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α-Ethynylation reaction of ketones using catalytic amounts of trialkylgallium base

Yoshio Nishimura, Ryo Amemiya and Masahiko Yamaguchi*

Department of Organic Chemistry, Graduate School of Pharmaceutical Sciences, Tohoku University, Aoba, Sendai 980-8578, Japan

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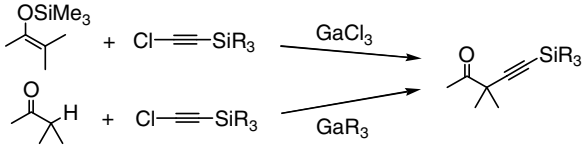
Abstract—Trialkylgalliums serve as a base to generate enolates from ketones. In the presence of catalytic amounts of a trialkylgallium (20–40 mol %) and 2,6-di(*t*-butyl)-4-methylpyridine (30–50 mol %), acyclic, and cyclic ketones were ethynylated at the α-carbon with chlorosilylethyne. The selective monoethynylation and diethynylation could be conducted for cyclic ketones by appropriate choices of the conditions, in which the addition of a catalytic amount of butyllithium (20–40 mol %) increased the yield.

The alkylation of ketone enolates is one of the most fundamental C–C bond forming reactions in organic synthesis. Alkynylation, however, was not well developed, and only one method was reported by Kende and co-workers, α-chloroethynylation of ketones using stoichiometric amounts of lithium diisopropylamide.[1,2] Previously, we developed stoichiometric[3] and catalytic[4] α-ethynylation reactions of silyl enol ethers derived from ketones with chlorosilylethyne in the presence of $GaCl_3$.[5] Although this method provided a convenient access to α-ethynyl ketones, silyl enol ethers needed to be prepared from ketones. We also reported a catalytic α-ethenylation reaction of ketones, in which gallium enolates were formed directly from ketones and $GaCl_3$.[6] Developed in this study is the α-ethynylation reaction of ketones using catalytic amounts of trialkylgalliums (Scheme 1). The organometallic compounds can be used as base to form enolates from ketones. Alkylgallium compounds have been used as alkylating reagent,[7] Lewis acid,[8] or reducing reagent[9] in organic synthesis, and use as base remains unexplored.[10]



Scheme 1.

Our investigation on the α-ethynylation reaction of ketones was started using $GaCl_3$. Under an argon atmosphere, a mixture of 2,5-dibenzylcyclopentanone **1** (cis:trans = 1:1.5), 2,6-di(*t*-butyl)-4-methylpyridine (100 mol %), $GaCl_3$ (20 mol %), and chlorotriethylsilylethyne **2** (2.5 equiv) in *o*-dichlorobenzene (4.0 M) reacted at 180 °C for 12 h, and 2,5-dibenzyl-2-(triethylsilyethynyl)cyclopentanone **3a** was obtained in 11% yield (Table 1, entry 1). After various trials, the addition of butyllithium (100 mol %) was found to increase the yield of **3a** to 40% (cis:trans = 1.5:1), which was accompanied by 2,5-bis(triethylsilylethynyl)-2,5-dibenzylcyclopentanone **4a** in 31% yield (cis:trans = 2.1:1) (entry 2). The cis-stereochemistry of the major isomer of **3a** was determined by reducing to (1*R**,2*S**,5*S**)-2,5-dibenzyl-2-(triethylsilylethynyl)cyclopentan-1-ol **5** as a single isomer, and observing the NOE between the 1-proton and the 2-benzyl protons and that between the 1-proton and the 5-proton (Scheme 2). To determine the stereochemistry of **4a**, two isomers were reduced to single isomers of *c*-2,5-bis(triethylsilylethynyl)-*t*-2,5-dibenzyl-*r*-1-cyclopentanol **6** and (2*R**,5*R**)-2,5-bis(triethylsilylethynyl)-2,5-dibenzylcyclopentan-1-ol, and the latter was acetylated leading to (2*S**,5*S**)-1-acetoxy-2,5-bis(triethylsilylethynyl)-2,5-dibenzylcyclopentane **7**. The ^{13}C NMR spectra of **6** and **7** showed 13 peaks and 25 peaks, respectively, which indicated **6** to be the meso-compound derived from *cis*-**4a**, and **7** the racemic compound

* Corresponding author at present address: Tohoku University, 21st Century COE Program CRESCENDO, Sendai, Japan. Tel.: +81 22 795 6812; fax: +81 22 795 6811; e-mail: yama@mail.pharm.tohoku.ac.jp

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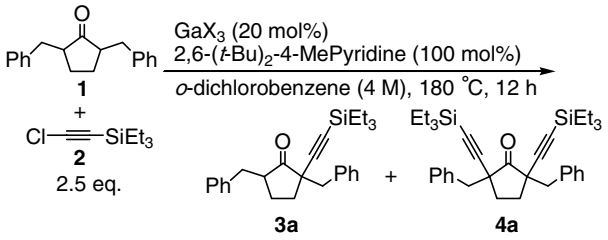
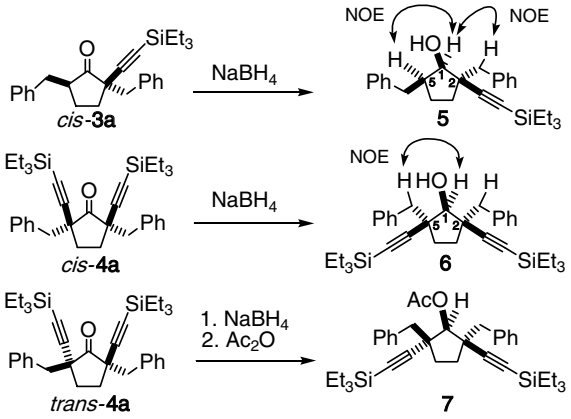
Table 1. α-Ethynylation of 2,5-dibenzylcyclopentanone **1**



Entry	GaX_3	Yield (%)	
		3a (cis:trans)	**4a** (cis:trans)
1	$GaCl_3$	11 (1.4:1)	Trace
2	$GaCl_3$–BuLi (100 mol %)	40 (1.5:1)	31 (2.1:1)
3	$GaMe_3$	44 (1.4:1)	20 (2.2:1)
4[a]	$GaMe_3$	23 (1.5:1)	3 (1.9:1)
5[b]	$GaMe_3$	Not detected	Not detected
6[b,c]	$GaMe_3$	28 (1.2:1)	12 (2.4:1)
7	$GaEt_3$	47 (1.5:1)	19 (2.2:1)

[a] The reaction was conducted at 140 °C.
[b] 2,6-Di(*t*-butyl)-4-methylpyridine was not added.
[c] Reaction time, 0.5 h.



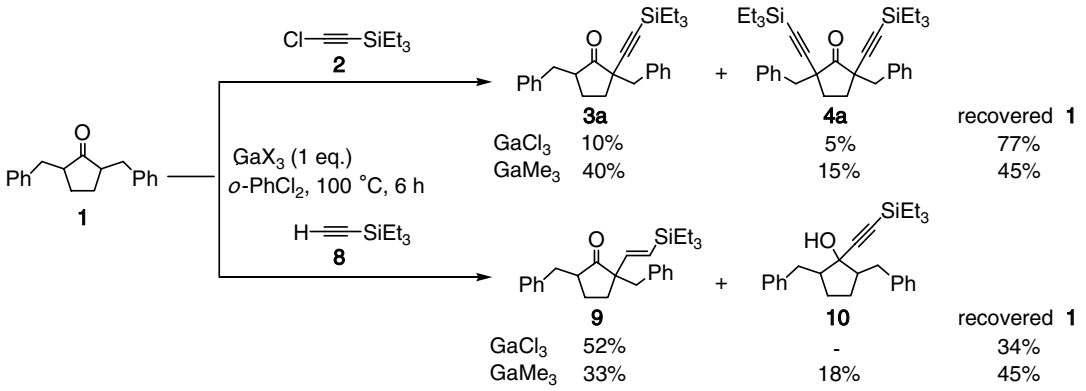
Scheme 2.

formed from *trans*-**4a**. The stereochemistry of **6** was determined by the NOE between the 1-proton and the 2,5-benzyl protons.

It was presumed that $GaBu_3$ generated from $GaCl_3$ and butyllithium was involved in the ethynylation reaction, and, in accordance, the treatment of **1** and **2** at 180 °C for 12 h in the presence of $GaMe_3$ (20 mol %) gave **3a** and **4a** in 40% and 22% yield, respectively (Table1, entry 3). Lowering the reaction temperature to 140 °C resulted in the decrease of the products (entry 4). The complete decomposition of the products and the starting materials occurred in the absence of 2,6-di(*t*-butyl)-4-methylpyridine (entry 5). It was noted, however, that the reaction for 0.5 h at the temperature in the absence of the pyridine gave considerable amounts of **3a** and **4a**, which indicated that $GaMe_3$ itself deprotonated at the carbonyl α-position (entry 6). $GaEt_3$ (20 mol %) gave a comparable result with $GaMe_3$ (entry 7). It is shown that alkylgallium compounds can be used as base to generate a gallium enolate from a ketone.

The reactivity of gallium enolates toward **2** was compared (Scheme 3). When **1** and **2** (1.5 equiv) reacted with $GaCl_3$ (1 equiv) in *o*-dichlorobenzene at 100 °C for 6 h, the ethynylated products **3a** and **4a** were obtained in only 10% and 5% yields, respectively, with recovered **1** in 77% (Scheme 2). Use of $GaMe_3$ (1 equiv) in place of $GaCl_3$ increased the yield of **3a** and **4a** to 40% and 15%, respectively, under the same conditions. The reactivity of **2** was compared with triethylsilylethyne **8**. When **1** and **8** (1.5 equiv) reacted with $GaCl_3$ (1 equiv) in *o*-dichlorobenzene at 100 °C for 6 h followed by workup with 10 M HCl at room temperature for 2 h, the silylethenylated product **9** was obtained in 52% yield. The results indicated that both $GaCl_3$ and $GaMe_3$ could effectively generate gallium enolate from **1**, and the reactivity of the dialkylgallium enolate was higher than the dichlorogallium enolate in the carbogallation with **2**. The dichlorogallium enolate reacted more effectively with **8** than **2**, which might be ascribed to the steric reasons. As for the ethenylation using $GaMe_3$, **9** was obtained in 33% yield, which was accompanied by a propargylic alcohol **10** in 18% yield. Although the dialkylgallium enolate underwent carbogallation with **8** as well as **2**, the reaction competed with the deprotonation of acetylene C–H.

The selective mono- and diethynylation of **1** were next examined. When **1** reacted with 2.5 equiv of **2** in the presence of $GaMe_3$ (40 mol %) and 2,6-di(*t*-butyl)-4-methylpyridine (50 mol %), diethynylated **4a** was obtained predominantly in 66% yield with monoethynylated **3a** in 26% yield. The addition of a catalytic amount of butyllithium (40 mol %) increased the yield of **4a** to 88%, and decreased **3a** (Table 2, entry 1).[11] The selective monoethynylation could be attained using an excess ketone. When 2 equiv of **1** reacted with **2** in the presence of $GaMe_3$ (20 mol %), butyllithium (20 mol %), and 2,6-di(*t*-butyl)-4-methylpyridine (30 mol %), **3a** was predominantly obtained in 58% yield based on **2**, which



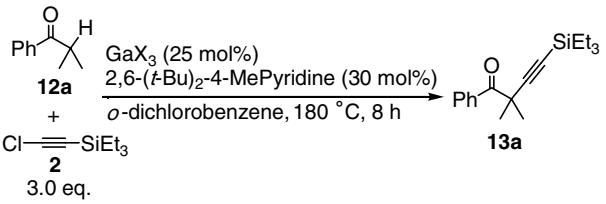
Scheme 3.

was accompanied by **4a** in 16% yield. Use of tributylsilyl derivative **11** improved the yield of **3b** to 72% with **4b** in 16% due to the less volatile nature of the chloroacetylene (entry 2). Without butyllithium, the yield of **3b** decreased to 51%.

The selective mono- and diethynylation of several five- or six-membered cyclic ketones were conducted employing these conditions (Table 2, entries 3–8).

Acyclic ketones were α-ethynylated under slightly modified conditions. In the presence of $GaEt_3$ (25 mol %) and 2,6-di(*t*-butyl)-4-methylpyridine (30 mol %), isobutyrophenone **12a** was converted to **13a** in 71% yield with recovered **12a** in 5% (Table 3, entry 1). When the reaction was conducted at a lower concentration (0.25 M), the yield of **13a** increased to 80% (entry 4).[12] Use of $GaEt_3$ gave the improved yields of **13a** compared to $GaMe_3$ in this case (entries 2 and 5), which might be related to the basicity of the organogallium compounds. The yield decreased to 21% using $GaCl_3$ under the same conditions as was in the case of cyclic ketones (entry 6).

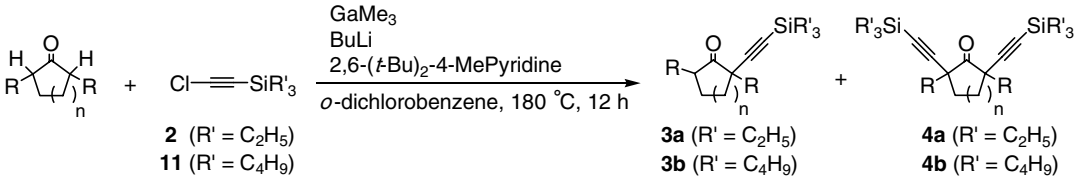
Table 3. α-Ethynylation of isobutyrophenone **12a**

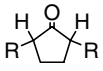
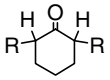


Entry	GaX_3	Concentration of **12a** (M)	Yield (%)
1	$GaEt_3$	4.0	71
2	$GaMe_3$	4.0	65
3	$GaEt_3$	1.0	76
4	$GaEt_3$	0.25	80
5	$GaMe_3$	0.25	64
6	$GaCl_3$	0.25	21

Various aromatic and aliphatic acyclic ketones were α-ethynylated in the presence of $GaEt_3$ (Table 4). The electronic effect of the aromatic *p*-substituents of iso-

Table 2. α-Ethynylation of cyclic ketones

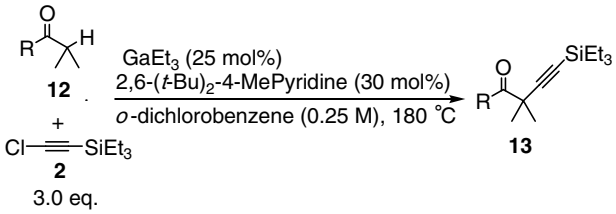


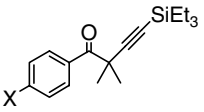
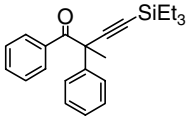
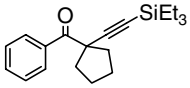
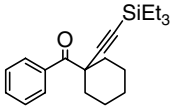
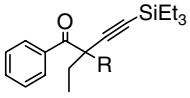
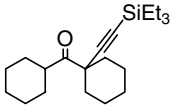
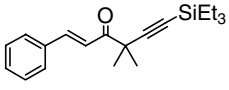
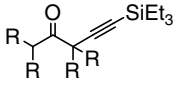
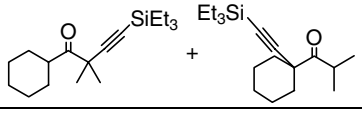
Entry	Ketone	R (cis:trans)	Acetylene	Conditions[a]	Yield (%)	
					3 (cis:trans)	**4** (cis:trans)
1		$PhCH_2$ (1:1.5)	**2**	A	—	88 (2.2:1)
2			**11**	B	72 (1.6:1)	16 (1.3:1)
3		*t*-$BuCH_2$ (1:2.3)	**2**	A	19 (4.2:1)	75 (1:2.5)
4			**11**	B	61 (3.0:1)	12 (1:4.6)
5[b]		$PhCH_2$ (cis isomer)	**2**	A	8 (1:8.6)	70 (2.3:1)
6			**11**	B	68 (1:14)	6 (1.2:1)
7		Ph (cis isomer)	**2**	A	—	67 (4.7:1)
8			**11**	B	71 (1:4.6)	4 (2.5:1)

[a] Conditions A: ketone and **2** (2.5 equiv) were reacted in the presence of $GaMe_3$ (40 mol %), butyllithium (40 mol %), and the pyridine (50 mol %). Isolated yields based on the ketone are shown. Conditions B: ketone (2.0 equiv) and **11** were reacted in the presence of $GaMe_3$ (20 mol %), butyllithium (20 mol %), and the pyridine (30 mol %). Isolated yields based on **11** are shown.

[b] 4.0 equiv of **2** was used.

Table 4. α-Ethynylation of acyclic ketones



Entry	Product **13**			Time (h)	Yield (%)
1		X = H	**a**	8	80
2		X = CF_3	**b**	6	73
3		X = OMe	**c**	12	64
4		X = Me	**d**	10	75
5			**e**	8	80
6			**f**	6	77
7			**g**	12	58
8		R = C_2H_5	**h**	24	36
9		R = C_4H_9	**i**	24	33
10			**j**	12	57
11			**k**	2.5	55
12		R = C_4H_9	**l**	24	43
13			**m**	10	53 and 21

butyrophenones **12a–d** exhibited a small effect on the yield (entries 1–4). α,β-Unsaturation did not interfere with the ethynylation as indicated by the reaction of **12k** (entry 11). The ethynylation of cyclohexyl isopropyl ketone **12m** took place at the isopropyl site preferentially (entry 13).

In summary, α-ethynylation reaction of ketones was developed using catalytic amounts of trialkylgalliums. It should be noted that trialkylgalliums can be used as base to deprotonate at the α-position of ketones generating gallium enolates.

Acknowledgements

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hedron Lett. **1982**, *23*, 2373; (c) Kende, A. S.; Fludzinski, P. *Synthesis* **1982**, 455.
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11. Under an argon atmosphere, to a mixture of **2** (2.25 mmol, 0.36 mL) and 2,6-di(*t*-butyl)-4-methylpyridine (0.38 mmol, 77 mg) in *o*-dichlorobenzene (0.19 mL) were added butyllithium (1.6 M solution in hexane, 0.3 mmol, 0.19 mL), $GaMe_3$ (1.0 M solution in hexane, 0.3 mmol, 0.3 mL), and **1** (cis:trans = 1:1.5) (0.75 mmol, 198 mg, 0.18 mL) at 0 °C. The mixture was stirred at 180 °C for 12 h, when water (10 mL) was added. The organic materials were extracted with ether, washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane–toluene = 2.5:1) to give *cis*-**4a** (246 mg, 61%) and *trans*-**4a** (110 mg, 27%).
12. Under an argon atmosphere, to a mixture of isobutyrophenone **12a** (1.0 mmol, 0.15 mL), **2** (3.0 mmol, 0.57 mL) and 2,6-di(*t*-butyl)-4-methylpyridine (0.3 mmol, 62 mg) in *o*-dichlorobenzene (4.0 mL) was added $GaEt_3$ (1.0 M solution in hexane, 0.25 mmol, 0.25 mL) at 0 °C. The mixture was stirred at 180 °C for 8 h, when water (10 mL) was added. The organic materials were extracted with ether, washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane–toluene = 3:1) to give **13a** (228 mg, 0.80 mmol, 80%).