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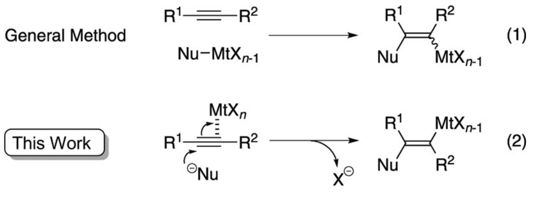
Carbogallation of Alkynes Using Gallium Tribromide and Silyl Ketene Acetals and Synthetic Application to Cross-Coupling with Aryl Iodides

Yoshihiro Nishimoto, Hiroki Ueda, Makoto Yasuda, and Akio Baba*[a]

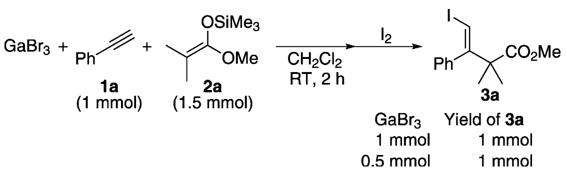
Alkenyl metals are valuable coupling partners for constructing conjugate systems. Therefore, preparation procedures for alkenyl metals have been extensively developed.[1] Oxidative addition of alkenyl halides to metals, metal–metal exchange, halogen–metal exchange, hydrogen–metal exchange, and hydrometalation or carbometalation of alkynes are representative synthetic methods. Among them, only carbometalation has the distinct advantage of simultaneous formation of both carbon–metal and carbon–carbon bonds.[2] Most carbometalations however, require the generation of organometallic nucleophiles before the addition to alkynes, which often limits compatible functional groups (Scheme 1, reaction (1)). In contrast, the separate introduction of a carbon nucleophile and a metal without the generation of organometallic nucleophiles as shown in Scheme 1, reaction (2) could expand the application area of carbometalation. We recently established this concept by using indium tribromide on the basis of its π-electrophilic Lewis acidity and low oxophilicity.[3] The present study has demonstrated an expansion of this concept toward the synthesis of alkenylgalliums bearing an ester moiety, which were found to be stable enough to achieve successive coupling reactions. Regio- and stereoselective carbogallation was achieved by a simple treatment of alkynes, $GaBr_3$, and ketene silyl acetals.[3,4] Results from the present study indicated the feasibility of similar syntheses for other alkenyl metals.



Scheme 1.

There are not many variations of carbogallation, even though the application of organogalliums to organic synthesis has attracted much attention.[5] Most traditional methods for carbogallation of alkynes have employed the addition of organogallium species, which are produced by the transmetalation between $GaCl_3$ and organosilane reagents, to alkynes (Scheme 1,reaction type-(1)), in which selective *syn*-addition took place.[6,7,8] Although Yamaguchi reported the carbogallation of alkynes using $GaCl_3$ and silyl enol ethers, an active organogallium species was generated in situ before carbogallation, and an alkyne was limited to only silylacetylene. In contrast, the present carbogallation is highly *anti* selective and applicable to various types of 1-alkynes to produce alkenylgalliums that were successively coupled with aryl iodides to produce trisubstituted alkenes. To the best of our knowledge, this is the first example of a reaction-(2)-type carbogallation (Scheme 1). The use of the carbogallation for the total synthesis of meroterpenoid nodosol is also presented.

First, the mixture of $GaBr_3$ and dimethylketene trimethylsilyl methyl acetal **2a** was monitored by ^1H, ^{13}C, and ^{29}Si NMR spectroscopy to confirm that there was no production of Me_3SiBr, which indicated that there was little if any transmetalation taking place. This result, which was in contrast to the easy transmetalation between $GaCl_3$ and silyl enol ethers reported by Yamaguchi,[6e] prompted the application of the combination of $GaBr_3$ and ketene silyl acetals to a new type of carbogallation as shown in Scheme 1, reaction (2). Next, the reaction using $GaBr_3$, phenylacetylene **1a**, and ketene silyl acetal **2a** was investigated (Scheme 2). Stirring the mixture that included one equivalent of $GaBr_3$ at room temperature for 2 h generated two types of gallium adducts, which was observed by ^1H NMR spectroscopy.[9] Quenching the reaction mixture with I_2 gave iodoalkene **3a** in a quantitative yield with complete regio- and stereoselectivity.[10] This result strongly indicated that both of the two types of adducts were transformed into **3a**. Even the use of 0.5



Scheme 2. Reaction between $GaBr_3$ and phenylacetylene **1a**, and ketene silyl acetal **2a** followed by quenching with I_2.

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[a] Dr. Y. Nishimoto, H. Ueda, Dr. M. Yasuda, Prof. Dr. A. Baba
Department of Applied Chemistry
Graduate School of Engineering
Osaka University, 2-1
Yamada-oka, Suita (Japan)
Fax: (+81) 6-6879-7387
E-mail: baba@chem.eng.osaka-u.ac.jp

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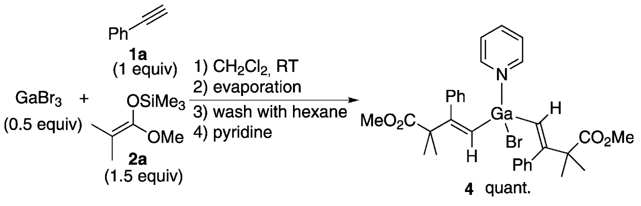
equivalent of $GaBr_3$ gave a quantitative yield of **3a** through generation of only one of the two adducts.[11] The pyridine complex of the adduct obtained from the reaction using 0.5 equivalent of $GaBr_3$ was successfully analyzed by X-ray crystallography and confirmed to be the dialkenylgallium species **4** with a *cis* conformation of gallium and phenyl moieties around the double bond (Scheme 3 and Figure 1). Therefore, it is believed that these two adducts are the mono- and dialkenylgallium species.



Scheme 3. Generation of dialkenylgallium pyridine complex **4**.

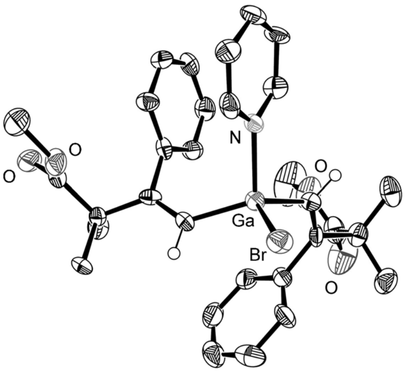
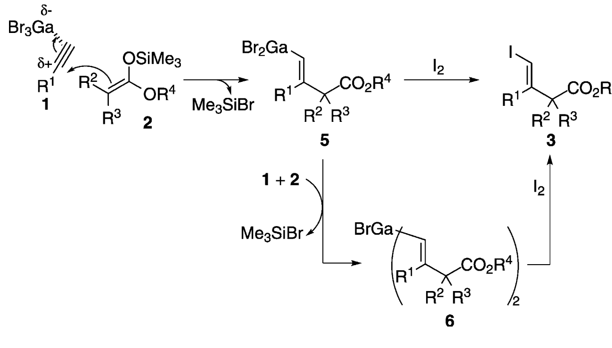


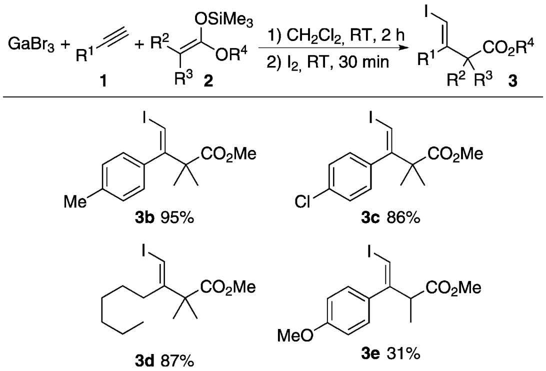
Figure 1. X-ray crystallographic analysis of dialkenylgallium pyridine complex **4**.

These results led to a plausible mechanism illustrated in Scheme 4. The interaction between $GaBr_3$ and alkyne **1** causes the nucleophilic attack of ketene silyl acetal **2** in an *anti* manner to give the monoalkenylgallium **5** with high regio- and stereoselectivity. When the resulting compound **5**, instead of $GaBr_3$, activates another alkyne to promote the further addition of **2**, dialkenylgallium **6** is produced. It is noteworthy that $GaBr_3$ effectively activates alkyne **1** without transmetalation with **2**. Therefore, $GaBr_3$ and **2** separately add to alkyne **1** from opposite sides. Adducts **5** and **6** are so stable that their formations are easily monitored by NMR spectroscopy. Finally, the addition of I_2 gives the transformation from both **5** and **6** to alkenyliodide **3**.



Scheme 4. Plausible mechanism of carbogallation and iodination.

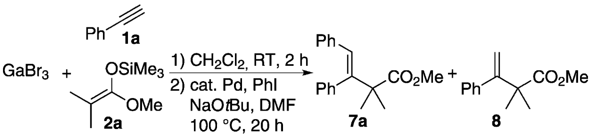
The scope of applicable 1-alkynes was next investigated (Scheme 5). Both electron-rich and -poor aromatic alkynes quantitatively gave the corresponding iodoalkenes **3b** and **3c**, respectively. Also, the carbogallation of 1-octyne occurred to give **3d** in 87% yield. The methyl-substituted ketene silyl acetal gave a moderate yield of **3e**, whereas an unsubstituted one failed in the carbogallation. These results demonstrated the selective formation of stable alkenylgalliums, which can be applied to further transformations.



Scheme 5. Halogenation of various alkenylgalliums. Reaction conditions: 1) $GaBr_3$ (1 mmol), **1** (1 mmol), **2** (1.5 mmol), and CH_2Cl_2 (2 mL), 2) I_2 (2 or 3 mmol) and Et_2O (3 mL). Yields of isolated products.

On the basis of the selective carbogallation, the successive palladium-catalyzed coupling of the alkenylgalliums with iodobenzene were examined (Table 1). After the treatment of $GaBr_3$ (1 mmol), **1a** (1 mmol), and **2a** (1.5 mmol) in CH_2Cl_2

Table 1. Optimization of carbogallation followed by Pd-catalyzed cross-coupling between alkenylgallium and iodobenzene.[a]

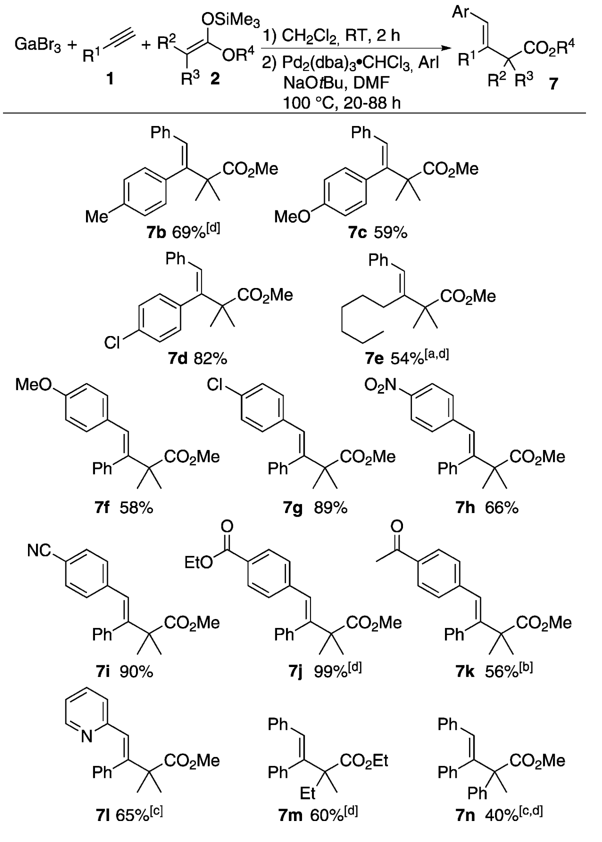


Entry	Pd catalyst	GaX_3	Yield [%][e] 7a	8
1	$Pd_2(dba)_3{\cdot}CHCl_3$	$GaBr_3$	90	10
2	$Pd(PPh_3)_4$	$GaBr_3$	46	39
3[b]	$Pd_2(dba)_3{\cdot}CHCl_3$	$GaBr_3$	18	22
4[c]	$Pd_2(dba)_3{\cdot}CHCl_3$	GaI_3	12	21
5[d]	$Pd_2(dba)_3{\cdot}CHCl_3$	$GaBr_3$	75	25

[a] $GaBr_3$ (1 mmol), **1a** (1 mmol), **2a** (1.5 mmol), CH_2Cl_2 (1 mL), cat. Pd (10 mol% Pd), PhI (3 mmol), NaO*t*Bu (3 mmol), DMF (3 mL). [b] The reaction was carried out in the absence of NaO*t*Bu. [c] Reaction time: 35 h. [d] $GaBr_3$ (0.5 mmol), reaction time: 25 h. [e] Yields were determined by ^1H NMR analysis by using an internal standard in crude products.

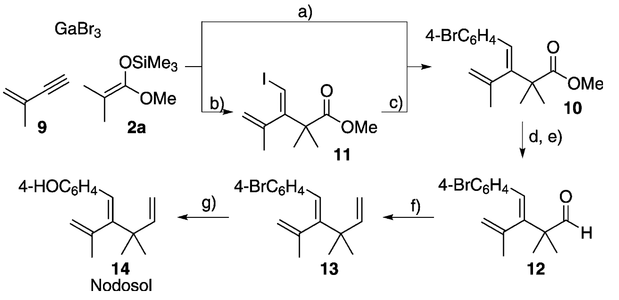
(1 mL) at room temperature for 2 h, the successive addition of $Pd_2(dba)_3{\cdot}CHCl_3$ (0.05 mmol), PhI (3 mmol), NaO*t*Bu (3 mmol), and DMF (3 mL) afforded a highly satisfactory 90 % yield of coupling product **7a** as a single isomer under heating at 100 °C (Table 1, entry 1).[12] $Pd(PPh_3)_4$ had less catalytic effect than $Pd_2(dba)_3{\cdot}CHCl_3$ (Table 1, entry 2). The cross-coupling without NaO*t*Bu resulted in a product yield of only 18 % (Table 1, entry 3). The reaction of GaI_3 gave a lower yield than that of $GaBr_3$ (Table 1, entry 4).[10] The use of 0.5 equivalent of $GaBr_3$ also produced a satisfactory yield (Table 1, entry 5).

Carbogallations and successive Pd-catalyzed couplings using various alkynes, ketene silyl acetals, and aryliodides are summarized in Scheme 6. Both aromatic alkynes with electron-donating and -withdrawing groups gave high yields (compounds **7b**, **7c**, and **7d**). 1-Octyne was also applicable to give the desired product **7e** in a 54 % yield. Various functional moieties, including methoxy, chloro, nitro, cyano, ester, and ketone groups, survived the coupling reactions to give moderate to excellent yields (Scheme 6, compounds **7f**, **7g**, **7h**, **7i**, **7j**, and **7k**). 3-Iodopyridine was used as a facile coupling partner (compound **7l**). Use of diethyl- and methylphenylketene silyl acetals were also successful (Scheme 6, **7m** and **7n**).



Scheme 6. Application of various alkynes, aryliodides, and ketene silyl acetals. Reaction conditions: 1) $GaBr_3$ (1 mmol), **1** (1 mmol), **2** (1.5 mmol), and CH_2Cl_2 (1 mL), 2) $Pd_2(dba)_3{\cdot}CHCl_3$ (0.05 mmol), ArI (1.5 mmol), NaO*t*Bu (3 mmol), and DMF (3 mL). Yields of isolated products. [a] HMPA (3 mL) was used instead of DMF. [b] **2a** (1.5 mmol), and NaOMe instead of NaO*t*Bu. [c] ArI (3 mmol). [d] Yields were determined by ^1H NMR analysis using internal standard in crude products.

Finally, we demonstrated the utility of trisubstituted alkene synthesis through carbogallation for the total synthesis of Nodosol, which is antibacterial active-meroterpenoid extracted from the seagrass *Cymodocea nodosa*.[13] The carbogallation using enyne **9** and ketene silyl acetal **2a** followed by Pd-catalyzed coupling between produced alkenylgallium and 4-bromoiodobenzene gave ester **10**, although the yield was only 15 %. Instead of direct coupling, the cross-coupling of 4-bromophenylboronic acid with iodoalkene **11**, which was produced by quenching with I_2 after the carbogallation, gave ester **10** effectively. Subsequent conversion to aldehyde **12** followed by a Wittig reaction produced triene **13**. Finally, the transformation from the bromoarene moiety to the phenol moiety of **13** by the treatment with *n*BuLi and O_2 provided Nodosol (**14**, Scheme 7).



Scheme 7. Total synthesis of meroterpenoid nodosol. Reagents and conditions: a) $GaBr_3$ (1 equiv), **8** (1 equiv), **2a** (1.5 equiv), CH_2Cl_2, RT, 2 h; $Pd_2(dba)_3{\cdot}CHCl_3$ (0.05 equiv), 4-bromoiodobenzene (1.5 equiv), NaO*t*Bu (3 equiv), DMF, 100 °C, 15 %; b) $GaBr_3$ (1 equiv), **8** (1 equiv), **2a** (1.5 equiv), CH_2Cl_2, RT, 2 h, and then, I_2 (1.5 equiv) and Et_2O, 81 %; c) 4-bromophenylboronic acid (4 equiv), $Pd(PPh_3)_4$ (0.1 equiv), Na_2CO_3 (4 equiv), toluene, MeOH, 59 %. d) DIBAL (3 equiv), THF, 76 %; e) Pyridinium chlorochromate (2 equiv), CH_2Cl_2, 64 %; f) Ph_3PCH_3I (1.6 equiv), *n*BuLi (2.1 equiv), 40 %; g) *n*BuLi, O_2, 29 %.

In summary, we have achieved a new type of carbogallation of alkynes. Quenching the produced alkenylgalliums with I_2 gave the corresponding iodoalkenes as a trisubstituted alkene. For the first time, alkenylgalliums produced by carbogallation were directly used on sequential Pd-catalyzed cross-coupling with a variety of aryl iodides to give the trisubstituted alkenes stereo- and regioselectively. These methods for synthesizing a trisubstituted alkene were used as key processes to accomplish the total synthesis of the meroterpenoid Nodosol. Results of the present study show that the concept developed in the previous carboindation was applicable to gallium salts, which indicates that this convenient procedure has the potential for application to other metals.

Experimental Section

General procedure: (Table 1, Entry 1): Phenylacetylene (**1a**, 1 mmol) was added to a solution of $GaBr_3$ (1 mmol) and dimethylketene methyl trimethylsilyl acetal (**2a**, 1.5 mmol) in dichloromethane (1 mL) under nitrogen. The reaction mixture was stirred at room temperature for 2 h. Then, DMF (3 mL), Pd$_2$(dba)$_3$ (0.05 mmol), NaO*t*Bu (3 mmol), and PhI (3 mmol) was added and the mixture was heated and maintained at 100 °C for 20 h. The reaction was then quenched with brine (5 mL), and more ethyl acetate (20 mL) was added. The organic layer was washed with brine and dried over MgSO$_4$. The evaporation of the volatiles left the crude product, which was analyzed by ^{1}H NMR spectroscopy.

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Keywords: alkynes · carbogallation · cross-coupling · gallium · ketene silyl acetals · synthetic methods

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[9] The details of NMR analysis is listed in the Supporting Information.

[10] GaCl$_3$ is poorly reproducible due to being very unstable and quite hard to handle, therefore the product yields varied when using GaCl$_3$. In fact, GaCl$_3$ occasionally gave a satisfying result, although we previously reported the low effect of GaCl$_3$ on carbogallation (see Ref. [3a]). GaI$_3$ also has a high effect, but Me$_3$SiI, which is a byproduct, decomposed the ester product. Therefore, we mainly used GaBr$_3$.

[11] The reaction using GaBr$_3$ (0.2 mmol), **1a** (1 mmol), and **2a** (1.5 mmol) gave **3a** (0.4 mmol) after the quench with I$_2$. This result shows no generation of the trialkenylgallium species.

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