

Reformatsky Type Reaction with New Aluminium Reagents Containing Al-Sn or Al-Pb Linkage¹⁾

Seijiro MATSUBARA, Noriyuki TSUBONIWA, Yoshitomi MORIZAWA,

Koichiro OSHIMA,* and Hitosi NOZAKI

Department of Industrial Chemistry, Faculty of Engineering Kyoto University, Yoshida, Kyoto 606

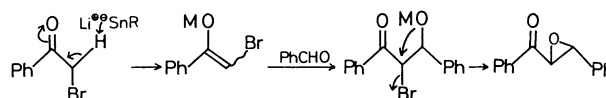
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Treatment of α -bromo carbonyl compounds with the reagent prepared from n -Bu₃SnLi and Et₂AlCl or from SnCl₂ and Et₂AlCl affords enolates which react with ketone or aldehyde to give β -hydroxy carbonyl compounds in good to excellent yields. The reactions proceed similarly with the reagents which are generated from R₃PbLi (R=Ph, n -Bu) and Et₂AlCl. Catalysis by the added Pd(PPh₃)₄ complex promotes the reduction effectively and improves the yields of the desired adducts. The regio- and stereoselectivities are disclosed.

Cross aldol condensation is one of the most versatile method of making a carbon-carbon bond. The old procedures, however, have some drawbacks of accompanying self aldol condensation and retro-aldol reaction, which provide undesired by-products.²⁾ During the past decade, numerous efforts have been made to overcome these shortages.³⁾ Among many metal enolates such as Li,²⁾ Mg,²⁾ Zn,²⁾ Ti,^{4a)} B,^{4b)} Al,^{4c, 4d, 4e)} Si,^{4f)} and Sn,^{4g)} having been explored, aluminium enolate is suitable for trapping the initially formed aldol adducts as stable chelates.^{4e)} Previously reported^{4e)} aldol reaction is based on the generation of the regiospecific aluminium enolate by the coupled attack of Et₂AlCl and Zn on the α -halo carbonyl compounds. Here we wish to describe another effective method for the regioselective formation of aluminium enolates which are sufficiently reactive to attack carbonyl components under mild conditions.

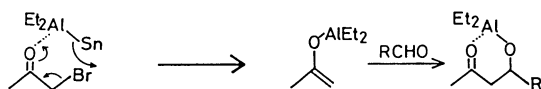
A novel reagent which is believed to have an aluminium-tin single bond⁵⁾ is produced by treatment of n -Bu₃SnLi⁶⁾ with an equimolar amount of Et₂AlCl. The aluminium atom should behave as a Lewis acid center, which will coordinate the carbonyl oxygen and will give rise to n -Bu₃Sn anion acting as a potent reductant (Scheme 1). In fact, treatment of an α -bromo

carbonyl compound with this reagent gave an enolate which reacted with a ketone or aldehyde to afford a β -hydroxy carbonyl compound in good yield after aqueous work-up. The success is ascribed to the strong affinity of tin for bromine⁷⁾ as well as that of aluminium for oxygen. Actually, treatment of a mixture of α -bromoacetophenone and benzaldehyde with n -Bu₃SnLi alone gave a small amount of β -hydroxy ketone (<5%) in addition to 1,3-diphenyl-2,3-epoxy-1-propanone (33% yield), a Darzens type product.⁸⁾ The latter compound was produced exclusively in 63% yield in the reaction of n -Bu₃SnLi-Me₃Al combination instead of n -Bu₃SnLi-Et₂AlCl. Strong basicity of the Sn⁻ anion accompanying Li⁺ ion explains the observed results (Scheme 2).

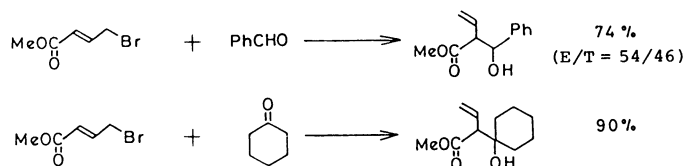


Scheme 2.

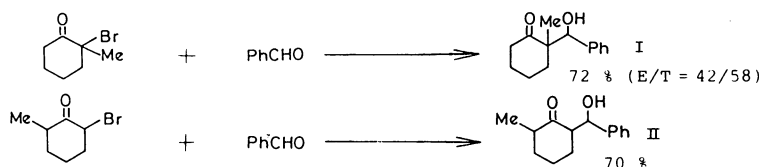
As shown in Table 1, the n -Bu₃SnLi-Et₂AlCl reagent can be applied equally well to the Reformatsky reaction⁹⁻¹¹⁾ of α -bromo esters. Reactions of methyl γ -bromocrotonate shown in Scheme 3 gave the α -adducts exclusively in contrast to the normal Reformatsky reactions producing mixtures of α -adducts and γ -adducts in roughly 7:3 ratios.¹²⁾ This high regioselectivity is a characteristic of the aluminium dienolate.^{4c, 4d)}



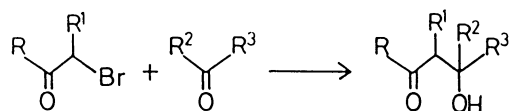
Scheme 1.



Scheme 3.



Scheme 4.

TABLE 1. REFORMATSKY TYPE REACTION WITH $n\text{-Bu}_3\text{SnLi-Et}_2\text{AlCl}$ SYSTEM

Run	R	R ¹	R ²	R ³	Additive	Yield/%	E/T
1	Ph	H	Ph	H	—	92 ^{a)}	—
2	Ph	H	—(CH ₂) ₅ —	H	—	76 ^{a)}	—
3	Ph	H	<i>n</i> -C ₈ H ₁₇	H	—	79	—
4	Ph	H	Ph-CH=CH-	H	—	54 ^{a, c)}	—
5	Ph	H	Ph-CH=CH-	H	Pd(PPh ₃) ₄ ^{b)}	70 ^{a, c)}	—
6	Ph	H	Me-CH=CH-	H	—	53 ^{c)}	—
7	Ph	H	Me-CH=CH-	H	Pd(PPh ₃) ₄ ^{b)}	77 ^{c)}	—
8	EtO	H	Ph	H	—	58 ^{a)}	—
9	EtO	H	—(CH ₂) ₅ —	H	—	87 ^{a)}	—
10	EtO	H	Ph-CH=CH-	H	—	54 ^{c)}	—
11	EtO	H	Ph-CH=CH-	H	Pd(PPh ₃) ₄ ^{b)}	75 ^{c)}	—
12	—(CH ₂) ₅ —	H	Ph	H	—	69 ^{a)}	25/75 ^{d)}
13	—(CH ₂) ₅ —	H	Ph	H	Pd(PPh ₃) ₄ ^{b)}	75 ^{a)}	26/74 ^{d)}
14	<i>n</i> -C ₆ H ₁₃	H	Ph	H	—	81	—
15	<i>n</i> -C ₆ H ₁₃	H	—(CH ₂) ₅ —	H	—	54	—
16	<i>n</i> -C ₆ H ₁₃	H	—(CH ₂) ₅ —	H	Pd(PPh ₃) ₄ ^{b)}	85	—
17	Et	Me	Ph	H	—	61 ^{e)}	50/50 ^{f)}

a) These compounds gave satisfactory spectra data. See Ref. 4c. b) A catalytic amount of Pd(PPh₃)₄ (5 mol%) was added. c) No 1,4-adduct was detected among the reaction mixture. d) The ratio of the stereoisomers (erythro and threo) was determined by an absorption due to the benzylic proton. See Ref. 4g. e) This compound was identical with the authentic sample. See Ref. 4f. f) Determined by nmr analysis. See Ref. 4f.

TABLE 2. REFORMATSKY TYPE REACTIONS WITH $\text{SnCl}_2\text{-Et}_2\text{AlCl}$ SYSTEM

Run	Bromo ketone or bromo ester	Ketone or aldehyde	Additive	Products	Yield/%
1	PhCOCH ₂ Br	PhCHO	—	PhCCH ₂ CHPh 	70
2	PhCOCH ₂ Br	PhCHO	Pd(PPh ₃) ₄ ^{a)}	PhCCH ₂ CHPh 	91
3	Ethyl bromoacetate	Cyclohexanone	Pd(PPh ₃) ₄ ^{a)}	Ph-CH(OH)-CH ₂ -C(=O)-Cyclohexyl 	89
4	Ethyl bromoacetate	PhCHO	Pd(PPh ₃) ₄ ^{a)}	EtOCCH ₂ CHPh 	88
5	Ethyl bromoacetate	Cyclohexanone	Pd(PPh ₃) ₄ ^{a)}	EtO-CH(OH)-CH ₂ -C(=O)-Cyclohexyl 	61
6	2-Bromocyclohexanone	PhCHO	Pd(PPh ₃) ₄ ^{a)}	Ph-CH(OH)-CH ₂ -C(=O)-Cyclohexyl 	95 (31/69) ^{b)}
7	Methyl γ-bromo-crotonate	PhCHO	— ^{c)}	MeO-CH(OH)-CH=CH-C(=O)-Ph 	80 (41/59) ^{d)}

a) A catalytic amount of Pd(PPh₃)₄ (5 mol%) was added. b) The ratio of the stereo isomers (erythro and threo) was determined by an absorption due to the benzylic proton. See Ref. 4g. c) Palladium catalyst was not effective. d) Erythro/threo ratio was determined by an absorption due to the methoxyl proton. See Ref. 4c.

TABLE 3. REFORMATSKY TYPE REACTIONS WITH $R_3PbLi-Et_2AlCl$ SYSTEM

Run	Bromo ketone or bromo ester	Ketone or aldehyde	Reagent	Products	Yield/%
1	$PhCOCH_2Br$	$PhCHO$	A	$PhC(=O)CH_2CH(Ph)OH$	86
2	$PhCOCH_2Br$	$PhCHO$	B	$PhC(=O)CH_2CH(Ph)OH$	78
3	$PhCOCH_2Br$	Cyclohexanone	A	$PhC(=O)CH_2CH_2C(OH)(Ph)C_5H_{10}$	61
4	$PhCOCH_2Br$	Cinnamaldehyde	B ^{a)}	$PhC(=O)CH_2CH(OH)CH=CHPh$	84
5	2-Bromocyclohexanone	$PhCHO$	A	$PhC(=O)CH_2C(OH)(Ph)C_5H_{10}$	77 (28/72) ^{b)}
6	Methyl γ -bromocrotonate	Cyclohexanone	A ^{a)}	$MeOOCCH=CHC(OH)(Ph)C_5H_{10}$	74
7	Methyl γ -bromocrotonate	Cyclohexanone	A	$MeOOCCH=CHC(OH)(Ph)C_5H_{10}$	56

Reagent A: $n-Bu_3PbLi-Et_2AlCl$; Reagent B: $Ph_3PbLi-Et_2AlCl$. a) A catalytic amount of $Pd(PPh_3)_4$ (5 mol%) was added. b) The ratio of the stereo isomers (erythro and threo) was determined by an absorption due to the benzylic proton. See Ref. 4g.

The regioselectivity of the reaction was demonstrated by the following two examples (Scheme 4). Treatment of a mixture of 2-bromo-2-methylcyclohexanone¹³⁾ and benzaldehyde with $n-Bu_3Sn-AlEt_2$ gave the expected β -hydroxy ketone I.^{4a)} Meanwhile, the reaction of 2-bromo-6-methylcyclohexanone¹⁴⁾ provided the regioisomer II^{4a)} exclusively. Each product I or II was obtained as a single product without any contamination of the opposite regioisomer. Since the starting bromides are prepared with high regioselectivity, the present method provided us with a simple route to the β -hydroxy ketones I and II.

It should be noted that these reactions proceeded more effectively in the presence of a catalytic amount of $Pd(PPh_3)_4$ (Run 5, 7, 11, 13, and 16). For instance, the yield of the adduct of α -bromoacetophenone and cinnamaldehyde was increased from 54% to 75% in the presence of a catalytic amount of $Pd(PPh_3)_4$.¹⁵⁾ We may safely assume that $Pd(0)$ facilitates the reduction of bromo ketone¹⁶⁾ to the aluminium enolate.

The addition of a hexane solution of Et_2AlCl to a suspension of anhydrous $SnCl_2$ in dichloromethane gave a dark red homogeneous solution.¹⁷⁾ The reagent thus prepared also was found to be effective for the Reformatsky type reaction (Table 2). The stereochemistry of the adducts and the regiochemistry of these reactions are similar to those with $n-Bu_3SnLi-Et_2AlCl$ reagent (Run 6, 7).

The use of $PhMe_2SiLi$ ¹⁸⁾ and Ph_3GeLi ¹⁹⁾ instead of $n-Bu_3SnLi$ resulted in a formation of only a small amount of desired β -hydroxy ketone in addition to unidentified products. The combination of R_3PbLi-

Et_2AlCl ²⁰⁾ ($R=n-Bu, Ph$), however, proved to be as effective as $n-Bu_3SnLi-Et_2AlCl$ system (Table 3). The stereochemical outcomes were almost same as those with $n-Bu_3SnLi-Et_2AlCl$ system.

Experimental

The IR spectra were determined on a Shimadzu IR-27-G spectrometer, the mass spectra on a Hitachi M-80 machine, and the NMR spectra on a Varian EM-390 spectrometer. The chemical shifts are given in δ , with TMS as an internal standard. The analyses were carried out by the staff at the Elemental Analyses Center of Kyoto University. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. Purification of products were performed by column chromatography on silica gel (Wakogel C-100) or preparative thin-layer chromatography (TLC). Analytical GLPC was performed with a Yanagimoto GCG-550-F and a Shimadzu GC-4CPT.

Preparation of β -Hydroxy Carbonyl Compounds with the Reagent Prepared from $n-Bu_3SnLi-Et_2AlCl$. A hexane solution of butyllithium (1.6 M[†], 3.8 ml, 6.0 mmol) was added to a suspension of anhydrous tin(II) chloride (0.38 g, 2.0 mmol) in THF (4 ml) at 0 °C. After being stirred for 20 min, the reaction mixture was treated with a hexane solution of diethylaluminum chloride (1.0 M, 2.0 ml, 2.0 mmol) at 0 °C. After the resulting mixture was stirred for another 20 min, a mixture of α -bromo carbonyl compound (1.0 mmol) and ketone or aldehyde (1.0 mmol) in THF (3 ml) was added [$Pd(PPh_3)_4$ (58 mg, 0.05 mmol) was added successively, if necessary] and the whole was stirred for 30 min. The reaction mixture was poured into 1M hydrochloric acid (20 ml) and

[†] 1 M = 1 mol dm⁻³.

extracted with ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The crude product was purified by silica-gel column chromatography (hexane-ethyl acetate, 2:1).

3-Hydroxy-1-phenyl-1-undecanone: Mp 41.5 °C (pentane); IR (nujol) 3500, 1672, 1205 cm⁻¹; NMR (CCl₄): δ =0.90 (t, *J*=6 Hz, 3H), 1.05–1.70 (m, 14H), 2.80–3.20 (m, 3H), 3.85–4.25 (m, 1H), 7.20–7.60 (m, 3H), 7.75–8.00 (m, 2H); MS *m/z* (%): 244 (30; M⁺–18), 220 (34), 120 (35) 105 (100); Found: C, 77.75; H, 10.22%. Calcd for C₁₇H₂₆O₂: C, 77.82; H, 9.99%.

(E)-3-Hydroxy-1-phenyl-4-hexen-1-one: Bp 80 °C (bath temp, 1 Torr^{††}); IR (neat): 3350, 2875, 1700, 1660, 1428 cm⁻¹; NMR (CCl₄): δ =1.68 (d, *J*=5.7 Hz, 3H), 2.80 (bs, 1H), 3.02 (d, *J*=6.0 Hz, 2H), 4.40–4.70 (m, 1H), 5.36–5.90 (m, 2H), 7.2–7.65 (m, 3H), 7.75–8.05 (m, 2H); MS *m/z* (%) 172 (2, M⁺–18), 120 (30), 105 (100), 77 (52); Found: C, 75.60; H, 7.50%. Calcd for C₁₂H₁₄O₂: C, 75.76; H, 7.42%.

Ethyl (E)-3-Hydroxy-5-phenyl-4-pentenoate: Bp 75 °C (bath temp, 1 Torr); IR (neat): 3400, 1705, 1150, 1020, 960 cm⁻¹; NMR (CCl₄): δ =1.25 (t, *J*=7.5 Hz, 3H), 2.50 (d, *J*=6 Hz, 2H), 2.90 (bs, 1H), 4.10 (q, *J*=7.5 Hz, 2H), 4.35–4.75 (m, 1H), 6.33 (d,d, *J*=6.7 Hz, 15.3 Hz, 1H), 6.90–7.40 (m, 6H); MS *m/z* (%): 220 (19, M⁺), 202 (25), 174 (15), 129 (71), 104 (100), 91 (19); Found: C, 71.04, H, 7.50%. Calcd for C₁₃H₁₆O₃: C, 70.89, H, 7.32%. Saponification and dehydration gave 5-phenylpentadienoic acid, which was identical with an authentic sample.²⁰

1-Hydroxy-1-phenyl-3-nonanone: Bp 104 °C (bath temp, 0.7 Torr); IR (neat): 3400, 2899, 1679, 1443 cm⁻¹; NMR (CCl₄): δ =0.90 (t, *J*=6 Hz, 3H), 1.05–1.70 (m, 8H), 2.35 (t, *J*=6.6 Hz, 2H), 2.60 (d, *J*=6 Hz, 1H), 2.63 (d, *J*=7.5 Hz, 1H), 3.15–3.45 (m, 1H), 4.8–5.1 (m, 1H), 6.95–7.30 (m, 5H); MS *m/z* (%): 234 (0.5, M⁺), 216 (3.8), 146 (69), 131 (100), 77 (13), 58 (26); Found: C, 77.05, H, 9.60%. Calcd for C₁₅H₂₂O₂: C, 76.88, H, 9.46%.

1-(1-Hydroxycyclohexyl)-2-octanone: Bp 58 °C (bath temp, 1 Torr); IR (neat): 3455, 1690, 1400, 970 cm⁻¹; NMR (CCl₄): δ =0.90 (t, *J*=6 Hz, 3H), 1.0–2.0 (m, 18H), 2.30 (t, *J*=6.6, 2H), 2.40 (s, 2H), 3.30 (bs, 1H); MS *m/z* (%): 226 (15, M⁺), 208 (35), 156 (8), 113 (100), 99 (51); Found: C, 74.38, H, 11.87%. Calcd for C₁₄H₂₆O₂: C, 74.29, H, 11.58%.

Methyl 2-(1-Hydroxycyclohexyl)-3-butenolate: Bp 51 °C (bath temp, 0.7 Torr); IR (neat): 3450, 1700, 1620, 1155, 985, 905 cm⁻¹; NMR (CCl₄): δ =0.80–1.90 (m, 10H), 2.82 (bs, 1H), 2.91 (t, *J*=9 Hz, 1H), 3.67 (s, 3H), 5.07 (d,d, *J*=16.5, 1.5 Hz, 1H), 5.13 (d,d, *J*=7.5, 1.5 Hz, 1H), 5.90 (d,d,d, *J*=16.5, 7.5, 1.5 Hz, 1H); MS *m/z* (%): 198 (0.76, M⁺), 183 (2.5), 155 (10), 100 (100), 99 (92), 81 (36), 69 (17), 68 (29); Found: C, 77.05, H, 9.60%. Calcd for C₁₁H₁₈O₃: C, 76.88, H, 9.46%.

Preparation of β -Hydroxy Carbonyl Compounds with the Reagent Prepared from SnCl₂-Et₂AlCl. A hexane solution of diethylaluminum chloride (1.0 M, 2.0 ml, 2.0 mmol) was added to a suspension of anhydrous tin (II) chloride (0.38 g, 2.0 mmol) in CH₂Cl₂ (5 ml) at 0 °C. The solution turned to red immediately. After being stirred for 20 min, a mixture of α -bromo carbonyl compound (1.0 mmol) and ketone or aldehyde (1.0 mmol) in CH₂Cl₂ (3 ml) was added [Pd(PPh₃)₄ (58 mg, 0.05 mmol) was added at the same time, if necessary] and the whole was stirred for 1 h. The reaction mixture was poured into 1M hydrochloric acid (30 ml) and extracted with ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The crude product was purified by silica-gel column chromatography (hexane-ethyl acetate, 2:1).

Preparation of β -Hydroxy Carbonyl Compounds with the Reagent Prepared from R₃PbLi-Et₂AlCl. A hexane solution of butyllithium (1.6 M, 3.8 ml, 6.0 mmol) or an ether solution

of phenyllithium (2.7 M, 2.2 ml, 6.0 mmol) was added to a suspension of a lead (II) chloride (0.56 g, 2.0 mmol) in THF (4 ml) at 0 °C. After being stirred for 20 min, the whole was cooled to –20 °C, and a hexane solution of diethylaluminum chloride (1.0 M, 2.0 ml, 2.0 mmol) was added at the same temperature. After the resulting mixture was stirred for another 20 min, a mixture of α -bromo carbonyl compound (1.0 mmol) and ketone or aldehyde (1.0 mmol) in THF (3 ml) was added [Pd(PPh₃)₄ (58 mg, 0.05 mmol) was added at this time, if necessary] and the whole was warmed up to 0 °C and stirred for 30 min. The reaction mixture was poured into 1 M hydrochloric acid and extracted with ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residual liquid was submitted to silica-gel column chromatography with hexane-ethyl acetate=2:1 as an eluent.

Darzens Type Reactions with *n*-Bu₃SnLi-Me₃Al System.

A hexane solution of trimethylaluminum (1.0 M, 2.0 ml, 2.0 mmol) was added to a solution of *n*-Bu₃SnLi prepared from *n*-BuLi (6.0 mmol) and SnCl₂ (0.38 g, 2.0 mmol) as described above, in THF (3.0 ml) at 0 °C. After stirring for 2 h, a mixture of α -bromoacetophenone (0.20 g, 1.0 mmol) and benzaldehyde (0.11 g, 1.0 mmol) in THF (2.0 ml) was added at 0 °C and the resulting mixture was stirred for another 20 min. The reaction mixture was poured into 1 M hydrochloric acid (30 min) and extracted with ether. The combined organic layers washed with brine, dried and concentrated. Purification by preparative TLC on silica-gel (hexane-ethyl acetate, 5:1) gave 1,3-diphenyl-2,3-epoxy-1-propanone in 63% yield.

1,3-Diphenyl-2,3-epoxy-1-propanone: Mp 88.5 °C (CH₂Cl₂/pentane); IR (CCl₄): 3000, 1680, 1590, 1500, 1210, 1000, 890 cm⁻¹; NMR (CCl₄): δ =3.90–4.05 (m, 2H) 6.90–7.60 (m, 3H), 7.27 (s, 5H), 7.80–8.10 (m, 2H); MS *m/z* (%): 224 (12.4, M⁺), 165 (9), 105 (100), 91 (23), 77 (64), 65 (16), 51 (31); Found C, 79.87, H, 5.30. Calcd for C₁₅H₁₂O₂: C, 80.34, H, 5.39%.

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^{††} 1 Torr≈133.322 Pa.

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