Trichlorogallium and trialkylgalliums in organic synthesis†

Masahiko Yamaguchi* and Yoshio Nishimura

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Organic gallium compounds formed by the interactions of organic compounds with trichlorogallium or trialkylgalliums exhibit various reactivities, and their use in organic synthesis is described.

1 Introduction

Over the past decades, a considerable number of studies have been conducted on the use of organic gallium compounds in organic synthesis. These compounds revealed reactivities quite different from those of other group 13 reagents, organic boron, aluminum, and indium compounds.[1–9] "Organic gallium compounds" here refers to organic compounds activated by gallium(III) reagents, which include both organogallium compounds with C–Ga bonds and gallium-activated organic compounds without C–Ga bonds. Summarized in this review are our studies of the use of gallium(III) reagents and catalysts, particularly trichlorogallium and trialkylgalliums, with emphasis on the formation and reactivity of organic gallium compounds.

The synthetic use of gallium(III) reagents and catalysts involves a two-step transformation: (1) the formation of organic gallium compounds and (2) the reaction of organic gallium compounds. Organic gallium compounds can be formed using several methods from organic compounds by treatment with trichlorogallium, trimethylgallium or triethylgallium, all of which are commercially available. In general, it is convenient to use stock solutions of these gallium(III) reagents in methylcyclohexane, since this solvent is liquid over a wide temperature range. The reactivity of organic gallium compounds is discussed focusing on protodegallation, carbometalation, carbonyl addition, and reactions of their π-complexes. Several typical synthetic organic transformations employing gallium(III) reagents and catalysts are described: (1) the vinylation of enolates and related compounds; (2) the ethynylation of enolates and related compounds; (3) the synthesis of polyethynylmethanes; (4) electrophilic aromatic alkenylation; and (5) electrophilic aromatic alkylation.

Department of Organic Chemistry, Graduate School of Pharmaceutical Sciences, Tohoku University, Aoba, Sendai, 980-8578, Japan. E-mail: yama@mail.pharm.tohoku.ac.jp
† This paper is dedicated to the late Professor Yoshihiko Ito.

2 Formation of organic gallium compounds

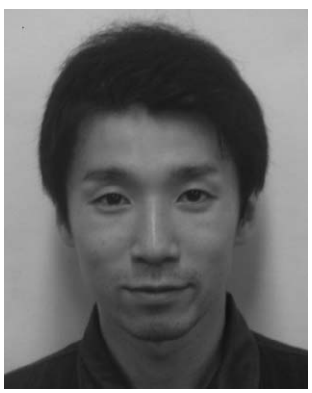
Organic gallium compounds are formed from organic compounds by (1) deprotonation, (2) transmetalation, (3) π-complexation, (4) oxidative addition, (5) hydride abstraction, and (6) heteroatom interaction.

2.1 Deprotonation

The deprotonation of organic compounds with gallium(III) reagents is a straightforward method of generating organogallium compounds. The use of trichlorogallium in such a process produces compounds with $GaCl_2$ moiety and liberates hydrogen chloride, whereas that of trialkylgalliums produces compounds with GaR_2 moiety with the concomitant formation of alkanes. The ligand exchange on the gallium metal then can produce equilibrium mixtures. Therefore, it is generally

Masahiko Yamaguchi

Masahiko Yamaguchi is a professor at Tohoku University. He received his BSc (1977) and PhD degrees (1982) from the University of Tokyo. He joined Kyushu Institute of Technology in 1982 as assistant professor and was promoted to associate professor in 1985. He became a member of the Department of Chemistry at Tohoku University in 1991. From 1987 to 1988 he worked as a post doctoral fellow at Yale University with Professor S. Danishefsky. In 1997, he was appointed professor in the Faculty of Pharmaceutical Sciences of Tohoku University. He received the Chemical Society of Young Chemists award in 1986. His research interests are in the area of synthetic methodology and functionally interesting compounds.



Yoshio Nishimura

Yoshio Nishimura is an assistant professor at Tohoku University. He was born in Fukuoka in 1978, and received his BSc (2002) and MSc degrees (2004) from Tohoku University. In 2006, he was appointed assistant professor in the Graduate School of Pharmaceutical Sciences, Tohoku University. His research interests are in the area of organogallium chemistry.

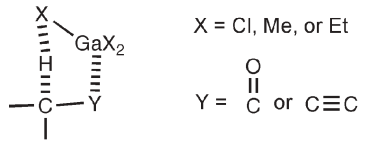


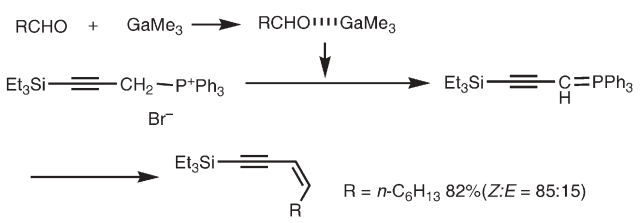
Fig. 1

difficult to determine which species is actually involved in subsequent reactions. However, it may reasonably be assumed in many cases that Lewis acids with the general formula $RGaCl_2$ are more reactive than other species, since they can activate various organic compounds.

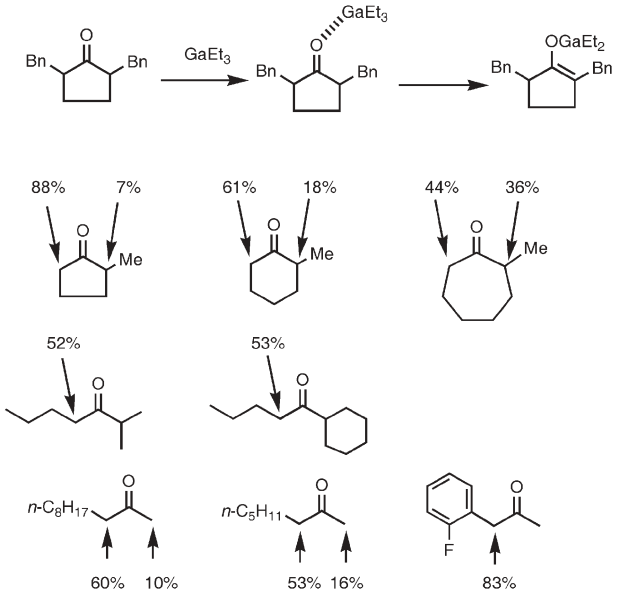
The mechanism of the above deprotonation reaction is another subject of interest. As indicated in our studies, it often happened that the initial coordination of Lewis acidic gallium centers with a Lewis basic sites Y in organic compound is followed by the intramolecular deprotonation of an adjacent C–H bond with gallium ligands X, either chloride or alkyl (Fig. 1). The groups Y are carbonyl or acetylene, and it is probable that other functional groups can also be used.

Propargylphosphonium salts are deprotonated with trimethylgallium at the propargyl position giving ylides, which undergo the Wittig reaction with aldehydes (Scheme 1).[10] When (3-triethylsilyl-2-propynyl)triphenylphosphonium salt is treated with an aldehyde and trimethylgallium in THF at room temperature, an enyne with the (*Z*)-configuration is obtained predominantly. The Wittig reaction of the stabilized propargyl ylides generally produces (*E*)-isomers, and the formation of a (*Z*)-isomer in this reaction is notable. Another observation is that the presence of an aldehyde is essential for deprotonation, and that the treatment of the phosphonium salt with trimethylgallium at room temperature followed by D_2O induces no deuteration. Thus, the coordination of a carbonyl with trimethylgallium must enhance the basicity of gallium(III) compounds.

Ketones are deprotonated at the α-position generating gallium enolates using either trialkylgalliums or trichlorogallium. When 2,5-dibenzylcyclopentanone is treated with triethylgallium at 125 °C, the corresponding gallium enolate is formed in quantitative yield as indicated by the results of a trapping experiment with acetic anhydride (Scheme 2).[11] No carbonyl addition products, *i.e.*, cyclopentanol and ethylcyclopentanol, are detected. For comparison, when the same ketone is reacted with triethylaluminium, low amounts of acetylated products are formed accompanied by considerable amounts of cyclopentanol and ethylcyclopentanol. Although triethylgallium is a non-nucleophilic base for ketone enolization, the corresponding aluminum compound exhibits



Scheme 1



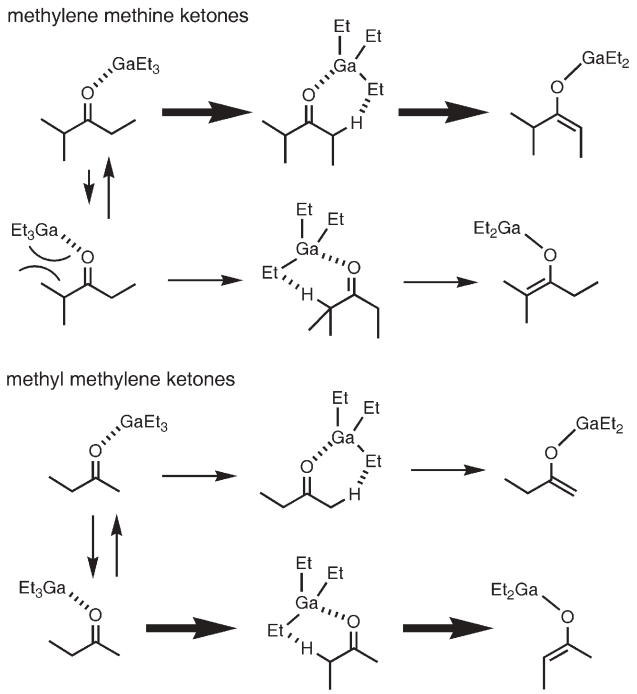
Scheme 2

nucleophilic and reducing characteristics. The use of alkylmetals for enolate formation has little precedent. Analogously to ylide formation, the initial coordination of the ketone carbonyl oxygen likely occurs with triethylgallium, which follows the deprotonation at an adjacent C–H bond.

Regioselectivity in the enolization of unsymmetrical ketones has been the focus of considerable interest, and thus gallium enolate formation was compared with conventional methods. The reaction of 2-methylcyclopentanone with triethylgallium at 125 °C followed by treatment with benzoyl chloride at room temperature gives 5-benzoyl and 2-benzoyl derivatives in 88 and 7% yields, respectively. Other α-substituted cyclic ketones with larger rings show similar tendencies, although their selectivities are lower. Acyclic ketones, namely, 2-methyl-3-heptanone and 1-cyclohexyl-1-pentanone, are exclusively deprotonated at the methylene site. Thus, methylene methine ketones are deprotonated at less hindered sites with triethylgallium.

The treatment of 2-undecanone and 2-octanone with triethylgallium at 150 °C followed by benzoyl chloride yields a *C*-benzoylated product that reacts at the methylene moiety (Scheme 2). Small amounts of self-aldols are formed, which are derived from deprotonation at the methyl group. Unsymmetrical ketones with α-methyl and α-methylene groups are deprotonated at the hindered methylene moiety.

Enolate formation using triethylgallium shows notable preference for methylenes. Both methylene methine ketones and methyl methylene ketones are deprotonated at the methylene moiety. The lack of serious deuterium scrambling in the reaction of 1,1,1-trideuterio-2-octanone is consistent with the formation of kinetic enolates. The methylene deprotonation that takes place at high temperatures under kinetic control is an interesting aspect of this method. The results are in contrast to the regioselectivity of bulky alkali-metal dialkylamides such as lithium diisopropylamide (LDA), which under kinetic control deprotonate ketones at less

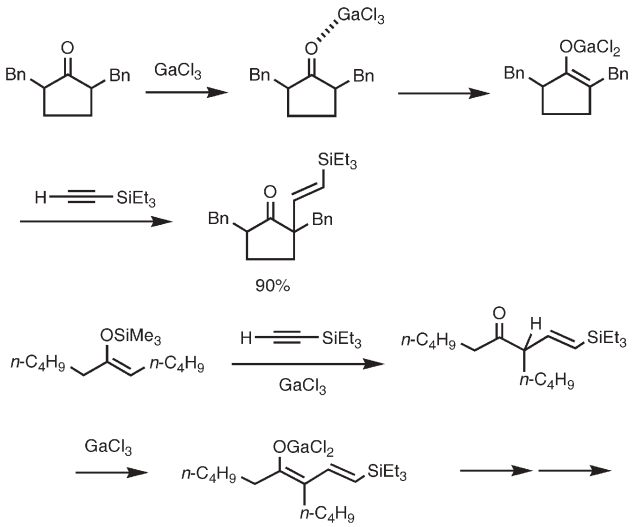


Scheme 3

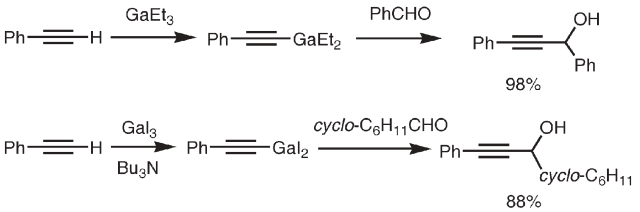
hindered sites. Although the origin of this regioselectivity is not clear, an explanation can be presented (Scheme 3). The initial step in enolization should be the coordination of triethylgallium with carbonyl n-electrons as suggested in the deprotonation of propargylphosphonium salt. For methylene methine ketones, the coordinated gallium Lewis acid should be directed to the methylene site to prevent steric repulsion with secondary alkyl groups, and the subsequent deprotonation occurs on the methylene side. When methyl methylene ketones interact with triethylgallium, the Lewis acid may approach from either direction, and at high temperatures enolization proceeds by the transition states forming thermodynamically stable substituted olefins.

LDA, generated from butyllithium and diisopropylamine, is employed as the base to enolize ketones, since butyllithium readily undergoes an addition reaction with carbonyls. The method, however, requires stoichiometric amounts of amines, which are not essential for transformation. The coordination of amines with metal enolates often complicates the analysis of the reaction. The use of trialkylgalliums for ketone enolization, which produce simple alkanes as the only byproduct, may have synthetic utility because of their operational simplicity. Although high temperatures are required for the enolization, the reactivity of gallium enolates which undergo acylation or aldol reaction below room temperature is high. This method therefore may be useful for reactions of unfunctionalized ketones.

Trichlorogallium can enolize ketones as well as the trialkylgalliums. The treatment of 2,6-dibenzylcyclopentanone with trichlorogallium gives gallium enolate, which undergoes silylvinylation with triethylsilylacetylene (Scheme 4).[12] It is again likely that coordination of the carbonyl with the Lewis acid trichlorogallium precedes deprotonation. Trichlorogallium also deprotonates acidic α-vinyl ketones to



Scheme 4

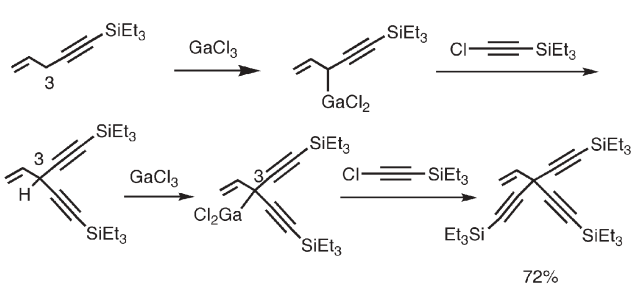


Scheme 5

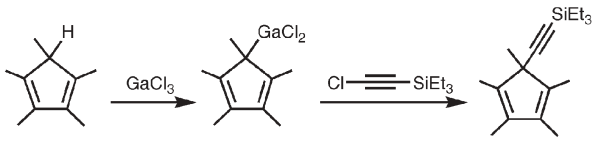
generate conjugated gallium enolates, which undergo a second vinylation at the α-position.[13]

The treatment of 1-alkynes with triethylgallium at room temperature generates gallioalkynes which add to aldehydes (Scheme 5).[14] 1-Alkynes can also be deprotonated with trihalogallium in the presence of amines, as examined by other researchers. The treatment of 1-alkynes with triiodogallium and tributylamine converts them to gallioalkynes which add to aldehydes (Scheme 5).[15] The acceleration of the allylgallation of 1-alkynes in the presence of diisopropylethylamine is attributed to the *in situ* formation of alkynylgallium.[16]

The deprotonation of 1,4-enynes proceeds at *ca.* 130 °C with trichlorogallium generating propargylgalliums (Scheme 6).[17] The organogallium intermediates undergo ethynylation with triethylsilylchloroacetylene at the 3-position giving vinyldiethynylmethanes, which is followed by the second deprotonation and ethynylation providing vinyltriethynylmethanes.



Scheme 6



Scheme 7

Because no diethynylmethanes are detected in the reaction mixture, the second deprotonation must be more rapid than the first ethynylation. It is likely that the deprotonation is initiated by the coordination of a triple bond with trichlorogallium, which enhances the basicity of the gallium(III) reagent and the acidity of the adjacent protons. As will be noted later, such interactions of trichlorogallium and silylacetylene were detected by low temperature NMR studies (Scheme 11). 1,4-Enynes are not deprotonated by trialkylgalliums, which might be due to the lower tendency of the gallium(III) reagent to form a π-complex with acetylene. Although 2,6-di(*tert*-butyl)-4-methylpyridine was added to the reaction mixture in order to improve the yield of the product, it was confirmed that trichlorogallium itself and not pyridine was involved in the deprotonation. Analogously, 1,4-diynes are deprotonated with trichlorogallium and diethynylated with triethylsilylchloroacetylene yielding tetraethynylmethanes.

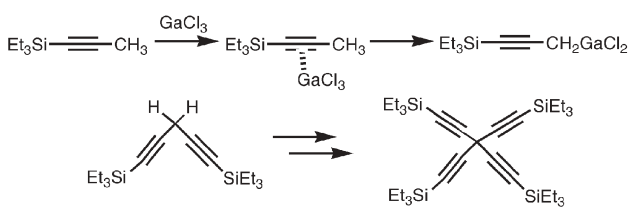
1,4-Dienes such as 1,4-pentadiene and 1-vinyl-2-cyclohexene are inert to deprotonation with trichlorogallium, which might be due to these substrates being less acidic than acetylenic derivatives. Highly acidic 1,2,3,4,5-pentamethylcyclopentadiene, however, reacts with triethylsilylchloroacetylene in the presence of trichlorogallium providing ethynylated cyclopentadiene (Scheme 7).[18] Acidity apparently plays an important role.

Even triethylsilylacetylenes can be deprotonated at the propargyl position with trichlorogallium, causing one-step triethynylation to proceed (Scheme 8).[19] The presence of a silyl group is essential, and no ethynylation proceeds with 4-octyne. The role of the silyl group may be to enhance the acidity of propargyl protons.

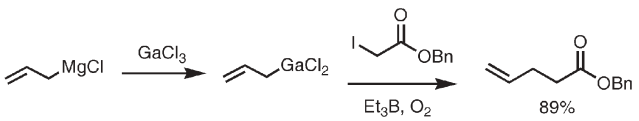
Thus, trichlorogallium and trialkylgalliums exhibit interesting properties as bases which can deprotonate various organic molecules.

2.2 Transmetalation

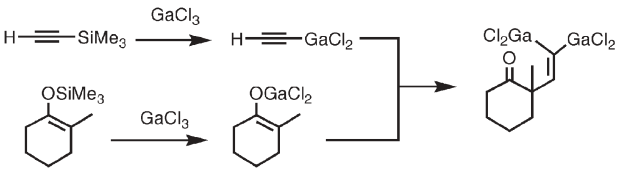
The transmetalation of readily available organometallic reagents with trichlorogallium is another convenient method of generating organogallium compounds. Reactive organolithium and organomagnesium compounds undergo transmetalation generally at room temperature. Examples are allyl-,[20]



Scheme 8



Scheme 9



Scheme 10

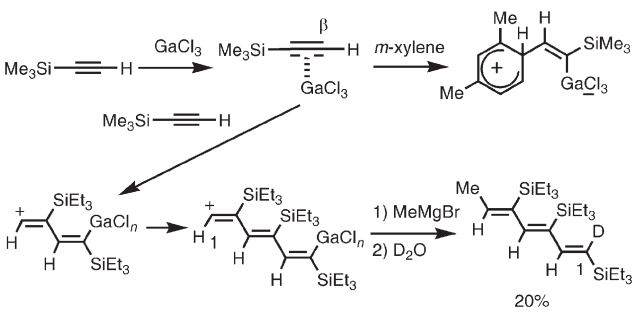
vinyl-,[21] alkynyl-,[22] 3-butenylmagnesium halides,[23] lithium acetylides,[24] lithiated phenols,[25] and lithiated anilines[26] (Scheme 9).

The transmetalation of organosilicon compounds with trichlorogallium generates organogallium species. The organosilicon compounds used included silyl enol ethers, ketene silyl acetals, allylsilanes, and silylacetylenes. Regioselectivity in transmetalation was retained in the reaction of unsymmetrical silyl enol ethers (Scheme 10).[27]

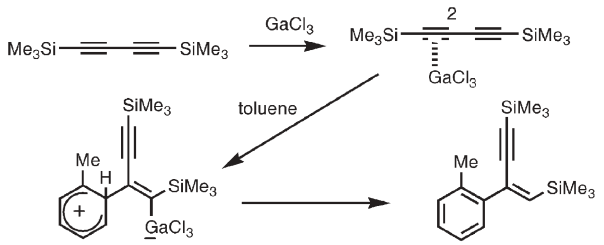
2.3 π-Complexation

An interesting feature of trichlorogallium as a Lewis acid among main group elements is that it can interact with unsaturated compounds. Trichlorogallium interacts with triethylsilylacetylene as indicated by the downfield shifts of ^{13}C and ^{1}H NMR peaks for acetylene carbons and protons at −70 °C (Scheme 11).[19,28] The β-carbon exhibits a larger shift suggesting its electron-deficient nature. Calculations indicates the formation of a π-complex with a tetrahedral gallium center and a Si–C–C–H moiety with an almost straight structure.[28]

The gallium complex is highly electrophilic and reacts with aromatic hydrocarbons at −78 °C. The nucleophilic attack occurs at the β-carbon of silylacetylene in accordance with the NMR shifts, and organogallium intermediates with a *cis*-configuration in terms of the arene and gallio group are formed. The arenium intermediates formed are stable at low temperatures, and unlike common arenium intermediates in electrophilic aromatic substitution reactions do not aromatize spontaneously at −78 °C. The existence of a Ga–C bond at the olefin moiety is confirmed by methylation with methyllithium giving 2-(dimethylgallio)vinylated arenes.



Scheme 11



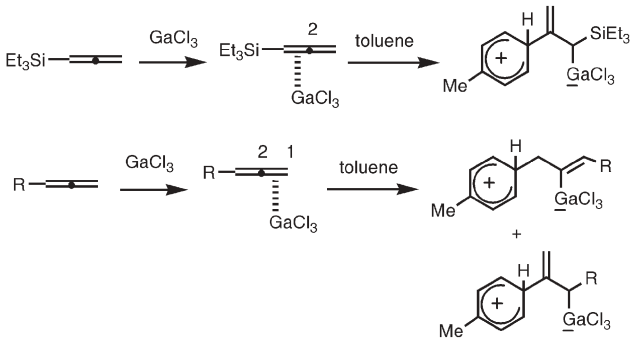
Scheme 12

In the absence of aromatic hydrocarbons, the π-complex formed from trichlorogallium and triethylsilylacetylene undergoes spontaneous trimerization (Scheme 11).[29] The first and second attacks of triethylsilylacetylene take place at the β-position of the silyl group with a *cis*-configuration in terms of the attacking silylacetylene and existing silyl group. An organogallium 1-hexatrienium cation is formed as indicated by NMR results; on treatment with methyllithium, the cation yields 1-gallio-1,3,5-heptatriene. The reaction with D_2O provides the corresponding 1-deuterated (1*E*,3*Z*,5*Z*)-heptatriene. Because no dimers or higher oligomers are isolated, the trimer must have higher thermodynamic stability than other oligomers.

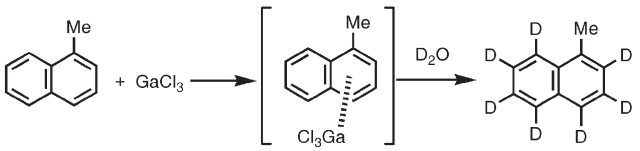
1,4-Disilylated 1,3-butadiyne activated with trichlorogallium also reacts with aromatic hydrocarbons at the 2-position (Scheme 12).[30] As will be noted later, this π-complex shows preference for reaction at the *o*-position of alkylbenzenes. The vinylgallium species, however, is not trapped by deuteration experiments, and thus proton transfer from the arenium intermediate to C–Ga bond might be rapid.

1-Triethylsilylallene formed a π-complex with trichlorogallium, and NMR experiments indicate complexation at a double bond adjacent to the silyl group, not at the terminal olefin (Scheme 13).[31] The complex is attacked by aromatic hydrocarbons at the 2-position giving 1-silyl-1-propen-2-ylated arenes. Proton transfer from the arenium intermediate to the organogallium again is rapid, and no deuterium trapping takes place. The reactivity of alkyl-substituted allenes is different, and aromatic hydrocarbons attack at the 1- and 2-positions giving 1-aryl-2-alkenes and 2-aryl-1-alkenes, respectively, with the former predominating. In this case, π-complex formation appears to occur at the terminal double bond.

Aromatic hydrocarbons form π-complexes as indicated by the formation of colored solutions when trichlorogallium is dissolved in benzene or toluene. Treatment of the π-complex



Scheme 13



Scheme 14

formed from 1-methylnaphthalene and trichlorogallium with D_2O results in random deuteration in the aromatic nuclei (Scheme 14).[32] No deuteration occurs at the methyl group. Because such deuteration takes place even when the complex is treated with alkaline D_2O, the results can not be ascribed to the acid-catalyzed hydrogen–deuterium exchange. The lack of appreciable selectivity in the deuteration suggests the formation of an organogallium intermediate.

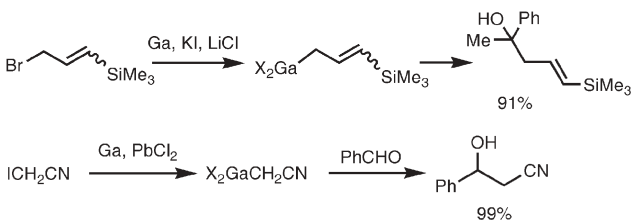
2.4 Oxidative addition

Organohalogen compounds can undergo oxidative addition with gallium metal to form organogallium halides, as has been reported by other researchers. Allyl halides, propargyl halides, and α-halo carbonyl compounds react in the presence of promoters such as alkali-metal halides, lead halide, and indium metal (Scheme 15). The reaction of allyl or propargyl halides under Barbier conditions with aldehydes or ketones yields unsaturated alcohols.[33,34] Gallium enolates are generated from metallic gallium and trichloroacetate or iodoacetonitrile in the presence of a catalytic amount of lead dichloride and also add to aldehydes.[35]

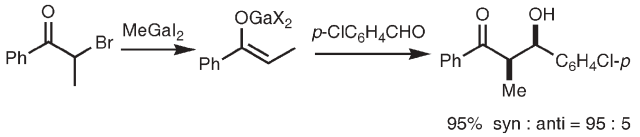
Halogen–metal exchange takes place with α-bromo ketones and triiodogallium, prepared *in situ* from gallium metal and iodine, and the enolates react with aldehydes or imines.[36] The use of methylgallium diiodide, prepared from gallium metal, iodine, and methyllithium, enhances the diastereoselectivity of the aldol reaction (Scheme 16).

2.5 Hydride abstraction

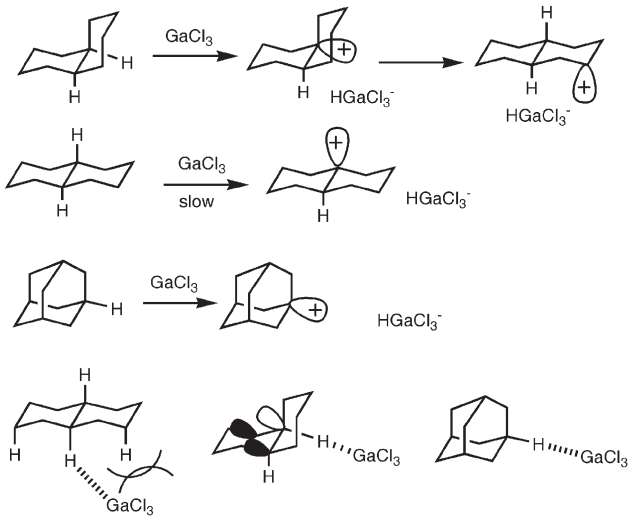
Trichlorogallium can abstract hydride from cycloalkanes generating carbocations with a tetrachlorogallate counteranion.[32,37] The organic gallium compounds undergo Friedel–Crafts alkylation with reactive aromatic hydrocarbons such as



Scheme 15



Scheme 16

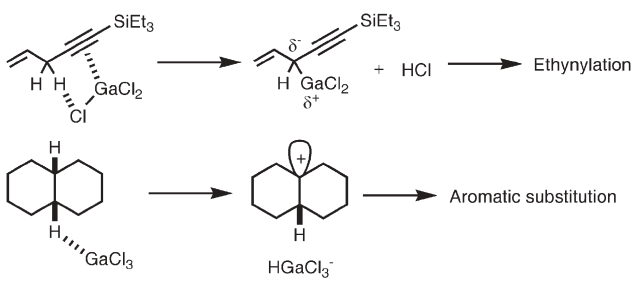


Scheme 17

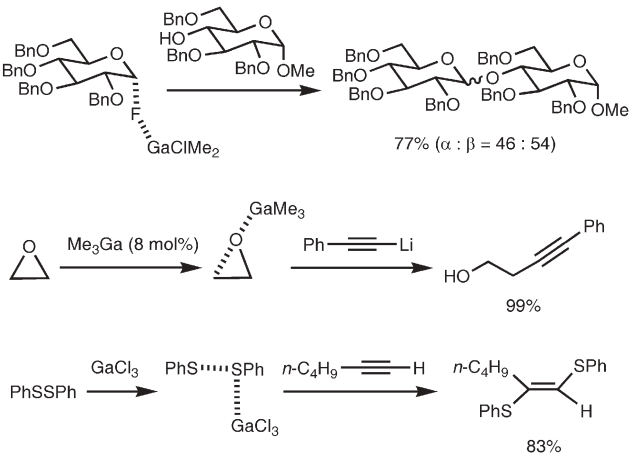
naphthalene. The reaction of *cis*-perhydronaphthalene and naphthalene in the presence of a catalytic amount of trichlorogallium yields 2-naphthylated *trans*-perhydronaphthalene; however, the *trans*-perhydronaphthalene reacts much less effectively (Scheme 17). The equatorial tertiary proton of perhydronaphthalene, rather than the axial proton, is activated selectively. Adamantane is also naphthylated at the 1-position from which the equatorial hydrogen is abstracted.

Trichlorogallium can access an equatorial C–H bond by either the side-on or front-side approach; the back-side approach is unlikely to occur in this case, taking the adamantane case into account. The side-on approach may be hindered for axial C–H *trans*-perhydronaphthalene by 1,3-diaxial interactions, and the transition state of the equatorial front-side approach may be stabilized by the hyperconjugation of adjacent C–C bonds.

Trichlorogallium can interact with hydrocarbon C–H bonds and abstract protons and hydrides as shown in the diethynylation of 1,4-enynes and the arylation of cycloalkanes, respectively (Scheme 18). In the former reaction, the π-complex formation of a carbon–carbon triple bond with trichlorogallium may play an important role. Proton abstraction at the relatively acidic methylene C–H generates nucleophilic propargylgallium, liberating hydrogen chloride. In the latter reaction, trichlorogallium is considered to directly interact with σ-electrons. Trichlorogallium exhibits dual reactivity against hydrocarbons, 1,4-enynes and cycloalkanes.



Scheme 18



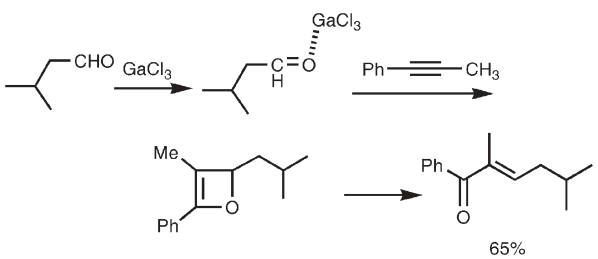
Scheme 19

2.6 Heteroatom interactions

Analogously to other metal Lewis acids, gallium(III) reagents interact with organoheteroatom compounds possessing n-electrons such as chloride, fluoride, oxygen, and sulfur. The resulting organic gallium compounds with weak carbon–heteroatom bonds exhibit high reactivity towards nucleophiles including aromatic hydrocarbons, alkynes, alkenes, isonitriles, water, alcohols, organolithium compounds, and organotin compounds, which have been extensively studied by other researchers.

Trichlorogallium has been used in the Friedel–Crafts alkylation as a Lewis acid, in which the reactions are initiated by the interactions of the Lewis acid with halogen n-electrons.[38,39] Interactions of gallium(III) with fluoride are employed for glycosidation using glucosyl fluorides in the presence of chlorodimethylgallium (Scheme 19).[40] Epoxides are also effectively activated by interactions of gallium(III) reagents at oxygen n-electrons. A catalytic amount of trimethylgallium promotes the alkynylation of oxiranes with lithium acetylides.[41] An additional adjacent oxygen functionality markedly accelerates the ring opening of epoxides with a trimethylgallium catalyst, which suggests the formation of pentacoordinate gallium species.[42] Arylisonitriles attack gallium-activated epoxides giving lactams.[43] The soft nature of gallium is used in the activation of disulfides, which are attacked by alkynes and alkenes.[44]

The interaction of carbonyls with trichlorogallium is another important activation mode, and various nucleophiles undergo attack at the carbonyl carbon (Scheme 20).[45–47] For example, the reaction with alkynes gives naphthalenes,[48]



Scheme 20

1,4-dienes,[49] or enones[50] depending on the structure of the substrate and the reaction conditions.

3 Reactivity of organic gallium compounds

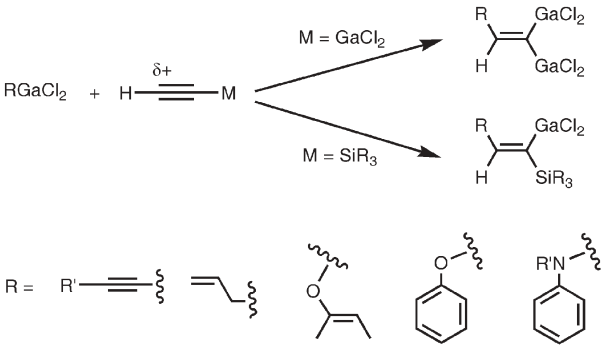
3.1 Protodegallation

The protodegallation of organogallium compounds is often not straightforward, which is in contrast to the protonation of organolithium or organoaluminium compounds. C–$GaCl_2$ bonds are relatively stable towards hydrolysis even in excess water at room temperature. It is therefore important to complete protodegallation before carrying out isolation procedures; otherwise, slow decomposition during purification results in low yields of the products. In general, aqueous acids, such as 6 M sulfuric acid, are effective for the protodegallation of C–$GaCl_2$ bonds compared with neutral water or aqueous bases. For example, the carbogallation of alkynes with gallium enolates provides vinylgallium intermediates, which are protodegallated with aqueous sulfuric acid (Scheme 27).[27] Treatment with silica gel may also be used. Alternatively, treatment with organolithium or magnesium reagents provides compounds possessing C–GaR_2 bonds, which are readily protodegallated with water.[28] The conditions for protodegallation depend on the functionality existing in the molecules, and sometimes optimization of the conditions for protodegallation is required.

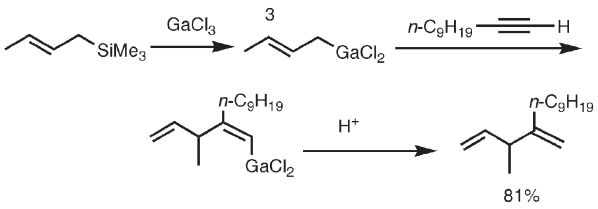
3.2 Carbometalation

An interesting reactivity of organogallium compounds is their ability to undergo carbometalation (carbogallation) with C–C triple bonds. In particular, alkyldichlorogalliums undergo facile carbometalation, which may be due to the Lewis acid nature of the gallium center and strong interactions with acetylene π-electrons (Scheme 21). The organogallium compounds that undergo carbometalation include alkynylgalliums, allylgalliums, propargylgalliums, gallium enolates, gallium phenoxides, and gallium anilides.

Carbogallation effectively proceeds with metalated acetylenes. The reaction of gallioacetylenes occurs below room temperature, whereas that of silylacetylenes occurs above 80 °C. The addition reaction of 1-alkynes is slow, and dialkylsubstituted alkynes are inert. 1-Gallation and 1-silylation activate the triple bond toward carbometalation, which may be due to the formation of electron-deficient triple bonds



Scheme 21



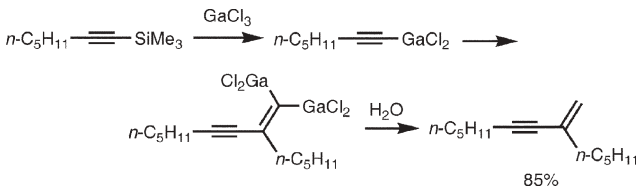
Scheme 22

induced by the inductive effect of the metals. The regiochemistry in carbogallation is in accordance with other carbometalation reactions, and 1,1-digallioalkenes or 1-gallio-1-silylalkenes are formed. *cis*-Addition generally occurs. The carbogallation of silylacetylenes is slower than that of gallioacetylenes, probably reflecting the less polarized nature of the C–C triple bond in the former compounds. The regioselectivity in the carbometalation of 1-alkynes, however, reverses, and the C–C bond forms at the 2-position and the gallio group is attached at the 1-position.

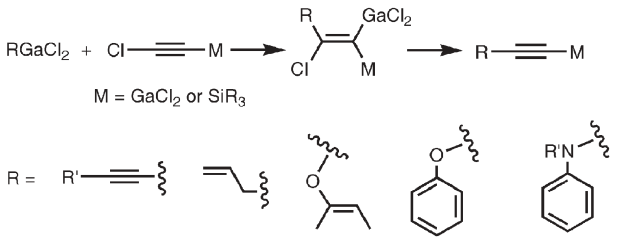
Allyldichlorogalliums add to 1-alkynes or silylated alkynes giving 1,4-dienes after protodegallation.[51] Although 1-silylalkynes undergo *cis*-addition, the stereochemistry for the reaction of 1-alkynes depends on the type of alkyl substituents. Smaller alkyl derivatives give comparable amounts of (*E*)- and (*Z*)-isomers, as indicated by results of the deuteration experiment; however, *cis*-addition predominates with cyclohexylacetylene. Crotylgallium undergoes carbometalation with acetylene at the 3-position rather than at the 1-position (Schemes 22).

Alkynyldichlorogalliums spontaneously dimerize in hydrocarbon solvents to give 1,1-digallio-1-alken-3-ynes, which are converted to 1,3-enynes by protodegallation (Scheme 23).[24] Such coupling also takes place with lithium acetylides in the presence of trichlorogallium. It is notable that a main-element-metalated 1-alkyne is unstable in hydrocarbon solutions, which may be ascribed to the strong interactions of the $GaCl_2$ group in gallioacetylene with a C–C triple bond of another gallioacetylene.

The carbometalation of gallium enolates and gallioacetylene derived from trimethylsilyl enol ethers and trimethysilylacetylene with trichlorogallium, respectively, proceeds below room temperature (Scheme 10).[27] The resulting γ,γ-digallio-β-enones are protodegallated giving α-vinylated ketones. Gallium enolates carbometalate with triethylsilylacetylene above 80 °C giving β-gallio-β-triethylsilylvinyl ketones (Scheme 34).[52] The slower transmetalation of triethylsilylacetylene with trichlorogallium than trimethylsilyl acetylene can be employed to develop a catalytic version of the reaction (Scheme 34). Gallium anilides[26] and gallium phenoxides[25] also undergo carbometalation.



Scheme 23



Scheme 24

The carbometalation of organogallium compounds proceeds with chloroacetylenes as well as acetylenes (Scheme 24). The reactivities of gallioacetylene and galliochloroacetylene are similar, and gallium enolates rapidly add to both compounds below room temperature. The regiochemistries and stereochemistries of both compounds are also similar, and 1,1-digallioalkenes or 1-silyl-1-gallioalkenes form in the *cis*-addition mode. The chloride appears to exert a small effect on carbogallation of alkynes. One difference is the fate of carbometalated adducts. Chloroacetylene adducts undergo facile β-elimination giving ethynylated products, which may be due to the *trans*-configuration of the gallio moiety and chloride formed by *cis*-carbometalation. The elimination, however, is not very rapid below room temperature, and the presence of nucleophilic ligands promotes β-elimination. In the reaction of gallium enolates and galliochloroacetylene, the addition of methanol or THF to the reaction mixtures produces α-ethynyl ketones, whereas the addition of a less nucleophilic but more acidic hexafluoroisopropanol yields α-(chlorovinyl) ketones (Scheme 35).[53] Spontaneous elimination proceeds only at higher temperatures, and under such conditions ketones,[12] *N*-benzylanilines,[26] phenols,[25] and alkylacetylenes[19] are catalytically silylethynylated with triethylsilylchloroacetylene.

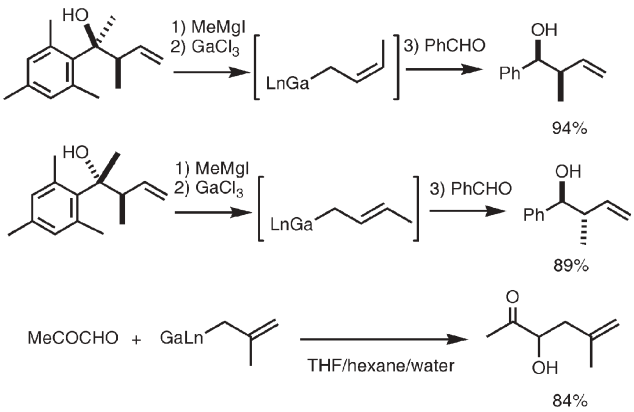
Propargyldichlorogallium undergoes carbometalation with triethylsilylchloroacetylene above 100 °C (Scheme 6).[17] The ethynylation takes place at the propargyl position giving alkynes; no allenes are formed.

3.3 Carbonyl addition

Trialkylgalliums are relatively unreactive to carbonyl addition compared with the organometallic reagents of lithium, magnesium, and aluminum; deprotonation competes (Scheme 2). In contrast, allyl or propargylgalliums react with aldehydes or ketones giving unsaturated alcohols as reported by Oshima and others.[54] The C–C bond formation of propargylgalliums generally takes place at the α-position giving acetylenic alcohols. The regioselectivity depends on the type of substituent in the allylgalliums: crotyl derivatives react at the γ-position, and silylallyl derivatives at the α-position (Scheme 25).[33,34] Taking advantage of the relative stability of allylgallium halides in water, allylation may be conducted in aqueous solvents.[55,56]

3.4 Reactions of π-complexes

π-Complexes formed from alkynes and trichlorogallium are highly electrophilic, and aromatic hydrocarbons[28] or alkynes[29]



Scheme 25

readily attack the complexes at −78 °C (Fig. 2). The reactivity is higher than that of alkenyl cations generated by the protonation of alkynes, which react with aromatic hydrocarbons only at room temperature. Silyl substitution on the alkyne generally increases the yields of the products and directs the nucleophilic attack to the β-position. The effect of a silyl group on stabilizing β-cations appears to be operating. Alkylacetylenes react at the α-carbon. *cis*-Addition stereochemistry regarding the attacking arenes and gallio group is observed.

π-Complexation enhances the acidity of the adjacent protons and basicity of trichlorogallium as shown by the deprotonation of enynes, diynes, and propynes.

4 Use of organic gallium compounds in organic synthesis

Using the above formation and reactivity of organic gallium compounds, novel and useful transformation methods have been developed which are not possible with other organometallic reagents.

4.1 Vinylation of enolates and related compounds

The alkylation of ketone enolates is a fundamental method in organic synthesis for constructing C–C bonds, and has been used to attach an sp^3-carbon at the carbonyl α-position. In contrast, vinylation and ethynylation, which attach sp^2- and sp-carbons, are not facile due to the difficulty in S_N2 and S_N1 reactions (Scheme 26). An exception to ketone enolate vinylation is a palladium-catalyzed reaction using vinyl halides, which involves oxidative addition for the activation of vinyl halides and reductive elimination to form a bond between enolate and olefin.[57] The scope of this method, however, is relatively limited. Thus, in order to introduce a vinyl group at the carbonyl α-position, stepwise methods have been employed.[58] Our group found that the carbometalation

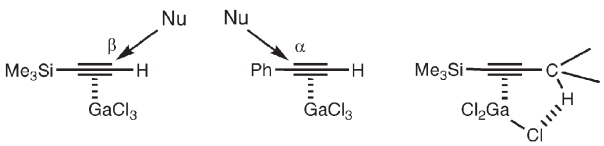
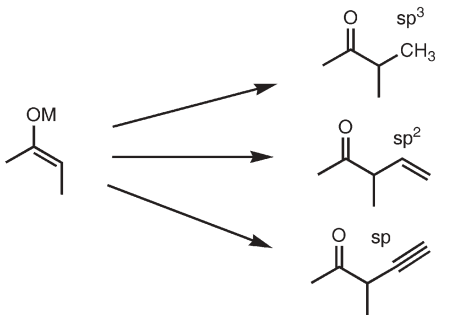


Fig. 2

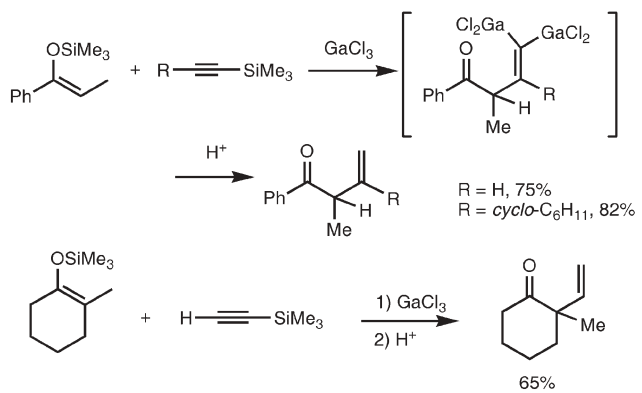


Scheme 26

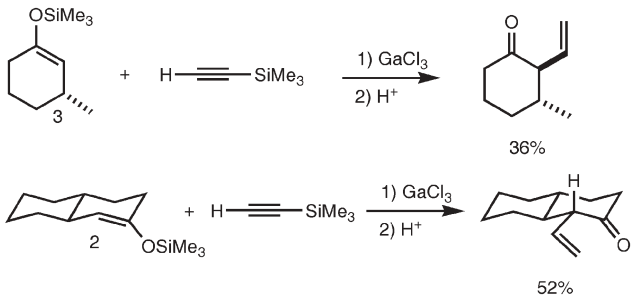
of gallium enolates and acetylenes is effective for the vinylation of enolates.

When trimethylsilyl enol ethers derived from ketones are reacted with trimethylsilylacetylene in the presence of trichlorogallium at room temperature, α-vinylated ketones are obtained after acid workup (Scheme 27).[27] The acid workup with aqueous sulfuric acid is crucial to obtain reproducible results for the protodegallation. The reaction can be applied to the synthesis of α-vinylated ketones with an acidic α-proton without isomerization to conjugated enones. Mechanistically, the reaction involves the formation of gallium enolate and gallioacetylene from a silyl enol ether and silylacetylene, respectively. Carbogallation gives γ,γ-digallio β-enones, followed by protodegallation giving α-ethenylated ketones (Scheme 3).

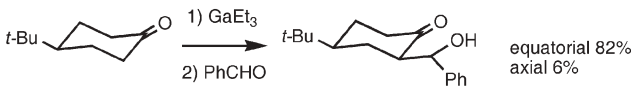
The vinylation of cyclic ketones reveals the stereochemical aspects of this reaction. 3-Alkyl substituted 1-trimethylsilyloxy-1-cyclohexenes are converted to 3-alkyl-2-ethenylcyclohexanone with the *trans*-configuration, which coincided with the stereochemistry in the alkylation of alkali-metal enolates (Scheme 28).[59] The reaction of a trimethylsilyl enol ether derived from *trans*-bicyclo[4.4.0]decan-3-one proceeds at the 2-position yielding exclusively an equatorial isomer. The stereochemistry is highly in contrast to that in the alkylation of the same bicyclic ketone alkali-metal enolate to give axial alkylated products. It is presumed that the actual species involved in the carbogallation is an α-gallio ketone and not gallium enolate; the sterically demanding dichlorogallio group occupies the equatorial position and undergoes carbogallation with the retention of the configuration.



Scheme 27



Scheme 28



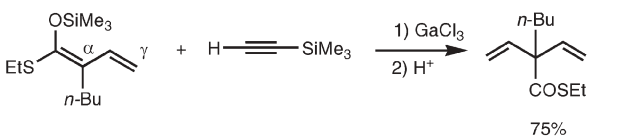
Scheme 29

Such equatorial stereoselectivity appears to be a general feature of gallium enolate reactions. The reaction of 4-(*tert*-butyl)cyclohexanone and triethylgallium forms gallium enolate, which reacts with benzaldehyde giving aldol products with equatorial isomers predominating (Scheme 29).[11] The stereochemistry is again contrasted to that of lithium enolates, which exhibit axial preferences.

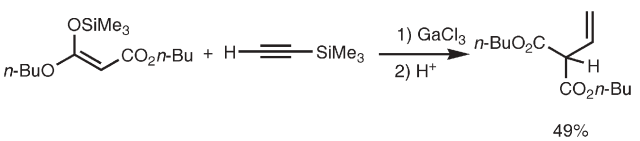
Although silyl enol ethers derived from esters cannot be vinylated under the conditions used, thioester trimethylsilyl ketene acetals are vinylated in the presence of trichlorogallium (Scheme 30).[60] In addition to ketones, products with acidic α-protons are obtained. Trimethylsilyl dienolates may be synthesized by the silylation of the products, and subsequent vinylation takes place at the α-position giving α,α-divinylated thioesters, which are not readily accessible by conventional methods.

Vinylation occurs with trimethylsilylated 1,3-dicarbonyl compounds (Scheme 31).[61] α-Substituted acetoacetates and malonates are converted to α-vinylated compounds with quaternary carbon atoms. Notably, vinylmalonates with an acidic α-proton are obtained by this method (Scheme 31). Vinylmalonate is relatively insensitive to acid; however, it rapidly isomerizes to a conjugated compound in the presence of triethylamine.

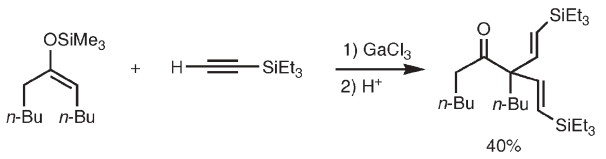
When silyl enol ethers derived from ketones possessing an α-methylene moiety are subjected to the vinylation reaction,



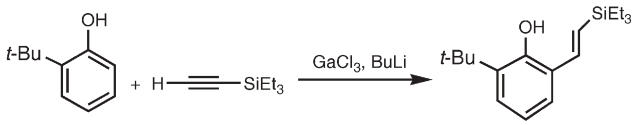
Scheme 30



Scheme 31



Scheme 32



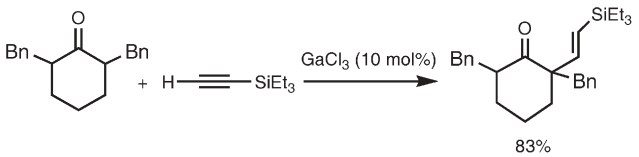
Scheme 33

α,α-divinylation takes place (Scheme 32).[13] Trimethylsilyl enol ether derived from 6-undecanone reacts with triethylsilylacetylene in the presence of trichlorogallium and 2,6-di(*tert*-butyl)-4-methylpyridine at 150 °C. The mixture may be treated with 6 M HCl in THF for 2 h to obtain α,α-bis(triethylsilylvinyl) ketones. The first vinylation proceeds *via* a gallium enolate formed by transmetalation, and the gallium enolate in the second vinylation is generated by the deprotonation of the acidic α-proton of α-vinylated ketone.

Gallium phenoxides possessing an analogous structure to gallium enolates undergo carbometalation with silylacetylene (Scheme 33). Phenoxides are generated by treatment with trichlorogallium and butyllithium and react with triethylsilylacetylene at 50 °C to give *o*-(β-silylvinyl)phenols (Scheme 34).[25] The reaction of phenols with bulkier *o*-substituents is faster, and the reaction of *o*-(*tert*-butyl)phenol reaches completion within 1 h.

The observation that triethylsilylacetylene undergoes carbometalation with gallium enolates and phenoxides without forming gallioacetylene led to the development of the catalytic version of enolate vinylation. The carbometalation of gallioacetylene provides 1,1-digalliovinyl compounds; however, it is difficult to regenerate trichlorogallium from an organogallium intermediate possessing two C–Ga bonds (Scheme 21). However, the carbogallation of silylacetylenes produces 1-gallio-1-silylalkenes which, on protonation of one C–Ga bond with hydrogen chloride, provide vinylated products with the regeneration of trichlorogallium.

α,α-Disubstituted cyclic ketones are catalytically α-triethylsilylvinylated by *in situ* protodegallation, thereby regenerating trichlorogallium.[52] The reaction of 2,5-dibenzylcyclohexanone and triethylsilylacetylene in the presence of trichlorogallium (10 mol%) and 2,6-di(*tert*-butyl)-4-methylpyridine (10 mol%) at 180 °C yields 2-(β-triethylsilylethenyl)cyclopentanone (Scheme 34). The added pyridine retards the decomposition of the products by trapping hydrogen chloride generated from



Scheme 34

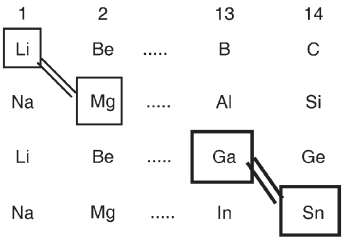


Fig. 3

a ketone and trichlorogallium. It is also likely that the pyridine hydrochloride functions as an efficient proton transfer reagent to the carbogallated intermediate. Higher temperature is required for this process.

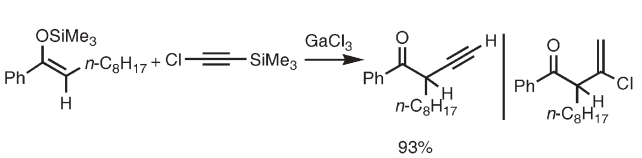
Our studies of organotin compounds revealed that they undergo similar carbometalation to organogallium compounds (Fig. 3).[62] Gallium and tin are located diagonally in the periodic table, which suggests that organometallic reagents of such elements exhibit similar reactivities, just as organolithium and organomagnesium compounds in carbonyl addition reactions.

4.2 Ethynylation of enolates and related compounds

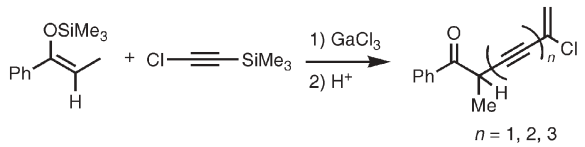
The ethynylation of ketone enolates, which results in the attachment of an sp-carbon atom at the carbonyl α-position, is more problematic than vinylation. Apart from several ethynylation reactions of active methylene compounds, the ethynylation of ketone enolates only proceeds through the reaction of lithium enolate and dichloroacetylene followed by reduction of the resulting chloroethynylated ketones.[63] The strongly basic reaction conditions employed for this process limit the scope of this method. Enolate ethynylation can be achieved using the gallium enolate method.

The ethynylation proceeds under similar conditions to vinylation, when a silylated chloroacetylene is used in place of silylacetylene. The reaction of trimethylsilyl enol ethers and trimethylsilylated chloroacetylene in methylcyclohexane at −40 °C followed by quenching with methanol gives α-ethynylated ketones (Scheme 35).[53] The β-elimination of the carbogallated intermediate takes place during the methanol treatment and not during the reaction, and the quenching conditions are crucial for the product. Quenching with 1,1,1,3,3,3-hexafluoro-2-propanol gives β-chlorovinylated ketones. The reaction can be applied to the synthesis of α-ethynylated ketones possessing acidic α-protons, which are obtained by careful isolation. The compounds are less stable towards conjugation than α-vinyl ketones, which may be due to their higher acidity.

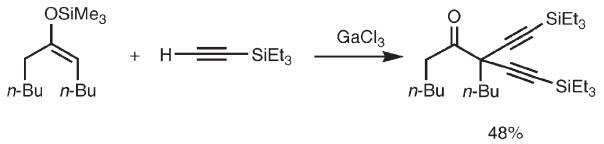
When the solvent for the reaction is switched from methylcyclohexane to dichloromethane, chlorovinylethynylated



Scheme 35



Scheme 36



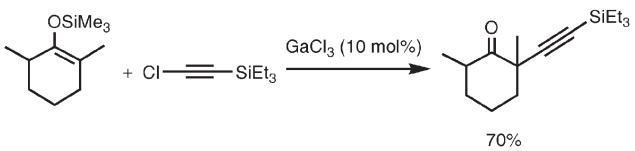
Scheme 37

ketones are obtained (Scheme 36). The products are formed by the carbometalation of gallioacetylene and gallioethynylated ketones followed by protodegallation.[64] As the reaction time lengthens, α-gallioethynylated ketones undergo further β-elimination and carbogallation with gallioacetylene sequentially yielding enynylation, endiynylation and entriynylation products. In the halogenated solvent, β-elimination occurs during the reaction, and the resulting ethynylgallium species undergoes sequential carbometalation.

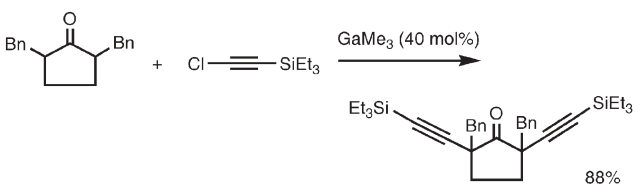
The α,α-bis(triethylsilylethynylation) of silyl enol ethers derived from methylene ketones proceeds similarly to divinylation (Scheme 32 and 37).[13] The reactivity of trimethylsilyl enol ethers derived from cyclic ketones is influenced by ring size, and large-membered-ring compounds give α,α-diethynylated ketones in acceptable yields.

α-Silylethynylation in principle is catalytic, since trichlorogallium is regenerated by β-elimination. The catalytic ethynylation of trimethylsilyl enol ethers may be conducted by treatment with triethylsilylchloroacetylene at 130 °C in the presence of 10 mol% trichlorogallium (Scheme 38).[65] Higher temperature is essential for the carbometalation of gallium enolate and triethylsilylacetylene. β-Elimination is much faster than carbogallation under these conditions because no chlorovinylated ketones are detected.

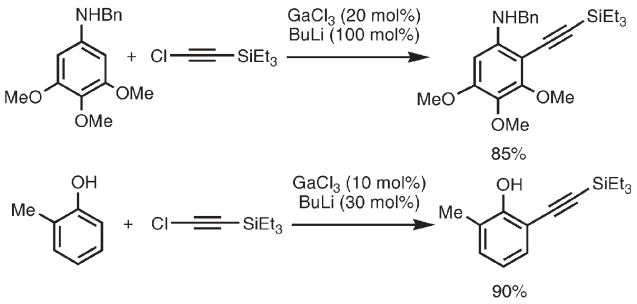
This synthesis uses silyl enol ethers as the transmetalation precursor of gallium enolates. Ketones are silylethynylated at 180 °C with triethylsilylchloroacetylene using a catalytic amount of triethylgallium (20–40 mol%) (Scheme 39).[66]



Scheme 38



Scheme 39



Scheme 40

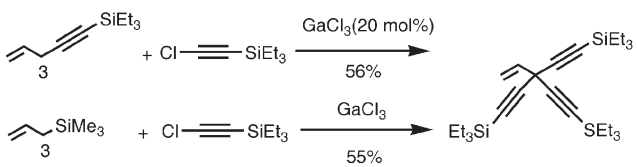
o-Ethynylanilines are versatile intermediates for the synthesis of indoles, and their preparation is generally conducted by the Sonogashira coupling of *o*-haloanilines, which must be prepared from anilines in a stepwise manner. The direct *o*-ethynylation of anilines is achieved using gallium chemistry. The reaction of lithiated *N*-benzylanilines and triethylsilylchloroacetylene in the presence of trichlorogallium (20 mol%) at 120 °C yields the corresponding *o*-ethynylanilines (Scheme 40).[26] *N*-Benzyl derivatives give higher yields of the products than *N*-methyl derivatives. The catalytic reaction of phenoxygallium with triethylsilylchloroethyne yields *o*-silylethynylated phenols.[67]

4.3 Synthesis of polyethynylmethanes

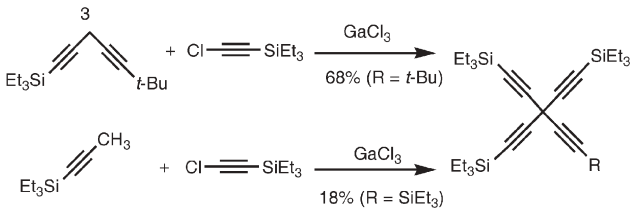
Tetraethynylmethanes and their partially hydrogenated derivatives are an interesting group of compounds possessing quaternary carbon centers with four fully functionalized substituents. They can be used for the preparation of high-carbon materials or as building blocks for functionally interesting compounds. The previous synthesis of such compounds employed multistep methods,[68] and it is conceivable that the ethynylation of 1,4-enynes or 1,4-diynes at the relatively acidic methylene moiety is straightforward. Trichlorogallium activates 3-methylene protons of 1,4-diynes and 1,4-enynes, and the ethynylation of the resulting propargylgallium intermediates gives polyethynylmethanes in one step.

The reaction of 1-triethylsilyl-4-penten-1-yne and triethylsilylchloroacetylene with trichlorogallium in the presence of trialkylsilanol and 2,6-di(*tert*-butyl)-4-methylpyridine at 130 °C produces triethynylvinylmethane (Scheme 41).[17] The added pyridine and silanol retard the decomposition of the substrates and product. Trichlorogallium deprotonates at the α-position generating propargylgallium, which undergoes addition and elimination reactions with triethylsilylchloroacetylene yielding the corresponding vinyltriethynylmethane.

This reaction proceeds regioselectively at the 3-position of the organogallium intermediates. The same reaction with 1,4-diynes yields the corresponding tetraethynylmethanes



Scheme 41



Scheme 42

(Scheme 42). The ethynylation of 1,4-enynes proceeds with a catalytic amount of trichlorogallium (20 mol%) at 150 °C; 1 mole of trichlorogallium may be used for more than 10 cycles of ethynylation.[19] The reaction of trimethylallylsilane and triethylsilylchloroacetylene directly gives the same triethynylvinylmethane *via* 1,4-enyne, which is formed by the ethynylation of allylsilane.

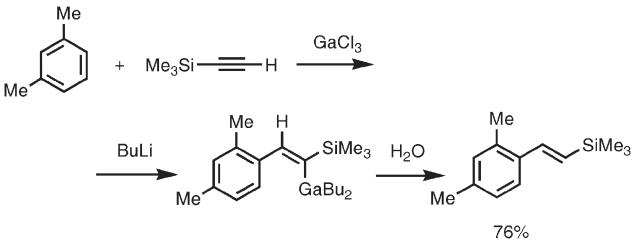
Ethynylation can be applied to even simple 1-triethylsilylacetylenes possessing less acidic propargyl protons, and exhaustive α-ethynylation occurs giving mono-, di-, and triethynylated products depending on the structure of the substrate.[19] For example, 1-triethylsilyl-1-propyne may be triethynylated to produce tetraethynylmethane.

Thus, organogallium chemistry is useful for the vinylation and ethynylation of various organic compounds.

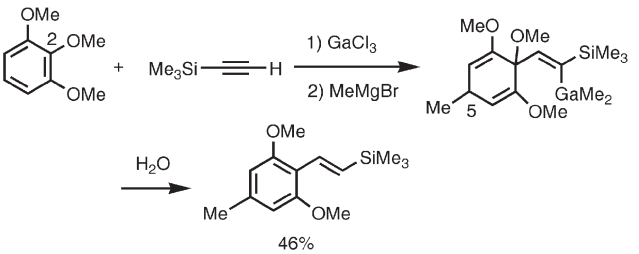
4.4 Electrophilic aromatic alkenylation

Friedel–Crafts alkylation is a fundamental transformation in organic synthesis and has been used to introduce alkyl groups to aromatic nuclei. Various Lewis acid catalysts have been used for this reaction including trichlorogallium.[38,39] The activity of trichlorogallium in the reaction using alkyl halides is in general comparable to or lower than that of trichloroaluminum. Trichlorogallium, however, exhibits interesting properties in electrophilic aromatic alkenylation reactions using alkynes.

In contrast to Friedel–Crafts alkylation reactions, alkenylation reactions have been less extensively examined because of the lower efficiency of the generation of alkenyl cations from either alkenyl halides or alkynes and the serious over-reactions of the alkenylated arenes toward further alkylation reactions. Several exceptions appear when highly substituted alkenyl halides or aryl substituted alkynes are reacted with a large excess of arenes, typically when the solvent is in the temperature range from 0 °C to room temperature in the presence of trichloroaluminium.[69] The π-complex of triethylsilylacetylene and trichlorogallium is highly electrophilic compared with that of conventional alkenyl cation reagents, and rapidly reacts with aromatic hydrocarbons at −78 °C (Scheme 43).[28] The resulting organogallium arenium intermediates do not liberate protons under the conditions used, and the addition of a base such as butyllithium or THF is required. Deprotonation generates an aromatized vinylgallium intermediate, and protodegallation by aqueous workup produces β-triethylsilylvinylated arenes. Usual orientations are observed for alkyl-substituted benzenes. A catalytic amount of trichlorogallium (10 mol%) was found by Chatani and Murai to promote the intramolecular reaction of acetylene and arene *via* the *in situ* protodegallation of an allylgallium intermediate.[70]



Scheme 43

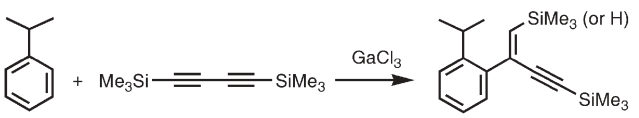


Scheme 44

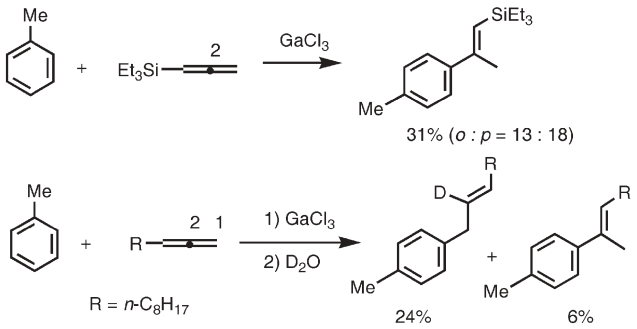
Ipso-substitution takes place with 1,2,3-trimethoxybenzene at the 2-position, and the treatment of the arenium intermediate with methylmagnesium bromide yields 2,5-dihydrobenzene methylated at the 5-position (Scheme 44).[28] Aqueous workup induces the protodegallation and elimination of methanol giving 1,4-dialkylated benzene derivatives. This is a unique addition reaction for aromatic nuclei promoted by a Lewis acid.

A unique orientation is observed in alkenylation using disilylated 1,3-butadiyne to produce 2-aryl-1,3-enynes.[30] The reaction of toluene and bis-silylated 1,3-butadiyne gives the *o*-substituted product exclusively, and even isopropylbenzene predominantly reacts at the *o*-position (Scheme 45). A possible explanation for this phenomenon is the ability of the π-complex formed from trichlorogallium and diyne to interact with alkyl C–H bonds on the aromatic ring.

Trichlorogallium interacts with silylallene as well as silylacetylene, and the complex reacts with aromatic hydrocarbons at low temperatures giving 1-silyl-1-propen-2-yl arenes (Scheme 46).[31] The formation of vinylsilane instead of allylsilane may be explained by the formation of an allylgallium intermediate and S_E2' protodegallation. As for the regioselectivity of arene, toluene yields *o*- and *p*-isomers in comparable amounts, which are the intermediates between disilylated 1,3-butadiyne and silylacetylene. The reaction of an alkyl substituted allene shows a different regioselectivity in terms of the allene, and C–C bond formation occurs predominantly at the 1-position and is accompanied by minor products that react at the 2-position. A 2-deuterated product is obtained from the former by the addition of D_2O to the



Scheme 45



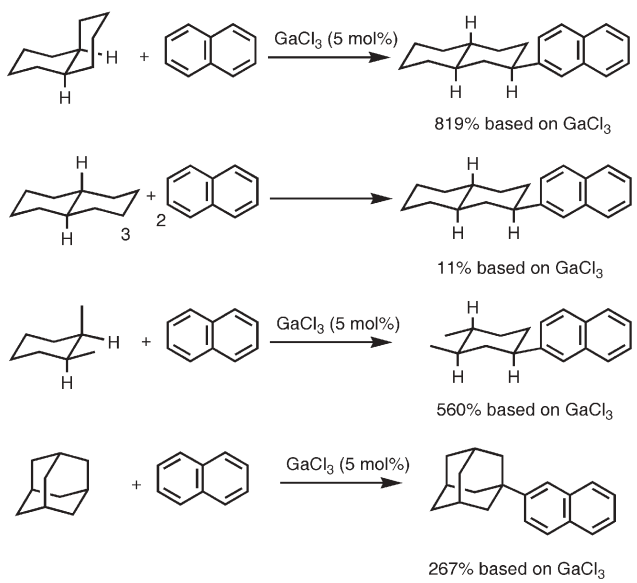
Scheme 46

reaction mixture, which confirms the formation of a vinylgallium intermediate in this reaction.

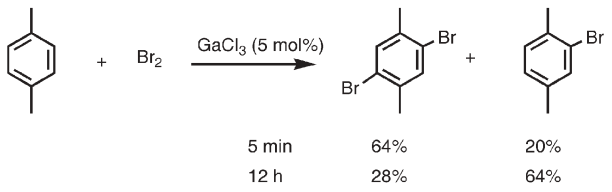
4.5 Electrophilic aromatic alkylation

Friedel–Crafts alkylation has generally been conducted using alkyl halides or alkenes. Only scattered examples have been reported of the use of alkanes, and the reactions were not efficient.[71] Trichlorogallium activates cycloalkane tertiary C–H and is a highly active catalyst for electrophilic aromatic alkylation using cycloalkanes.[6]

The reaction of *cis*-perhydronaphthalene and naphthalene in the presence of a catalytic amount of trichlorogallium (5 mol%) yields 2-naphthylated *trans*-perhydronaphthalene as the major product.[32,37] The turnover number (TON) based on the C–C bond formed exceeds 10 (Scheme 47). The C–C bond formation predominantly takes place at the 2-position of naphthalene and the 3-position of perhydronaphthalene. The thermodynamically most stable compounds are formed by aryl migration under the conditions used. *cis*-Perhydronaphthalene yields naphthylated *trans*-perhydronaphthalene, which may be explained by initial hydride abstraction at the tertiary C–H followed by cation migration. Accordingly, *cis*-perhydronaphthalene isomerizes to its *trans*-isomer under the conditions used. Notably,



Scheme 47



Scheme 48

cis-perhydronaphthalene reacts much more effectively than its *trans*-isomer, which reacts at a TON less than 1. This indicates that the equatorial tertiary hydrogen of cycloalkanes rather than the axial hydrogen is activated. 1,2-Dimethylcyclohexane exhibits a similar reactivity, and the TON of its *cis*-isomer is considerably higher than that of its *trans*-isomer. Adamantane is also naphthylated at the 1-position, which again possesses an equatorial hydrogen. In this case, no carbocation migration takes place, which is characteristic of the 1-adamantyl cation. Alkanes can be efficient alkylating reagents for aromatic nuclei in the presence of trichlorogallium.

Trichlorogallium exhibits a unique property in the electrophilic bromination of alkylbenzenes.[72] The reaction of xylene produces dibrominated products within 5 min, which then isomerize to monobromo derivatives within 12 h (Scheme 48). The origin of this tendency is ascribed to the C–H interaction of either trichlorogallium or trichlorogallium-activated species with aromatic methyl protons.

Trichlorogallium can electrophilically activate alkynes and alkanes, and some of its properties can be understood based on its tendency to interact with C–H.

Conclusions

Gallium(III) compounds, particularly trichlorogallium and trialkylgalliums, exhibit various reactivities with organic compounds both as bases or acids, and such diversity of reactivities is useful in organic synthesis.

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