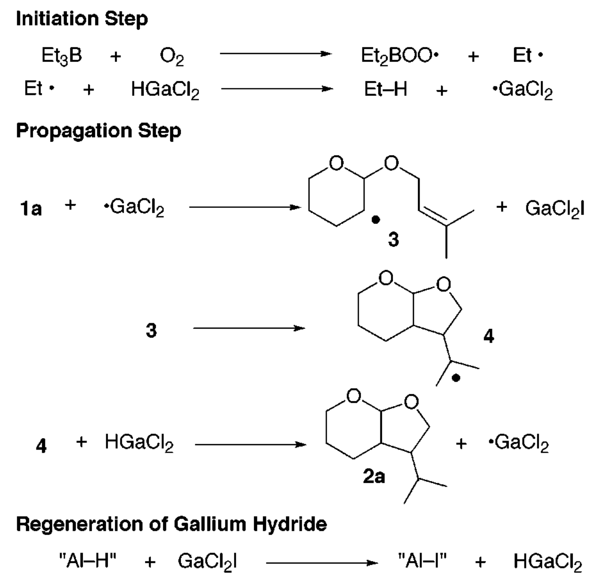
[a] Red-Al was added slowly over 2 h, and the resulting mixture was stirred additionally for the indicated time. [b] Isolated yield. Diastereomer ratios are in parentheses.

an additional 1 h to yield **2a** in 79% yield. Slow addition was essential for the success of the catalytic reaction. Exposure of $GaCl_3$ to excess Red-Al at one time resulted in poor conversion (**2a**, 10%; **1a**, 65% recovered). Gallane (GaH_3) would be unstable under these reaction conditions.[11c]

We are tempted to assume the catalytic mechanism as shown in Scheme 1, in analogy with the reaction with tributyltin hydride. An ethyl radical, generated from Et_3B by the action of a trace amount of oxygen, would abstract hydrogen homolytically from $HGaCl_2$ to give divalent gallium radical $^{\bullet}GaCl_2$.[15] Halogen abstraction by $^{\bullet}GaCl_2$ from substrate **1a**, for example, affords $GaCl_2I$ and radical **3**. Ring closure followed by hydride donation from $HGaCl_2$ to the radical **4** provides the product **2a** and regenerates $^{\bullet}GaCl_2$. $GaCl_2I$, formed in the propagation step, is transformed into $HGaCl_2$ by the action of aluminum hydride, and the gallium hydride works again as a hydride source for the carbon-centered radical.

(15) Gallium-centered radical anion was reported: Brand, J. C.; Roberts, B. P. *J. Chem. Soc., Chem. Commun.* **1984**, 109−110.

Scheme 1



In summary, we have revealed that the gallium hydride reagent, $HGaCl_2$, works well as a chain carrier in place of tributyltin hydride. Removal of residual gallium compound is easy and no special technique is necessary.

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Supporting Information Available: Detailed experimental procedures and characterization data of **2a**−**2i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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