A facile preparation of indium enolates and their Reformatsky- and Darzens-type reactions

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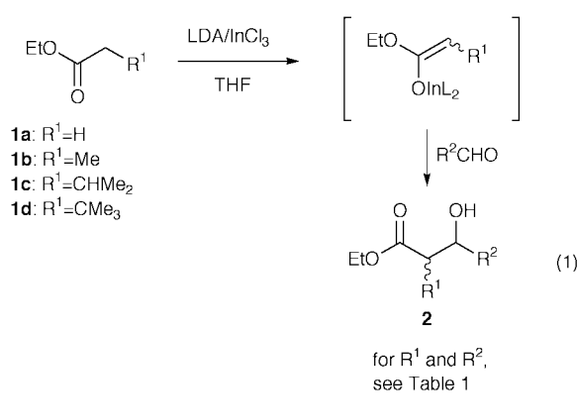
Indium enolates were readily prepared by transmetalation of lithium enolates with indium trichloride, and were subsequently reacted with aldehydes to give β-hydroxy esters in high yields. Indium α-bromo enolates were also prepared and reacted with carbonyl compounds to give Darzens-type α,β-epoxy carbonyl products.

Introduction

The Reformatsky reaction is a useful method for carbon–carbon bond formation. Besides the classical zinc enolate, various metal enolates have been examined so far, of which indium enolate was first introduced to organic synthesis only in 1975.[1] It was reported that activated indium powder, prepared by the reduction of indium trichloride with potassium metal, is useful for the Reformatsky reaction between α-bromo esters and carbonyl compounds, where indium enolates were generated *in situ*. Later, our group found that commercially available indium powder is equally useful for the Reformatsky reaction,[2] and this reaction was developed for the asymmetric synthesis of β-hydroxy esters through the use of chiral amino alcohols.[3] Although the indium-mediated Reformatsky reaction proceeds under mild conditions, α-iodo esters are essential to give high yields of β-hydroxy esters.[4a,b] Otherwise, addition of iodine and heating are required to generate indium enolates from α-bromo esters with metallic indium.[4c–e] α-Chloro esters resist oxidative addition of indium and, therefore, cannot be used for the preparation of organoindium reagents. In this paper we report a new and facile preparation of indium enolates and indium α-bromo enolates *via* transmetalation of the corresponding lithium enolates. Their reactions with carbonyl compounds are also disclosed.

Results and discussion

The lithium enolate of ethyl acetate **1a** was readily transmetalated with indium trichloride in THF at −78 °C to give the corresponding indium enolate. Further reaction with benzaldehyde and usual chromatographic separation gave the β-hydroxy ester **2a** in 48% yield, together with ethyl cinnamate in 19% yield [eqn. (1)]. The results with the various esters **1a**–**d** and aldehydes are summarized in Table 1, which shows that both



1a: R^1=H
1b: R^1=Me
1c: R^1=$CHMe_2$
1d: R^1=CMe_3

(1)

Table 1 Synthesis of β-hydroxy esters[a]

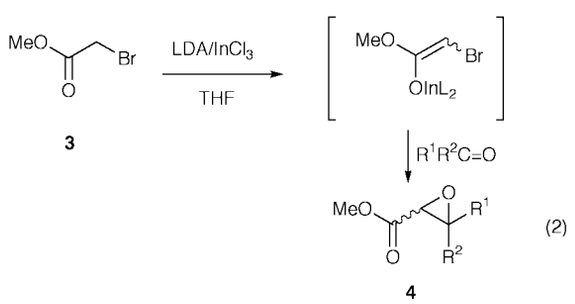
Entry	R^1	R^2	Product	Yield[b] (%)	*syn*:*anti*[c]
1	H	Ph	**2a**	48[d]	—
2	H	2-$(OH)C_6H_4$	**2b**	57	—
3	Me	Ph	**2c**	79	66:34
4[e]	Me	Ph	**2c**	78	56:44
5[f]	Me	2-$(OH)C_6H_4$	**2d**	70	67:33[g]
6	Me	$Me(CH_2)_6$	**2e**	88	60:40
7	Me	(*E*)-PhCH=CH	**2f**	83	64:36
8	Me_2CH	Ph	**2g**	86	35:65
9	Me_2CH	$Me(CH_2)_6$	**2h**	75	55:45[g]
10	Me_2CH	(*E*)-PhCH=CH	**2i**	88	50:50
11	Me_3C	Ph	**2j**	61	14:86
12	Me_3C	$Me(CH_2)_6$	**2k**	56	56:44[g]
13	Me_3C	(*E*)-PhCH=CH	**2l**	67	50:50

[a] All reactions were carried out with the appropriate ester (3 mmol), indium trichloride (1 mmol), lithium dicyclohexylamide (3 mmol), and corresponding aldehyde (1.5 mmol) overnight at room temperature. [b] Isolated yield. [c] On the basis of ^{1}H NMR analysis. [d] Ethyl cinnamate was also obtained in 19% yield. [e] Ethanol (3 mmol) was added before the coupling reaction. When a large excess of ethanol (70 mmol) was used, the yield of **2c** was 31% (*syn*:*anti* = 65:35). [f] This reaction was carried out over 3 days at room temperature. [g] Major:minor.

aromatic and aliphatic aldehydes give the corresponding β-hydroxy esters **2** in good yields without formation of the Claisen condensation products. The coupling with salicylaldehyde, which has a free hydroxy group, gave products **2b** and **2d** in good yields (entries 2 and 5). Moreover, the addition of ethanol before the coupling reaction with the aldehyde did not decrease the yield (entry 4). These facts support the intermediacy of indium enolates in these reactions, because organoindium reagents are known to be tolerable to active hydrogen, whereas lithium enolates are easily quenched. Although the diastereoselectivity of the present reaction is, in general, not very high, the substituent effect of indium enolates on the diastereoselectivity was observed for the reactions with benzaldehyde. As the substituent on ester **1** becomes sterically demanding, the *anti* selectivity of the products becomes higher (entries 3, 8 and 11). Such a steric effect was not evident in the cases of octanal and cinnamaldehyde. Acetophenone, as a representative ketone, gave no cross-coupling product under similar conditions. It is worth comparing this chemoselectivity with that of the indium-mediated Reformatsky reaction reported previously,[2] where even acetophenone gave the corresponding β-hydroxy ester in moderate yield.

In order to compare the reactions of indium enolates with those of lithium enolates, the reaction of the lithium enolate of ethyl propanoate with benzaldehyde was carried out under similar conditions but in the absence of indium trichloride. Without the addition of ethanol, **2a** could be obtained in 63% yield (*syn*:*anti*, 50:50) (*cf.* entry 3). On the other hand, in the presence of an equimolar amount of ethanol (*cf.* entry 4), **2a** did not form at all. The reaction of the lithium enolate with salicylaldehyde gave no trace of **2d**.

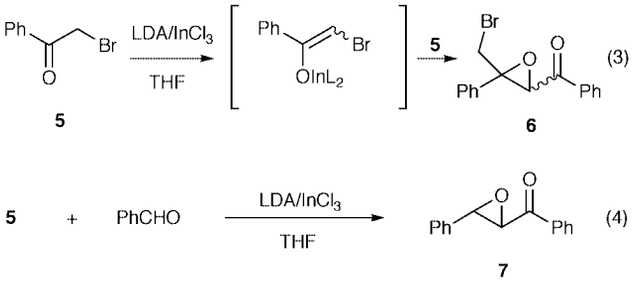
The Darzens reaction is a well-known synthetic method for generating α,β-epoxy esters and ketones from α-halo carbonyl compounds.[5] The preparation and the reactions of indium α-bromo enolates were examined in the same manner described above [eqn. (2)]. As expected, the Darzens products **4a–d**



(2)

were obtained by starting with α-bromo acetate **3** (Table 2). Benzaldehyde gave a high yield, whereas the reactions with octanal and cinnamaldehyde were sluggish and the yields were lower. In contrast to the results in Table 1, acetophenone gave the corresponding epoxy ester **4d** in a modest yield. The reaction of the corresponding lithium enolate with benzaldehyde at −78 °C gave a mixture of the oxirane **4a** (35% yield, *cis*:*trans* 27:73) and methyl 2-bromo-3-hydroxy-3-phenylpropanoate (26% yield, *syn* only).

The attempted coupling of the indium α-bromo enolate derived from phenacyl bromide (**5**) with benzaldehyde did not give the cross-coupling product. Instead, the self-coupling product **6** was obtained in 97% yield with a *cis*:*trans* ratio of 64:36 [eqn. (3)]. Without indium trichloride, the corresponding lithium enolate decomposed and **6** was not obtained. This self-coupling is considered to occur before the addition of the aldehyde. Then, in order to avoid the self-coupling of **5**, the reaction was carried out in a Barbier-type fashion. Thus, lithium dicyclohexylamide was added to a mixture of **5**, indium trichloride and benzaldehyde in THF. The expected cross-coupling product **7** was obtained in 77% yield with complete *trans* selectivity [eqn. (4)].



In summary, a new preparative route to indium enolates directly from esters by deprotonation with lithium amide followed by transmetalation with indium trichloride has been developed. This method provides easier access to indium enolates compared with the existing procedures that need α-halo esters. The tolerance of indium enolates to protic solvents and substrates confers on them a greater advantage over conventional lithium enolates. β-Hydroxy esters were obtained free from Claisen condensation products by the coupling of the indium enolates of esters with aldehydes. This reaction proceeded even in alcoholic media. Indium α-bromo enolates were also prepared and Darzens-type products, α,β-epoxy esters, were readily obtained. The self- and cross-coupling reactions of phenacyl bromide (**5**) were achieved *via* the corresponding indium α-bromo enolate.

Experimental

General

All reactions were carried out under a positive pressure of argon. THF was distilled from lithium aluminium hydride. Anhydrous indium trichloride was purchased from the Katayama Chemical Co. and used as received. Infrared spectra were recorded on a JASCO IRA-102 spectrometer. ^{1}H NMR spectra were recorded on a Varian Gemini-300 spectrometer (300 MHz). All NMR data were obtained in $CDCl_3$ solutions containing tetramethylsilane as an internal standard; *J* values are given in Hz. Elemental analyses were performed at the Elemental Analysis Centre of Kyoto University.

Table 2 Synthesis of α,β-epoxy esters[a]

Entry	R^1	R^2	Product	Yield[b] (%)	*cis*:*trans*[c]
1	Ph	H	**4a**	80	44:56
2	$Me(CH_2)_6$	H	**4b**	49	48:52
3	(*E*)-PhCH=CH	H	**4c**	23	18:82
4	Ph	Me	**4d**	27	18:82

[a] All reactions were carried out similarly to those in Table 1 unless stated otherwise. [b] Isolated yield. [c] On the basis of ^{1}H NMR analysis.

Typical procedure for the reaction of indium enolates and carbonyl compounds

The following reaction (entry 3 in Table 1) represents the general procedure. Lithium dicyclohexylamide, prepared from dicyclohexylamine (0.6 mL, 3.0 mmol) and *n*-butyllithium (1.6 M, 2.0 mL, 3.1 mmol) in THF (4 mL) was added to a stirred solution of anhydrous indium trichloride (221 mg, 1.0 mmol) and ethyl propanoate (344 μL, 3.0 mmol) in THF (6 mL) at −78 °C. The mixture was stirred for 10 min, after which time benzaldehyde (152 μL, 1.5 mmol) was added. The reaction mixture was warmed to room temperature and left overnight. The reaction was quenched with 1 M HCl (6 mL), and the product was extracted with diethyl ether. The organic extracts were washed with water and brine, and concentrated. The residue was purified by column chromatography on silica gel (elution with hexane–EtOAc, 9:1) to give ethyl 3-hydroxy-2-methyl-3-phenylpropanoate (**2c**)[6] (245 mg, 79%; *syn*:*anti*, 66:34).

The products **2a**,[2] **2b**,[2] **2e**,[7] **2f**,[8] **2g**[9] and **2j**[9] are known compounds.

Ethyl 3-hydroxy-3-(2-hydroxyphenyl)-2-methylpropanoate (2d). (Entry 5 in Table 1): ν_{max}(film)/cm^{-1}: 3370, 2990, 1706, 1610, 1582, 1490, 1458, 1378, 1344, 1242, 1190, 1100, 1052, 1020, 930, 860, 754, 732; major isomer: δ_H 1.26 (3 H, d, *J* 7.2, Me), 1.27 (3 H, t, *J* 7.2, Me), 3.02 (1 H, qd, *J* 9.0 and 7.2, C*H*Me), 4.18 (2 H, q, *J* 7.2, OC*H*$_2$Me), 4.18 (1 H, d, *J* 3.6, CHO*H*), 4.89 (1 H, dd, *J* 9.0 and 3.6, C*H*OH), 6.80–6.99 (3 H, m, aromatic), 7.13–7.23 (1 H, m, aromatic), 7.88 (1 H, d, *J* 1.8, OH); minor isomer: δ_H 1.04 (3 H, d, *J* 7.2, Me), 1.31 (3 H, t, *J* 7.2, Me), 2.81 (1 H, qd, *J* 7.2 and 3.2, C*H*Me), 4.21 (1 H, d, *J* 2.6, CHO*H*), 4.23 (2 H, q, *J* 7.2, OC*H*$_2$Me), 5.33 (1 H, dd, *J* 3.2 and 2.6, C*H*OH), 6.80–6.99 (3 H, m, aromatic), 7.13–7.23 (1 H, m, aromatic), 8.53 (1 H, s, OH) (Found: C, 64.49; H, 7.01. $C_{12}H_{16}O_4$ requires C, 64.27; H, 7.19%).

Ethyl 3-hydroxy-2-isopropyldecanoate (2h). (Entry 9 in Table 1): ν_{max}(film)/cm^{-1}: 3450, 2940, 1725, 1462, 1368, 1350, 1238, 1180, 1160, 1120, 1096, 1030, 720; a mixture of *syn* and *anti* isomers: δ_H 0.85–1.03 (9 H, m, 3 × Me), 1.25–1.31 (15 H, m, $(CH_2)_6$ and OCH$_2$*Me*), 2.11 (1 H, m, C*H*(*i*-Pr), minor isomer), 2.16 (1 H, m, C*H*Me$_2$), 2.33 (1 H, dd, *J* 6.9 and 6.0, C*H*(*i*-Pr), major isomer), 2.60–2.80 (1 H, br s, OH), 3.70–3.80 (1 H, m, C*H*OH, minor isomer), 3.86–3.92 (1 H, m, C*H*OH, major isomer), 4.13–4.22 (2 H, m, OC*H*$_2$Me) (Found: C, 69.61; H, 11.93. $C_{15}H_{30}O_3$ requires C, 69.72; H, 11.70%).

Ethyl (*E*)-3-hydroxy-2-isopropyl-5-phenylpent-4-enoate (2i). (Entry 10 in Table 1): ν_{max}(film)/cm^{-1}: 3450, 2960, 1725, 1600, 1578, 1495, 1460, 1445, 1390, 1370, 1300, 1240, 1180, 1160, 1098, 1026, 968, 750, 694; a mixture of *syn* and *anti* isomers: δ_H 0.97 (3 H, d, *J* 6.6, Me), 1.00 (3 H, d, *J* 6.9, Me), 1.02 (3 H, d, *J* 6.9, Me), 1.08 (3 H, d, *J* 6.6, Me), 1.22 (3 H, t, *J* 7.2, OCH$_2$*Me*), 1.25 (3 H, t, *J* 7.2, OCH$_2$*Me*), 2.11–2.24 (1 H, m, OH), 2.11–2.24 (1 H, m, C*H*Me$_2$), 2.32 (1 H, dd, *J* 8.4 and 4.8, C*H*(*i*-Pr)), 2.53 (1 H, dd, *J* 6.9 and 6.6, C*H*(*i*-Pr)), 3.09 (1 H, s, OH), 4.12 (2 H, q, *J* 7.2, OC*H*$_2$Me), 4.15 (2 H, q, *J* 7.2, OC*H*$_2$Me), 4.50–4.62 (1 H, m, C*H*OH), 6.18 (1 H, dd, *J* 15.9 and 5.4, PhCH=C*H*), 6.35 (1 H, dd, *J* 15.9 and 7.2, PhCH=C*H*), 6.64 (1 H, d, *J* 15.9, PhC*H*=), 6.66 (1 H, d, *J* 15.9, PhC*H*=), 7.20–7.41 (5 H, m, Ph) (Found C, 72.53; H, 8.53. $C_{16}H_{22}O_3$ requires C, 73.25; H, 8.45%).

Ethyl 2-*tert*-butyl-3-hydroxydecanoate (2k). (Entry 12 in Table 1): ν_{max}(film)/cm^{-1}: 3460, 2950, 1730, 1710, 1465, 1398, 1370, 1348, 1300, 1260, 1218, 1200, 1155, 1096, 1026, 720; major isomer: δ_H 0.88 (3 H, t, *J* 6.9, Me), 1.08 (9 H, s, 3 × Me), 1.25–1.32 (15 H, m, $(CH_2)_6$ and OCH$_2$*Me*), 2.31 (1 H, d, *J* 8.4, C*H*(*t*-Bu)), 3.20–3.30 (1 H, m, OH), 4.13 (2 H, q, *J* 7.2, OC*H*$_2$Me), 3.90–3.98 (1 H, m, C*H*OH); minor isomer: δ_H 0.88 (3 H, t, *J* 6.9, Me), 1.07 (9 H, s, 3 × Me), 1.25–1.32 (15 H, m, $(CH_2)_6$ and OCH$_2$*Me*), 2.21 (1 H, d, *J* 1.8, C*H*(*t*-Bu)), 3.20–3.30 (1 H, m, OH), 4.20 (2 H, q, *J* 7.2, OC*H*$_2$Me), 3.82–3.89 (1 H, m, C*H*OH) (Found C, 70.62; H, 12.08. $C_{16}H_{32}O_3$ requires C, 70.54; H, 11.84%).

Ethyl (*E*)-2-*tert*-butyl-3-hydroxy-5-phenylpent-4-enoate (2l). (Entry 13 in Table 1): ν_{max}(film)/cm^{-1}: 3450, 2960, 1724, 1630, 1600, 1580, 1496, 1480, 1445, 1396, 1368, 1330, 1254, 1194, 1152, 1112, 1100, 1072, 1028, 970, 748, 696; a mixture of *syn* and *anti* isomers: δ_H 1.11 (9 H, s, 3 × Me), 1.12 (9 H, s, 3 × Me), 1.20 (3 H, t, *J* 7.1, OCH$_2$*Me*), 1.23 (3 H, t, *J* 7.2, OCH$_2$*Me*), 2.42 (1 H, d, *J* 3.6, C*H*(*t*-Bu)), 2.57 (1 H, d, *J* 7.8, C*H*(*t*-Bu)), 3.46 (1 H, br s, OH), 4.08 (2 H, q, *J* 7.1, OC*H*$_2$Me), 4.16 (2 H, q, *J* 7.2, OC*H*$_2$Me), 4.59–4.69 (1 H, m, C*H*OH), 6.18 (1 H, dd, *J* 15.9 and 5.4, PhCH=C*H*), 6.38 (1 H, dd, *J* 15.9 and 7.8, PhCH=C*H*), 6.59 (1 H, d, *J* 15.9, PhC*H*=), 6.63 (1 H, d, *J* 15.9, PhC*H*=), 7.20–7.42 (5 H, m, Ph) (Found C, 74.09; H, 8.94. $C_{17}H_{24}O_3$ requires C, 73.88; H, 8.75%).

The products **4a**,[10] **4b**,[11] **4c**,[12] and **4d**[13] were known compounds.

The reaction of the lithium enolate of ethyl propanoate with benzaldehyde

Lithium dicyclohexylamide, prepared from dicyclohexylamine (0.6 mL, 3.0 mmol) and *n*-butyllithium (1.6 M, 2.0 mL, 3.1 mmol) in THF (4 mL) was added to a stirred solution of ethyl propanoate (344 μL, 3.0 mmol) and benzaldehyde (152 μL, 1.5 mmol) in THF (6 mL), at −78 °C. The reaction mixture was stirred for 3 h at this temperature and was subsequently quenched with saturated aqueous ammonium chloride. After the white precipitate had been removed by filtration, the product was extracted with diethyl ether. The organic extracts were washed with water and brine, and concentrated. The residue was purified by column chromatography on silica gel (elution with hexane–dichloromethane, 1:1 and then dichloromethane) to give **2c** (198 mg, 63% yield; *syn*:*anti*, 50:50).

The reaction of the lithium enolate of methyl bromoacetate with benzaldehyde was carried out similarly, and oxirane **4a** (35% yield, *cis*:*trans*, 27:73) and methyl 2-bromo-3-hydroxy-3-phenylpropanoate[14] (26% yield, *syn* 100%) were obtained.

The self-coupling reaction of 5 [eqn. (3)]

To a stirred mixture of anhydrous indium trichloride (221 mg, 1.0 mmol) and **5** (597 mg, 3.0 mmol) in THF (6 mL), lithium dicyclohexylamide prepared from dicyclohexylamine (0.6 mL, 3.0 mmol) and *n*-butyllithium (1.6 M, 2.0 mL, 3.1 mmol) in THF (4 mL), was added at −78 °C. The mixture was stirred for 10 min and benzaldehyde (152 μL, 1.5 mmol) was added. The reaction mixture was warmed to room temperature and the reaction was continued at room temperature for 3 h. The mixture was quenched with 1 M HCl (6 mL), and the product was extracted with diethyl ether. The organic extracts were washed with water and brine, and concentrated. The residue was purified by column chromatography on silica gel (elution with hexane–EtOAc, 9:1) to give 4-bromo-2,3-epoxy-1,3-diphenylbutan-1-one (**6**)[15] (462 mg, 97%, *cis*:*trans*, 64:36). The unreacted benzaldehyde was recovered.

The cross-coupling reaction of 5 with benzaldehyde [eqn. (4)]

This reaction was performed as described above by changing the addition of lithium dicyclohexylamide to a mixture of indium trichloride, **5** and benzaldehyde. 2,3-Epoxy-1,3-diphenylpropan-1-one (**7**)[16] (258 mg, 77%, *trans* 100%) was obtained.

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