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A Straightforward, Efficient and Versatile Preparation of Propargylic Alcohols from 1- Alkynes and Aldehydes via GaI_3 and Amine

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Abstract: The straightforward additions of 1-alkynes to aldehydes in the presence of GaI_3 and an amine give propargylic alcohol in moderate to high yields.

The addition of alkynylmetals to aldehydes to produce propargylic alcohols is one of the useful methods in organic synthesis. In the synthesis of many natural products such as prostaglandins[1], steroids[2], carotenoids[3], leukotrienes[4] etc., propargylic alcohols are often key intermediates. Many alkynylmetals, including alkynyl- Li, Na, K, Mg and Zn[5] etc. , have been employed for this purpose. However these alkynylmetals commonly possess high reactivity and strong basicity, so as to sometimes cause undesired side reactions. Several improved procedures have been reported. For example, alkynyl- B[6], Al[7], Ce[8], and V[9], prepared from the transmetalation of alkali or alkali-earth metal derivative, reacted with carbonyl compounds to yield propargylic alcohols. However, these methods are not straightforward. In order to overcome this problem, Yamaguchi et al. reported $Sn(OTf)_2$ or $SnCl_4$-promoted addition reactions of 1-alkynes to aldehydes[10]. Recently, in continuation of our studies on the synthetic application of metallic gallium and its compounds[11], we found that gallium triiodide, generated *in situ* from the reaction of metallic gallium and iodine in THF, can promote the reaction of 1-alkynes and aldehydes in the presence of an amine, producing propargylic alcohols in moderate to high yields.

Scheme

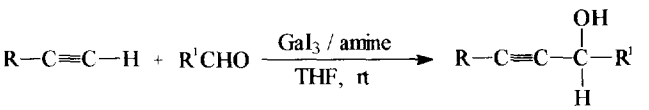
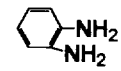


Table 1. The Straightforward Addition of 1-Alkynes to Aldehydes Promoted by GaI_3 and Amines

Entry	R	Aldehyde	Amine	Yield(%)[a]
1	Ph	^{t}BuCHO	DBU	8
2	Ph	^{t}BuCHO		5
3	Ph	^{t}BuCHO		0
4	Ph	^{t}BuCHO	Et_3N	80
5	Ph	^{t}BuCHO	Et_2NPh	77
6	Ph	^{t}BuCHO	Bu_3N	85
7	Ph	^{t}BuCHO	$(Me_2CH)_2NH$	64
8	Ph	PhCHO	Bu_3N	80
9	Ph	p-ClC_6H_4CHO	Bu_3N	82
10	Ph	p-$O_2NC_6H_4CHO$	Bu_3N	62
11	Ph	c-$C_6H_{11}CHO$	Bu_3N	88
12	PhCH=CH	^{t}BuCHO	Bu_3N	49
13	p-$MeO_2CC_6H_4$	p-FC_6H_4CHO	Bu_3N	60[13]
14	p-$MeO_2CC_6H_4$	^{t}BuCHO	Bu_3N	51[13]
15	n-C_5H_{11}	PhCHO	Bu_3N	64
16	n-C_5H_{11}	c-$C_6H_{11}CHO$	Bu_3N	69
17	n-C_5H_{11}	^{t}BuCHO	Bu_3N	74
18	Ph	PhCHO	Bu_3N	76
		$PhCOCH_3$		94[b]

[a] Isolated yields based on the aldehyde. All the resulting compounds gave satisfactory ^{1}H NMR, IR, MS spectral data, unknown compounds gave satisfactory elementary analyses or HRMS. [b] $PhCOCH_3$ was recovered in 94% yield.

When a mixture of 1-alkyne(2 mmol), GaI_3(2 mmol) and amine(2 mmol) in THF was treated with an aldehyde(1 mmol), the addition took place smoothly at rt., giving propargylic alcohol (**Table 1**). The reaction is general for both aliphatic and aromatic substrates, and is highly chemoselective in the presence of other functional groups such as olefin, esters, and nitro group. The reaction is also chemoselective for aldehyde in the presence of a ketone(**Entry 18**). In addition, it is necessary that two equivalents of the reagents(GaI_3, alkyne, and amine) were used in the reactions, if not, yields were reduced using 1.5 or 1 equiv. of the reagents.

In order to find optimum conditions, we examined the various kinds of amines. **Entries 4-7 in Table 1** show that Et_3N and Bu_3N are the most efficient bases. Diisopropyl amine containing an active hydrogen is efficient also. Under the same conditions, other Lewis acids are inefficient in the reaction (**Table 2**).

Table 2. Reaction Results of Phenylacetylene and Trimethylacetaldehyde in the Presence of Lewis Acid and Amine[a]

Entry	Lewis acid [b]	Amine	Yield(%) [c]
1	GaI_3	Bu_3N	85%
2	$GaCl_3$	Bu_3N	0
3	AlI_3	Bu_3N	trace
4	InI_3	Bu_3N	trace
5	ZnI_2	Bu_3N	0

[a] The reaction was carried out with Lewis acid (2 mmol), amine (2 mmol), phenylacetylene (2 mmol) and trimethylacetaldehyde (1 mmol) at room temperature. [b] All of Lewis acids were prepared from metal and iodine *in situ* in THF except for gallium trichloride. [c] Isolated yield based on aldehyde.

Although the mechanism of GaI_3 / amine promoted addition of 1-alkynes and aldehydes has not yet been clarified, a possible nucleophilic organometallic species, such as "R-C≡C-GaI_2", is most likely as the reactive intermediate.

It is very interesting that, unlike $SnCl_4$-amine, GaI_3-NBu_3 can not promote the reaction of 1-alkyne and aldehyde to yield propargylic alcohols at rt. in CH_2Cl_2. In fact, the reaction of 1-alkyne with aldehyde was carried out to produce conjugated enones in the presence of GaI_3-NBu_3 in CH_2Cl_2 [12].

In conclusion, we have described a novel, simple and efficient preparation of propargylic alcohols from 1-alkynes and aldehydes mediated by gallium triiodide in the presence of an amine. Its advantages lie on:(1) the straightforward and simplicity of the procedure, (2) the mildness of the reaction conditions, and (3) high chemoselectivity. Further studies to determine the scope, limitations, and mechanism of this efficient and flexible synthesis of propargylic alcohols are under active investigation and will be reported in due course.

Typical procedure: Under an argon atmosphere, phenylacetylene(204 mg, 2 mmol) and tributyl amine(370 mg, 2 mmol) were added to gallium triiodide(450 mg, 2 mmol), prepared from gallium (140 mg, 2 mmol) and iodine (762 mg, 3 mmol) in 4 ml THF for 30 min. at rt, and the mixture was further stirred at rt. for 30 min. A THF (2 ml) solution of 4-chlorophenylaldehyde (140 mg, 1 mmol) was added, and stirring was continued for 16 h at the same temperature. The reaction mixture was filtered by means of a silica gel column (hydrolysis), and product (199 mg, 82%) obtained by a standard work-up.

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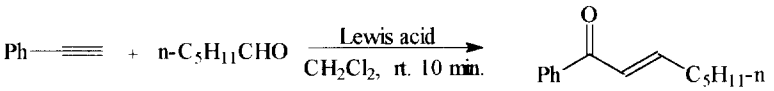
12. In the presence of Lewis acids, the addition reactions of alkynes to aldehydes or ketones have been reported. Hayashi, A.; Yamaguchi, M.; Hirama, M., *Synlett.*, **1995**, 195 and references cited therein. We found that GaI_3-NBu_3, GaI_3, $GaCl_3$, $AlCl_3$ can promote the reactions of phenylacetylene with hexanal to obtain exclusively (E)-α,β- unsaturated ketone.



Lewis acid	Yield(%)
GaI_3-NBu_3	21
GaI_3	25
$GaCl_3$	47
$AlCl_3$	62

13. Selected spectroscopic data of products of **Entry 13** and **14: Entry 13**: *1-(4'-Flurophenyl)-3-(4''-carbomethoxyphenyl)-proparg-2-yn-1-ol*, m.p. 88-90°C. ^{1}H NMR (90 MHz, $CDCl_3$), δ 2.40 (br, 1H, OH), 3.90 (s, 3H, OCH_3), 5.63 (s, 1H, -C≡C-CH), 7.18 (m, 2 H), 7.47 (m, 4H), 7.97 (m, 2 H); m/z 285 (M+1, 10.48), 284 (M^+, 55.56), 269 (M-CH_3, 41.00), 253 (M-OCH_3, 30.65), 225 (M-CO_2CH_3, 96.9), 207 (M-CO_2CH_3-H_2O, 22.69), 149 (M-$C_6H_4CO_2CH_3$, 100.00); ν_{max} (CCl_4, cm^{-1}), 3400br; Found: C, 71.4; H, 4.2%; $C_{17}H_{13}FO_3$ requires C, 71.82; H, 4.61%. HRMS: 284.0827; requires 284.0821.

Entry 14*: 1-(4'-Carbomethoxyphenyl)-4,4-dimethyl-pent-1-yn-3-ol.* m.p. 58-60°C. ^{1}H NMR (90 MHz, $CDCl_3$), δ 1.07 [s, 9H, -$C(CH_3)_3$], 2.10 (br, 1H, OH), 3.91 (s, 3H, -OCH_3), 4.10 (s, 1H, -C≡C-CH), 7.45 (d, 2 H, J = 9.0Hz), 7.93 (d, 2 H, J = 8.0Hz); m/z 247 (M+1, 0.94), 246 (M^+, 3.10), 231 (M-CH_3, 4.62), 215 (M-OCH_3, 6.82), 190 [M- H_2C=$C(CH_3)$, 100.00], 189 [M-$C(CH_3)_3$, 36.18); ν_{max} (CCl_4, cm^{-1}), 3400br; HRMS: 246.1220; $C_{15}H_{18}O_3$ requires 246.1256.

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