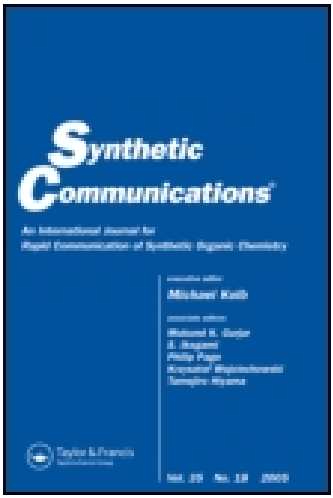

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Gallium-Mediated Highly Regioselective Reaction of Allyl-Type Bromide and Propargyl-Type Bromide With Aldehyde

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GALLIUM-MEDIATED HIGHLY REGIOSELECTIVE REACTION OF ALLYL-TYPE BROMIDE AND PROPARGYL-TYPE BROMIDE WITH ALDEHYDE

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ABSTRACT: In the presence of potassium iodide and lithium chloride, the one-pot reaction of gallium powder, allyl-type bromide and aldehyde shows very high selectivity favoring α-adducts. Under the same condition, the reaction of propargylic bromide with aldehyde exhibit high acetylenic selectivity.

Selective nucleophilic allylation or propargylation of carbonyl compounds remain an important research objective in organic synthesis[1]. The reaction of allenyl and propargyl metal derivatives has been reported and these derivatives are in equilibrium in solution and react differently with carbonyl compounds[2]. Recently, in continuation of our studies on the synthetic application of metallic gallium and its compounds[3], we have reported gallium-mediated highly regioselective reactions of trimethylsilylpropargyl bromide and trimethylsilylallyl bromide with carbonyl

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Table 1. Regioselective synthesis of homoallylic alcohols and homopropargylic alcohols

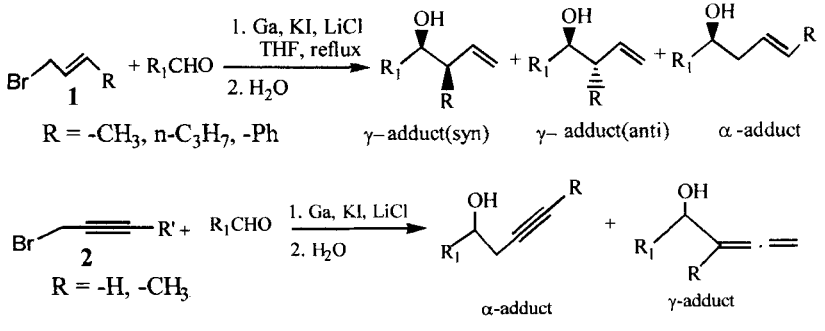
Entry	R_1CHO	Bromo-compound	adduct[a] γ/α	adduct[a] syn/anti	yield(%)[b]
1	PhCHO	$BrCH_2CH{=}CHCH_3$	>99/1	54/46	94
2	2,4-$Cl_2C_6H_3CHO$	$BrCH_2CH{=}CHCH_3$	>99/1	45/55	97
3	p-MeC_6H_4CHO	$BrCH_2CH{=}CHCH_3$	>99/1	55/45	94
4	p-$NO_2C_6H_4CHO$	$BrCH_2CH{=}CHCH_3$	>99/1	43/57	68
5	p-ClC_6H_4CHO	$BrCH_2CH{=}CHCH_3$	>99/1	59/41	91
6	$CH_3(CH_2)_8CHO$	$BrCH_2CH{=}CHCH_3$	>99/1	------	89
7	p-ClC_6H_4CHO	$BrCH_2CH{=}CH$-(n-C_3H_7)	79/21	40/60	87
8	p-ClC_6H_4CHO	$BrCH_2CH{=}CHPh$	60/40	5/95	81
9	PhCHO	$BrCH_2C{\equiv}CH$	<1/99		90
10	p-ClC_6H_4CHO	$BrCH_2C{\equiv}CH$	<1/99		96
11	p-MeC_6H_4CHO	$BrCH_2C{\equiv}CH$	<1/99		86
12	p-$MeOC_6H_4CHO$	$BrCH_2C{\equiv}CH$	<1/99		77
13	p-FC_6H_4CHO	$BrCH_2C{\equiv}CH$	<1/99		97
14	c-$C_6H_{11}CHO$	$BrCH_2C{\equiv}CH$	<1/99		89
15	$CH_3(CH_2)_8CHO$	$BrCH_2C{\equiv}CH$	<1/99		94
16	trans-PhCH=CHCHO	$BrCH_2C{\equiv}CH$	2/98		81
17	$CH_3(CH_2)_8CHO$	$BrCH_2C{\equiv}CCH_3$	42/58		89
18	c-$C_6H_{11}CHO$	$BrCH_2C{\equiv}CCH_3$	52/48		96

[a] Ratios were determined by 300 MHz ^1H NMR. [b] Isolated yields based on carbonyl compounds.

compounds[3a] . In this communication we would like to report the regioselective synthesis of α-methylhomoallylic alcohol and homopropargylic alcohols mediated by gallium. It was found that some Lewis acids could improve greatly the yields.

The reaction of 1-bromo-2-butene and aldehyde in the presence of KI and LiCl (**Entry 1-6**) mediated by gallium show very high γ / α regioselectivity (>99 / 1). Clearly, R in allyl bromide **1** affects not only γ/α selectivity, but also syn / anti selectivity (**Entry 7-8**). Also, the reaction of propargyl bromide with aldehyde exhibits high α/γ regioselectivity under same condition. Regioselectivity dramatically reduce to almost 1:1 after $-CH_3$ replace -H in R'. All of them give the corresponding products in high yields.

KI and LiCl are very important to these reactions. We studied that p-chlorobenzaldehyde reacted with propargyl bromide mediated by gallium in the presence of Lewis acid. We found that yield of the reaction was increased greatly in the presence of Lewis acid (**Table 2, Entry 2-6**) without altering the



Scheme 1

Table 2. Effect of various Lewis acids to the reaction of p-chlorobenzalde - hyde with propargyl bromide mediated by gallium in the presence of KI[a]

Entry	Lewis acid	Time(h)	γ/α Adduct[b]	Total yield(%)[c]
1	none	10	>99/1	18
2	LiCl	2	>99/1	95
3	$MgCl_2$	2	>99/1	89
4	LiBr	2	>99/1	96
5	$MgBr_2$	2	>99/1	86
6	BF_3 OEt_2	2	>99/1	78

[a] All of reactions gave same product, 1-(p-Chlorophenyl)-3-butyn-1-ol. Ratios were determined by 300MHz ^{1}H NMR. [b]Isolated yields based on carbonyl compounds.

regioselectivity. In the absence of Lewis acid, the yield was quite low (18%), even refluxing 10h (**Table 2, Entry 1**). Effect of a number of Lewis acids to the reaction was shown in **Table 2**. Although the reasons for Lewis acids to improve the yields have not yet been clarified, we believe that it presumably involves the reaction of the C-Br bond to become C-I bond promoted by Lewis acid, and the coordination of Lewis acids to carbonyl group results in activating the carbonyl group and increasing yields.

Experimental

^{1}H NMR spectral were determined in $CDCl_3$ on a Bruke 300 M Hz or a Varian EM 390 M Hz spectrometer with $SiMe_4$ as the internal standard. J-Values are

given in Hz. IR spectra were recorded on a Shimadzu IR-440 instrument. Mass spectral data were obtained by electron ionization(EI) on GC-HP5989 spectrometer.

General procedure: Into a suspension of gallium power (70mg, 1 mmol)[4] in THF(4 ml) was added potassium iodide (249mg, 1.5 mmol), lithium chloride (42.5mg, 1mmol), allyl bromide or propargyl bromide (1.5mmol) and aldehyde (1mmol). The mixture was refluxed for 2-4 h under argon. After aqueous work-up and chromatography (petroleum ether:ethyl acetate = 5:1), pure product was obtained. *2-Methyl-1-phenyl-3-buten-1-ol* **(Entry 1)** (94%)[5]. syn-form. δ_H 1.02(3H, d, J 6.8), 2.05 (1H, br), 2.61(1H, m), 4.63(1H, d, J 5.5), 5.08(2H, m), 5.83(1H, m), 7.31(5H, m); ν_{max}(neat)/cm^{-1} 3400v; m/z(%) 161(M-1, 0.59), 145(M-OH, 41.42), 107(M-CH_3-CH-CH=CH_2, 100.0); anti-form δ_H 0.90(3H, d, J 6.82), 2.51(1H, m), 4.39(1H, d, J 7.83), 5.24(1H, m). The data of IR and MS are the same as syn-form.

1-(2,4-dichlorophenyl)-2-methyl-3-buten-1-ol **(Entry 2)** (97%), anti-form: δ_H 0.96(3H, d, J 6.9), 2.16(1H, br), 2.68(1H, m), 4.91(1H, d, J 6.5), 5.14(2H, m), 5.86(1H, m), 7.26(1H, m), 7.34(1H, t, J 2.1), 7.45(1H, m); ν_{max}(neat)/cm^{-1} 3400v; m/z(%) 213(M-OH, 2.82), 175 (M-CH_3-CH-CH=CH_2, 100.0); (Found: C, 56.84; H, 5.02. $C_{11}H_{12}Cl_2O$ requires C, 57.16; H, 5.23%). syn-form: δ_H 1.02(3H, d, J 6.9), 2.16 (1H, br), 2.53(1H, m), 5.06(1H, d, J 4.6), 5.20(2H, m), 5.70(1H, m), 7.26(1H, m), 7.34(1H, t, J 2.1), 7.45(1H, m); The data of IR and MS are the same as anti-form.

2-Methyl-1-[p-methylphenyl-3-buten-1-ol **(Entry 3)** (94%)[5]. syn-form: δ_H 1.01(3H, d, J 6.8), 2.01(1H, br), 2.33(1H, s), 2.54(1H, m), 4.54(1H, d, J 5.7), 5.10(2H, m), 5.77(1H, m), 7.16(4H, m); ν_{max}(neat)/cm^{-1} , 3400v; m/z (%) 175(M-1, 0.41), 159(M-OH, 39.35), 121[M-$CH(CH_3)CH{=}CH_2$, 100.00]. anti-form δ_H 0.86(3H, d, J 6.8), 2.01(1H, br), 2.33(1H, s), 2.47(1H,m), 4.32(1H, d, J 7.9), 5.10(2H, m), 5.80(1H, m), 7.16(4H, m). The data of IR and MS are the same as anti-form.

1-(p-Nitrophenyl)-2-methyl-3-buten-1-ol(**Entry 4**) (68%). anti-form: δ_H 0.94(3H, d, J 6.8), 2.32(1H, br), 2.48(1H, m), 4.54(1H, d, J 7.1), 5.12(2H, m), 5.75(1H, m), 7.51(2H, m), 8.20(2H, m); ν_{max}(neat)/cm^{-1} 3450v; m/z (%) 208(M+1, 71.81), 190(M-OH, 21.54), 152[M-$CH(CH_3)CH{=}CH_2$, 100.00]. HRMS 207.0853, require: 207.0896. syn-form: δ_H 0.98(3H, d, J 6.9), 2.32(1H, br), 2.61(1H, m), 4.78(1H, d, J 5.01),), 5.12(2H, m), 5.75(1H, m), 7.51(2H, m), 8.20(2H, m); The data of IR and MS are the same as anti-form.

1-(p-Chlorophenyl)-2-methyl-3-buten-1-ol **(Entry 5)** (91%)[5]. syn-form: δ_H 1.01(3H, d, J 6.9), 2.10(1H, br), 2.63(1H, m), 4.65(1H, d, J 5.6), 5.10(2H, m), 5.86(1H, m), 7.32(2H, m), 7.42(2H, m); IR(neat): 3400(v) cm^{-1}; m/z (%) 197(M+1, 21.81), 179(M-OH, 11.44), 151[M-$CH(CH_3)CH{=}CH_2$, 100.00]. anti-form: δ_H 0.92(3H, d, J 6.8), 2.10(1H, br), 2.53(m, 1H), 4.51(1H, d, J 6.9), 5.10(2H, m), 5.86(1H, m), 7.32(2H, m), 7.42(2H, m); The data of IR and MS are the same as syn-form.

3-Methyl-1-tridecen-4-ol **(Entry 6)** (89 %)[6]. Mixture of syn-form anti-form, δ_H 0.88 (3H, t, J 6.9),1.02(3H, d, J 3.0), 1.27-1.50(17H, m), 2.25(1H, m), 3.49(1H,

m), 5.09(2H, m), 5.78(1H, m); ν_{max}(neat)/cm^{-1} 3400v; m/z(%), 213(M+1, 0.05), 212(M^+, 0.21), 195(M-OH, 0.13), 157[(M- $CH(CH_3)CH{=}CH_2$), 100.00].

1-(p-Chlorophenyl)-2-propyl-3-buten-1-ol **(Entry 7)** (87%)[5]. anti-form δ_H 0.87(3H, m), 1.13(2H, m), 1.36(2H, m), 2.04(1H, br), 2.37(1H, m), 4.59(1H, d, J 7.8), 5.10(2H, m), 5.60(1H, m), 7.25(4H, m); ν_{max}(neat)/cm^{-1} 3400v; m/z(%), 207(M-OH, 1.69), 141[M-$CH(CH_3)CH{=}CH_2$, 100.0]; syn-form δ_H 0.87(3H, m), 1.13(2H, m), 1.36(2H, m), 2.04(1H, br), 2.37(1H, m), 4.69(1H, d, J 5.8), 5.10(2H, m), 5.60(1H, m), 7.25(4H, m); The data of IR and MS are the same as anti-form.

1-(p-Chlorophenyl)-2-phenyl-3-buten-1-ol **(Entry 8)** (81%). anti-form δ_H 2.01(1H, br), 3.48(1H, m), 4.82(1H, d, J 7.8), 5.25 (2H, m), 6.23(1H, m), 7.06(4H, m), 7.18(5H, m); ν_{max}(neat)/cm^{-1} 3400v; m/z(%), 241(M-OH, 9.53); (Found: C, 74.58; H, 5.68. $C_{16}H_{15}ClO$ requires C, 74.26; H, 5.86%). syn-form δ_H 2.01(1H, br), 3.48(1H, m), 5.0(1H, d, J 7.0), 5.25 (2H, m), 6.23(1H, m), 7.06(4H, m), 7.18(5H, m); The data of IR and MS are the same as anti-form.

1-Phenyl-3-butyn-1-ol **(Entry 9)** (90%)[6]. δ_H 2.07(1H, t, J 2.6), 2.46 (1H, br), 2.65(2H, dd, J_1 2.8, J_2 6.5), 4.87(1H, t, J 6.4), 7.39(5H, m); ν_{max} (neat)/cm^{-1} 3350v, 2100w. m/z(%) 146(M^+, 31.45), 145(M-1, 49.64), 129(M-OH, 6.81).

1-(p-Chlorophenyl)-3-butyn-1-ol **(Entry 10)** (96%)[6]. δ_H 2.07 (1H, t, J 2.7), 2.52(1H, br), 2.60(2H, m), 4.83(1H, t, J 6.3), 7.34(4H, s); ν_{max} (neat)/cm^{-1} 3350vs, 2110w. m/z(%) 180(M^+, 8.25), 179(M-1, 12.64), 164(M-OH, 6.81).

1-(p-Methylphenyl) -3-butyn-1-ol **(Entry 11)** (90%)[7]. δ_H 2.04(1H, t, J 2.6), 2.34(3H, s), 2.30(1H, br), 2.61(2H, dd, J_1 2.8, J_2 6.6), 4.82 (1H, t, J 6.3), 7.15

(2H, d, J 8.0), 7.25(2H, m); ν_{max} (neat)/cm^{-1} 3350v, 2100w. m/z(%) 160(M^+, 11.85), 159(M-1, 9.60), 143(M-OH, 55.09).

1-(p-Methyoxyphenyl)-3-butyn-1-ol **(Entry 12)** (77%)[7]. δ_H 2.01 (1H, t, J 2.6), 2.40(1H, br), 2.61(2H, dd, J_1 2.6, J_2 6.4), 3.84 (3H, s), 4.82(1H, t, J 6.3), 6.90(2H, d, J 8.5), 7.30(2H, d, J 8.6); ν_{max} (neat)/cm^{-1} 3350vs, 2110w. m/z(%) 176(M^+, 39.78), 175(M-1, 19.84), 159(M-OH, 14.21).

1-(p-Flurophenyl)-3-butyn-1-ol **(Entry 13)** (97%). δ_H 2.07(1H, t, J 2.6), 2.53(1H, br), 2.61 (2H, dd, J_1 2.6, J_2 6.3), 4.84(1H, t, J 6.3), 7.04(2H, m), 7.35(2H, m); ν_{max} (neat)/cm^{-1} 3350vs, 2115w; m/z (%) 164(M^+, 43.0), 163 (M-1, 33) ; HRMS 164.0661, $C_{10}H_9FO$, requies 164.0637.

1-Cyclohexyl-3-butyn-1-ol ***(Entry 14)***(89%)[8]. δ_H 1.13 (6H, m), 1.48(1H, m), 1.75(5H, m), 1.93(1H, br), 2.04(1H, t, J 2.6), 2.40(2H, m), 3.49(1H, m); ν_{max}(neat)/cm^{-1}, 3400v. m/z(%) 146(M^+, 31.45), 145(M-1, 49.64), 129(M-OH, 6.81).

1-Tridecyn-4-ol **(Entry 15)**(94%)[6], δ_H 0.88 (3H, t, J 7.1), 1.30(14H, m), 1.50(2H, m), 1.94(1H, br), 2.05(1H , t, J 2.6), 2.35(2H, m), 3.76(1H, m); ν_{max}(neat)/ cm^{-1} 3340v, 2110w. m/z(%) 198(M^+, 1.97), 181(M-OH, 13.23).

1-phenyl-1-hexen-5-yn-3-ol **(Entry 16)**(81%)[8], δ_H 2.10(1H, t, J 2.3), 2.15(1H, br), 2.60(2H, m), 4.50(1H, m), 6.30(1H, dd, J_3 6.4, J_4 16.0), 6.70(1H, d, J 15.9), 7.35(5H, m); ν_{max}(neat)/cm^{-1} 3350v, 2110w. m/z(%) 172(M^+, 5.75), 171(M-1, 57.82), 155(M-OH, 16.51).

2-Tetradecyn-5-ol **(Entry 17)** (89%). α-adduct: δ_H 0.88(3H, t, J 7.0), 1.28(16H, m), 1.80(3H, t, J 2.3), 1.88(1H, br), 2.30(2H, m), 3.69(1H, m); ν_{max}(neat)/cm^{-1}

3400v; m/z(%) 210(M^+, 7.15), 192(M-H_2O, 2.10). HRMS, 210.1989, $C_{14}H_{26}O$, requies, 210.1984. γ-adduct: δ_H 0.88(3H, t, J 7.0), 1.28(16H, m), 1.70(3H, t, J 3.1), 1.88(1H, br), 4.03(1H, m), 4.61(2H, m); ν_{max}(neat)/cm^{-1} 3400v, 1960m.

1- Cyclohexyl-3-pentyn-1-ol **(Entry 18)** (96%)[9]. α-adduct: δ_H 0.90-1.80(10H, m), 1.76(3H, t, J 2.5), 2.28(2H, m), 1.70(1H, br), 3.40(1H, m); ν_{max}(neat)/cm^{-1} 3400v, 2275w. γ-adduct: δ_H 0.90-1.80(10H, m), 1.62(3H, m), 1.70(1H, br), 3.75(1H, m), 4.70(2H, m); ν_{max}(neat)/cm^{-1} 3400v, 1960m.

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4. Preparation of Gallium powder: 20g Gallium bar (m.p. 29.8°C) was placed

into 30 mL dried toluene in a 50 mL Schlenk flask under nitrogen. The mixture was vigorously stirred at 110°C for 30 min., then cooled to room temperature and kept stirring. After solvent was poured out and dried by vacuum, gallium powder is obtained.

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