

## Enantioselective Synthesis of $\beta$ -Hydroxy Esters by Indium-induced Reformatsky Reaction

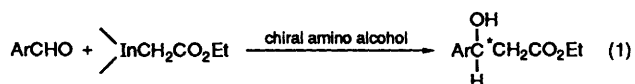
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Indium-induced Reformatsky reaction, with stoichiometric amounts of chiral amino alcohols such as cinchonine and cinchonidine, gave optically active  $\beta$ -hydroxy esters in 40–70% e.e.

The Reformatsky reaction is one of the fundamental reactions in organic synthesis. Recent rapid progress in the chemistry of the Reformatsky reaction, *i.e.* variation and activation of metals, selection of solvents, and structural modification of reagents and substrates, has greatly extended its applicability and versatility.<sup>1</sup> However, despite increasing interest in diastereo- and enantio-selective syntheses, synthesis of optically active  $\beta$ -hydroxy esters by stereocontrolled Reformatsky reaction has been but scarcely studied. Diastereoselective condensation of carbonyl compounds with chiral Reformatsky reagents, prepared from zinc metal and bromoacetates of chiral alcohols, showed low diastereoselectivity.<sup>2</sup> Examples of the addition of Reformatsky reagents to chiral substrates such as aldehydes<sup>3</sup> and imines<sup>2b</sup> are known. Aside from these intramolecular asymmetric inductions, intermolecular transfer of asymmetry utilizing external chiral ligands has received very little attention in studies of the Reformatsky reaction, which is in contrast to the cases of rapidly developing asymmetric aldol reactions and enantioselective addition of dialkylzinc to carbonyl compounds.<sup>4</sup> This methodology is particularly fascinating, because the selection and modification of substrates and reagents are quite easy. A few examples of such enantioselective addition of Reformatsky reagent to prochiral carbonyl compounds have been performed in the presence of (–)-sparteine<sup>5</sup> or *N,N,N',N',2,3*-hexamethylbutane-1,4-diamine<sup>6</sup> as chiral ligands, but the reported chemical and/or optical yields were generally poor.

We recently reported that organoindium reagents, prepared from iodoacetate and metallic indium, readily react with aldehydes and ketones to give  $\beta$ -hydroxy esters.<sup>7</sup> Now, this indium-induced Reformatsky reaction has been extended to enantioselective reactions simply by the addition of chiral ligands; when the reaction was conducted in the presence of external chiral amino alcohols such as cinchonine and cinchonidine, moderate yields of  $\beta$ -hydroxy esters were obtained in 40–70% e.e. [eqn. (1)].



### Results and Discussion

The organoindium reagent, prepared from ethyl iodoacetate and indium powder, was treated with benzaldehyde in the presence of a stoichiometric amount of cinchonine in a tetrahydrofuran (THF)/pentane mixture at between  $-7.5^\circ\text{C}$  and room temperature. Usual chromatographic separation gave the expected  $\beta$ -hydroxy ester in 63% yield. The e.e. was estimated to be 71% by HPLC on a chiral column, and the absolute configuration of the major enantiomer was determined

to be *S* based on the  $[\alpha]_D$ -value ( $-37.2$ )<sup>†</sup> (Table 1). Replacement of the ligand from cinchonine to cinchonidine afforded the *R* enantiomer predominantly (64% e.e.). Results for other aromatic aldehydes are summarized in Table 1. A *p*-methoxy substituent did not show a significant effect either on the chemical or the optical yields (entries 3 and 4), but electron-withdrawing chloro and nitro groups decreased the e.e. (entries 5–7). *o*-Methoxy- and *o*-chloro-benzaldehyde (entries 8–10) gave lower e.e.s than did those of the corresponding *para*-isomers.  $\beta$ -Naphthaldehyde also gave the (–)- $\beta$ -hydroxy ester with 68% optical purity in 64% yield when cinchonine was used (entry 11). The chemical yield could be easily increased by using a two-fold excess of the reagent (entry 12). With cinchonidine the (+)-enantiomer was obtained in 57% e.e. (entry 13). It is interesting to note here that cinchonidine sodium salt showed the opposite enantioselectivity [(–)-isomer predominant], though the chemical and optical yields were lower. A quinidine–quinine pair showed similar results (entries 14 and 15), but the stereoselectivities were lower than those of the cinchonine–cinchonidine case. In contrast with the smooth reaction with uncomplexed indium-based Reformatsky reagent,<sup>7a</sup> ketones did not react with the indium-Reformatsky reagent in the presence of the chiral amino alcohols, probably owing to the increased bulk of the chelated Reformatsky reagents. Zinc-Reformatsky reagent in place of indium-Reformatsky reagent gave no trace of  $\beta$ -hydroxy esters under the same reaction conditions as described above, because zinc-Reformatsky reagent is not compatible with the hydroxy group in the amino alcohols.

Other chiral ligands, including (–)-sparteine, (–)-norephedrine, (+)-(1-methylpyrrolidin-2-yl)diphenylmethanol, (+)-dibutyl tartrate and (+)-1,1'-bi-2-naphthol, were also examined for our indium-induced Reformatsky reaction; however, the chemical yield and/or enantioselectivities were quite modest.

Optically active 3-hydroxy esters are an important class of compounds and have hitherto been prepared by the asymmetric reduction of 3-oxo esters.<sup>8</sup> The enantioselectivities of our Reformatsky-based procedure are not very high and only aromatic aldehydes give satisfactory results. Nevertheless, the method is useful and convenient, because the experimental operations are simple, both enantiomers are obtainable simply by changing the ligands, and the chiral sources are easy to obtain.

### Experimental

IR spectra were recorded for neat oils on a JASCO A-102 spectrophotometer. <sup>1</sup>H NMR spectra were obtained for solutions in CDCl<sub>3</sub> on a Hitachi R-90 spectrometer (90 MHz) with Me<sub>4</sub>Si as internal standard; *J*-values are given in Hz. HPLC

<sup>†</sup> New units for  $[\alpha]_D$ -values:  $10^{-1}$  deg cm<sup>2</sup> g<sup>-1</sup>.

**Table 1** Reformatsky reaction with chiral amino alcohols<sup>a</sup>

Entry	Aldehyde	Alcohol <sup>b</sup>	Yield (%)	$[\alpha]_D^{20}$ (c) <sup>d</sup>	e.e.(%) <sup>e</sup> Config.
1	PhCHO	A	63	-37.2 (3.15)	71(75) <sup>f</sup> S <sup>f</sup>
2	PhCHO	B	57	+32.8 (2.95)	64(66) <sup>f</sup> R <sup>f</sup>
3	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> CHO	A	58	-30.7 (2.50)	71(72) <sup>g</sup>
4	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> CHO	B	56	+28.2 (1.85)	63(66) <sup>g</sup>
5	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> CHO	A	53	-28.9 (2.05)	66
6	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> CHO	B	58	+26.8 (2.35)	60
7	<i>p</i> -O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> CHO	A	52	-15.2 (5.25)	42
8	<i>o</i> -MeOC <sub>6</sub> H <sub>4</sub> CHO	A	60	-42.0 (2.30)	68
9	<i>o</i> -MeOC <sub>6</sub> H <sub>4</sub> CHO	B	57	+41.3 (2.00)	62
10	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub> CHO	A	68	-36.5 (4.45)	42
11	2-Naphthaldehyde	A	64	-31.0 (2.90)	68
12 <sup>h</sup>	2-Naphthaldehyde	A	90	-31.4 (3.50)	71
13	2-Naphthaldehyde	B	56	+26.6 (1.45)	57
14	2-Naphthaldehyde	C	69	-30.1 (2.60)	63
15	2-Naphthaldehyde	D	49	+23.2 (2.50)	49

<sup>a</sup> Reactions were carried out in THF-pentane at between -75 and 18 °C for 15 h under molar proportions of In:ICH<sub>2</sub>CO<sub>2</sub>Et:amino alcohol:aldehyde of 1:1.6:1:1. <sup>b</sup> A: cinchonine; B: cinchonidine; C: quinidine; D: quinine. <sup>c</sup>  $[\alpha]_D$ -Values are given in units of 10<sup>-1</sup> deg cm<sup>2</sup> g<sup>-1</sup>. <sup>d</sup> Solvent: CHCl<sub>3</sub>. <sup>e</sup> Determined by HPLC using Chiralcel OB. <sup>f</sup> Based on the reported value of *R*-enantiomer  $\{[\alpha]_D^{22} + 49.5$  (c 3.11, CHCl<sub>3</sub>), ref. 8b}. <sup>g</sup> Based on the reported value  $[\alpha]_D^{22} + 42.5$  (c 5.26, CHCl<sub>3</sub>), ref. 8b. <sup>h</sup> Two-fold excess of the reagent was used.

analyses were carried out on a JASCO TRI ROTAR-II with a chiral column (Chiralcel OB, Daicel Chemical Industries) and a JASCO UVIDEC-100 UF detector for determination of the optical purity of the products. Optical rotations were measured on material isolated by bulb-to-bulb distillation, by using a JASCO DIP-4 digital polarimeter with a 1.0 dm path length cell. All chemicals used in this work were purchased from Nacalai Tesque Co. All reactions were carried out under argon.

**Enantioselective Reformatsky Reaction using Chiral Amines.**—Typical experimental procedure. To a stirred suspension of indium powder (114 mg, 1 mmol) in THF (3 cm<sup>3</sup>) at 0 °C was added ethyl iodoacetate (185 mm<sup>3</sup>, 1.6 mmol) over a period of 5 min. The mixture was stirred at 0 °C for 30 min and then at 18 °C for 20 min. The reaction mixture was then chilled to -75 °C and this was followed by the addition of well dried cinchonine (295 mg, 1 mmol). The mixture was stirred for 10 min at -75 °C and pentane (1 cm<sup>3</sup>) was then added. 2-Naphthaldehyde (156 mg, 1 mmol) was then added and the whole mixture was stirred for 15 h while the temperature was allowed to increase to 18 °C spontaneously. The solvent was removed under reduced pressure, and water (3 cm<sup>3</sup>) and dichloromethane (10 cm<sup>3</sup>) were added. The mixture was stirred for 15 min and filtered. The organic layer was separated and the aqueous layer was extracted with dichloromethane (5 cm<sup>3</sup> × 5). After the extracts had been combined and dried (Na<sub>2</sub>SO<sub>4</sub>), the solvent was removed. The residue was purified by preparative TLC [silica gel; hexane-ethyl acetate (8:2)] and then bulb-to-bulb distillation to give pure ethyl 3-hydroxy-3-(2-naphthyl)propanoate (157 mg, 64%). All other reactions were carried out and worked up similarly. The structures of the products were determined by <sup>1</sup>H NMR and IR spectra.

**Ethyl 3-hydroxy-3-phenylpropanoate.**<sup>5,8b</sup> B.p. 130–140 °C/3 mmHg (bath temp.);  $v_{\max}/\text{cm}^{-1}$  3275 (OH) and 1720 (C=O);  $\delta_{\text{H}}$  1.26 (3 H, t, *J* 7, Me), 2.73 (2 H, m, CH<sub>2</sub>), 3.12 (1 H, br d, *J* 3, OH), 4.18 (2 H, q, *J* 7, CH<sub>2</sub>), 5.10 (1 H, m, CH) and 7.32 (5 H, m, Ph).

**Ethyl 3-hydroxy-3-(*p*-methoxyphenyl)propanoate.**<sup>8b,9</sup> B.p. 145–155 °C/3 mmHg (bath temp.);  $v_{\max}/\text{cm}^{-1}$  3450 (OH) and 1722 (C=O);  $\delta_{\text{H}}$  1.26 (3 H, t, *J* 7, Me), 2.70 (2 H, m, CH<sub>2</sub>), 3.10 (1 H, d, *J* 3, OH), 3.80 (3 H, s, OMe), 4.20 (2 H, q, *J* 7, CH<sub>2</sub>), 5.08 (1 H, m, CH), 6.88 (2 H, d, *J* 9, ArH) and 7.25 (2 H, d, *J* 9, ArH).

**Ethyl 3-(*p*-chlorophenyl)-3-hydroxypropanoate.**<sup>9</sup> B.p. 150–160 °C/3 mmHg (bath temp.);  $v_{\max}/\text{cm}^{-1}$  3440 (OH) and 1720

(C=O);  $\delta_{\text{H}}$  1.26 (3 H, t, *J* 7, Me), 2.69 (2 H, d, *J* 6, CH<sub>2</sub>), 3.32 (1 H, br s, OH), 4.19 (2 H, q, *J* 7, CH<sub>2</sub>), 5.10 (1 H, t, *J* 6, CH) and 7.31 (4 H, m, ArH).

**Ethyl 3-hydroxy-3-(*p*-nitrophenyl)propanoate.**<sup>9</sup> B.p. 190–200 °C/3 mmHg (bath temp.);  $v_{\max}/\text{cm}^{-1}$  3450 (OH), 1720 (C=O), 1518 (NO<sub>2</sub>) and 1342 (NO<sub>2</sub>);  $\delta_{\text{H}}$  1.28 (3 H, t, *J* 7, Me), 2.73 (2 H, d, *J* 6, CH<sub>2</sub>), 3.58 (1 H, d, *J* 3, OH), 4.20 (2 H, q, *J* 7, CH<sub>2</sub>), 5.20 (1 H, m, CH), 7.56 (2 H, d, *J* 9, ArH) and 8.20 (2 H, d, *J* 9, ArH).

**Ethyl 3-hydroxy-3-(*o*-methoxyphenyl)propanoate.**<sup>9</sup> B.p. 140–150 °C/3 mmHg (bath temp.);  $v_{\max}/\text{cm}^{-1}$  3475 (OH) and 1720 (C=O);  $\delta_{\text{H}}$  1.22 (3 H, t, *J* 7, Me), 2.72 (2 H, m, CH<sub>2</sub>), 3.42 (1 H, br d, *J* 3, OH), 3.84 (3 H, s, OMe), 4.17 (2 H, q, *J* 7, CH<sub>2</sub>), 5.38 (1 H, m, CH) and 6.80–7.50 (4 H, m, ArH).

**Ethyl 3-(*o*-chlorophenyl)-3-hydroxypropanoate.**<sup>9</sup> B.p. 145–155 °C/3 mmHg (bath temp.);  $v_{\max}/\text{cm}^{-1}$  3450 (OH) and 1720 (C=O);  $\delta_{\text{H}}$  1.23 (3 H, t, *J* 7, Me), 2.55 (1 H, dd, *J* 17 and 9, CHH), 2.85 (1 H, dd, *J* 17 and 3, CHH), 3.55 (1 H, br s, OH), 4.20 (2 H, q, *J* 7, CH<sub>2</sub>), 5.45 (1 H, m, CH), 7.30 (3 H, m, ArH) and 7.65 (1 H, m, ArH).

**Ethyl 3-hydroxy-3-(2-naphthyl)propanoate.**<sup>10</sup> B.p. 190–200 °C/3 mmHg (bath temp.);  $v_{\max}/\text{cm}^{-1}$  3450 (OH) and 1720 (C=O);  $\delta_{\text{H}}$  1.26 (3 H, t, *J* 7, Me), 2.82 (2 H, d, *J* 6, CH<sub>2</sub>), 3.36 (1 H, d, *J* 3, OH), 4.19 (2 H, q, *J* 7, CH<sub>2</sub>), 5.28 (1 H, m, CH), 7.50 (3 H, m, ArH) and 7.84 (4 H, m, ArH).

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