Recent applications of gallium and gallium halides as reagents in organic synthesis

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This review highlights the application of gallium metal and gallium halides as reagents in organic synthesis. Owing to their unique catalytic properties, gallium trihalides are considered effective Lewis acids which can activate several functional groups under extremely mild conditions. Gallium halides have been successfully employed as Lewis acid catalysts in various organic transformations such as alkylation, allylation, radical reactions, cycloaddition reactions, Friedel Craft's reactions and various coupling reactions. This review seeks to update organic chemists about the potential application of gallium halides in the synthesis of a wide variety of chemical building blocks.

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1. Introduction

Carbon-carbon bond formation is the most fundamental reaction for the construction of molecular frameworks and remains a major focus of research in organic chemistry.[1-3] During the past few years, synthetic organic chemistry has grown enormously with the development of new methodologies for the construction of carbon-carbon bonds and functional group transformations, as well as the development of new reagents, catalysts and strategies often involving the concepts of atom economy and selectivity. Since the successful introduction of indium metal in various organic transformations, the utilisation of other related metals for organic synthesis has attracted widespread interest. One of these recent additions is gallium. Gallium has emerged as a metal of high potential in organic synthesis because of certain unique properties which it possesses. Its low ionisation energy of 5.99 eV (e.g. Li 5.39 eV, Mg 7.65 eV) makes it useful for single electron transfer reactions which, combined with its low vapour pressure and the fact that it is liquid at low temperatures (mp 29.8 °C), makes it an attractive candidate for metal-mediated organic transformations. As testament to the growing interest in gallium-mediated reactions, this topic has been subject to a number of reviews notably by Yamaguchi.[4, 5] In this article, we review the broad application of gallium and gallium halides in organic synthesis, including some of our contributions to this area, and lay special emphasis on recent developments in this field.

2. Gallium and its halides: A Brief Outline

The French chemist, Boisbau Dran, discovered gallium metal spectroscopically in 1875.[6] The name gallium is coined from the Latin word ‘gallio’, the former name of France. Gallium is stable in air and is not attacked by water unless free oxygen is present. Gallium trihalides have a bridged dimer molecular lattice as shown in Figure 1. These dimeric molecules are arranged in sheets and the low intermolecular forces are responsible for their low melting points.[7]

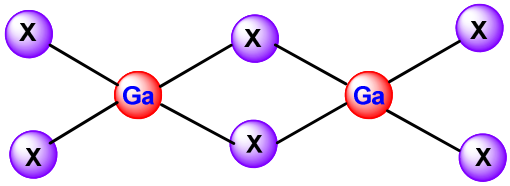


Figure 1

The halides of gallium ($GaCl_3$, $GaBr_3$ and GaI_3) are largely covalent in nature when anhydrous. The dimeric formula is retained when the halides are dissolved in non-polar solvents such as benzene, chloroform and dichloromethane etc. Gallium halides are weaker acids than aluminum trichloride and may be used in organic synthesis without affecting acid sensitive groups. Reactions involving gallium halides are generally faster and higher yielding than traditional Lewis acids.[8, 9]

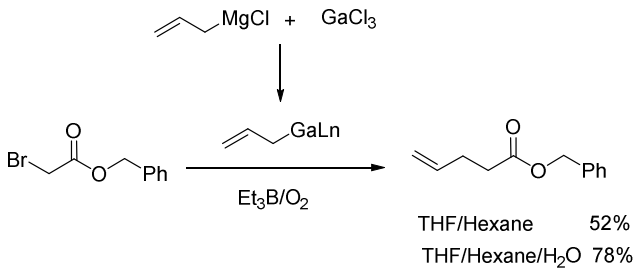
Several gallium halides are commercially available e.g. gallium (III) chloride, gallium (III) bromides and gallium (III) iodides. Gallium (III) chloride can be prepared by burning gallium in a stream of Cl_2 or by the action of HCl or $SOCl_2$ (> ca 200 ^oC) on

Ga_2O_3.[10-12] The pure anhydrous compound can be obtained by redistillation in a stream of Cl_2 (Cl_2/N_2) followed by vacuum sublimation or zone refining.[11]

2.1 Allylation Reactions

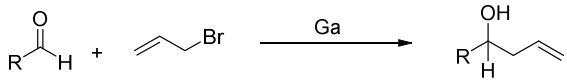
Radical allylation reactions provide a mild and efficient method for introducing allylic groups into organic molecules bearing ionically labile functionalities.[13-15] Usugi *et al.* have reported an efficient and effective allylation methodology employing an allylgallium reagent in an aqueous medium.[16] Radical allylation proceeded smoothly in the presence of allylgallium reagents with triethylborane as a radical initiator (Scheme 1).

The allylgallium reagent was prepared by reacting allylmagnesium chloride and gallium trichloride in THF/hexane under an argon atmosphere. It was suggested that the reaction proceeded by a radical mechanism as complete inhibition was observed when radical scavengers such as galvinoxyl and 2,2,6,6-tetramethylpiperidine-*N*-oxyl were added. The use of water as co-solvent enhanced the reaction yield possibly due to a change in structure of the reacting alkylgallium species.



Scheme 1

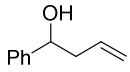
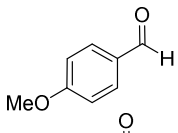
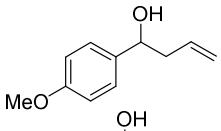
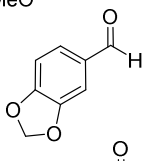
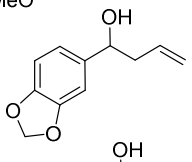
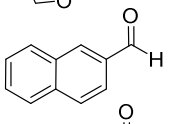
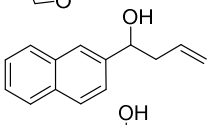
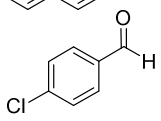
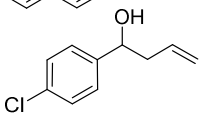
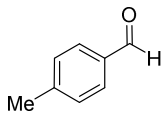
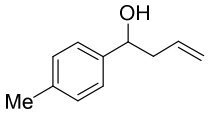
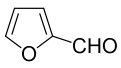
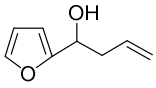
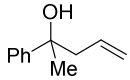
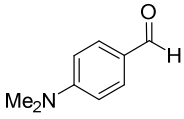
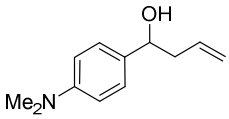
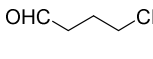
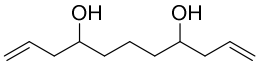
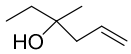
Wang *et al.* also investigated water as a solvent medium for the gallium-mediated allylation of aldehydes and ketones. Both aromatic and aliphatic aldehydes as well as ketones were converted to their corresponding homoallylic alcohols without recourse to acidic media or sonication (Scheme 2).[17]



Scheme 2

Reactions were smooth and side reactions such as reductions and couplings were not observed. Notably, acid sensitive groups such as acetals remained intact under these mild reaction conditions. (Table 1).

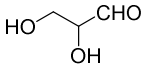
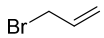
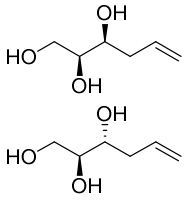
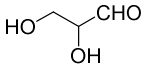
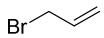
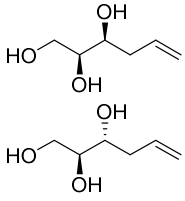
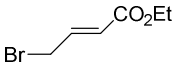
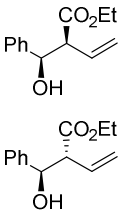
Table 1. Allylation reactions mediated by Ga in water

entry	substrate	product	yield(%)[a]
a			76
b			82
c			79
d			64
e			73
f			80
g			68
h			61
i			42
j			57
k			46

[a]isolated yields

The diastereoselectivities of these gallium-catalysed allylations were also studied. Allylation of 2,3-dihydroxy propanal with allylbromide in the presence of gallium gave the corresponding products with diastereoselectivity dependent on the reaction solvent. When the reaction was carried out in water, the dominant product was the *syn*-isomer (Table 2). By contrast, the *anti*-isomer was the dominant product when THF was employed as the reaction medium. The *syn*-isomer was regarded as the chelation-controlled product due to hydrogen bonding between the two hydroxyl groups while an aqueous environment favours chelation of the α-hydroxy group.

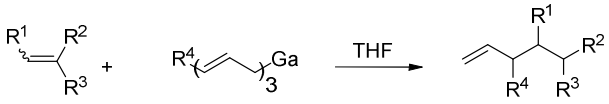
Table 2. Diastereoselective allylation catalysed by Ga in different solvents

entry	aldehyde	halide	product (*syn/anti*)	*syn/anti* yield[a]	reaction conditions
a				8.3/1 86%	Ga / H_2O 45 °C / 16 h
b				1/4.2 74%	Ga / THF 45 °C / 16 h
c	PhCHO			1/2.2 67%	Ga / H_2O 45 °C / 16 h

[a]isolated yields.

Research into organogalliums has revealed that these compounds often display different selectivity from that of conventional Grignard and organolithium reagents. An example of this is the allylgallation of electron-deficient alkenes reported by Araki *et al.*[18] They found that triallylgallium reagents may be employed to successfully allylate 1,3-unsaturated nitrile and carbonyl compounds regioselectively affording the 1,4-addition products. The high 1,4-selectivity is not completely understood, though it may be explainable in terms of the softness of these reagents. In addition, the allylgallium reagent was found to add from the *trans*-face, avoiding steric repulsion from the substituent on the 3-carbon (Tables 3 and 4).

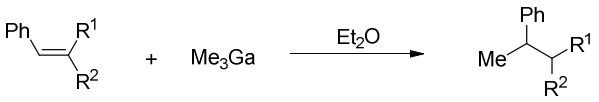
Table 3. Allylation of electron deficient alkenes with triallylgallium



entry	alkene R^1	R^2	R^3	allylgallium R^4	yield(%)[a]
a	Et	CN	CN	H	76
b	Ph	CN	CN	H	78
c	Ph	CN	CN	Ph	76 (70 : 30)
d	Ph	CO_2Me	CO_2Me	H	95
e	Ph	CO_2Et	CO_2Et	H	89
f[b]	Ph	CO_2Me	CO_2Et	H	95 (61 : 39)
g[c]	Ph	CN	CO_2Et	H	74 (59 : 41)

[a]Figures in parentheses refer to diastereomeric ratio. [b]A mixture of geometric alkenes (*E:Z* = 54:46) was used. [c]Pure *E*-alkene was used.

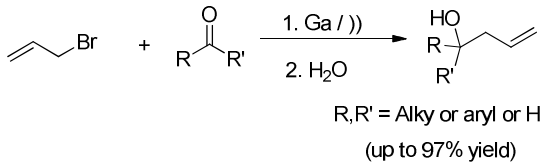
Table 4. Methylation of electron deficient alkenes with trimethylgallium



entry	alkene R^1	alkene R^2	yield(%)[a]
a	CN	CN	27
b	CO_2Me	CO_2Me	71
c[b]	CN	CO_2Et	87 (58:42)
d[c]	CHO_2Me	CO_2Et	87 (60:40)

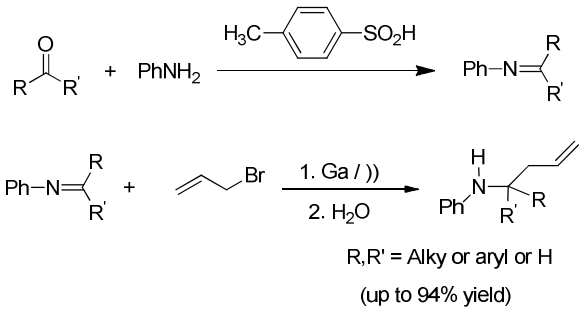
[a]Figures in parentheses refer to diasteroemeric ratio. [b]Geometrically pure *E*-alkene was used. [c]Alkene (*E*:*Z* = 37:63) was used.

Solvent-free reactions offer some considerable benefits to industry, primarily as these alternatives obviate entirely the need to dispose of, or recycle, the reaction medium. Allylation of both carbonyl compounds and imines affording the corresponding homoallylic alcohols and amines using gallium metal under solvent free conditions was reported by Andrews *et al.*[19] Under sonication, the reactions proceeded smoothly and efficiently with yields ranging from 74% to 97% for aromatic, methoxy substituted aromatic and aliphatic aldehydes (Scheme 3).



Scheme 3

The same methodology was successfully applied to the allylation reaction of imines, derived from the corresponding aldehydes or ketones, and proceeded proceeded smoothly affording homoallylic amines in yields ranging from 32% to 94% (Scheme 4).

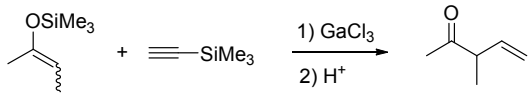


Scheme 4

2.2 Alkenylation Reactions

Ethenylation (*i.e.* C_2-olefination) is an underdeveloped reaction. The few known examples are only applicable to the synthesis of unenolisable ethenylated products, which do not possess an acidic α-proton. Stepwise methods have traditionally been employed for enolate ethenylation using reagents such as vinyl sulfones, ethenylsulfone,

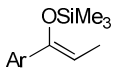
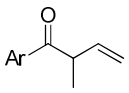
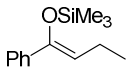
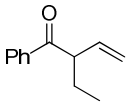
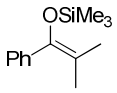
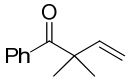
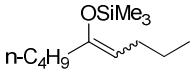
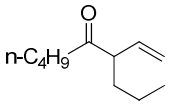
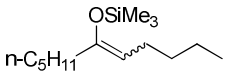
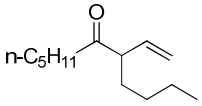
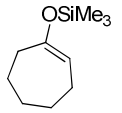
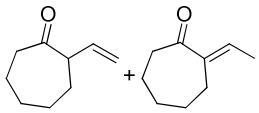
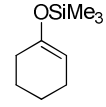
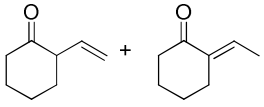
trichloroethylene, α-phenylselenylacetaldehyde, α-trimethylsilylaldehyde, or vinyl ether-iron complexes to generate the ethenyl group.[20-23] A direct method for the ethenylation of silyl enol ethers with trimethylsilylethyne in the presence of $GaCl_3$ has been developed by Yamaguchi *et al.* (Scheme 5). Importantly, the reaction can be applied to the synthesis of not only unenolisable R-ethenylated ketones, but also enolisable products.[24]



Scheme 5

Both acyclic and cyclic ketones can be ethenylated in this manner (Table 5). The configuration of the silyl enol ether was found to be unimportant with the β-enone being the major product.

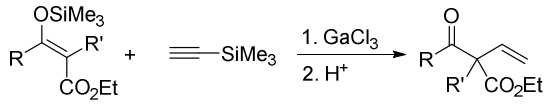
Table 5. α-Ethenylation of silyl enol ethers

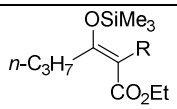
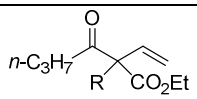
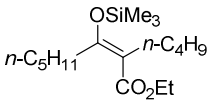
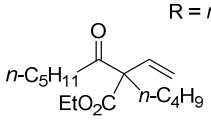
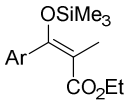
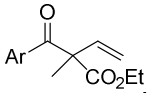
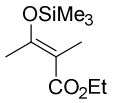
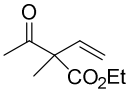
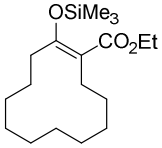
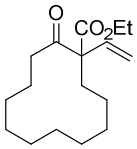
substrate	product	yield (%)
		
	Ar = C_6H_5	75
	Ar = *p*-FC_6H_4	72
	Ar = *p*-$MeOC_6H_4$	70
		76
		74
		74
		77
		53+10[a]
		11+46[a]

[a]Yields of β-enone and α-enone are shown.

α-Substituted β-ketoesters and malonates may be ethenylated in a similar fashion.[25] A notable aspect of this methodology is its application to the synthesis of ethenylmalonates possessing acidic α-protons (Table 6). The reaction is very rapid at 0 °C and is completed within 15 seconds. It was also observed that addition of a small amount of *t*.-butyl alcohol increases the overall yield.

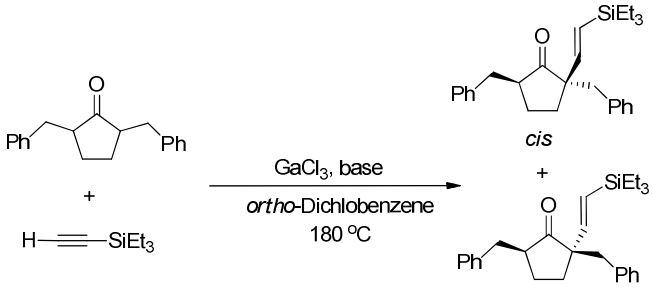
Table 6. Ethenylation of silylated β-ketoester with silylethyne[a]



substrate	product		yield(%)
		R = Me	74 37[a]
		R = Et	84
		R = *n*-C_3H_7	85 83[b]
			92
		Ar = C_6H_5	55
		Ar = *p*-MeC_6H_4	72
		Ar = *p*-FC_6H_4	65
			67
			88

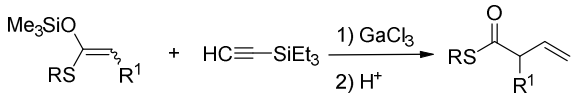
[a]The reaction was carried out without *t*-BuOH. [b]The reaction was carried out in 5 mmol scale.

Later, the same group demonstrated that five- or six-membered cyclic ketones possessing α,α′-disubstituents may be ethenylated at the α-carbon in the presence of $GaCl_3$ and 2,6-di(*t*-butyl)-4-methylpyridine.[26] The base has two roles, both preventing decomposition of the products as well as promoting protodegallation of the organogallium intermediates. In a typical example, 2,5-dibenzylcyclopentanone and triethylsilylethyne were reacted in the presence of $GaCl_3$ and base to provide 2,5-dibenzyl-2-(2-triethylsilylethenyl)cyclopentanone in a combined yield of 24% for both diastereomers (Scheme 6). The stereochemical configuration of the *cis* product was determined by converting it to (*1R*,2R*,5R*,E*)-2,5-dibenzyl-2-(2-triethylsilylethenyl)-1-cyclopentanone and observing the nOe interaction between the 5-position and 2-benzyl protons, and the additional interaction between the 1-proton and the vinyl proton.



Scheme 6

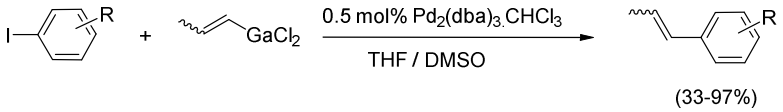
Sulfur-containing compounds are similarly amenable to ethenylation by this approach. The reaction of *S*-alkyl or *S*-aryl thioesters with trimethylsilylethyne in the presence of $GaCl_3$ proceeds in high yield affording α-ethenylthioesters (Scheme 7).[27] Both α-mono- and α,α-disubstituted thioesters proved suitable substrates under these conditions with no isomerisaton to α,β-unsaturated thioesters being observed. The authors also outlined how thioester dienolates may be converted to their corresponding α,α-diethenyl thioesters.



R = Et	$R^1 = CH_2Ph$	85%
R = Et	$R^1 = n\text{-}C_4H_9$	83%
R = Et	$R^1 = n\text{-}C_6H_{13}$	83%
R = Et	$R^1 = i\text{-}C_3H_7$	76%
R = Et	$R^1 = t\text{-}C_4H_9$	72%
$R = Ph(CH_2)_2$	$R^1 = i\text{-}C_3H_7$	70%
R = *cyclo*-C_6H_{11}	R^1 = Me	81%
R = *cyclo*-C_6H_{11}	$R^1 = i\text{-}C_3H_7$	92%

Scheme 7

Many organometallic reagents - organoboron compounds in particular - have proven to be highly effective for the transition-metal catalysed cross-coupling reaction with alkenyl halides and aryl halides. By contrast, the related coupling of organogallium compounds is not yet well developed, even though boron and gallium belong to the same group in the periodic table. Oshima *et al*. demonstrated the coupling of alkenylgallium reagents with aryl iodides in the presence of a palladium catalyst (Scheme 8).[28] Coupling of 1-propenylgallium with a range of aryliodides bearing electron donating as well as electron withdrawing groups proceeded smoothly with good yields. Substrates with acidic protons, such as iodophenol and iodobenzoic acid, were similarly compatible with these conditions.



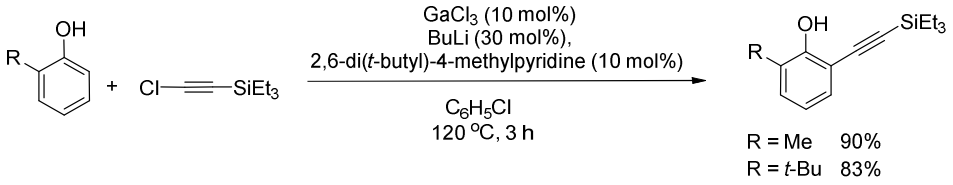
R = *m*-OMe, *p*-NO_2, *p*-$COCH_3$, *p*-CO_2H, *m*-OH, *o*-CH_2OH, *p*-NH_2, *p*-NMe_2,1-Naphthyl, *p*-CN, *o*-CHO, *o*-Br

Scheme 8

2.3 Ethynylation Reactions

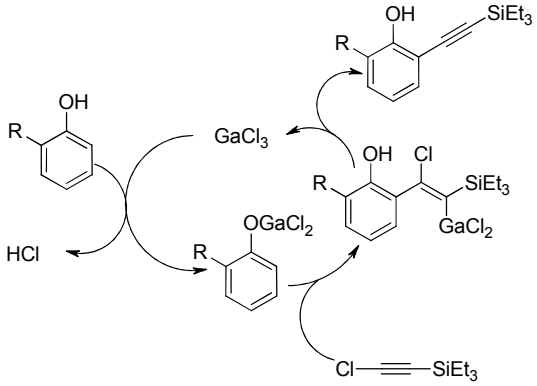
The most common method for the introduction of the ethynyl group is the nucleophilic reaction of an ethynyl metal reagent with carbonyls, halogens, or oxiranes.[29] Stepwise transformations, as exemplified by the Corey-Fuchs method or Julia coupling, are also often employed.[30] Electrophilic ethynylation of carbon nucleophiles is another attractive methodology, since organometallic species with C-M bonds can, in some cases, be generated directly by activation of C-H bonds. Kobayashi *et al.* investigated the *ortho*-ethynylation of phenol with triethylsilylchloroethyne using a catalytic amount of gallium chloride which resulted in the replacement of the phenol *ortho*-hydrogen atom by an ethynyl group.[31] Several *ortho*-ethynyl phenols were made directly from phenols using a novel catalysts system of $GaCl_3$ (10 mol%), 2,6-di(*tert*-butyl)-4-methylpyridine (10 mol%),and butyllithium (30 mol%) at high temperatures (Scheme 9). The authors note

that the amount of butyllithium is critical for successful catalysis. While the use of 40 mol% butyllithium inhibits the reaction, 20 mol% results in a significant decrease in yield. Catalytic ethynylation does not proceed in the absence of butyllithium.



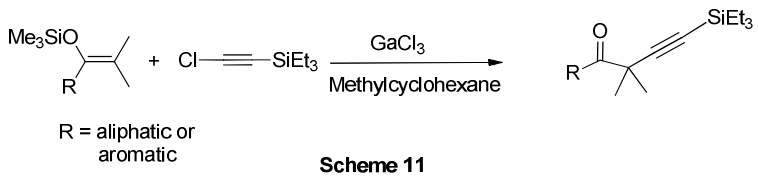
Scheme 9

The postulated mechanism for this catalytic ethynylation most likely involves carbogallation of the phenoxygallium intermediate and triethylsilylchloroethyne followed by β-elimination to afford the desired product (Scheme 10).



Scheme 10

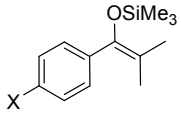
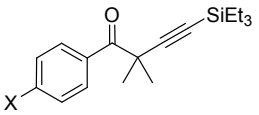
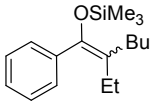
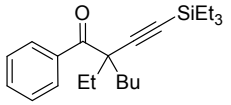
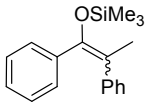
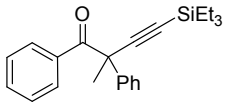
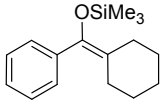
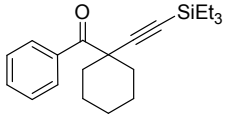
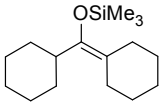
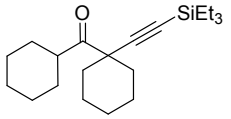
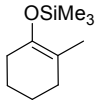
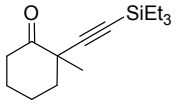
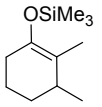
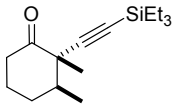
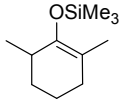
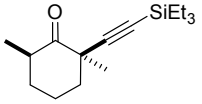
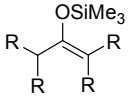
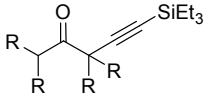
Having previously demonstrated the successful ethenylation of silyl enol ethers, Yamguchi *et al*. extended this methodology to the ethynylation of silyl enol ethers using triethylsilylchloroethyne in the presence of a catalytic amount of $GaCl_3$ to give α-ethynylated ketones (Scheme 11).[32]



Scheme 11

This catalytic reaction could be applied to several silyl enol ethers derived from both aromatic and aliphatic ketones, and α-ethynylated ketones were obtained in high yields (Table 7). However, the reaction did not take place with silyl enol ethers which are not fully-substituted at the α-carbon. For example, neither α-monoethynylated ketone nor its isomerised allene was obtained by the reaction of 6-trimethylsilyloxy-5-undecene and only the starting ketone was instead recovered.

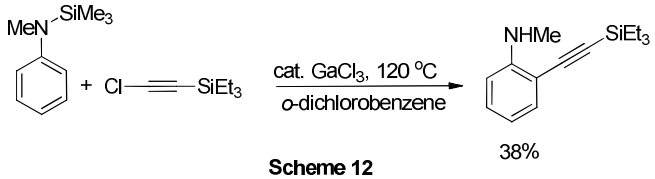
Table 7. Catalytic α-ethynylation of silyl enol ethers

entry	substrate	product	yield(%)
			
1	X=H		83
2	X=F		80
3	X=OMe		80
4[a]			80
5[b]			96
6			72
7			93
8[c]			54
9			37
10			70[d]
			70
11	R = CH_3		98
12	R = *n*-Bu		36

[a]E/Z = 1:1. [b]E/Z = 1:2. [c]A 9:1 mixture with 2-methyl and 6-methyl-1-trimethylsilyloxy-1-cyclohexene. [d]A mixture of *trans:cis* - 8:1 as determined by ^{1}H-NMR.

o-Ethynylanilines are versatile intermediates for the synthesis of indoles.[33, 34] The most common methods for the preparation of ethynylamines include the Sonogashira coupling reaction of *ortho*-haloanilines with terminal alkynes and the Stille coupling using stannylated alkynes.[35, 36] These methods, however, require multistep preparations of the halogenated substrates, particularly in the case of substituted anilines. Therefore, a straightforward method for the ethynylation of *N*-benzyl aniline is much sought after. When *N*-trimethylsilyl-*N*-methylaniline was reacted with (chloroethynyl)triethylsilane and a catalytic amount of $GaCl_3$ (20 mol%) in *o*-dichlorobenzene at 90 ^oC for 1 hour, the

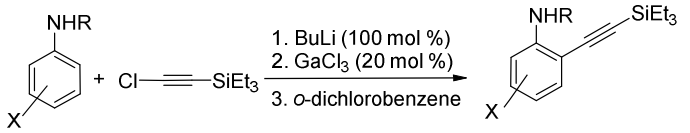
product, *N*-methyl-2-((triethylsilyl)ethynyl)aniline, was obtained in 20% yield.[37] The yield was increased to 38% by heating to 120 °C (Scheme 12).



Scheme 12

When direct *o*-ethynylation of *N*-alkylanilines was attempted, *N*-benzyl anilines were found to be unreactive. However, addition of butyllithium to a solution of *N*-benzyl aniline in *o*-dichlorobenzene followed by $GaCl_3$ (1 eq.) and (chloroethynyl)triethylsilane (3 eq.), furnished *N*-benzyl-2-(triethylsilylethynyl)aniline in 65% yield. The amount of $GaCl_3$ could be reduced to 20 mol%, when the temperature was elevated to 120°C affording the product in 58% yield after 3 hours. This catalytic reaction could also be applied to substituted *N*-benzylanilines (Table 8). Substrates possessing electron donating substituents at the aniline nuclei gave the *ortho*-ethynylanilines in higher yields and TON. However, the yields decreased when halogen groups were attached at the *para*-position.

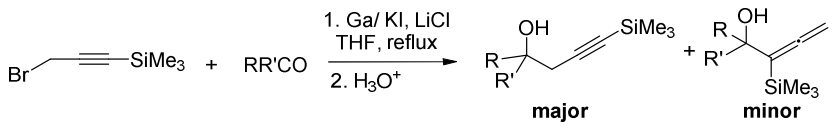
Table 8. *ortho*-Ethenylation reactions of *N*-alkylanilines



entry	R	X	yield(%)
1[a]	$PhCH_2$	H	65
2	$PhCH_2$	H	58
3[a]	Me	H	55
4	Me	H	19
5	*n*-C_4H_9	H	52
6	*p*-$MeOC_6H_4CH_2$	H	60
7	*p*-$FC_6H_4CH_2$	H	59
8	$PhCH_2$	3,4,5-MeO	85
9	$PhCH_2$	4-MeO	75
10	$PhCH_2$	4-Me	74
11	$PhCH_2$	3,5-MeO	59
12	$PhCH_2$	3,5-Me	60
13	$PhCH_2$	4-F	47
14	$PhCH_2$	4-Cl	38
15	$PhCH_2$	3-Me	70 (41+29)[b]

[a]Reaction was conducted at 90°C for 1 h with 100 mol% of $GaCl_3$.
[b]Yields of 1,2,5-substituted and 1,2,3-substituted anilines

A one-pot reaction for the selective propargylation of aldehydes and ketones has been reported by Han & Huang.[38] Gallium powder and triethylsilylpropargyl bromide were added to the appropriate aldehyde or ketone in the presence KI or LiCl, affording the acetylenic silyl ether as the major product (Scheme 13). In the absence of LiCl or Lewis acid, the reaction progressed sluggishly with poor yields following prolonged heating to reflux. Although the role of the Lewis acids in improving the yield was not definitively clarified, the authors postulate that coordination of the lithium ion or Lewis acids to the carbonyl oxygen activates the carbonyl group.

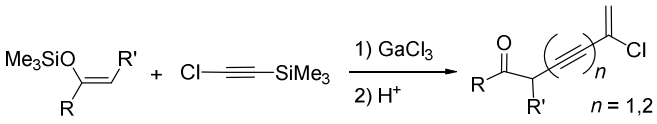


R'RCO = C_6H_5CHO	92% (>99:1)
R'RCO = *p*-$CH_3C_6H_4CHO$	97% (99:1)
R'RCO = *p*-ClC_6H_4CO	99% (>99:1)
R'RCO = *p*-FC_6H_4CHO	91% (>99:1)
R'RCO = $C_6H_5CH{=}CHCHO$	78% (98:2)
R'RCO = *n*-$C_5H_{11}CHO$	87% (97:3)
R'RCO = *n*-$C_9H_{19}CHO$	82% (>99:1)
R'RCO = $(CH_2)_5CO$	85% (>99:1)
R'RCO = $C_6H_5COCH_3$	87% (>99:1)

Scheme 13

Yamaguchi has developed a one-pot methodology which will be of interest to those intending to prepare conjugated polyyne compounds. In the presence of $GaCl_3$, silyl enol ethers may be sequentially ethynylated at the α-carbon atom with chlorotrimethyl silylethyne giving α-ethynylated, α-endiynylated and even α-entriynylated ketones.[39] The length of the alkyl chain of phenyl alkyl ketone enolates was observed to have some effect on the overall yield (Table 9). Substrates with shorter alkyl groups typically gave higher yields of the α-endiynylated products (entries 1–5). Aromatic silyl enol ethers with electron withdrawing *p*-substituents afforded the desired products in higher yields (entries 6 and 7) compared to those possessing electron donating groups (entries 9-11).

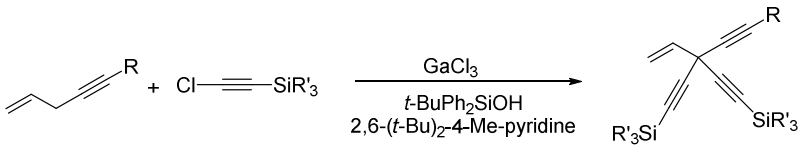
Table 9. Ethenylation of silyl enol ethers with chlorotrimethylsilylethyne



entry	R	R'	yield(%) n = 1	n = 2
1	Ph	CH_3	45	14
2	Ph	$CH_2CH(CH_3)_2$	49	9
3	Ph	*n*-C_3H_7	66	4
4	Ph	*n*-C_5H_{11}	74	0
5	Ph	*n*-C_8H_{17}	73	0
6	*p*-FC_6H_4	*n*-C_7H_{15}	71	0
7	*p*-$CF_3C_6H_4$	*n*-C_7H_{15}	50	0
8	*p*-$MeOC_6H_4$	*n*-C_7H_{15}	5	6[a]
9 [b]	*p*-$MeOC_6H_4$	*n*-C_7H_{15}	37	15
10	*p*-MeC_6H_4	*n*-C_7H_{15}	13	9[c]
11 [d]	*p*-MeC_6H_4	*n*-C_7H_{15}	37	21
12	1-Naphthyl	*n*-C_7H_{15}	58	7

[a]Allenyl ketone was obtained in 54% yield. [b]Reaction temp of -20°C.
[c]Allenyl ketone was obtained in 65% yield. [d]Reaction temp of -10°C.

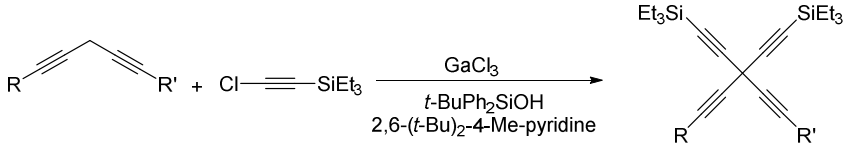
In related work on the preparation of polyethynylmethanes, the same research group reported a one-step synthesis of triethynylvinylmethanes by $GaCl_3$-promoted diethynylation of 1,4-enynes (Scheme 14).[40] They discovered that $GaCl_3$ activates the C-H bond of the hydrocarbon substrate, and that the resultant organogallium compounds readily undergo ethynylation with chloroethynes.



R = $SiEt_3$; R' = Et	72%
R = $SiEt_3$; R' = *n*-Bu	72%
R = $Si(n\text{-}Bu)_3$; R' = Et	76%
R = $Si(t\text{-}Bu)Me_2$; R' = Et	66%
R = 1-adamantyl; R' = Et	49%
R = cyclohexyl; R' = Et	52%
R = *n*-Bu; R' = Et	32%

Scheme 14

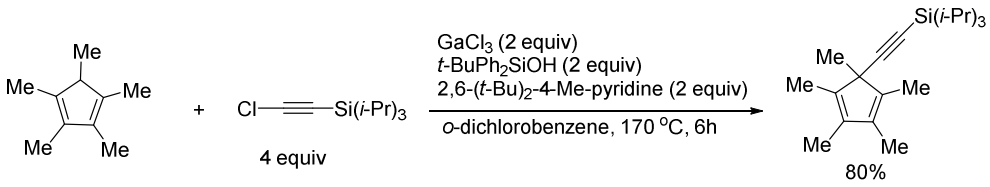
Tetraethynylmethanes were similarly obtained by the regioselective diethynylation of 1,4-diynes (Schemes 15).



R = $SiEt_3$; R' = *t*-Bu	65%
R = $SiEt_3$; R' = 1-adamantyl	69%
R = $SiEt_3$; R' = cyclohexyl	63%
R = *t*-Bu; R' = *t*-Bu	47%
R = *t*-Bu; R' = 1-adamantyl	49%
R = $SiEt_3$; R' = $SiEt_3$	22%

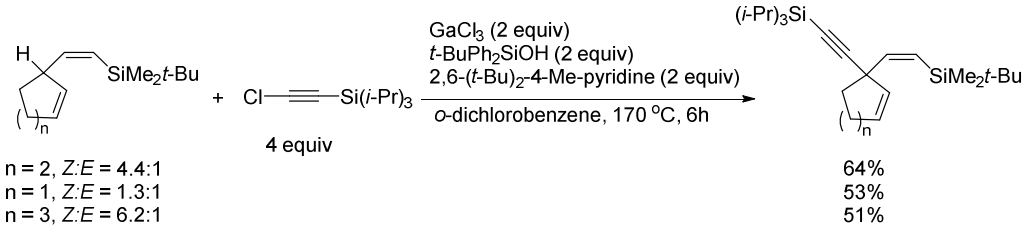
Scheme 15

Yamaguchi and co-workers later applied this methodology to cyclopentadienes and silylated 1,4-dienes.[41] The acidity of the allylic protons determines whether the reaction proceeds or not, with reactions involving indene and 1,4-nonadience proving unsuccessful. By contrast, when 1,2,3,4,5-pentamethylcyclopenta-1,3-diene, which possesses highly acidic protons, and chlorotriisopropyl-silylacetylene were heated in the presence of gallium trichloride, *tert*-butyldiphenylsilanol and 2,6-di(*tert*-butyl)-4-methylpyridine, an 80% yield of 5-(triisopropylsilylethynyl)-1,2,3,4,5-pentamethylcyclopentadiene was obtained (Scheme 16).



Scheme 16

Various 1,4-dienes were subjected to these same conditions and proved to be good substrates (Scheme 17). For example, isomeric 1-[2-(*tert*-butyldimethylsilyl)ethenyl]-2-cyclohexene (*Z*:*E* = 4.4:1) was converted to (*E*)-1-(triisopropylsilylethynyl)-1-[2-(*tert*-butyldimethylsilyl)ethenyl]-2-cyclohexene in 64% yield. The exclusive formation of the (*E*)-isomer indicated that the silylethenyl group isomerised from (*Z*)- to (*E*)-geometry during the ethynylation reaction which is consistent with the formation of a dienylgallium intermediate.

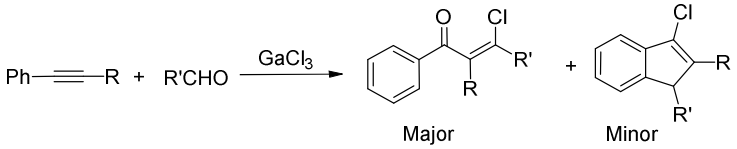


Scheme 17

2.4 Coupling Reactions

Coupling reactions of alkynes (and alkynylmetallic reagents) and aldehydes are important transformations in organic synthesis as they generate new carbon-carbon bonds. Recently, progress has been made on the addition of terminal acetylenes to aldehydes or ketones with propargylic alcohols being the primary products. Li and Viswanathan reported an unusual coupling reaction of terminal alkynes with a variety of aldehydes resulting in α,β-unsaturated ketones and small amounts of [4+1] annulation indene derivatives (Table 10).[42]

Table 10. $GaCl_3$-mediated coupling of phenyl alkynes with aldehydes

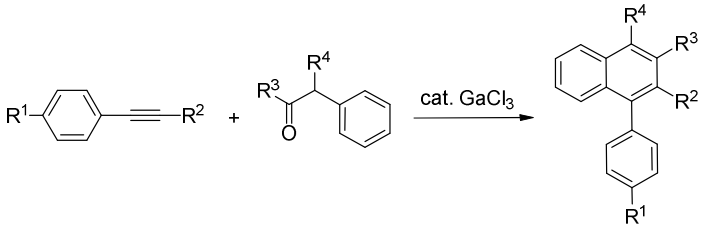


entry	R	R'	yield(%) major	yield(%) minor
1	Me	CH_2CH_3	60	<5
2	Me	$CH_2CH_2CH_3$	53	19
3	Me	$CH_2CH(CH_3)_2$	65	13
4	Me	$CH(CH_3)CH_2CH_3$	55	12
5	Me	$C(CH_3)_3$	47[a]	7
6	Me	$(CH_2)_4CH_3$	46	24
7	Me	$(CH_2)_5CH_3$	35	22
8	Me	$(CH_2)_4CH_2Br$	25	10
9	Me	3-F-C_6H_4	18	6
10	Pr	$CH(CH_2)_2$	40	-
11	Pr	$CH_2CH(CH_3)_2$	64	<4

[a] *E:Z* = 15:1, and in all other cases *E:Z* > 15:1

Li *et al.* also described the synthesis of polysubstituted naphthalene derivatives through a $GaCl_3$-catalysed alkyne-aldehyde coupling.[43] They discovered that the cyclisation reaction between an aromatic alkyne and phenyl acetone catalysed by gallium trichloride gave naphthalene derivatives with complete regioselectivity of all substituents (Table 11). Several aromatic alkynes were treated with substituted and unsubstituted aryl acetaldehydes to give the products ranging from 40-70% yield.

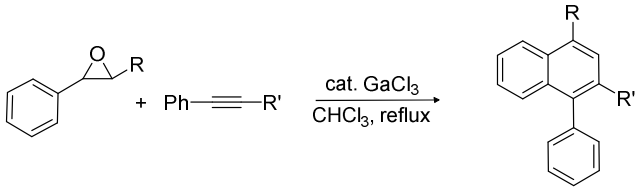
Table 11. $GaCl_3$-mediated alkyne-aldehyde coupling



entry	R^1	R^2	R^3	R^4	catalyst (mol%)	yield(%)
1	H	H	H	H	7.7	50
2	H	Me	H	H	7.8	61
3	H	Et	H	H	5.5	64
4	H	Pr	H	H	6.0	62
5	H	Bu	H	H	5.5	52
6	CH_3	H	H	H	5.5	46
7	Br	H	H	H	5.5	49
8	H	H	H	Me	4.9	51
9	H	Me	H	Me	13.0	70
10	H	Ph	H	H	7.7	25[a]
11	H	H	H	Ph	14.0	55[b]
12	H	Pr	H	Me	8.6	63
13	H	Et	H	Ph	12.4	68
14	H	H	Me	Ph	15.3	10

[a]The crude reaction mixture contained a large amount of unreacted diphenylacetylene after reflux for 24h. [b]Yield at RT.

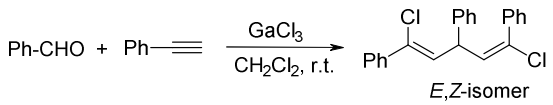
In related work, Li and Viswanathan described the synthesis of naphthalene derivatives by reacting epoxides with alkynes in the presence of $GaCl_3$ (Scheme 21).[44] The reaction displays excellent regiocontrol and proceeds smoothly with substituted epoxides and alkynes in good yields. As the same products were obtained when employing a gallium trichloride-catalysed cyclisation between the aromatic alkynes and the corresponding phenyl acetaldehydes, this would appear to indicate that the epoxides are undergoing isomerisation to form β,γ-unsaturated aldehydes *in situ* before reacting with the alkynes.



R = H; R' = H	65%
R = H; R' = Me	69%
R = H; R' = Et	63%
R = H; R' = Pr	47%
R = Ph; R' = H	49%
R = Ph; R' = Me	22%
R = Ph; R' = Et	22%

Scheme 18

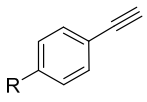
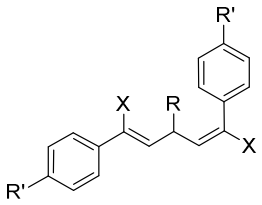
Yadav *et al.* have been actively engaged in the study of gallium(III) halides as catalysts for various organic transformations. The coupling of aldehydes and phenyl acetylene to give 1,3,5-triaryl-1,5-dihalo-1,4-pentadienes is one such example.[45] The condensation of phenyl acetylene with benzaldehyde in the presence of $GaCl_3$ affords triaryl-1,5-dichloro-1,4-pentadiene in good yields (Scheme 19).



Scheme 19

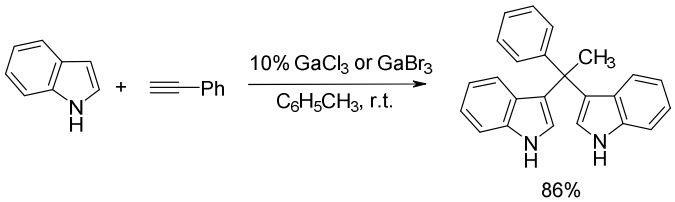
p-Chloro-, *p*-methyl-, *p*-cyano-and *m*-phenoxybenzaldehydes underwent smooth coupling with phenylacetylene to furnish the corresponding 1,5-dichloro-1,4-pentadienes (Table 12). Like gallium trichloride, gallium tribromide and gallium triiodide gave the respective bromo- and iodo-adducts under similar conditions. The reaction displayed a high level of stereocontrol, affording exclusively *E,Z*-isomers in most cases except for the reactions of *p*-chloro and *p*-cyanobenzaldehyde.

Table 12. $GaCl_3$-promoted streoselective synthesis of triaryl 1,5-dihalo-1,4-pentadienes

entry	aldehyde	alkyne	product	time (h)	yield(%)[a]
	R-CHO				
a	R=C_6H_5	R=H	R=C_6H_5; R'=H; X=Cl	2.0	87
b	R=4-ClC_6H_4	R=H	R=4-ClC_6H_4; R'=H; X=Cl	2.0	85[b]
c	R=4-MeC_6H_4	R=H	R=4-MeC_6H_4; R'=H; X=Cl	1.5	89
d	R=4-NCC_6H_4	R=H	R=4-NCC_6H_4; R'=H; X=Cl	2.0	60[b]
e	R=3-$PhOC_6H_4$	R=H	R=3-$PhOC_6H_4$; R'=H; X=Cl	1.5	50
f	R=C_6H_5	R=H	R=C_6H_5; R'=H; X=Br	0.5	86
g	R=C_6H_5	R=H	R=C_6H_5; R'=H; X=I	1.5	85
h	R=C_6H_5	R=H	R=4-NCC_6H_4; R'=H; X=Br	2.0	87
i	R=C_2H_5	R=H	R=C_2H_5; R'=H; X=Cl	1.5	80
j	R=*n*-C_5H_{11}	R=H	R=*n*-C_5H_{11}; R'=H; X=Br	1.5	80
k	R=*n*-C_5H_{11}	R=H	R=n-C_5H_{11}; R'=H; X=I	2.0	78
l	R=C_6H_5	R=Me	R=C_6H_5; R'=Me; X=Cl	2.0	91
m	R=4-FC_6H_4	R=Me	R=4-FC_6H_4; R'=Me; X=Cl	2.5	90
n	R=4-ClC_6H_4	R=Me	R=4-ClC_6H_4; R'=Me; X=Cl	1.0	89

[a]Yield refers to the isolated pure products. [b]*E,Z : Z,Z* -isomers obtained after column chromatography.

The coupling of indoles with phenylacetylene was developed by Yadav *et al.* as a short route to bis(indole) products.[46] Bis(indoles) are found in many natural products of biological significance.[47, 48] The treatment of indole with phenylacetylene in the presence of gallium(III) chloride or gallium(III) bromide, for example, afforded the bis(indolyl)phenyl ethane product in 86% yield (Scheme 20).

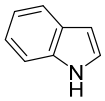
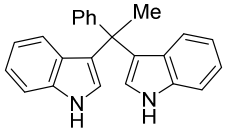
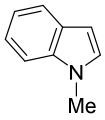
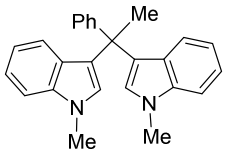
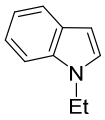
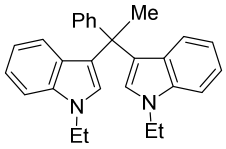
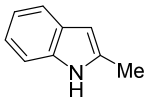
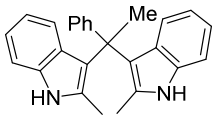
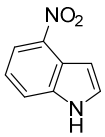
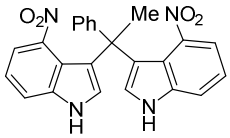
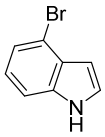
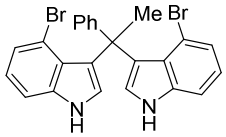
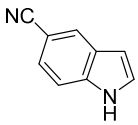
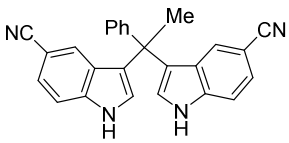
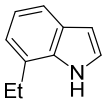
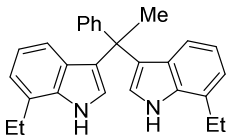
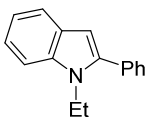
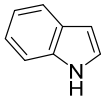
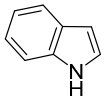


Scheme 20

Several substituted indoles such as *N*-methyl-, *N*-ethyl-, 2-methyl-, 4-nitro-, 4-bromo-, 5-cyano- and 7-ethyl-indoles underwent smooth coupling with phenylacetylene to afford the corresponding bis(indolyl)phenylethanes in high yields at room temperature (Table 13). However, 1-ethyl-2-phenyl indole did not react with phenylacetylene under these conditions. Neither diphenylacetylene nor alkyl-substituted alkynes (e.g. noctyne) gave

the desired products even on prolonged heating which is most likely a result of their intrinsically lower reactivity.

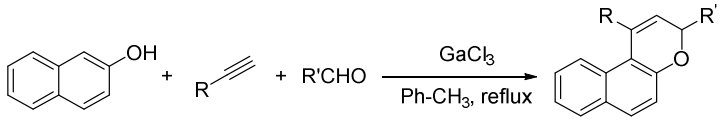
Table 13. Gallium(III) halide-catalyzed coupling of indoles with phenyl acetylene

entry	indole	alkyne	product	time (h)	yield(%)[a]
a				6.0	86
b				8.0	75
c				6.5	84
d				7.5	80
e				6.0	82
f				6.5	88
g				7.0	83
h				6.0	85
i			No Reaction	30.0	-
j			No Reaction	23.0	-
k			No Reaction	24.0	-

[a]Yield refers to the isolated pure products after column chromatography.

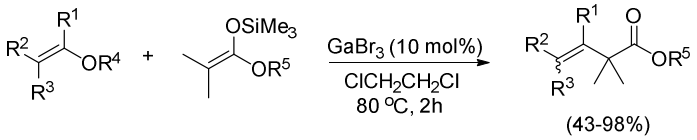
Yadav *et al*. further described a three-component coupling of naphthol, alkyne and aldehyde in the presence of 10 mol% gallium(III) chloride in toluene under reflux conditions to afford the corresponding 1,3-disubstituted-3*H*-benzo[*f*]chromenes in good yields.[49] A wide variety of aldehydes such as cyclohexanecarboxaldehyde, 1-octanal, 4-methoxy-benzaldehyde, 2- bromobenzaldehyde, cinnamaldehyde and geranial underwent smooth coupling with 2-naphthol and phenyl acetylene (Table 14). Other alkynes such as 1-ethynyl-4-methylbenzene and 1-octyne also underwent coupling with naphthol and benzaldehyde to give the corresponding chromene derivatives in good yields.

Table 14. $GaCl_3$-catalysed coupling of naphthol, alkyne and aldehyde



entry	R	R'	yield(%)
1	Ph	Ph	75
2	4-Me-C_6H_4	Ph	72
3	Ph	Cy	75
4	Ph	$CH_3(CH_2)_6$	70
5	Ph	4-MeO-C_6H_4	69
6	Ph	2-Br-C_6H_4	76
7	Ph	Ph-CH_2=CH_2	68
8	Ph	geranial	70
9	$CH_3(CH_2)_5$	Ph	68

The coupling reaction of alkenyl electrophiles with organometallics is an area of considerable interest as it is a powerful tool for the construction of π-conjugated carbon framework. Baba *et al.* have developed a novel coupling reaction of alkenyl ethers with ketene silyl acetals (Scheme 21).[9] Following an initial focus on indium-based systems, they subsequently discovered that $GaBr_3$ was a more effective catalyst affording α-vinyl esters in high yields across a range of substrates.

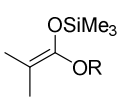
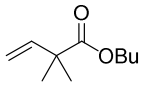
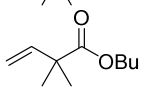
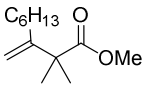
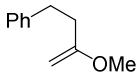
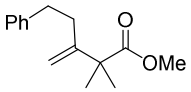
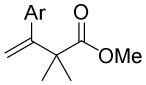
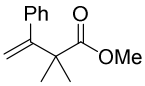
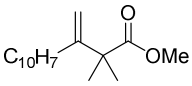
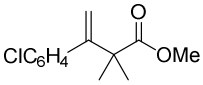
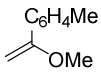
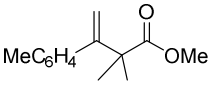
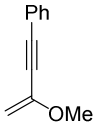
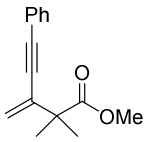
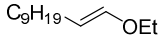
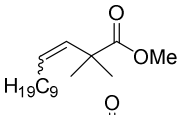
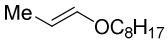
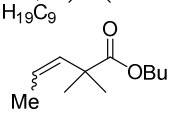
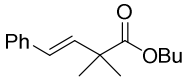


R^1 = H, Alkyl, Aryl
R^2 = H, Alkyl
R^3 = H, Aryl
R^4 = Me, *i*Pr, Ph, Et, C_8H_{17}
R^5 = Me, Bu

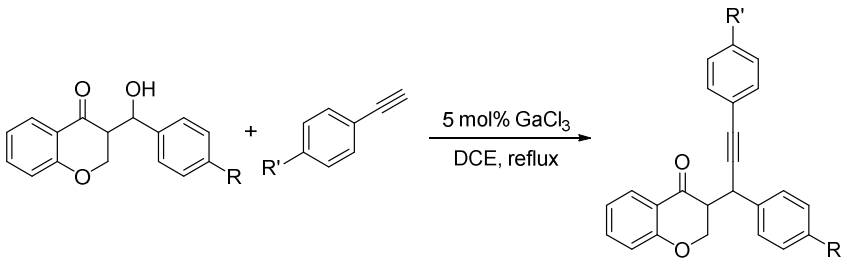
Scheme 21

1-Alkylated 1-methoxyethenes reacted to give the corresponding α-alkenylated esters in moderate yields (Table 15, entries c and d). 1-Phenyl- and 1-naphtyl-1-methoxyethenes gave the desired products in 43% and 59% yields (entries e and f) while 1-aryl-1-methoxyethenes possessing either electron withdrawing or electron donating substituents were also found to be suitable coupling partners (entries g and h).

Table 15. Gallium tribromide catalyzed coupling reaction of alkenyl ethers with ketene silyl acetals

entry	alkenyl ether	ketene silyl acetal 	product	yield (%)
a		R=Bu		50
b		R=Bu		98
c		R=Me		77
d		R=Me		69
		R=Me		
e		R=Me		43
f		R=Me		59
g		R=Me		61
h		R=Me		43
i		R=Me		73
j		R=Me		91 Z/E=54:46
k		R=Bu		100 Z/E=63:37
l		R=Bu		58

Morita-Baylis-Hillman alcohols, which possess both allylic hydroxyls and Michael acceptor units, are valuable synthons and useful starting materials for the synthesis of many biologically active molecules.[50] Liu *et al.* reported a $GaCl_3$-catalysed dehydrative coupling reaction of chromone-derived Morita-Baylis-Hillman alcohols with terminal alkynes (Scheme 22).[51] These reactions were exclusively α-regioselective and furnished alkyne-substituted products in good yields. While $GaCl_3$ catalysis generally afforded lower yields than the corresponding $FeCl_3$-mediated reactions, lower catalyst loadings were required in the case of $GaCl_3$ (5 mol% vs. 10 mol%).

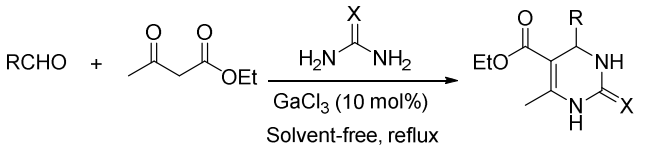


R = F; R' = H 53%
R = Br; R' = H 50%
R = H; R' = Br 62%
R = H; R' = F 63%

Scheme 22

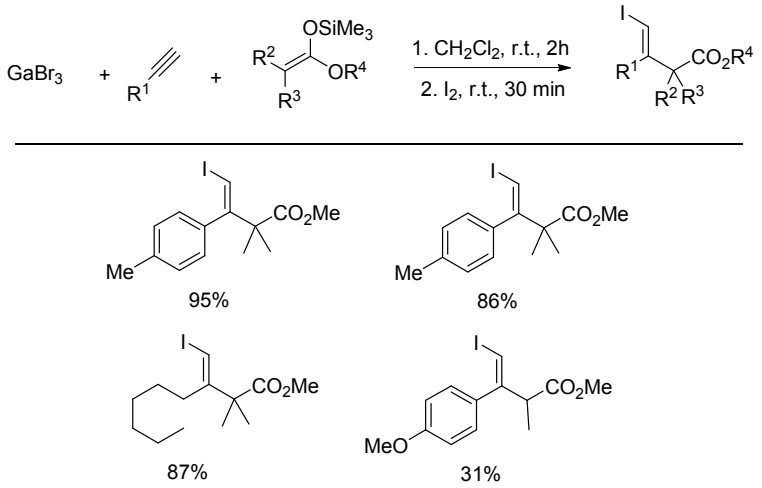
The dihydropyrimidinone motif appears in many pharmacologically active compounds including calcium channel modulators, α_{1a}-antagonists, anticancer drugs, and anti-HIV marine natural products.[52] Jianping *et al.* have described a novel route to dihydropyrimidine-2(1*H*)-ones using gallium catalysis.[53] Biginelli-type condensation of ethyl acetoacetate/cycloketone, aldehyde and urea/thiourea under solvent-free condition catalysed by 10% gallium(III) iodide affords dihydropyrimidine-2(1*H*)-one derivatives in good to excellent yields with a simple procedure and short reaction times. Both aromatic and aliphatic aldehydes as well as α,β-unsaturated aldehydes proved suitable substrates (Table 16, entries 1-9). When thiourea was used instead of urea, the expected sulfur-containing product was obtained in 90% yield (entry 10).

Table 16. GaI_3-catalysed Biginelli reaction under solvent-free conditions



entry	R	X	yield(%)
1	Ph	O	95
2	4-ClC_6H_4	O	90
3	4-NCC_6H_4	O	91
4	4-$NO_2C_6H_4$	O	90
5	4-FC_6H_4	O	92
6	4-$CHOC_6H_4$	O	79
7	CH_3	O	84
8	$CH_3(CH_2)_5$	O	82
9	Ph-CH_2=CH_2	O	87
10	Ph	S	90

A new methodology for the carbogallation of alkynes has been reported by Baba *et al.*[54] Reaction of an appropriate silyl ketene acetal, arylacetylene and gallium tribromide generates an alkenylgallium intermediate which is subsequently quenched with iodine to furnish the final iodoalkene product (Scheme 23). Both electron-rich and electron-poor aromatic alkynes react quantitatively to give the corresponding iodoalkenes. Carbogallation of 1-octyne proceeded in 87% yield while methyl-substituted ketene silyl acetal gave a moderate 31% yield of the desired product. The authors further describe the successive palladium-catalysed *in situ* coupling of these alkenylgalliums with various aryliodides.

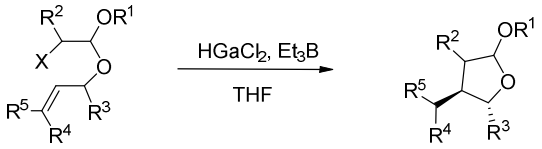


Scheme 23

2.5 Radical Reactions

The gallium hydride reagent $HGaCl_2$ is an efficient radical mediator. Mikami *et al.* investigated the reduction of alkyl halides with this reagent which provided the corresponding dehalogenated products in excellent yields.[55] This work was expanded to include the radical cyclisation of haloacetals. Selected haloacetals underwent 5-*exo* reductive cyclisation in the presence of dichlorogallane and triethylborane as outlined in Table 17. 2,2,6,6-Tetramethylpiperidine-*N*-oxyl completely inhibited the reaction suggesting that the reaction proceeds *via* a radical mechanism.

Table 17. Radical cyclisation of halo acetals



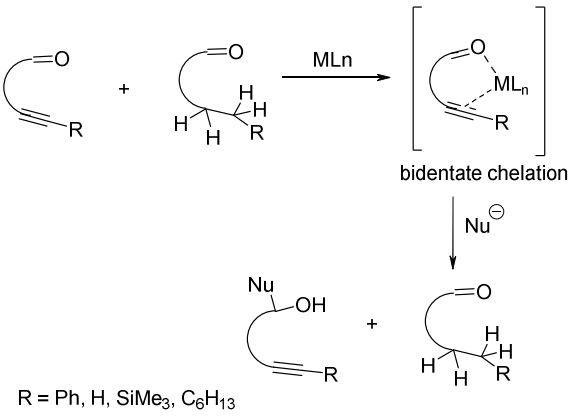
X	R^1	R^2	R^3	R^4	R^5	Yield(%)[a]
I	$(CH_2)_3$		H	Me	Me	87 (70/30)[b]
Br	$(CH_2)_3$		H	Me	Me	82 (71/29)[c]
I	$(CH_2)_3$		H	*n*-Pr	H	85 (84/16)[b]
Br	$(CH_2)_3$		H	*n*-Pr	H	80 (84/16)[b]
I	$(CH_2)_3$		*n*-Pen	H	H	85 (57/43)[b]
Br	$(CH_2)_3$		*n*-Pen	H	H	80 (56/44)[c]
I	*n*-Bu	H	H	*n*-Pr	H	97 (84/16)[b]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

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

2.6 Reduction Reactions

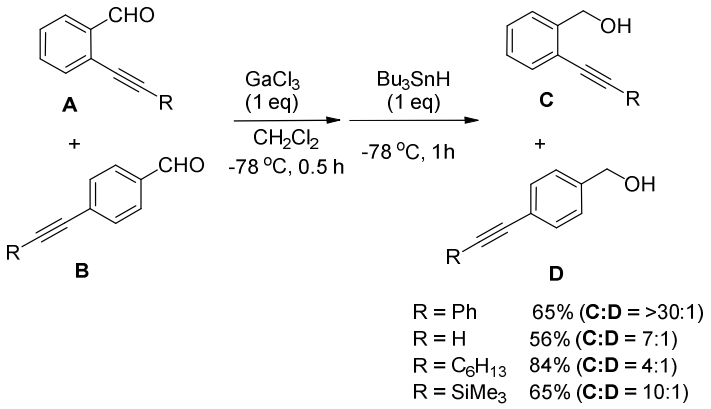
Lewis acid-mediated chelation control is one of the most fundamental concepts in modern organic chemistry. [56] Chelation-controlled reactions generally proceed through the co-ordination of a Lewis acid to a heteroatom lone pair such as the oxygen atom of

aldehydes or the nitrogen atom of imines. Yamamoto *et al.* reported a novel procedure for a chelation controlled reduction which proceeds *via* the coordination of Lewis acids to the π–electrons of C-C multiple bonds.[57] The reactions are both chemo- and regioselective and are most likely controlled by chelation of the π–electrons of the acetylenic bond as outlined in Scheme 24.



Scheme 24

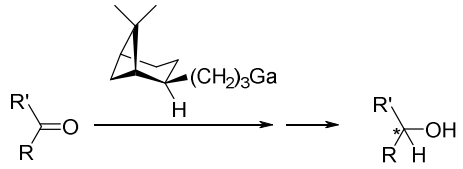
An example of this chemoselectivity is shown in Scheme 25, where an equimolar mixture of **A** (R = Ph) and its *para*-isomer (**B**) were treated with tributyltin hydride in the presence of $GaCl_3$. High chemoselectivity was observed in the case of **A** and a 63% yield of **C** was obtained along with recovered **A** (32%). By contrast, **D** was obtained in only 2% yield along with recovered **B** (92%). This trend was also observed for other substrates (R = C_6H_{13}, H or $SiMe_3$) and the authors conclude that this high selectivity is most likely due to effective bidendate chelation of the Lewis acid to the alkynyl groups.



Scheme 25

The asymmetric reduction of ketones using organogallium complexes was reported by Giacomelli *et al.*[58] The chiral organogallium derivative (prepared by reaction of *cis*-myrtanylmagnesium chloride with $GaCl_3$) reacted slowly in the absence of solvent at 50 °C with ketones, affording the corresponding optically active carbinols after hydrolysis (Table 18). It was noted that the steric hindrance of the substituent on the carbonyl carbon atom had a negative influence on reaction kinetics and the reduction rate dropped significantly on passing from ethyl phenyl ketone to *i*-propyl phenyl ketone.

Table 18. Reduction of ketones by tris(*cis*-myrtanyl)gallium

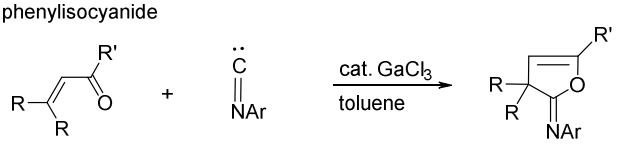


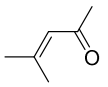
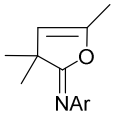
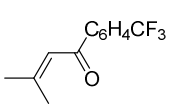
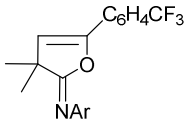
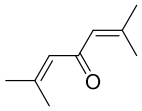
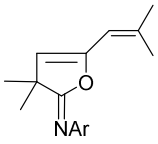
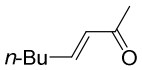
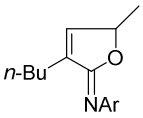
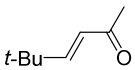
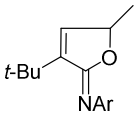
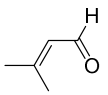
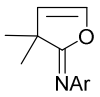
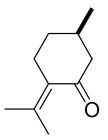
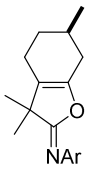
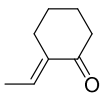
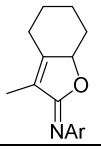
substrate	Carbinol		
	conversion (%)	time (h)	*ee* (%)
Ethyl phenyl ketone	77	24	21 (*R*)
1-Propyl phenyl ketone	58	48	51 (*R*)
2-Propyl-4-nonyn-3-one	79	24	75 (*R*)
2,2-Dimethyl-4-nonyn-3-one	89	24	54 (*R*)

2.7 Cycloaddition Reactions

Isocyanides are recognized as useful building blocks in organic synthesis as well as in polymer science.[59, 60] The characteristic features of isocyanide chemistry include high acidity of the α C-H bond and high reactivity toward cations, anions, and radicals. A $GaCl_3$-catalysed [4+1] cycloaddition reaction of α,β-unsaturated carbonyl compounds and isocyanides was investigated by Chatani *et al*. (Table 19).[61, 62] The presence of geminal substituents at the β-position led to the expected products in high yields (entries 2 and 3). Addditonally, it appears that the substituent at the β-position must be sufficiently sterically bulky (e.g *t*-Bu versus *n*-Bu) for the reaction to proceed efficiently (entries 4 and 5).

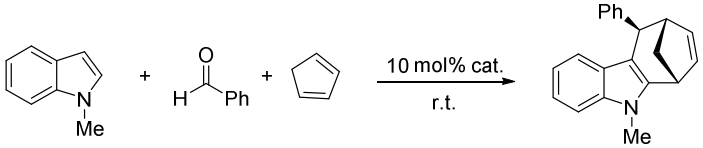
Table 19. $GaCl_3$-catalysed reaction of ketones with 2,6-Dimethyl-phenylisocyanide



entry	enone	product	yield (%)
1			94
2			95
3			78
4			20
5			73
6			41
7			91
8			44

Recently, Wu *et al*. described a gallium(III)-catalysed three-component [4+3] cycloaddition for the preparation of cyclohepta[*b*]indoles in high yields (Table 20).[63] These reactions occurred in a single step at room temperature without the need for Schlenk techniques, glove boxes, or an inert atmosphere. Both $Ga(OTf)_3$ and $GaBr_3$ were effective in promoting the desired reaction. While $Ga(OTf)_3$ was qualitatively the more reactive catalyst, it also formed a by-product (not formed with the use of $GaBr_3$) which was difficult to remove. The reaction was also sensitive to the choice of solvent (entries 3 and 4) while $GaCl_3$ catalysis proved unsuccessful (entry 5). As each of the three coupling components (i.e. indole, aldehyde/ketone, diene) can be independently varied, this methodology provides rapid access to a diverse library of cyclohepta[*b*]indole derivatives.

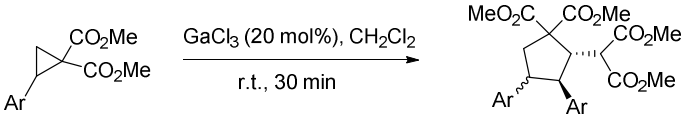
Table 20. Gallium(III)-catalysed three-component [4+3] cycloadditions



entry	catalyst	yield
1[b]	$Ga(OTf)_3$	91%
2	$GaBr_3$	94%
3[c]	$GaBr_3$	84%
4[d]	$GaBr_3$	-
5	$GaCl_3$	-

[a] 10 mol % catalyst, 2 equiv benzaldehyde, 5 equiv cyclopenta-1,3-diene, r.t, CH_2Cl_2 (all reactions stopped at 2 h). [b] Reaction time 35 min. [c] Toluene as solvent. [d] THF or Et_2O

Nefedov *et al.* reported a gallium trichloride-catalysed reaction of 2-arylcyclopropane-1,1-dicarboxylates affording polysubstituted *E*,*E*- and *E*,*Z*-cyclopentanes (Scheme 26).[64] Good yields were obtained from substrates containing halogen atoms in the *ortho*- and *meta*-positions of the phenyl ring. Naphthyl-substituted substrates also furnished the desired products albeit in more modest yields.

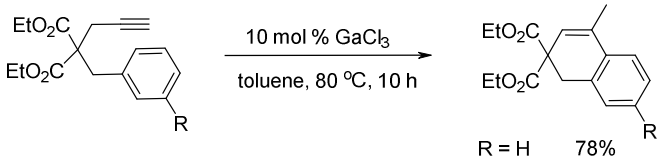


Ar = Ph	60%
Ar = 2-ClC_6H_4	91%
Ar = 3-ClC_6H_4	86%
Ar = 3-BrC_6H_4	80%
Ar = 4-MeC_6H_4	57%
Ar = 4-FC_6H_4	68%
Ar = 4-ClC_6H_4	69%
Ar = 4-BrC_6H_4	65%
Ar = 1-naphthyl	50%
Ar = 2-naphthyl	48%

Scheme 26

2.8 Cycloisomerisation Reactions

A $GaCl_3$-catalysed cycloisomerisation of ω-aryl alkynes has been developed by Murai *et al.*[65] A range of functionalised ω-aryl alkynes was cycloisomerised in the presence of $GaCl_3$ to form the corresponding dihydronaphthalene derivatives in excellent yields and with high site selectivity (Scheme 27). Both electron donating and electron withdrawing substituents were tolerated although elevated temperatures were required to achieve good conversion for the latter.

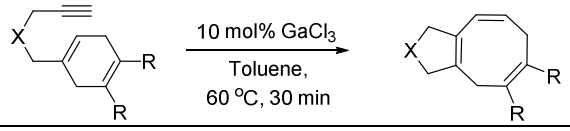


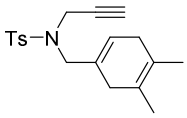
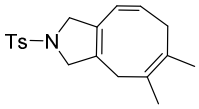
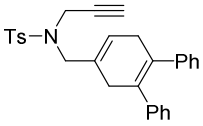
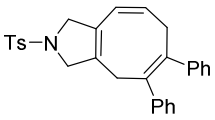
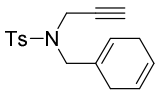
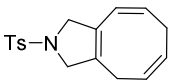
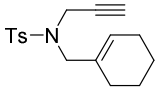
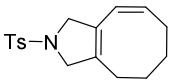
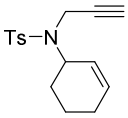
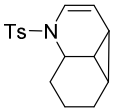
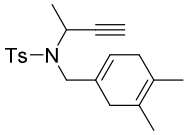
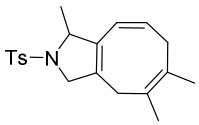
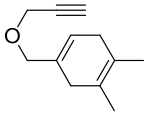
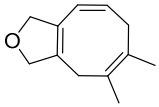
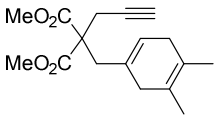
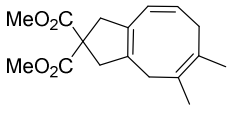
R = H 78%
R = OMe 80%
R = Me 79%
R = Cl 69%

Scheme 27

A $GaCl_3$-catalysed method has been reported by Chung *et al.* for the formation of eight-membered rings from enynes bearing a cyclic olefin.[66] This reaction represents a versatile new catalytic method for the synthesis of eight-membered bicyclic compounds (Table 21). Enynes bearing a cyclic diene with an NTs tether group (entries 1-3) were particularly good substrates for this cycloisomerisation. By contrast, enynes containing a cyclic monoene proved inferior (entry 4). Interestingly, reaction of an enyne with no spacer between an N atom and cyclohexene afforded an unexpected tricyclic product (entry 5). Oxygen and carbon were also tolerated as tether atoms (entries 7 and 8).

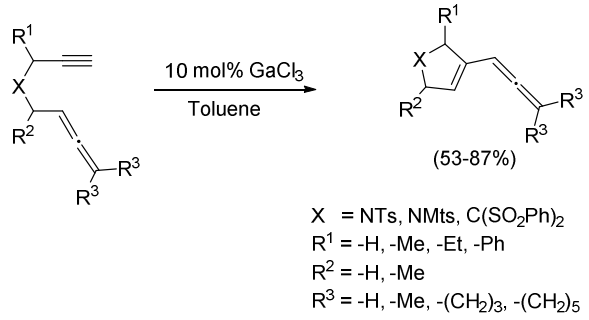
Table 21. $GaCl_3$-catalysed ring-opening metathesis of cylic enynes



entry	enone	product	yield (%)
1			91
2			63
3			75
4			39
5			12
6			16
7			88
8			33

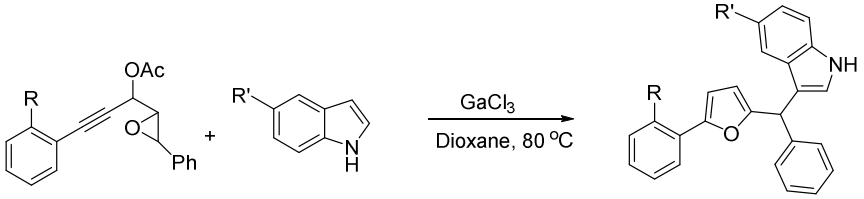
Chung *et al*. also demonstrated the gallium-mediated cycloisomerisation of allenynes to allenenes.[67] This catalytic system was quite effective for terminal 1,6-allenynes, and allenenes were obtained in moderate to high yields (Scheme 28). Terminal allenynes also served as good substrates while 3- and 5-substituted allenynes proved similarly amenable

to these reaction conditions. However, no reaction was observed for allenynes having a substituent on the alkyne terminal postion.



Scheme 28

A tandem cycloisomerisation/Friedel–Crafts alkylation of indoles has been achieved by Yadav *et al.* in a one-pot process to produce 2,5-disubstituted furans.[68] The reaction proceeds *via* the activation of both the alkyne and epoxide by gallium(III) (Scheme 29). This is followed by the addition of the nucleophile on the epoxide and subsequent isomerisation of the propargylic acetate results in the formation of the desired 2,5-disubstituted furan. The reaction proceeds efficiently under mild conditions with complete regioselectivity to afford the substituted furan derivatives in good yields with high diversity.



R = H; R' = H	65%
R = H; R' = Cl	69%
R = H; R' = Br	63%
R = H; R' = NO_2	47%
R = OMe; R' = H	49%
R = OMe; R' = Cl	22%
R = OMe; R' = Br	22%
R = OMe; R' = NO_2	22%

Scheme 29

Sarpong and Simmons have reported a general approach to the construction of the tricyclic core of the icetexane family of natural products *via* the cycloisomerization of alkynyl indenes using $GaCl_3$.[69, 70] Having initially screened several platinum- and ruthenium-based catalyst systems, they discovered that $GaCl_3$ effected the skeletal reorganisation of a variety of enynes under mild conditions. This approach was successfully applied to the preparation of a key intermediate in the synthesis of salviasperanol and sets the stage for access to other members of this family of diterpenoids (Scheme 30).

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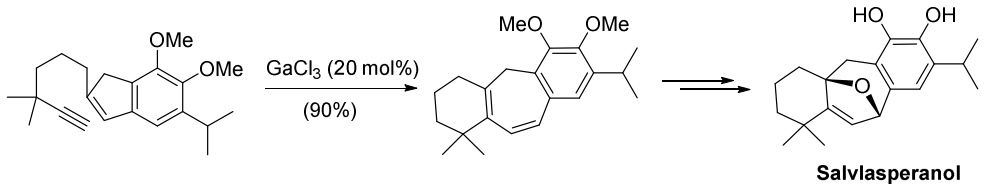
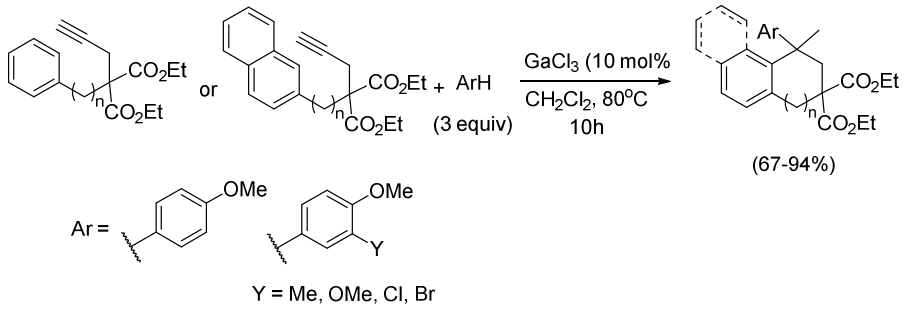


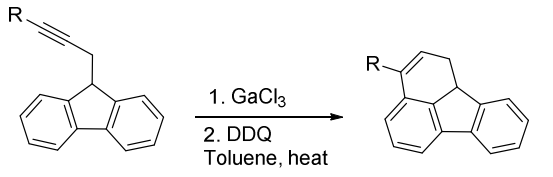
Scheme 30

$GaCl_3$ is known as powerful σ- and π-Lewis acid.[71] Gandon *et al.* have exploited this fact to excellent effect and have developed a polyhydroarylation protocol based on their discovery that $GaCl_3$ not only catalyses the cycloisomerisation of arenynes, but also traps the intermediates by electron-rich arenes, even in an intermolecular fashion.[72] Some examples are presented in Scheme 31.



Scheme 31

$GaCl_3$-catalysed synthesis of fluoranthenes by intramolecular hydroarylation of alkynes was reported by Echavarren *et al.*[73] The reaction proceeded satisfactorily with aryl-substituted substrates bearing either electron donating (*p*-Me, *o*-OMe) or electron withdrawing (*p*-Cl, *p*-Br, *p*-CN, *p*-NO_2) groups (Scheme 40). However, no reaction was observed for the substrate bearing an *n*-butyl substituent. $GaCl_3$ was found to a superior to Au(I)-based catalysts in all cases.



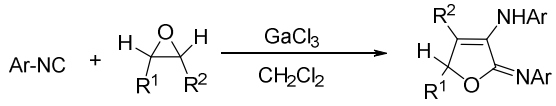
R = *p*-Tol	45%
R = *p*-ClC_6H_4	71%
R = *p*-NCC_6H_4	88%
R = *p*-$NO_2C_6H_4$	92%
R = *o*-$MeOC_6H_4$	57%
R = *o*-BrC_6H_4	44%
R = C_6F_5	74%
R = Br	21%

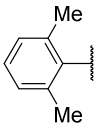
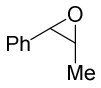
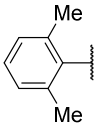
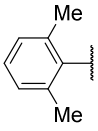
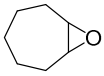
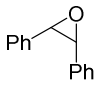
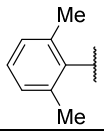
Scheme 32

2.9 Insertion Reactions

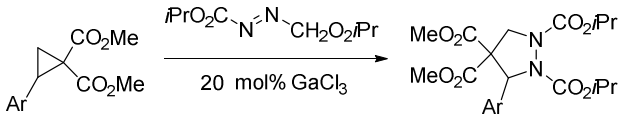
Epoxides are versatile building blocks in organic synthesis due to the high reactivity of their three-membered rings.[74] Although isocyanides are quite reactive toward cations, anions and radicals, they do not react with epoxides in the absence of a promoter. Bez and Zhao have described the double insertion of aryl isocyanides into disubstituted epoxides leading to α,β-unsaturated α-iminolactones (3-amino-2-imino-2,5-dihydrofurans) using $GaCl_3$ catalysis in a single step operation (Table 22).[75] The products of this reaction are potential substrates for the synthesis of sotolone type natural products.[76]

Table 22. Insertion of isocyanides into epoxides



entry	epoxide	Ar	yield (%)
1			31
2			61
3			73
4			14
5			51
6			68

$GaCl_3$ has been found to efficiently catalyse the formal cycloadditions of diazene derivatives onto 2-arylcyclopropane-1,1-dicarboxylates giving rise to substituted pyrazolidine derivatives.[77] The insertion into the cyclopropane ring proceeds with complete regioselectivity to furnish 5-arylpyrazolidine-1,2,3,3-tetracarboxylates exclusively (Scheme 33).

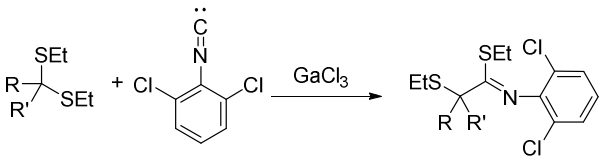


Ar = Ph 63%
Ar = 4-MeC_6H_4 52%
Ar = 4-BrC_6H_4 46%
Ar = 4-ClC_6H_4 67%
Ar = 4-$MeOC_6H_4$ 43%

Scheme 33

Insertion reactions into the C-S bond of dithioacetals, which afford products bearing two sulfur-based functionalities, have not been thoroughly investigated, and successful examples are limited to intramolecular processes.[78] An investigation into the $GaCl_3$-catalysed insertion reaction of isocyanides into the C-S bonds of dithioacetals has recently been carried out by Chatani *et al.*[79] They found that a variety of different dithioacetals, both aliphatic and aromatic, could be readily converted to the

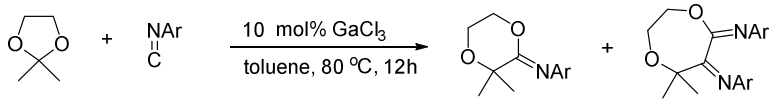
corresponding thioimidates using $GaCl_3$ catalysis (Scheme 34). Of the latter, electron-rich systems (e.g. dithioacetals derived from *para*-methoxybenzaldehye) displayed noticeably higher reactivity.



R = *n*-C_5H_{11}; R' = H	65%
R = Ph; R' = H	62%
R = 4-ClC_6H_4; R' = H	65%
R = 4-$MeOC_6H_4$; R' = H	84%
R = *n*-C_6H_{13}; R' = Me	47%
R = *t*-Bu; R' = Me	47%

Scheme 34

In a related study, Chatani *et al.* demonstrated the $GaCl_3$-catalysed insertion reaction of isocyanides into the carbon-oxygen bond of cyclic ketals and acetals, affording iminolactone derivatives (Scheme 35).[80] Over the course of the work, it was discovered that increasing the steric demand of the isocyanide had little effect on the efficiency of the reaction. However, electron withdrawing atoms such as chlorine and bromine on the phenyl ring of the aryl isocyanide led to a marked improvement in both yield and selectivity for the monoinsertion product.

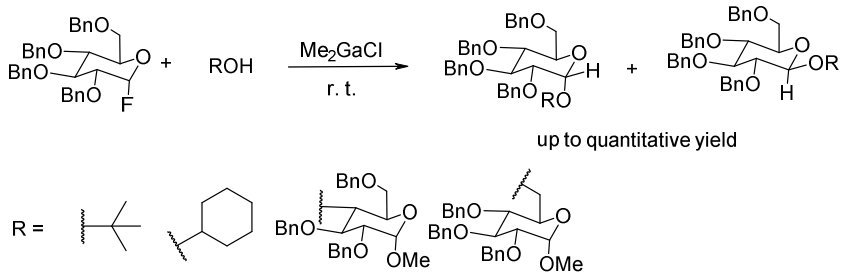


Ar = 2,6-$Me_2C_6H_3$	47%	5%
Ar = 2,6-*i*-$Pr_2C_6H_3$	46%	trace
Ar = 2,6-$Cl_2C_6H_3$	81%	0%
Ar = 2,6-$Br_2C_6H_3$	81%	5%

Scheme 35

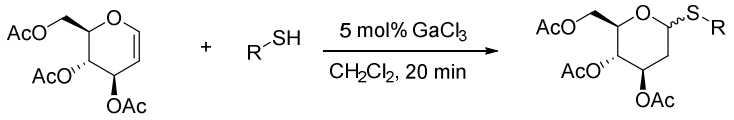
2.10 Glycosidation Reactions

A variety of glycosidation methods have been developed since the classical Koenigs-Knorr synthesis, but even now, the development of more selective or milder glycosidation reactions is still one of the most challenging topics in carbohydrate chemistry.[81] Kobayashi *et al.* have reported for the first time the use of gallium compounds for glycosidation reactions.[82] Dimethyl galliumchloride and dimethylgallium triflate were found to efficiently promote the glycosidation of several glycopyranosyl fluorides (Scheme 36). The reaction was solvent dependent with dichloromethane and acetonitrile resulting in relatively high β-selectivity. However, the glycosidation proceeded very slowly in acetonitrile, probably because of the coordination of the lone pair electrons of the solvent to the gallium ion.



Scheme 36

Yadav *et al.* found that gallium(III) chloride efficiently catalyses the addition of thiols to glycals under extremely mild conditions affording 2-deoxy thioglycosides in high yields with a good α-selectivity (Scheme 37).[83] Several substituted thiophenols underwent addition reactions to glycals to provide the respective thioglycosides with high α-selectivity. The influence of donating and withdrawing substituents on the aromatic ring of the thiols was also studied and it was discovered that electron withdrawing halogen substituents led to depressed overall yields.



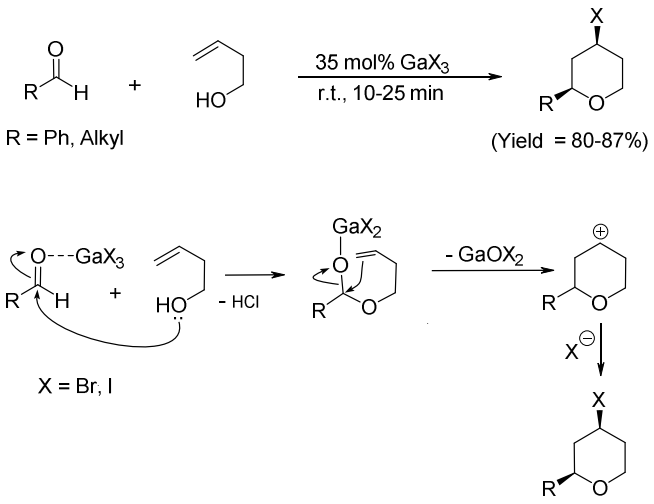
R = 1-naphthyl 90%
R = 4-$MeOC_6H_4$ 95%
R = 4-BrC_6H_4 46%
R = 4-ClC_6H_4 67%
R = Et 43%
R = cyclohexyl 43%

Scheme 37

3. Miscellaneous

3.1 Synthesis of 4-Halotetrahydropyrans

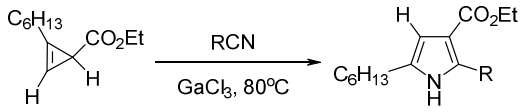
The tetrahydropyran skeleton is a core structure in various natural products such as avermectins, aplysiatoxins, oscillatoxins, latrunculins, talaromycins and acutiphycins.[84] Yadav *et al.* developed a modified Prins cyclisation for the rapid coupling of aldehydes with 3-buten-1-ol in the presence of 35 mol% gallium(III) bromide and gallium(III) iodide.[85] A range of 4-halotetrahydropyran derivatives was isolated under mild conditions in excellent yields and with high selectivity. The formation of the products may be accounted for by initial hemi-acetal formation followed by subsequent Prins-type cyclisation (Scheme 38).



Scheme 38

3.2 Synthesis of Pyrroles

Araki *et al.* have described a novel synthesis of pyrroles by the condensation of cyclopropenes and nitriles mediated by gallium trihalides.[86] When the reaction of cyclopropenes with $GaCl_3$ was first attempted in acetonitrile, no chlorogallation occurred. However, a small amount of a pyrrole derivative was isolated from the reaction mixture. It was later discovered that this pyrrole was formed by the condensation of cyclopropene and the acetonitrile solvent. This unexpected result prompted a systematic investigation of the reaction of various cyclopropenes with nitriles mediated by $GaCl_3$ (Scheme 39). Although the yields are moderate for some substrates, the selective formation of a single isomer of pyrrole makes this methodology attractive.

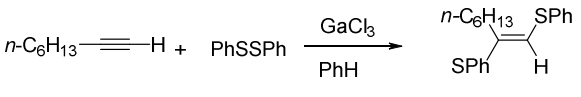


R = Me	90%
R = $Ph(CH_2)_3$	95%
R = 2-thiophenyl	46%
R = 2-CF_3-C_6H_4	67%

Scheme 39

3.3 Disulfidation of Alkynes and Alkenes

Vinylsulfides have synthetic utility in organic chemistry and can be readily prepared by the stereoselective sulfidation of alkynes.[87, 88] Usigi *et al.* found that treatment of diphenyl disulfide and terminal alkynes with gallium chloride affords (*E*)-1,2-diphenylthio-1-alkenes selectively (Scheme 40).[89]

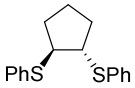
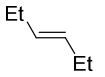
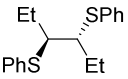
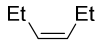
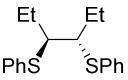
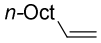
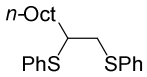
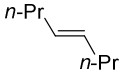
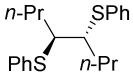
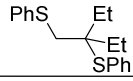


Scheme 40

Alkenes can be transformed in a similar fashion, affording the *trans* adduct. The results of the addition of diphenyl disulfide to various alkenes in the presence of Ga(III) chloride

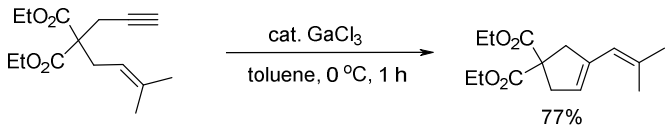
are summarised in Table 23. While mono- and disubstituted alkenes proved suitable substrates, an attempt to react diphenyldisulfide with tri- and tetrasubstituted alkenes failed to give the desired di(phenylthio)alkanes.

Table 23. Disulfidation of various alkenes with Gallium(III) chloride

entry	alkene	product	yield(%)
a			87
b			93
c			88
d			65
e			71
f			74

3.4 Skeletal Reorganisation of Enynes

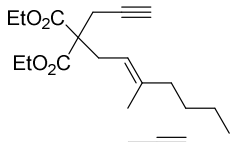
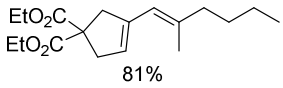
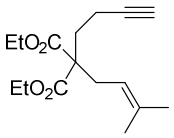
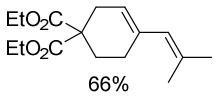
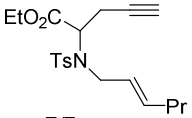
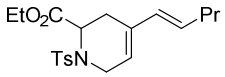
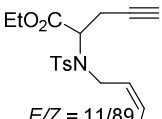
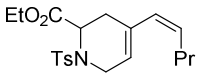
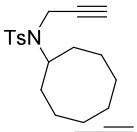
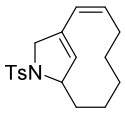
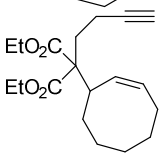
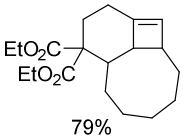
The transformation of enynes into 1-vinylcycloalkenes provides a powerful method for the construction of a useful ring system by means of a simple operation. Chatani *et al.* investigated the reaction of a 1,6-enyne with a catalytic amount of $GaCl_3$ which afforded a 1-vinylcyclopentene derivative in 77% yield (Scheme 41).[90]



Scheme 41

Disubstituted enynes were found to serve as good substrates (Table 24, entries 1-2) while this approach was also applicable to the formation of 1-vinylcyclohexenes (entries 2-4). Notably, the skeletal reorganisation of enynes, which contain a monosubstituent at the olefinic terminal carbon, proceeds in a stereospecific manner under $GaCl_3$ catalysis (entry 3-4). This is in contrast to previously reported results on the Ru(II)- and Pt(II)-catalysed reaction of enynes, where *trans* isomers were obtained irrespective of the geometry of the starting materials.[91]

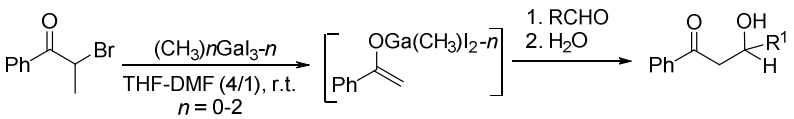
Table 24. Skeletal reorganisation of enynes catalysed by $GaCl_3$[a]

entry	enynes	conditions	products
1		0 °C 30 min[b]	 81%
2		40 °C 30 min	 66%
3[c]	 *E/Z* = 88/12	60 °C 2 h	 69% *E/Z* = 93/7
4	 *E/Z* = 11/89	40 °C 2 h	 87% *E/Z* = 5/95
5		60 °C 3 h	 72%
6		40 °C 2 h	 79%

[a]Reaction conditions: enyne (0.5 mmol), $GaCl_3$ (0.05 mmol, 1.0 M in methylcyclohexane), and toluene (2.5 mL) under N_2. [b]Solvent: methylcyclohexane. [c]A small amount (4% yield) of a six-membered by-product was also formed.

3.5 Aldol and Addition Reactions

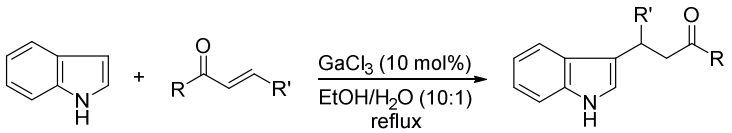
The aldol reaction remains one of the key C-C bond forming reactions in modern organic synthesis.[92] A mild and efficient reductive diastereoselective dehalogenation and aldol condensation of α-bromoketones with gallium halides has been studied by Han and Huang.[93] When an aldehyde or ketone was added to this mixture, the cross-aldol reaction proceeded under mild conditions and β-hydroxyketones were obtained in good yields (Scheme 42). An improvement in yield was noted when gallium triiodide was replaced with either gallium methyl iodide or dimethyl gallium iodide.



R = Ph; n=0	86%
R = *p*-ClC_6H_4; n=0	82%
R = Et; n=0	64%
R = *p*-$NO_2C_6H_4$; n=0	74%
R = *p*-ClC_6H_4; n=1	94%
R = *p*-ClC_6H_4; n=2	95%

Scheme 42

While several Lewis acids have been employed as catalysts in the Michael addition of indoles and pyrroles, the majority of these catalysts require dry, organic solvents. Ding *et al.* have reported a $GaCl_3$-catalysed Michael addition of indole which can be carried out in aqueous media.[94] A selection of the indole reactions are outlined in Scheme 43. These Michael additions proceeded smoothly to produce the corresponding 3-alkyl products in good yields without the formation of any side products such as *N*-alkylation products. Neither electron donating nor electron withdrawing groups on the aromatic ring affected the reaction significantly either in terms of yields or rate of the reaction.

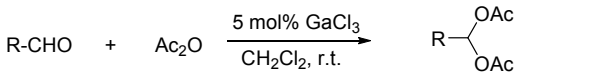


R = Ph; R' = Ph	93%
R = Ph; R' = 4-$CH_3OC_6H_4$	87%
R = Ph; R' = 4-$CH_3C_6H_4$	85%
R = Ph; R' = 4-BrC_6H_4	84%
R = Ph; R' = 3,4-$OCH_2OC_6H_3$	47%
R = 4-$CH_3C_6H_4$; R' = 4-ClC_6H_4	47%

Scheme 43

3.6 Preparation of *gem*-diacetates from aldehydes

gem-Diacetates are useful synthons and have found application in an array of different reactions including Grignard, Barbier, Prins and Knoevenagel condensations among others. A solvent-free methodology for the preparation of these versatile compounds has been developed by Sandhu *et al.* employing $GaCl_3$ catalysis.[95] Their solvent-free methodology afforded the desired products in higher yields and shorter reaction times than the corresponding reaction in solvents such as dichloromethane. A variety of aliphatic and aromatic aldehydes could be converted under these conditions in excellent yields including aromatic aldehydes bearing either electron donating or electron withdrawing substitents (Scheme 44). Ketones, however, did not react under these conditions.

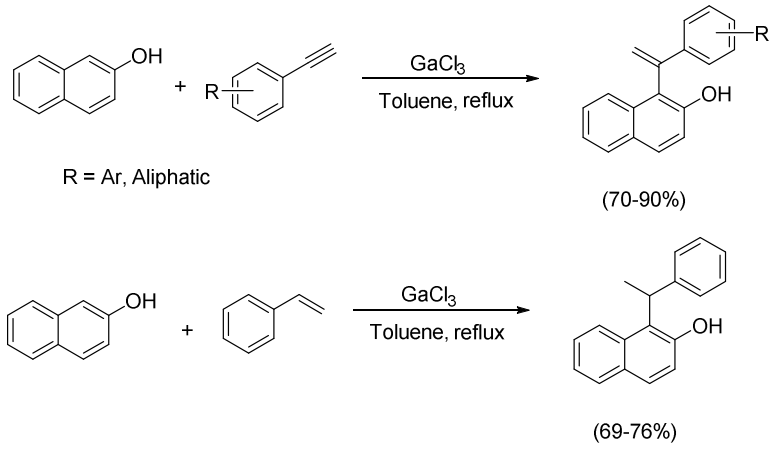


R = Ph	98%
R = 4-MeC_6H_4	98%
R = 4-$MeOC_6H_4$	95%
R = 4-ClC_6H_4	97%
R = 3-$NO_2C_6H_4$	89%
R = 4-$NO_2C_6H_4$	91%
R = PhCH=CH	86%
R = Pr	90%
R = $CH_3(CH_2)_4$	91%

Scheme 44

3.7 Hydroarylation of Arylacetylenes

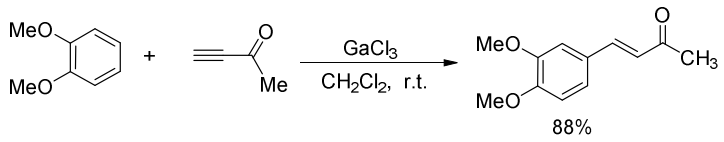
Traditionally, Friedel–Crafts alkylation and acylation, nitration, and halogenation reactions have been employed in the functionalisation of arenes. These methods, however, are characterised by strongly acidic conditions, high temperatures, poor regioselectivity, and the formation of large amounts of by-products. A mild method of hydroarylation of arylacetylenes in the presence of $GaCl_3$ has been described by Yadav *et al.*[96] Arylacetylenes were found to undergo smooth hydroarylation with naphthols and phenols in the presence of 10 mol% gallium(III) chloride in refluxing toluene to afford the corresponding 2-vinylnaphthols and 2-vinylphenols in good yields with high regioselectivity (Scheme 45). Styrenes similarly underwent hydroarylation with naphthols and phenols to provide substituted naphthols and phenols.



Scheme 45

3.8 Stereoselective Synthesis of *E*-Configured α,β-Unsaturated Ketones

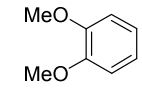
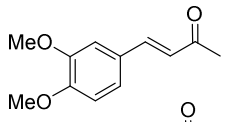
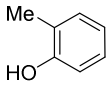
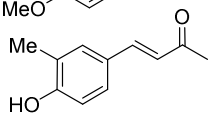
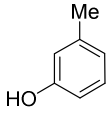
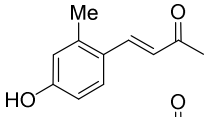
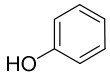
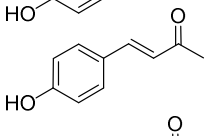
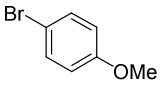
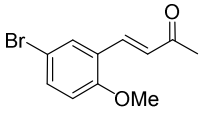
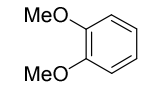
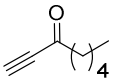
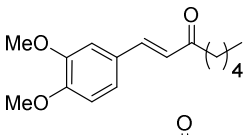
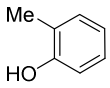
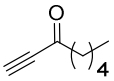
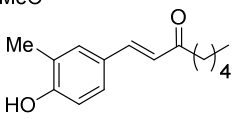
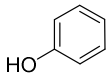
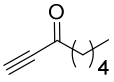
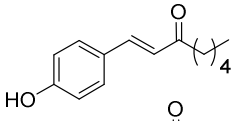
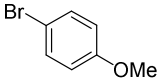
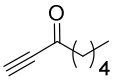
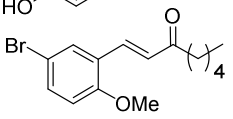
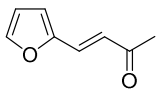
Gallium(III) compounds are particularly effective at activating alkynes under extremely mild conditions.[43] Yadav *et al.* have exploited this property of gallium(III) to considerable effect in their highly stereoselective method for the synthesis of *E*-configured α,β-unsaturated ketones from ynones (Scheme 46).[97]



Scheme 46

This procedure offers significant advantages over previous methods such as high conversions, short reaction times together with mild reaction conditions (Table 25). This reaction was highly regioselective, with none of the *Z*-isomer products being formed. Interestingly, no reaction was observed with methyl propiolate although the authors ascribe this to the intrinsically lower reactivity of methyl propiolate in comparison to the other substrates.

Table 25. Gallium(III) chloride-catalysed synthesis of α,β-unsaturated ketones

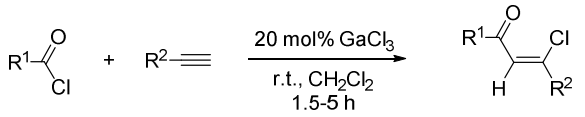
entry	substrate	alkynes	product[a]	time (min)	yield (%)[b]
a				40	88
b				45	89
c				35	85
d				30	80
e				30	90
f				30	90
g				35	81
h				30	85
i				35	91
j				45	89

[a]All products were characterized by NMR, IR and ESI/MS.
[b]Isolated yields after column chromatography.

3.9 Chloroacylation of Alkynes

The Friedel–Crafts addition of acid chloride–$AlCl_3$ complexes to acetylenes leading to β-chlorovinyl ketones has been known since the early 1970s.[98] The major products of this reaction typically have the chlorine and the carbonyl groups configured in a *trans* relationship.[99] Huang *et al.* have reported a novel procedure for the preparation of β-chlorovinyl ketones in which the major products are of the *cis* configuration. In contrast to the alternative Friedel–Crafts acylation, only a catalytic amount of $GaCl_3$ is needed to afford the target products with good stereoselectivity (Table 26).[100] The authors noted that the *trans* isomers could be isolated in cases when sterically non-hindered or aromatic acid chlorides were employed.

Table 26. Synthesis of β-chlorovinyl ketones *via* tha $GaCl_3$-catalysed chloroacylation of alkynes[a]

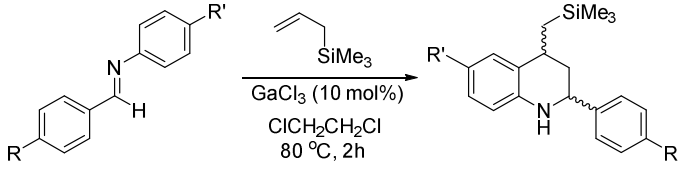


	R^1	R^2	Yield (%); *cis/trans* ratio[c]
	n-Pent	Ph	65
	n-Pent	*n*-Pent	61
	n-Pent	*n*-Pent	58
	n-Hex	*n*-Pent	62
	n-Hex	Ph	66
	Me[d]	*n*-Pent	62 (50:50)
	Et[d]	*n*-Pent	57 (69:31)
	Et[d]	*n*-Bu	55 (55:45)
	Ph	$BrCH_2CH_2$	52 (88:12)
	Ph	Ph	61 (89:11)
	p-Tol	Ph	62 (87:13)
	Et[d]	*n*-Pent	55 (62:38)
	Et[d]	*n*-Bu	59 (52:48)
	Ph	$BrCH_2CH_2$	58 (83:17)
	Ph	Ph	58 (82:18)
	p-Tol	Ph	55 (84:16)

[a]All reactions were carried out using 1 (0.6 mmol), 2 (0.5 mmol) and $GaCl_3$ (0.1 mmol) in CH_2Cl_2 (5 mL at r.t).
[b]Isolated product yield after chromatography.
[c]The cis/trans ratios were determined by NMR spectroscopy.
[d]Acid chloride (1 mmol) was used.

3. 10 Annulation Reactions

Tetrahydroquinolines are generally prepared by the aza-Diels–Alder reaction of arylimines with dienophiles or the reaction of Schiff bases with allyl Grignard reagents, followed by a ring closure under acidic conditions.[101, 102] Hirashita *et al.* have demonstrated that the $GaCl_3$-catalysed reaction of allyltrimethylsilane and aldimines is a practical alternative for the preparation of tetrahydroquinolines in good yields (Scheme 47).[103] While other Lewis acids such as $BF_3.OEt_2$, $Sc(OTf)_3$ and $Yb(OTf)_3$, were also investigated, $GaCl_3$ proved to be a superior reagent in all cases.

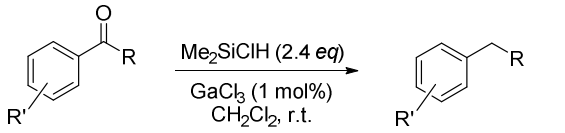


R = H; R' = H	93%
R = NO_2; R' = H	87%
R = CN; R' = H	85%
R = Me; R' = H	84%
R = OMe; R' = H	47%
R = NO_2; R' = OMe	47%

Scheme 47

3.11 Deoxygenation of Aryl Ketones

Reduction of the carbonyl group of aldehydes and ketones to the corresponding methylene derivatives can be accomplished by several chemical methods such as Clemmensen reduction, Wolff-Kishner reduction, $LiAlH_4$-$AlCl$ or $NaBH_4$-CF_3CO_2H among others. However, because of the harsh conditions involved or the requirement for large amounts of Lewis acid, many of these methods are restricted from use with compounds containing acid sensitive functional groups. A mild and efficient direct deoxygenation of aryl ketones using $GaCl_3$ as a Lewis acid and chlorodimethylsilane as a hydride donor was reported by Kang *et al.* with potential for application with acid labile compounds (Scheme 48).[104] While acetophenone, propiophenone, and butyrophenone were readily reduced to the corresponding methylenes, the authors noted that the yields decreased with the increasing length of the acyl side chain.



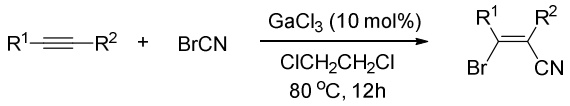
R = Me; R' = H	99%
R = Et; R' = H	94%
R = Pr; R' = H	79%
R = Bu; R' = H	75%
R = Ph; R' = H	64%
R = CH_3; R' = *p*-OCH_3	95%
R = CH_3; R' = *p*-NO_2	37%

Scheme 48

3.12 Bromocyanation and Cyanation Reactions

(*Z*)-β-Bromoacrylonitriles are versatile synthons which can be converted to a wide range of α,β-unsaturated nitriles.[105] Ohe *et al.* have developed a $GaCl_3$-mediated bromocyanation of alkynes with cyanogen bromide affording (*Z*)-β-bromoacrylonitriles in good yields.[106] This method enables the regio- and stereoselective introduction of the bromo- and cyano-functionalities to carbon-carbon triple bonds in single operation. While a broad array of arylacetylenes proved suitable substrates under these conditions (Table 27), reactions with internal aliphatic or alicyclic alkynes, such as 4-octyne and cyclooctyne, gave complex mixtures.

Table 27. $GaCl_3$-catalysed bromocyanation of alkynes using BrCN[a]

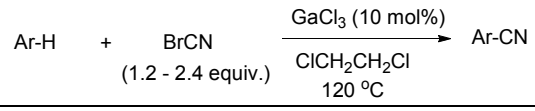


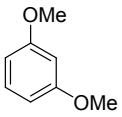
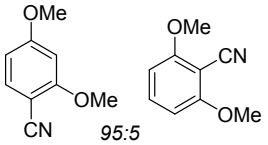
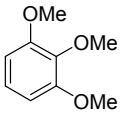
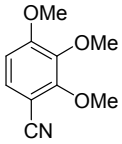
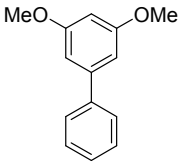
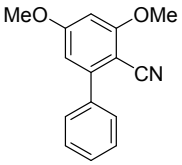
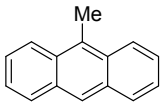
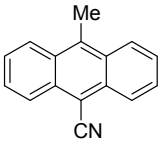
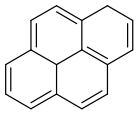
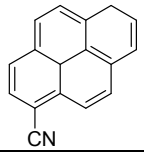
entry	R^1	R^2	Isolated yield (%)	$Z : E$ [b]
1	4-$CH_3C_6H_4$	H	70	95:5
2	2-$CH_3C_6H_4$	H	61	98:2
3	2-Naph	H	55	95:5
4	4-FC_6H_4	H	71	91:9
5	4-ClC_6H_4	H	68	90:10
6	4-BrC_6H_4	H	68	91:9
7	4-$CF_3C_6H_4$	H	20	92:8
8	Ph	CH_3	70	95:5
9	Ph	*n*-Bu	72	91:9
10[c]	Ph	Ph	56	99:1

[a]*Reaction conditions*: alkynes (0.48 mmol) and BrCN (0.40 mmol) in $ClCH_2CH_2Cl$ (1.6 mL) were heated in the presence of $GaCl_3$ (10 mol%). [b]Determined by NMR. [c]Reaction carried out in toluene at 100 °C.

More recently the same group has described the direct cyanation of aromatic and heteroaromatic C–H bonds with cyanogen bromide catalysed by gallium(III) halides.[107] Highly electron rich dimethoxy- and trimethoxyarenes were transformed into the corresponding aromatic nitriles in high yields, while polycyclic aromatic compounds such as anthracene and pyrene also afforded the desired products as single regioisomers (Table 28).

Table 28. Gallium-catalysed cyanation of arenes with cyanogen bromide[a]

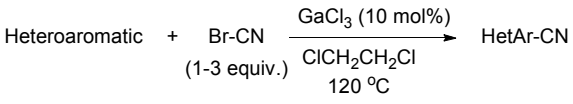


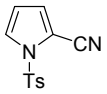
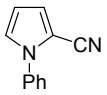
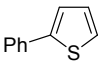
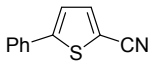
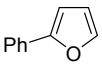
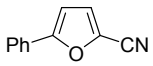
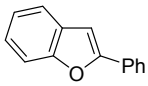
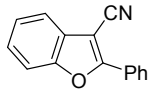
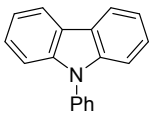
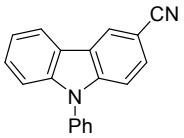
Substrate	Cyanation products	Yields (%)
	 *95:5*	82
		83
		78
		85
		88

[a]Reactions were carried out with arenes (0.40 mmol, 1.0 equiv.), cyanogen bromide (0.48 mmol, 1.2 equiv.), and $GaCl_3$ (10 mol%) in $ClCH_2CH_2Cl$ (1.6 mL).

This methodology is equally applicable to heteroaromatic compounds. A range of heteroarenes, including pyrroles, furans, thiophenes, benzofurans and carbazoles underwent electrophilic cyanation in good to excellent yields (Table 29). The cyanation proceeded with a high degree of regioselectivity, with 5-membered rings reacting exclusively at the 2-position.

Table 29. Gallium-catalysed cyanation of heteroarenes with cyanogen bromide[a]



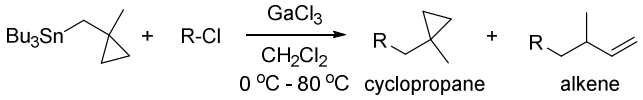
Substrate	Cyanation products	Yield (%)
		80
		73
		83
		50
		90
		80

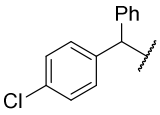
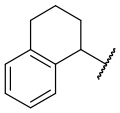
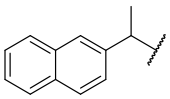
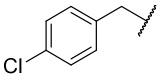
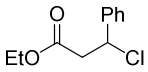
[a]Reactions were carried out with heteroarenes (0.40 mmol, 1.0 equiv.), cyanogen bromide (0.48 mmol, 1.2 equiv.), and $GaCl_3$ (10 mol%) in $ClCH_2CH_2Cl$ (1.6 mL).

3.13 Cyclopropylmethylation of Alkyl chlorides

Although butenyl metal species are considered useful reagents for the construction of cyclopropyl rings, their low nucleophilicity has limited their synthetic application.[108] Recently, Baba *et al.* have studied a $GaCl_3$-catalysed cyclopropylmethylation of alkyl chlorides with cyclopropylmethylstannane.[109] Various secondary benzylic chlorides were converted to the cyclopropylated products in moderate to high yields (Table 30). 3-Chlorocyclohexene and β-chloroesters could also be transformed in this manner, albeit in more modest yields (entries 6 and 8).

Table 30. $GaCl_3$-catalysed cyclopropylmethylation of alkyl chlorides

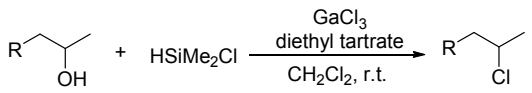


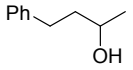
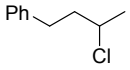
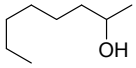
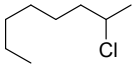
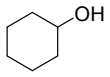
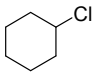
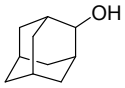
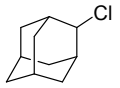
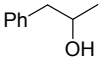
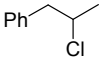
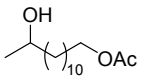
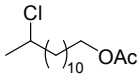
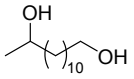
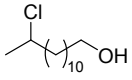
entry	R	yield (%) cyclopropane	alkene
1		72	16
2		59	21
3		56	22
4		63	15
5		73	20
6		45	12
7		36	46
8		40	22

3.14 Direct Chlorination of Alcohols

Numerous methods exist for the chlorination of organic alcohols. The majority of these reactions, however, are carried out in acidic conditions which precludes their application to acid labile substrates. Baba *et al.* have reported a neutral system for chlorination of alcohols using dimethylchlorosilane, dimethyl tartrate and $GaCl_3$.[110] Various secondary alcohols, including 2-octanol, cyclohexanol, 2-adamantanol and 3-phenyl-2-propanol gave the corresponding chlorides in high yields (Table 31). Acid sensitive substrates, such as acetate esters, were cleanly converted to the desired products without unwanted side reactions (entry 7). The chlorination conditions displayed high chemoselectivity, with alcohols bearing both secondary and primary hydroxyls sites reacting exclusively at the secondary site (entry 8).

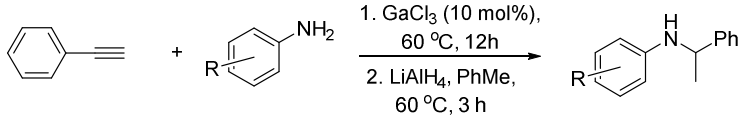
Table 31. Chlorination of secondary alcohols



entry	alcohol	product	yield (%)
1			75
2			36
3			57
4			89
5			69
6			62
7			53
8			39

3.15 Hydroamination Reaction

The direct hydroamination of alkynes remains an underdeveloped reaction.[111] The successful application, therefore, of gallium(III) catalysis to the hydroamination of hydroamination of alkynes with aromatic amines as reported by Li *et al.* represents a considerable step forward.[112] Primary aromatic amines, containing different functionalities such as halogens and methoxyls, were transformed in high yields with exclusive formation of the Markovnikov products (Scheme 50). Secondary aromatic amines similarly underwent hydroamination, but in more moderate yields.



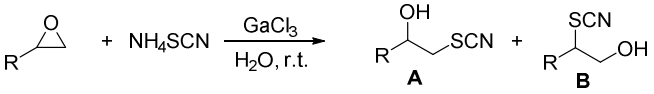
R = *o*-Cl 98%
R = *m*-Cl 98%
R = *p*-Cl 95%
R = *p*-Br 89%
R = *o*-F 91%
R = *p*-F 86%
R = *p*-MeO 90%
R = H 91%

Scheme 49

3.16 Ring Opening of Epoxides

An improved method for the preparation of β-hydroxy thiocyanates from epoxides has been described by Su *et al.* In the presence of NH_4SCN and $GaCl_3$, a range of substituted epoxides were converted to the corresponding β-hydroxy thiocyanates in excellent yields (Table 32). The reaction displays high regioselectivity with monoaryl-substituted epoxides undergoing preferential attach of thiocyanate at the more substituted position (entries 1-3). By contrast, thiocyanate attacked monoalkyl-substituted epoxides at the less hindered position (entries 4-7).

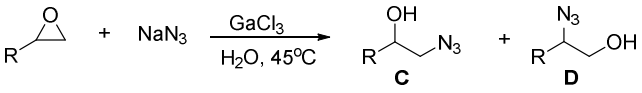
Table 32. Reaction of various epoxides with NH_4SCN in the presence of $GaCl_3$



entry	R	product	yield (%)
1	Ph	**1B**	92
2	4-Cl-Ph	**2B**	87
3	4-Br-Ph	**3B**	89
4	$PhCH_2OCH_2$	**4A**	90
5	$PhOCH_2$	**5A**	88
6	4-Cl-$PhOCH_2$	**6A**	89
7	CH_2=$CH(CH_2)_6$	**7A**	87

Gallium(III)-mediated azidolysis of epoxides could be carried out with exclusive regioselectivity in a similar manner. The azido ion was observed to attack monoaryl-substituted epoxides at the benzylic carbon (Table 33, entries 1-3) while good regioselectivity was also observed for monoalkyl-substituted epoxides (entries 4-6). This methodology offers the additional benefit of an environmentally friendly reaction medium (i.e. water).

Table 33. $GaCl_3$-promoted azidolysis of epoxides with NaN_3



entry	R	product	yield (%)
1	Ph	**1D**	93
2	4-Cl-Ph	**2D**	88
3	4-Br-Ph	**3D**	87
4	$PhCH_2OCH_2$	**5C**	93
5	$PhOCH_2$	**5C**	93
6	4-Cl-$PhOCH_2$	**6C**	89

4. Conclusion

Organic chemists are continually uncovering new uses for gallium metal and gallium trihalide reagents, most especially as substitutes for standard Lewis acids. It is clearly evident from this review that gallium halides are highly versatile compounds with potential application in a myriad of different organic transformations. While the study of gallium and gallium halide mediated reactions is still in its infancy, the examples described in this review highlight the usefulness and wide ranging applicability of these reagents. We hope that this review will encourage more researchers to become involved in this fascinating field of chemistry.

Acknowledgement

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