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$GaCl_3$ in Organic Synthesis

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$GaCl_3$ and organogallium compounds generated from $GaCl_3$ possess novel properties that can be used in organic synthesis. This microreview summarizes our studies on the use of $GaCl_3$ as 1) a reagent to generate organogallium compounds, which can carbometalate unactivated unsaturated bonds, and 2) a Lewis acid which can activate organic molecules by interacting with the π-, n-, and σ-electrons. Carbometalation of carbon–carbon triple bonds (carbogallation) is a characteristic reaction of organogallium compounds. Carbogallation of gallioacetylenes occurs at lower temperatures than with silylacetylenes, and addition to 1-alkynes is slow. The regiochemistry and stereochemistry are in accordance with other carbometalation reactions, giving 1,1-digallio or 1-gallio-1-silyl intermediates in the *cis*-addition mode. Carbogallation of enolates and acetylenes is effective for the α-ethenylation of ketones, and a catalytic version of the reaction has been developed. When chloroacetylenes are used, α-ethynylation of ketones proceeds by addition and β-elimination. Aniline and phenols can be ethenylated or ethynylated at the *o*-position of the heteroatom groups. $GaCl_3$ has been used not only for the ethynylation of heteroatom compounds but also hydrocarbons such as 1,4-enynes or 1,4-diynes by C–H activation, and triethynylvinylmethanes and tetraethynylmethanes are obtained in one step via nucleophilic propargylgallium intermediates. As a Lewis acid, $GaCl_3$ has the ability to interact with π-acids such as silylacetylenes. The resulting gallium complexes are sufficiently electrophilic to react with aromatic hydrocarbons, even at –78 °C, to give an organogallium arenium intermediate. Arenium cations or vinyl cations appear to be stabilized in the presence of $GaCl_3$. An unusual orientation has been observed in electrophilic aromatic substitution with $GaCl_3$. $GaCl_3$ activates even cycloalkane C–H bonds at σ-electrons, and the reaction of *cis*-perhydronaphthalene and naphthalene catalytically gives 2-naphthylated *trans*-perhydronaphthalene. Two C–H activation reactions of hydrocarbons with $GaCl_3$ are notable as they generate nucleophilic and electrophilic species.

Introduction

$GaCl_3$ is a group 13 Lewis acid that for a long time was considered to be analogous to $AlCl_3$ but with a lower reactivity. Recent studies, however, have revealed that $GaCl_3$ and organogallium compounds generated from $GaCl_3$ exhibit novel properties in organic synthesis, whereas $AlCl_3$ does not.[1,2] In the present microreview, we summarize our studies on the use of $GaCl_3$ as 1) a reagent for generating organogallium compounds, which can carbometalate unactivated unsaturated bonds, and 2) a Lewis acid that can acti-

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MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

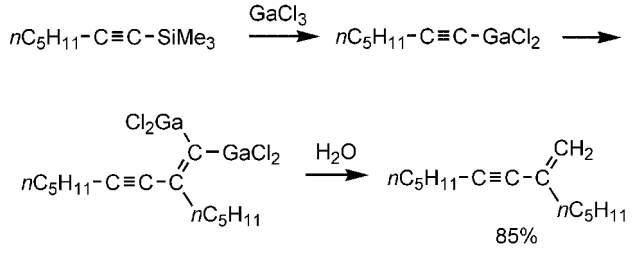
vate organic molecules by interacting with π-, n-, and σ-electrons. As $GaCl_3$ is soluble in hydrocarbons it is often used as a stock solution in methylcyclohexane. Although the toxicity of many organogallium compounds is not known, data for $Ga(NO_3)_3$ provide some information [LD_{50} = 55 mg/kg (mice, iv)].[1,2]

1. Carbometalation of Organogallium Compounds

1.1. Carbogallation

Carbometalation is the addition of organometallic compounds to C–C multiple bonds, and has attracted considerable interest as a method for constructing a new C–C bond at unactivated unsaturated bonds and generating a new organometallic species. This addition reaction and the fate of the resulting organometallic species are highly dependent on the type of metal species. Carbometalation of carbon–carbon triple bonds is a characteristic reaction of organogallium compounds (carbogallation), and proceeds more effectively than that of organoaluminum compounds. In general, carbogallation to gallioacetylenes occurs at lower temperatures than with silylacetylenes, and addition to 1-alkynes is relatively slow. The regiochemistry and stereochemistry in carbogallation are in accordance with other carbometalation reactions, giving 1,1-digallio- or 1-gallio-1-silylalkenes in the *cis*-addition mode.

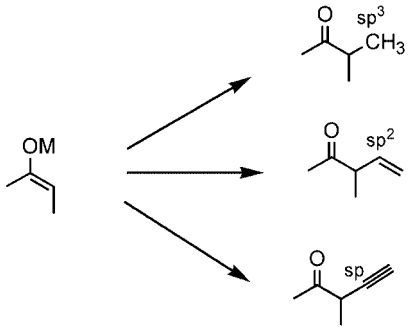
Carbogallation of a carbon–carbon triple bond was first found in the dimerization of an alkynylgallium:[3] the treatment of silylated 1-alkynes with a stoichiometric amount of $GaCl_3$ gave an enyne (Scheme 1). A gallioacetylene generated by transmetalation spontaneously dimerized to give a bisgallated enyne, which was converted to an enyne by protodegallation. The C–C bond formation occurred at the internal carbon atom. This is an unusual dimerization of a main group element metal acetylide. Allylgalliums, generated from allylsilanes and $GaCl_3$, add to 1-alkynes or silylated alkynes to give 1,4-dienes after protodegallation.[4]



Scheme 1.

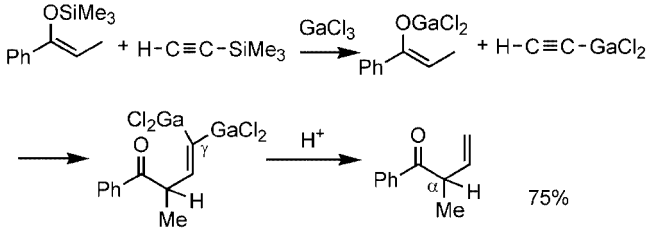
1.2. Enolate Ethenylation

The alkylation of enolates is a fundamental method for constructing a C–C bond, and is used to attach an sp^3 carbon at the carbonyl α-position. In contrast, ethenylation and ethynylation, which attach sp^2 and sp carbons, respectively, are not easy (Scheme 2). This is because of the difficulty of performing an S_N2 or S_N1 reaction at sp^2 and sp carbons. The carbogallation of enolates and acetylenes turned out to be effective for this transformation. Taking advantage of the addition reaction, catalytic ethenylation and ethynylation have also been attained.



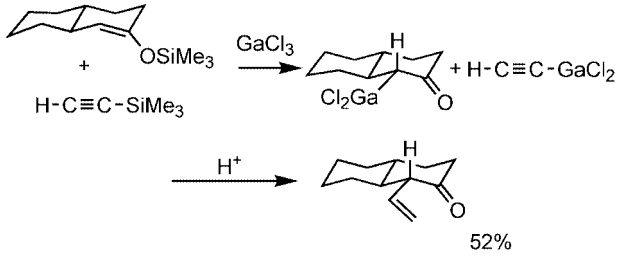
Scheme 2.

Gallium enolate and ethynylgallium, generated, respectively, from silyl enol ether and silylacetylene by treatment with $GaCl_3$, undergo carbogallation at room temperature within 5 min to give γ,γ-digallio enones, and α-ethenylated ketones are obtained after workup with an aqueous acid (Scheme 3).[5,6] The reaction can be applied to the synthesis of α-ethenyl ketones possessing an acidic α-proton; isomerization to thermodynamically stable conjugated enones is generally not observed.



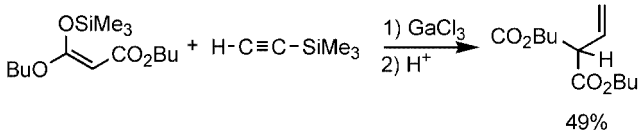
Scheme 3.

Equatorial preferences have been observed in the ethenylation of cyclohexanone enolates; for example, the ethenylation of a silyl enol ether derived from *trans*-3-decalone predominantly gives the equatorial isomer (Scheme 4).[7] This is in contrast to the stereochemistry of enolate alkylation, which takes place at the axial site of the enolate plane. The actual species involved in the carbogallation is presumably the α-gallio ketone and not the gallium enolate; the sterically demanding dichlorogallium group occupies the equatorial position, which undergoes carbogallation



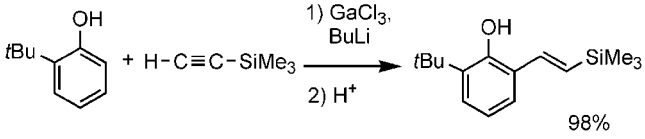
Scheme 4.

with retention of its configuration. Ethenylation occurs with silylated malonate to give ethenyl malonate (Scheme 5).[8]



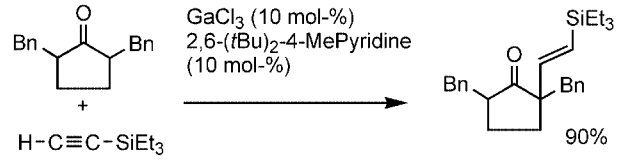
Scheme 5.

The gallium phenoxide generated from phenol, $GaCl_3$, and butyllithium reacts with silylacetylene at 50 °C in methylcyclohexane to give *o*-(β-silylethenyl)phenol after protodegallation (Scheme 6).[9]



Scheme 6.

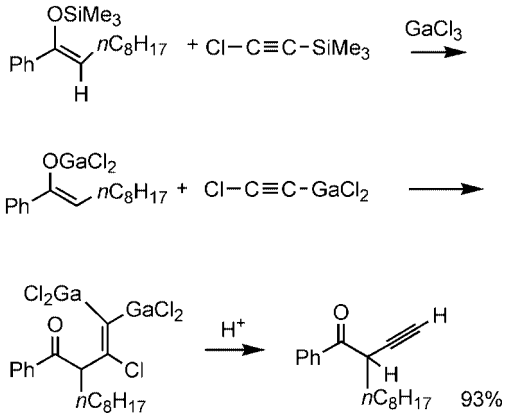
Cyclic ketones can be catalytically α-ethenylated in a reaction where the carbogallated product undergoes in situ protodegallation with an acid to regenerate $GaCl_3$.[10] The reaction of a 2,5-disubstituted cyclopentanone with triethylsilylacetylene in the presence of $GaCl_3$ (10 mol-%) and 2,6-di(*tert*-butyl)-4-methylpyridine (10 mol-%) at 180 °C in *o*-dichlorobenzene gives the corresponding 2-(β-silylethenyl)-cyclopentanone (Scheme 7). The added pyridine retards the decomposition of the products by trapping hydrogen chloride generated from the ketone and $GaCl_3$. It is also conceivable that pyridine hydrochloride functions as an efficient proton-transfer reagent for the carbogallated intermediate, thereby providing the ethenylated ketone and the regeneration of $GaCl_3$, although a higher temperature is required for this process. Since the ethenylation takes place in the absence of pyridine, it was confirmed that the gallium enolate can be generated from the ketone by treatment with $GaCl_3$. Enolate ethenylation using an addition reaction to acetylene compares well with the substitution reaction of vinyl halides. In terms of atom efficiency, the former method should be more favorable, since by-products derived from the leaving group do not form.



Scheme 7.

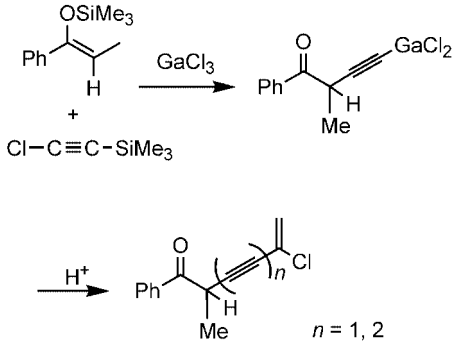
1.3. Enolate Ethynylation

The ease of the carbogallation between enolates and acetylenes led us to the idea that enolate ethynylation could proceed by addition and elimination to chloroacetylenes. Trimethylsilylated chloroacetylene was therefore treated with a silyl enol ether in the presence of $GaCl_3$ in methylcyclohexane at –40 °C, followed by the addition of methanol, to give an α-ethynylated ketone (Scheme 8).[11] The β-elimination took place upon methanol addition and ethynylated ketones with an acidic α-proton were obtained by careful isolation.



Scheme 8.

The reaction in dichloromethane gives α-enynylated ketones and α-endiynylated ketones (Scheme 9).[12] In the halogenated solvent, β-elimination occurs in situ during the reaction to generate ethynylgallium species, which undergo sequential carbon–carbon bond formations.

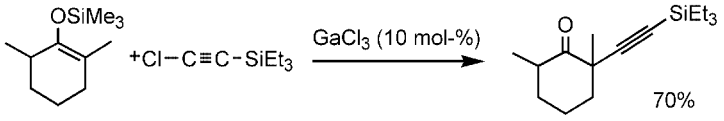


Scheme 9.

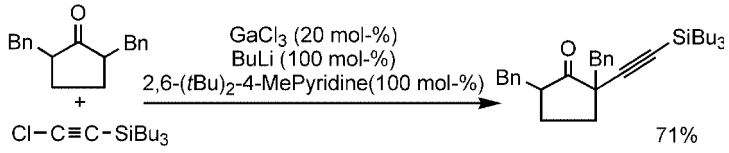
Since $GaCl_3$ was regenerated by β-elimination, the ethynylation could, in principle, be catalytic. The catalytic ethynylation of silyl enol ethers was conducted at 130 °C in methylcyclohexane in the presence of 10 mol-% $GaCl_3$ (Scheme 10).[13] A higher temperature is essential for the carbogallation of gallium enolate and silylated acetylene, which turned out to be less reactive than gallioacetylene. β-Elimination is much faster than carbogallation under these conditions.

It has recently been found that catalytic ethynylation can also be conducted with ketones in the presence of $GaCl_3$, BuLi, and 2,6-di(*tert*-butyl)-4-methylpyridine (Scheme 11).[14]

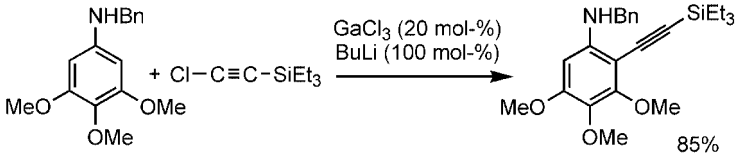
o-Ethynylanilines are versatile intermediates for the synthesis of indoles, and various methods have been examined for their cyclization. The substrate is generally prepared by the acetylenic coupling of *o*-haloanilines, which need to be



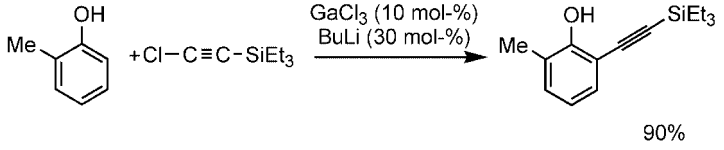
Scheme 10.



Scheme 11.



Scheme 12.

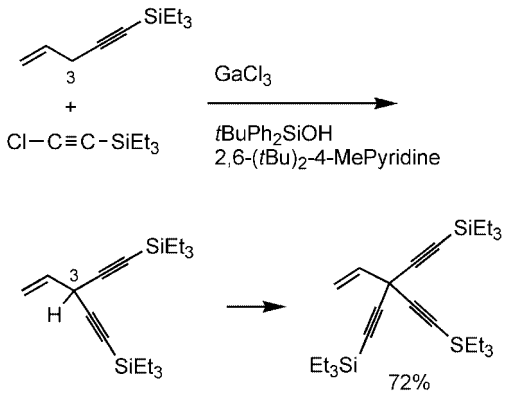


Scheme 13.

prepared in a stepwise manner from anilines. It is obvious that the direct *o*-ethynylation of anilines is straightforward: *N*-Alkylaniline undergoes *o*-ethynylation in the presence of a catalytic amount of $GaCl_3$. The reaction of lithiated *N*-benzylanilines and chloroacetylene in the presence of $GaCl_3$ (20 mol-%) at 120 °C in *o*-dichlorobenzene gives the corresponding *o*-ethynylanilines (Scheme 12).[15] *N*-Benzyl derivatives give higher yields of the products than *N*-methyl derivatives. Analogously, the catalytic reaction of phenoxygallium with chloroacetylene gives *o*-ethynylated phenols (Scheme 13).[16]

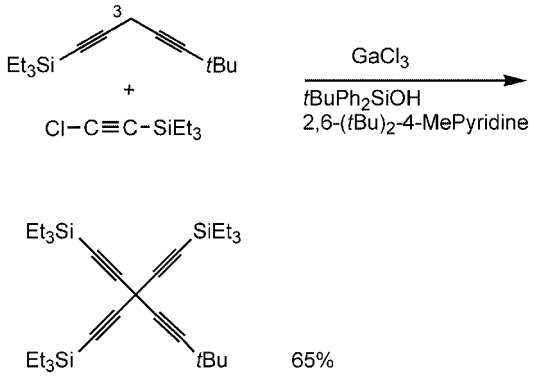
1.4. Propargylic Ethynylation

Some of the above ethenylation and ethynylation reactions involve C–H activation at relatively acidic protons adjacent to heteroatomic functional groups such as ketone, phenol, and aniline. The enolate formation reactions of ketones and $GaCl_3$, for example, most likely involve the initial complex formation of carbonyl n-electrons and $GaCl_3$ followed by deprotonation at the carbonyl α-position. Such complexation–deprotonation also proceeds for propargyl derivatives lacking heteroatoms. The reaction of 1,4-enyne and chloroacetylene in the presence of $GaCl_3$, trialkylsilanol, and 2,6-di(*tert*-butyl)-4-methylpyridine in *o*-dichlorobenzene at 130 °C, for example, gives triethynylvinylmethane (Scheme 14).[17] The added silanol and pyridine retard the decomposition of the substrates and product. $GaCl_3$ could interact with the acetylene π-electrons (vide infra), and these activated 1,4-enynes then undergo deprotonation at the α-position to generate propargylgalliums, which then undergo an addition/elimination with chloroacetylene to give the products. It was confirmed that $GaCl_3$ itself and not pyridine is involved in the C–H activation. The intermediate diethynylvinylmethane could not be detected, and the second ethynylation should be much faster than the first. Another notable feature of this reaction is



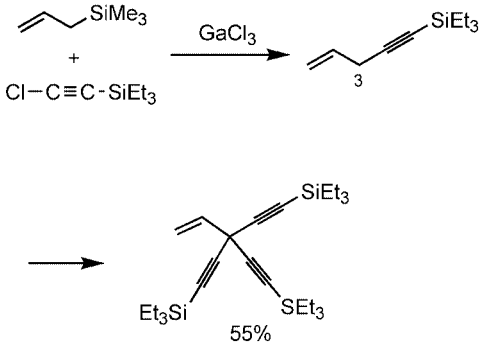
Scheme 14.

the regioselectivity in the ethynylation: the C–C bond formation proceeds at the 3-position of the organogallium intermediates. The same reaction with 1,4-diynes gives the corresponding tetraethynylmethanes (Scheme 15).



Scheme 15.

The reaction of allylsilane and chloroacetylene gives triethynylvinylmethane directly via an enyne by three C–C bond formations (Scheme 16).

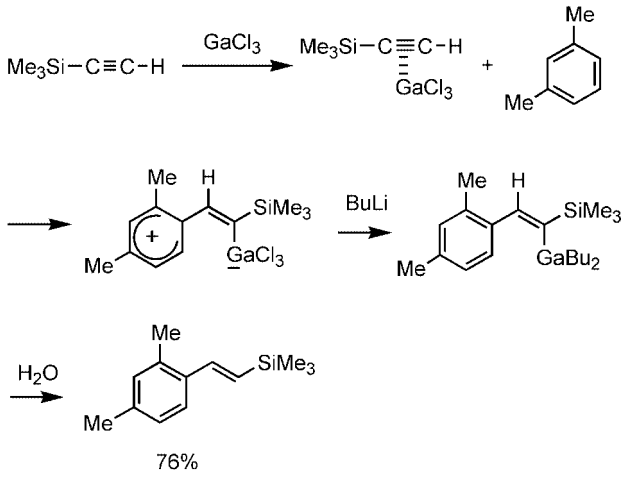


Scheme 16.

It has been observed that various organogallium dichlorides undergo carbometalation with acetylenes, and this reaction can be used for catalytic ethenylation and ethynylation of organic compounds. The introduction of such reactive functional groups is an important transformation in organic synthesis.

2. Activation of Organic Molecules by Interaction of $GaCl_3$ with π- or σ-Electrons

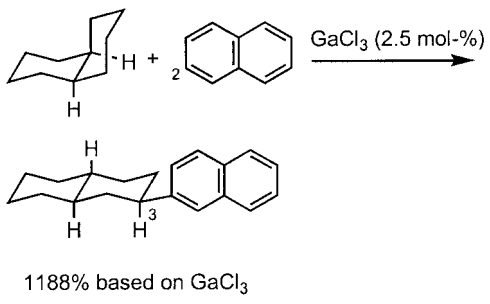
As a Lewis acid, $GaCl_3$ has the ability to interact with π-acids such as silylacetylene[18–20] or silylallene,[21] as shown by spectroscopic studies. The gallium complexes are sufficiently electrophilic to react with aromatic hydrocarbons, even at –78 °C, to give organogallium arenium intermediates (Scheme 17).[18–20] The addition of bases such as butyllithium or THF results in deprotonation to generate vinylgallium intermediates; finally, protodegallation produces β-silylethenylated arenes. In the absence of aromatic hydrocarbons, the silylacetylene–$GaCl_3$ complex spontaneously trimerizes to a conjugated trienyl cation, which, upon treatment with organolithium or magnesium compounds, is converted into an alkylated triene.[22] Arenium cations or vinyl cations, with which organometallic reagents can react, seem to be stabilized in the presence of $GaCl_3$. It should also be noted that such π complexation of an $RGaCl_2$ reagent with acetylenes facilitates the carbogallation described in the previous section.



Scheme 17.

Unusual orientations have sometimes been observed in electrophilic aromatic substitutions using $GaCl_3$. The reaction of toluene and a disilylated 1,3-butadiyne in the presence of $GaCl_3$, gives, for example an *o*-substituted product exclusively, and even isopropylbenzene predominantly reacts at the *o*-position.[23] The electrophilic bromination of xylenes with $GaCl_3$ initially produces dibrominated products, which react further to give monobromo derivatives.[24] The origin of the regioselectivities in these reactions has been ascribed to the C–H interaction of either $GaCl_3$ or $GaCl_3$-activated electrophiles with aromatic methyl protons.

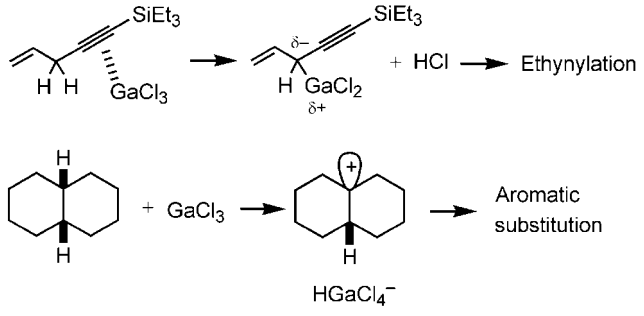
$GaCl_3$ activates the σ-electrons of cycloalkane C–H bonds, and this can be used for catalytic aromatic alkylation. The reaction of *cis*-perhydronaphthalene and naphthalene in the presence of a catalytic amount of $GaCl_3$ (5 mol-%) gives 2-naphthylated *trans*-perhydronaphthalene (Scheme 18) with a turnover number exceeding 10.[25,26] The carbon–carbon bond formation predominantly takes place at the 2-position of naphthalene and the 3-position of perhydronaphthalene. Notably, *cis*-perhydronaphthalene reacts much more effectively than the *trans* isomer. This observation indicates that the equatorial tertiary proton of the cy-



Scheme 18.

cloalkane, rather than the axial proton, is activated selectively, and the carbocation resulting from the migration reacts with naphthalene. This is an interesting example of the stereoselective C–H activation of alkanes.

Two C–H activation reactions of hydrocarbons with $GaCl_3$ are also known: the diethynylation of 1,4-enynes (Scheme 14) and arylation of cycloalkanes (Scheme 18). In the former, the complex formation of a carbon–carbon triple bond with $GaCl_3$ may play an important role (Scheme 19). Proton abstraction at the relatively acidic methylene C–H then generates a nucleophilic propargylgallium and liberates HCl. This C–H activation is very much in contrast to that of cycloalkanes, in which the resultant organogallium intermediate undergoes electrophilic aromatic substitution. In the latter, the active species has an electron-deficient carbon center. It should be noted that $GaCl_3$ generates organogallium intermediates with apparently different natures with hydrocarbons, 1,4-enynes, and cycloalkanes.



Scheme 19.

Organogallium reagents have become popular in organic synthesis in the past five years. However, we consider that gallium chemistry is still young and that other interesting synthetic applications of $GaCl_3$ will emerge.

[1] M. Yamaguchi, in *Science of Synthesis, Houben-Weyl, Methods of Molecular Transformations*, vol. 7 (Eds.: R. Noyori, H. Yamamoto), Georg Thieme Verlag, Stuttgart, **2004**, p. 387–412.
[2] M. Yamaguchi, in *Main Group Metals in Organic Synthesis* (Eds.: H. Yamamoto, K. Oshima), Wiley-VCH Verlag, Weinheim, **2004**, p. 307–322.
[3] M. Yamaguchi, A. Hayashi, M. Hirama, *Chem. Lett.* **1995**, 1093–1094.
[4] M. Yamaguchi, T. Sotokawa, M. Hirama, *Chem. Commun.* **1997**, 743–744.
[5] M. Yamaguchi, T. Tsukagoshi, M. Arisawa, *J. Am. Chem. Soc.* **1999**, *121*, 4074–4075.
[6] M. Arisawa, C. Miyagawa, S. Yoshimura, Y. Kido, M. Yamaguchi, *Chem. Lett.* **2001**, 1080–1081.
[7] M. Arisawa, C. Miyagawa, M. Yamaguchi, *Synthesis* **2002**, 138–145.
[8] M. Arisawa, K. Akamatsu, M. Yamaguchi, *Org. Lett.* **2001**, *3*, 789–790.
[9] K. Kobayashi, M. Arisawa, M. Yamaguchi, *Inorg. Chim. Acta* **1999**, *296*, 67–71.
[10] R. Amemiya, Y. Nishimura, M. Yamaguchi, *Synthesis* **2004**, 1307–1314.
[11] M. Arisawa, R. Amemiya, M. Yamaguchi, *Org. Lett.* **2002**, *4*, 2209–2211.
[12] R. Amemiya, A. Fujii, M. Arisawa, M. Yamaguchi, *Chem. Lett.* **2003**, 298–299.
[13] R. Amemiya, A. Fujii, M. Arisawa, M. Yamaguchi, *J. Organomet. Chem.* **2003**, *686*, 94–100.
[14] Y. Nishimura, R. Amemiya, M. Yamaguchi, manuscript in preparation.
[15] R. Amemiya, A. Fujii, M. Yamaguchi, *Tetrahedron Lett.* **2004**, *45*, 4333–4335.
[16] K. Kobayashi, M. Arisawa, M. Yamaguchi, *J. Am. Chem. Soc.* **2002**, *124*, 8528–8529.
[17] R. Amemiya, K. Suwa, J. Toriyama, Y. Nishimura, M. Yamaguchi, *J. Am. Chem. Soc.* **2005**, *127*, 8252–8253.
[18] M. Yamaguchi, Y. Kido, A. Hayashi, M. Hirama, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1313–1315.
[19] Y. Kido, S. Yoshimura, M. Yamaguchi, T. Uchimaru, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1445–1458.
[20] Y. Kido, M. Arisawa, M. Yamaguchi, *J. Synth. Org. Chem. Jpn.* **2000**, *58*, 1030–1036.
[21] Y. Kido, F. Yonehara, M. Yamaguchi, *Tetrahedron* **2001**, *57*, 827–833.
[22] Y. Kido, M. Yamaguchi, *J. Org. Chem.* **1998**, *63*, 8086–8087.
[23] F. Yonehara, Y. Kido, M. Yamaguchi, *Chem. Commun.* **2000**, 1189–1190.
[24] M. Arisawa, A. Suwa, M. Ashikawa, M. Yamaguchi, *ARKIVOC* **2003**, 24–34.
[25] F. Yonehara, Y. Kido, S. Morita, M. Yamaguchi, *J. Am. Chem. Soc.* **2001**, *123*, 11310–11311.
[26] F. Yonehara, Y. Kido, H. Sugimoto, S. Morita, M. Yamaguchi, *J. Org. Chem.* **2003**, *68*, 6752–6759.

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