Regioselective Addition Reactions of Propargyl Bromides to Carbonyl Compounds with Gallium Catalyzed by Indium

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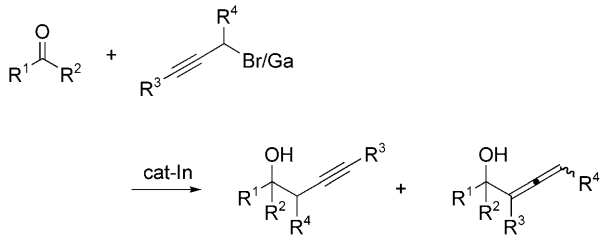
Abstract: Reactions of organogallium reagents generated from propargyl bromides having substituents at the γ-position and gallium in the presence of 5 mol % of indium with aldehydes and ketones selectively produced homoallenyl alcohols in good to excellent yields. Treatment of organogallium reagents obtained from propargyl bromide or propargyl bromides having substituents at the α-position and gallium in the presence of 5 mol % of indium with carbonyl compounds selectively afforded homopropargyl alcohols.

Keywords: allenylation; gallium; indium; propargylation; regioselectivity



R^1 = *n*-C_8H_{17}, $PhCH_2CH_2$, C_6H_{11}, Ph; R^2 = H, Me

R^3 = Me, Et, Ph, TMS; R^4 = H, Me

Scheme 1.

Selective nucleophilic allenylations or propargylations to carbonyl compounds in the syntheses of either homoallenyl alcohols or homopropargyl alcohols are a very important class of organic transformations.[1] To date various methods have been developed on the basis of the nucleophilic character of propargylmetal species obtained from propargyl halides and metals (Ti, Al, Si, Sc, In, Sn, Zn, Bi, Cd, and Sb).[1,2] Recently, a reagent derived from the treatment of 3-bromo-1-(trimethylsilyl)-1-propyne with Ga/KI/LiCl in THF selectively gave propargyl products in the reaction with carbonyl compounds.[3] The selective preparations of either the homoallenyl alcohols or homopropargyl alcohols using cat-In/InX_3 (X = F and Br)-mediated reactions of 3-bromo-1-(trialkylsilyl)-1-propynes with various aldehydes were reported.[4] Surprisingly, although organoindium reagents obtained from the reaction of indium with allyl halides, allyl acetates, and propargyl halides have been used extensively in carbonyl addition reactions,[5] additions to C–C multiple bonds and nitriles,[6] and cross-coupling reactions,[7] organogallium reagents prepared from gallium and allyl halides and propargyl halides have not been explored to a great extent in organic syntheses.[8] The preparation of allylgalliums *via* direct reduction of allylic bromides using a catalytic amount of indium[9] and selective allene formation[7i,10] using organoindium reagents generated from indium and γ-substituted propargyl bromides led us to investigate the efficient and regioselective, indium-catalyzed addition reactions of propargyl bromides to carbonyl compounds with gallium (Scheme 1).

First, the reactivity and regioselectivity of a variety of organogallium reagents derived from propargyl bromide and 3-bromo-1-(trimethylsilyl)-1-propyne were examined in the reactions with benzaldehyde and their results were compared to references (Table 1). Although the propargylindium reagent gave addition products in 72% yield (α:γ = 86:14) in H_2O-MeOH (entry 3), gallium reagents in aqueous media were not effective to produce the desired products (entries 1, 2, 4, and 5). Organogallium reagent generated from propargyl bromide and gallium in THF did not afford the addition product (entry 7). However, the use of 1 equivalent of gallium with 5 mol % of indium (THF, 25 °C, 1 h) regioselectively gave homopropargyl alcohol in 96% yield (α:γ = 100:0) (entry 9),[11] whereas the propargylindium reagent afforded the addition products in 94% yield (α:γ = 84:16) in THF at 25 °C for 2 h (entry 6) and the propargylgallium reagent produced the desired products in 90% yield (α:γ = > 99:1) in THF at 67 °C for 4 h (entry 11).[3b] Although 10 mol % and 1 mol % indium selectively furnished the homopropargyl alcohol, the desired product was produced in moderate yields (74% and 77%, respectively) (entries 8 and 10). The use of DMF as a solvent and application of ultrasonic irradiation in DMF failed to generate addition products (entries 12 and 13). When 3-bromo-1-(trimethylsilyl)-1-propyne was used, organoindium (entry 16) and orga-

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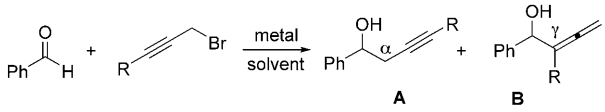
Table 1. Reaction optimization.[a]



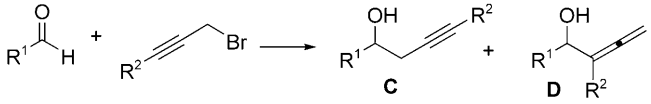
Entry	R	Metal	Solvent	Temp [°C]	Time [h]	Yield [%(**A** : **B**)][b]
1	H	Ga	H_2O	25	12	0
2[c]	H	cat-In/Ga	H_2O	25	12	0
3[d,e]	H	In	H_2O/MeOH	25	12	72(86 : 14)
4[e]	H	Ga	H_2O/MeOH	25	12	0
5[c,e]	H	cat-In/Ga	H_2O/MeOH	25	12	17(86 : 14)
6	H	In	THF	25	2	94(84 : 16)
7	H	Ga	THF	25	12	0
8[f]	H	cat-In/Ga	THF	25	1	74(100 : 0)
9[c]	**H**	**cat-In/Ga**	**THF**	**25**	**1**	**96(100 : 0)**
10[g]	H	cat-In/Ga	THF	25	1	77(100 : 0)
11[h]	H	Ga/KI/LiCl	THF	67	4	90(>99 : 1)
12	H	cat-In/Ga	DMF	25	6	0
13[i]	H	cat-In/Ga	DMF	25	6	0
14[j]	TMS	In	H_2O	25	7	60(20:80)
15[c]	TMS	cat-In/Ga	H_2O	25	12	0
16	TMS	In	THF	25	4	81(100 : 0)
17	TMS	Ga	THF	25	12	0
18[c]	**TMS**	**cat-In/Ga**	**THF**	**25**	**4**	**81(100 : 0)[k]**
19[l]	TMS	In/$InBr_3$	THF	67	20	92(99 : 1)
20[l]	TMS	In/InF_3	THF	67	9	92(99 : 1)
21[m]	TMS	Ga/KI/LiCl	THF	67	2	92(>99 : 1)

[a] Reactions of the Grignard-type performed in the presence of 1 equivalent of metal (In or Ga), 1.0 equivalent of benzaldehyde, and 2.0 equivalents of propargyl bromide in solvent (0.3 M) at 25 °C. 0% yield means that both Grignard- and Barbier-type reactions did not proceed.
[b] Yield of isolated product. Ratios were obtained on the basis of an internal standard (dodecane) in GC.
[c] 5 mol % of In and 1 equiv. of Ga were used.
[d] Ref.[2k]
[e] Ratio of H_2O to MeOH = 2 : 1.
[f] 10 mol % of In and 1 equiv. of Ga were used.
[g] 1 mol % of In and 1 equiv. of Ga were used.
[h] Ref.[3b]
[i] Ultrasonic irradiation was used.
[j] Ref.[2h]
[k] This reaction proceeded in a Barbier-type manner.
[l] Ref.[4]
[m] Ref.[3a]

nogallium reagents (entry 18) in the presence of 5 mol % of indium gave the same results in yield (81%) and selectivity (α-attack). The organogallium reagent derived from gallium and 3-bromo-1-(trimethylsilyl)-1-propyne did not produce the addition product in THF (entry 17).

We applied the optimum conditions (cat-In/Ga/THF) to various propargyl halides and carbonyl compounds to

Table 2. Regioselectivity comparison of cat-In/Ga with Ga/KI/LiCl.

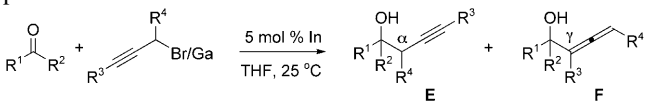


Entry	R^1	R^2	cat-In/Ga THF/25 °C/1 h **C**	cat-In/Ga THF/25 °C/1 h **D**	Ga/KI/LiCl THF/67 °C/4 h **C**	Ga/KI/LiCl THF/67 °C/4 h **D**
1	*n*-C_8H_{17}	H	100	0		
2	*n*-C_8H_{17}	CH_3	0	100		
3	C_6H_{11}	H	100	0	>99	1
4	C_6H_{11}	CH_3	0	100	48	52
5	*n*-C_9H_{19}	H			>99	1
6	*n*-C_9H_{19}	CH_3			58	42

demonstrate the efficiency and scope of the present methods. The results are summarized in Table 3. For the propargyl bromide as precursor of the nucleophile, both aliphatic and aromatic aldehydes selectively gave homopropargyl alcohols *via* α-attack in good to excellent yields (entries 1, 4, 6, 12, 14, 17 and 18). Contrary to the reaction of propargyl bromide, the reactions of propargyl bromides having various alkyl and aryl substituents at the γ-position with aldehydes and ketones produced homoallenyl alcohols as a major product (entries 2 and 3, 5, 7–9, 15 and 16, 19, and 22). Although introduction of a methyl group at the γ-position of the organogallium reagents obtained from propargyl bromide and Ga/KI/LiCl dramatically reduced the regioselectivity (*n*-$C_9H_{19}CHO$; α : γ = > 99 : 1 to 58 : 42, $C_6H_{11}CHO$; α : γ = > 99 : 1 to 48 : 52),[3b] the present conditions gave regioselectively reversed homoallenyl alcohols (entry 1 *vs.* 2 and entry 3 *vs.* 4, Table 2).

A methyl substituent at the γ- position afforded better selectivity than ethyl and phenyl groups (entries 7–9). However, the organogallium reagent derived from gallium and 3-bromo-1-(trimethylsilyl)-1-propyne selectively gave rise to homopropargyl alcohols, albeit with the γ-trimethylsilyl substituent (entries 10 and 23). Under the present conditions, the reaction of 4-methoxybenzaldehyde with 1-bromo-2-butyne exceptionally produced the propargyl alcohol in 82% yield even with γ-methyl substituent (entry 13). Variation of electron density on the aromatic rings did not diminish the efficiency and selectivity (entries 12–17). A hydroxy group is tolerated on the benzaldehyde (entry 17). The organogallium reagent derived from 3-bromo-1-butyne having a α-methyl substituent selectively afforded a homopropargyl alcohol, which is clearly different from the γ-selectivity of 1-bromo-2-butyne having a γ-methyl substituent (entries 11 and 7). A similar trend of reactivity and regioselectivity was obtained from the reactions of aliphatic and aromatic ketones with organogallium reagents in the presence of 5 mol % of indium (entries 19–24).

Table 3. Reactions of propargyl bromides with carbonyl compounds with cat-In/Ga.[a]

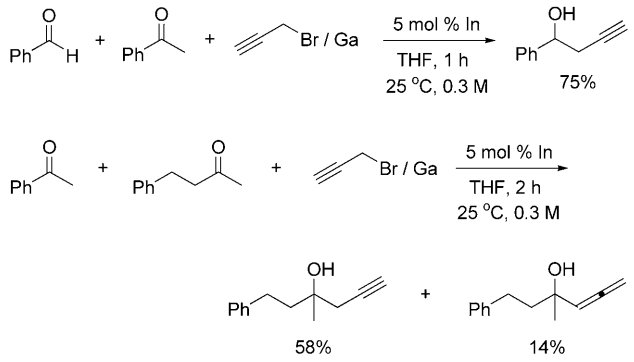


Entry	R^1	R^2	R^3	R^4	Time [h]	Yield [%(E:F)][b]
1	*n*-C_8H_{17}	H	H	H	1	65 (100:0)
2	*n*-C_8H_{17}	H	Me	H	1	75 (0:100)
3	*n*-C_8H_{17}	H	Ph	H	1	73 (39:61)
4	C_6H_{11}	H	H	H	1	87 (100:0)
5	C_6H_{11}	H	Me	H	1	80 (0:100)
6	Ph	H	H	H	1	96 (100:0)
7	Ph	H	Me	H	1	99 (5:95)
8	Ph	H	Et	H	1	64 (25:75)
9	Ph	H	Ph	H	1	76 (35:65)
10[c]	Ph	H	TMS	H	4	81 (100:0)
11	Ph	H	H	Me	1	96 (100:0)
12	4-MeO-Ph	H	H	H	1	70 (100:0)
13	4-MeO-Ph	H	Me	H	1	82 (93:7)
14	4-NO_2-Ph	H	H	H	1	80 (92:8)
15	4-NO_2-Ph	H	Me	H	1	87 (0:100)
16	4-NO_2-Ph	H	Ph	H	1	72 (0:100)
17	3-HO-Ph	H	H	H	1	91 (100:0)
18	PhCH=CH	H	H	H	1	83 (100:0)
19	$PhCH_2CH_2$	Me	Me	H	1	84 (29:71)
20	$PhCH_2CH_2$	Me	H	Me	2	75 (100:0)
21	Ph	Me	H	H	2	80 (97:3)
22	Ph	Me	Me	H	2	62 (33:67)
23[c]	Ph	Me	TMS	H	4	77 (100:0)
24	Ph	Me	H	Me	2	72 (100:0)

[a] Reactions of the Grignard-type performed in the presence of 5 mol % of In, 1.0 equivalent of carbonyl compound, 2.0 equivalents of propargyl bromide, and 1.0 equivalent of Ga in THF (0.3 M).
[b] Yield of isolated product. Ratios were obtained on the basis of an internal standard (dodecane) in GC.
[c] Reactions proceeded in Barbier-type manner.

To investigate the reactivity of aromatic aldehydes and ketones toward organogallium reagents, an excess of a mixture of benzaldehyde and acetophenone was treated with the propargylgallium reagent in the presence of 5 mol % of indium, producing chemoselectively 1-phenyl-3-butyn-1-ol in 75% yield (Scheme 2). Exposure of an excess of a mixture of acetophenone and 4-phenyl-2-butanone with the propargylgallium reagent gave 6-phenyl-1-hexyn-4-ol in 58% yield and 6-phenyl-1,2-hexadien-4-ol in 14% yield. These results mean that the relative order of reactivity of carbonyl compounds toward organogallium reagents in the presence of 5 mol % of indium is aromatic aldehyde > aliphatic ketone > aromatic ketone.

In conclusion, we have demonstrated the efficient and regioselective addition reactions of propargyl bromides to carbonyl compounds with gallium catalyzed by indium. Reactions of organogallium reagents generated from propargyl bromides having substituents at the γ-position and gallium in the presence of 5 mol % of indium with aldehydes and ketones selectively produced homoallenyl alcohols in good to excellent yields. However, treatment of organogallium reagents obtained from propargyl bromide or propargyl bromides having substituents at the α-position and gallium in the presence of 5 mol % of indium with carbonyl compounds selectively afforded homopropargyl alcohols. Because organogallium reagents generated *in situ* from propargyl bromides and gallium with cat-indium were not previously applied to metal-catalyzed organic reactions, these results should provide more opportunities for the discovery of efficient and selective C–C bond-forming reactions. Further studies to explain the utility and mechanism of this reaction are in progress.



Scheme 2. Competition reaction of benzaldehyde and acetophenone and acetophenone and 4-phenyl-2-butanone under the present conditions.

Experimental Section

Typical Experimental Procedure

To a solution of a catalytic amount of indium powder (5.7 mg, 5 mol %) and gallium ingots (69.7 mg, 1.0 mmol, cut into small pieces) in THF (3 mL) was added propargyl bromide (237.9 mg, 2.0 mmol) under a nitrogen atmosphere at 10 °C. After the gallium ingot had dissolved for 1 h at 10 °C, benzaldehyde (106.1 mg, 1.0 mmol) was added to the reaction mixture. After being stirred at 25 °C for 1 h, the reaction mixture was poured into aqueous saturated $NaHCO_3$ (20 mL). The aqueous layer was extracted with ether (3 × 5 mL) and the combined organic layers were washed with brine (20 mL), dried with $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 7/1) to give 1-phenyl-3-butyn-1-ol; yield: 141.0 mg (96%).

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