Allylation of Carbonyl Compounds with Allylic Gallium Reagents

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Allylic gallium reagents, prepared from gallium trichloride and the corresponding allylic Grignard reagents, allylated carbonyl compounds in good yields in an aqueous medium as well as in organic solvent.

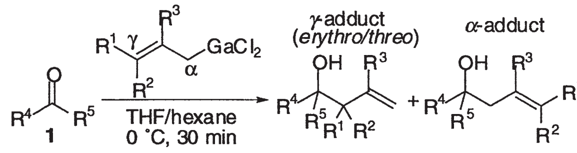
Allylation of carbonyl compounds is a fundamental reaction in organic synthesis. Various allylic metals have been developed and used for stereo- and regio-selective reactions.[1] Among them, allylic indium species are known for their stability in aqueous media.[2] The usefulness of allylic indium compounds is illustrated in syntheses of natural products, especially a concise synthesis of a sialic acid starting from allylation of unprotected mannose.[3] On the other hand, allylation with allylic gallium[4] in the presence of water is not known to our knowledge.[5,6] Here we wish to report allylation of carbonyl compounds with allylic gallium reagents in aqueous media as well as in organic solvent.

We first examined the allylation in THF. The allylgallium reagent used here was prepared by mixing gallium trichloride and an equimolar amount of allylmagnesium chloride. Allylmagnesium chloride (0.8 M THF solution, 1.9 mL, 1.5 mmol) was added to gallium trichloride (1.0 M hexane solution, 1.5 mL, 1.5 mmol, diluted with 3 mL of THF) at 0 °C. After the mixture was stirred for 5 min, benzaldehyde (**1a**, 1.0 mmol) was added to the allylgallium reagent. The resulting mixture was stirred for 30 min at 0 °C. Workup and silica gel column purification provided 1-phenyl-3-buten-1-ol in 94% yield.

Reactions of allylic gallium reagents including crotyl-,[7] methallyl-, and prenylgallium reagents are summarized in Table 1. Decanal (**1b**) also reacted efficiently with the allylgallium reagent (Entry 2). However, ketone was less reactive. Acetophenone (**1c**) underwent allylation to provide the corresponding homoallylic alcohol in 35% yield at 0 °C, and in 73% yield even at elevated temperature (Entries 3 and 4).[8] γ–Allylation proceeded predominantly in the reactions with the crotyl- and prenylgallium reagents (Entries 5, 6, 8, and 9). The reaction with the gallium reagent, prepared from allenylmagnesium bromide[9] and gallium trichloride, yielded the corresponding homopropargylic alcohols (Scheme 1).

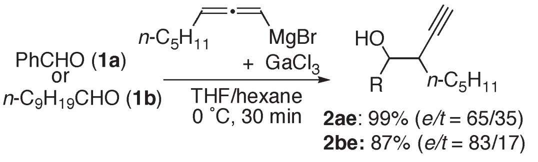
Allylation of various aldehydes was examined, and the results are shown in Table 2. Selective allylation of the formyl moieties of nitro-, cyano-, and methoxycarbonylbenzaldehyde was successfully achieved. Interestingly, aldehydes having a hydroxy or a carboxyl group were also allylated efficiently (Entries 5 and 6). Treatment of *o*-phthalaldehydic acid (**3g**) with 1.5 molar amounts of the allylgallium reagent furnished a mixture of hydroxy carboxylic acid **4g** and lactone **5** (Scheme 2). The mixture was stirred in 1M HCl to afford **5** in 86% overall yield. Treatment of cinnamaldehyde with allylgallium dichloride afforded the 1,2-adduct selectively in 97% yield.

Table 1. Allylation of benzaldehyde (**1a**), decanal (**1b**), and acetophenone (**1c**) with allylic gallium reagents.



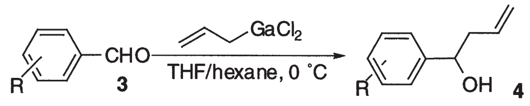
Entry	R¹	R²	R³	1	R⁴	R⁵	Product	Yield/%
1	H	H	H	**1a**	Ph	H	**2aa**	94
2	H	H	H	**1b**	n-C_9H_{19}	H	**2ba**	94
3	H	H	H	**1c**	Ph	Me	**2ca**	35
4	H	H	H	**1c**	Ph	Me	**2ca**	73[a]
5	Me(H)	H(Me)	H	**1a**	Ph	H	**2ab**	82[b]
6	Me	Me	H	**1a**	Ph	H	**2ac**	78[c]
7	H	H	Me	**1a**	Ph	H	**2ad**	100
8	Me(H)	H(Me)	H	**1b**	n-C_9H_{19}	H	**2bb**	98[d]
9	Me	Me	H	**1b**	n-C_9H_{19}	H	**2bc**	86[e]
10	H	H	Me	**1b**	n-C_9H_{19}	H	**2bd**	83

[a]Reaction at reflux. [b]$e/t/\alpha$ = 60/38/2. [c]γ/α = 99/1. [d]e/t = 52/48. [e]γ/α = 81/19.



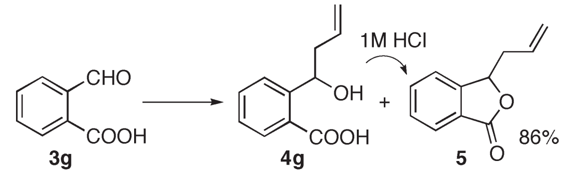
Scheme 1.

Table 2. Allylation of aromatic aldehydes with the allylgallium reagents.

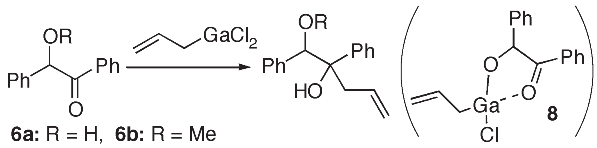


Entry	3	R	Time/h	4	Yield/%
1	**3a**	p-NO_2	0.5	**4a**	95
2	**3b**	p-CN	0.5	**4b**	100
3	**3c**	p-COOMe	0.5	**4c**	89
4	**3d**	2-Pyridinecarbaldehyde	0.5	**4d**	88
5	**3e**	o-OH	1	**4e**	66
6	**3f**	p-COOH	0.8	**4f**	100

Allylation of benzoin (**6a**) proceeded smoothly to yield *erythro*-**7a** as a single diastereomer (Scheme 3). On the other hand, benzoin methyl ether (**6b**) was less reactive. Heating a reaction mixture at reflux in THF was required to give a mixture of diastereomers. These contrastive results suggest the formation of gallium alkoxide **8** and the efficient activation of the carbonyl group.



Scheme 2.



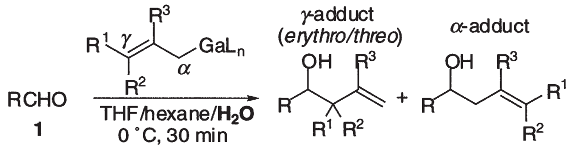
6a: R = H, 6b: R = Me

7a: R = H, 0 °C, 1 h 96%, *e*/*t* = >99/1
7b: R = Me, reflux, 1.5 h 98%, *e*/*t* = 73/27

Scheme 3.

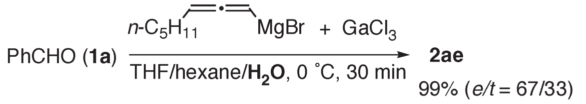
We turned our attention to the reaction in aqueous media. The allylgalliums were prepared as described above. The reagents were treated with water (1 mL) prior to addition of aldehyde. The results are summarized in Table 3 and Scheme 4. Although we anticipated some changes in stereo- and/or regioselectivity, the allylation in aqueous media proceeded efficiently with similar selectivity. In similar fashion to the reaction in anhydrous organic solvent, allylation of cinnamaldehyde provided the 1,2-adduct in the presence of water (99% yield).

Table 3. Allylation of aldehyde with allylic gallium reagents in aqueous media



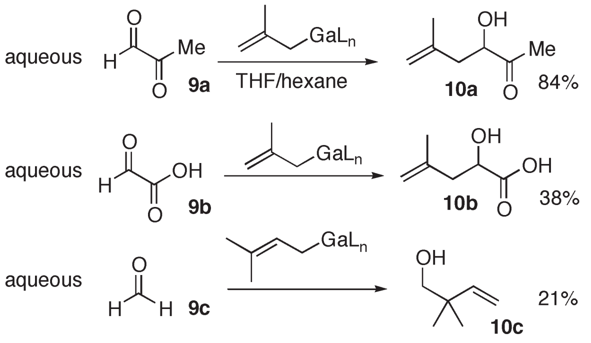
Entry	1	R	R^1	R^2	R^3	Product	Yield/%
1	**1a**	Ph	H	H	H	**2aa**	97
2	**1a**	Ph	Me(H)	H(Me)	H	**2ab**	90^{a}
3	**1a**	Ph	Me	Me	H	**2ac**	81^{b}
4	**1a**	Ph	H	H	Me	**2ad**	97
5	**1b**	n-C_9H_{19}	Me	Me	H	**2bc**	90^{c}

[a] $e/t/\alpha = 47/42/11$. [b] $\gamma/\alpha = 98/2$. [c] $\gamma/\alpha = 89/11$.

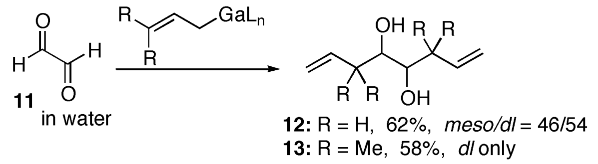


Scheme 4.

Commercially available aqueous aldehydes could be used for the allylation with the allylic galliums (Scheme 5). For instance, an aqueous solution of pyruvaldehyde (**9a**) was added to methallylgallium dichloride in THF/hexane. Selective allylation took place to yield α-hydroxy ketone **10a** in excellent yield. However, reactions of aqueous solutions of glyoxylic acid (**9b**) and formaldehyde (**9c**) were unsatisfactory. Treatment of glyoxal (**11**) solution with three equimolar amounts of the allylgallium species provided diol **12** in 62% yield as a mixture of diastereomers (Scheme 6). In contrast, reaction of **11** with the prenylgallium reagent afforded *dl*-diol **13** exclusively. The control of facial selectivity by the chelation would operate in this system as in the case of Scheme 3.



Scheme 5.



12: R = H, 62%, *meso*/*dl* = 46/54
13: R = Me, 58%, *dl* only

Scheme 6.

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Dedicated to Prof. Teruaki Mukaiyama on the occasion of his 75th birthday.

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7 Formation of the crotylgallium reagent, not 1-methyl-2-propenyl form, was confirmed. See Ref. 5.
8 Allylation of ketone with allylic indium and bismuth reagents proceeded smoothly. See Refs. 3b and 6a.
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