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Gallium Enolate-Mediated Intermolecular Aldol Reaction and Addition Reaction of α-Bromoketone with Imine

Ying Han and Yao-Zeng Huang*

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences,
354 Fenglin Lu, Shanghai 200032, China

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Abstract: Treatment of α-bromoketone with gallium triiodide or methyl galliumiodide prepared in *situ* provides gallium enolates which react with carbonyl compounds or imines to give β - hydroxy ketones or β -phenylamino ketones effectively in moderate yields

Carbon-carbon bond formation *via* selective reduction of the carbon halogen bond, one of the most important operations in synthetic organic chemistry, is often accomplished by the aldol reaction.[1] Much attention has been paid to the enolates of Si, Fe, P, Al and Sn[2] generated by reductive dehalogenation of α-haloketones, but there has been little reported on the use of gallium enolates in organic synthesis. In continuation of our studies on the synthetic application of metallic gallium and its compounds,[3] we found a straightforward, efficient and versatile preparation of propargylic alcohols from 1-alkynes and aldehydes via gallium triiodide.[3c] In this communication, we would like to report the utility of gallium triiodide or gallium methyl iodide as a mild and diastereoselective reagent for efficient reductive dehalogenation, aldol condensation of α-bromoketone and addition reaction of α-bromoketone with imine via *situ* generation of a gallium enolate intermediate which is the first example of gallium enolate (**Scheme 1**).

Scheme 1

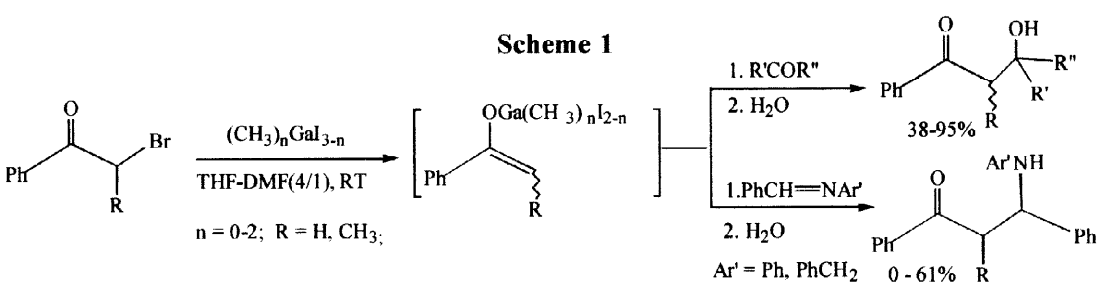

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Table 1. Gallium enolate-mediated intermolecular aldol type reactions and addition reactions of α-bromoketones with imines[a]

Entry	α -Bromoketone	$(CH_3)_nGaI_{3-n}$	Electrophile	Product	Yield(%)[b]
1	$PhCOCH_2Br$	n = 0	PhCHO	$PhCOCH_2CH(OH)Ph$	86
2	$PhCOCH_2Br$	n = 0	p-ClC_6H_4CHO	$PhCOCH_2CH(OH)C_6H_4Cl$-p	82
3	$PhCOCH_2Br$	n = 0	p-$NO_2C_6H_4CHO$	$PhCOCH_2CH(OH)C_6H_4NO_2$-p	74
4	$PhCOCH_2Br$	n = 0	trans-$C_6H_5CHCHCHO$	$PhCOCH_2CH(OH)CHCHPh$	83
5	$PhCOCH_2Br$	n = 0	CH_3CH_2CHO	$PhCOCH_2CH(OH)CH_2CH_3$	90
6	$PhCOCH_2Br$	n = 0	$(CH_2)_5CO$	$PhCOCH_2C(OH)(CH_2)_5$	64
7	$PhCOCH(CH_3)Br$	n = 0	p-ClC_6H_4CHO	$PhCOCH(CH_3)CH(OH)C_6H_4Cl$-p	38[c]
8	$PhCOCH_2Br$	n = 1	p-ClC_6H_4CHO	$PhCOCH_2CH(OH)C_6H_4Cl$-p	95
9	$PhCOCH_2Br$	n = 2	p-ClC_6H_4CHO	$PhCOCH_2CH(OH)C_6H_4Cl$-p	94
10	$PhCOCH_2Br$	n = 1	PhCH=NPh	$PhCOCH_2CH(NHPh)Ph$	61
11	$PhCOCH(CH_3)Br$	n = 2	PhCH=NPh	$PhCOCH(CH_3)CH(NHPh)Ph$	46[d]
12	$PhCOCH_2Br$	n = 1	PhCH=NBn	$PhCOCH_2CH(NHBn)Ph$	53
13	$PhCOCH(CH_3)Br$	n = 2	PhCH=NBn	$PhCOCH(CH_3)CH(NHBn)Ph$	42[d]
14	$PhCOCH_2Br$	n = 0	PhCH=NPh	$PhCOCH_2CH(NHPh)Ph$	0

[a]All reactions were performed with α-bromoketone (1.5 mmol), carbonyl compound (1 mmol) and $(CH_3)_nGaI_{3-n}$ (1.5 mmol) in THF / DMF (4 / 1) at rt. [b] Isolated yields based on aldehyde, ketone or imine, and products were determined by ^1H NMR, IR, MS and HRMS. [c] syn / anti isomers were determined by 300 MHz ^1H NMR (see **Scheme 2**). [d] The ratio of syn / anti isomers was 50 / 50, determined by 300 MHz ^1H NMR.

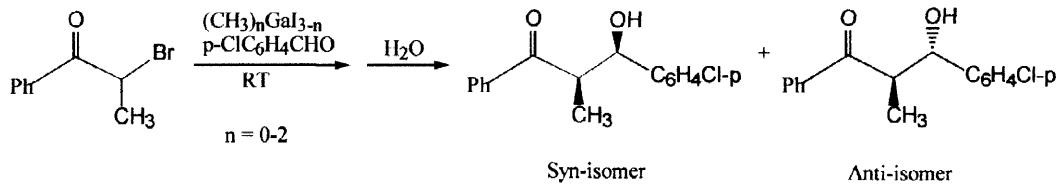
When α-bromoketone was treated with gallium triiodide, methyl gallium iodide or dimethyl gallium iodide in THF / DMF at room temperature,[4] followed by addition of electrophiles the corresponding products were isolated in moderate yields (38-95% except for **Entry 14**). While aldehyde or ketone was added into the mixture to trap intermediate, a cross - aldol reaction was performed under mild conditions and β-hydroxyl ketones were obtained in good yields (**Entry 1-9**). β-Phenylamino ketones were yielded after adding imine to the reaction (**Entry 10-13**). The results are summarized in **Table 1**.

It is particularly noteworthy that, unlike CeI_3,[5] GaI_3 can promote the aldol reaction of 2-bromo-1phenyl propanone with aldehyde and show high syn / anti selectivity (**Entry 7**). In fact, the yields and stereo selectivity of β-hydroxy ketone have improved when gallium methyl diiodide or dimethyl gallium iodide was used. Some dramatic results (**Scheme 2**) were obtained after the solvent was changed.

The reasons for this improved stereo-chemistry and yield by changing solvent and reagent are not clear at present. It is possible that the gallium atom in $MeGaI_2$, Me_2GaI and GaI_3 behaves as a Lewis acid which co-

ordinates with carbonyl oxygen and promotes debromination by iodide anion from gallium reagents. Formation of iodide anion from $MeGaI_2$ or Me_2GaI is easier than GaI_3.

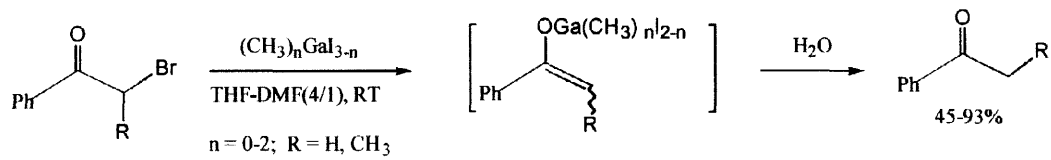
Scheme 2



Solvent	$(CH_3)_nGaI_{3-n}$	syn / anti	yield
THF / DMF	n = 0	81 / 19	38%
THF	n = 1	25 / 75	96%
DMF	n = 1	95 / 5	95%
DME	n = 1	46 / 54	92%
Dioxane	n = 1	28 / 72	88%
THF	n = 2	20 / 80	98%

In the absent of electrophile, a ketone was isolated from the reaction by adding water. This indicates that the first step of the reaction is dehalogenation by $(CH_3)_nGaI_{3-n}$ and the reacting species is the gallium enolate. Results are shown in **Scheme 3**.

Scheme 3



α-Bromoketone	$(CH_3)_nGaI_{3-n}$	Product	Yield
$PhCOCH_2Br$	n = 0	$PhCOCH_3$	91%
$PhCOCH(CH_3)Br$	n = 0	$PhCOCH_2CH_3$	45%
$PhCOCH(CH_3)Br$	n = 1	$PhCOCH_2CH_3$	93%
$PhCOCH(CH_3)Br$	n = 2	$PhCOCH_2CH_3$	89%

In conclusion, gallium triiodide -or methyl gallium iodide-mediated intermolecular aldol reaction and addition reaction of imine clearly revealed the facile formation of gallium enolate. Obviously the solvents affect the diastereoselectivity of the aldol reaction. The reaction would broaden the scope of utility of gallium reagents in organic chemistry.

The following experimental procedure is typical: Under an atmosphere of nitrogen, a mixture of 2-bromoacetophenone (299 mg, 1.5 mmol), and 4-chlorobenzaldehyde (140 mg, 1 mmol) was added to gallium triiodide in 4 mL THF, prepared from gallium (105 mg, 1.5 mmol) and iodine (572 mg, 2.25 mmol). 1 mL

DMF was added dropwise into the mixture. The reaction was stirred at room temperature for 4 h. Then the mixture was passed a silica gel column (15x3 cm, ca. 50 mL ethyl acetate), and the solvents were evaporated in vacuum. The residue was chromatographed on a plate of silica gel (20 x 20 cm) or column (ethyl acetate / light petroleum 60-90 °C = 5 / 1) to give the corresponding product in 82%.

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4. The preparation of GaI_3, $MeGaI_2$ and Me_2GaI:

   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.

   Gallium triiodide: The mixture of gallium powder (105 mg, 1.5 mmol) and iodine (572 mg, 2.25 mmol) in 4 mL dried THF in a Schlenk flask under nitrogen was stirred at room temperature until the color of iodine disappeared completely (10-15 min.).

   Methyl gallium diiodide: To a solution of gallium triiodide (1.5 mmol) in dried THF was slowly added methyl lithium (1.5 mmol in hexane) at room temperature under nitrogen. The solution was stirred for 15 min.

   Dimethyl gallium iodide: To a solution of gallium triiodide (1.5 mmol) in dried THF was slowly added methyl lithium (3.0 mmol in hexane) at room temperature under nitrogen. The solution was stirred for 15 min.
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