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Indolinylmethanol catalyzed enantioselective Reformatsky reaction with ketones

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This paper is dedicated to celebrate the 60th birthday of Professor Albert S. C. Chan

ABSTRACT

A series of chiral indolinylmethanol ligands have been applied for the first time in the asymmetric Reformatsky reaction of an α-bromoester with ketones. In the presence of $NiBr_2$ and zinc powder, up to 75% yield and 87% ee were obtained for a variety of aromatic and aliphatic ketones. The use of $Ni(acac)_2$ resulted in 96% ee although the corresponding yield was low. This process provided a convenient method to access synthetically useful chiral β-hydroxyesters.

1. Introduction

The Reformatsky reaction was realized in 1887 and is still widely used in organic synthesis.[1–3] It involves the zinc-induced formation of β-hydroxy alkanoates from α-halocarbonyl compounds and aldehydes or ketones. The mild reaction conditions, the excellent functional group tolerance, and the use of inexpensive non-toxic metals have made it an important alternative to the base-catalyzed aldol reaction. However, the usual heterogeneous reaction conditions have made the development of catalytic stereoselective variants quite difficult. Recently, significant improvements have been achieved in the enantioselective Reformatsky reaction with aldehydes,[4,5] but only a few examples of ketones have been reported[6,7] due to the low reactivity and decreased steric discrimination even though the resulting chiral tertiary alcohols are important structural units present in many biologically active compounds and synthetic intermediates.

Cozzi et al. described the first practical catalytic enantioselective Reformatsky reaction to ketones using 20 mol % ClMn(salen) **1** (Fig. 1) as the chiral catalyst.[8,9] Later, they developed an efficient dimethylzinc mediated, air promoted Reformatsky reaction of both aldehydes and ketones, employing commercially available (1*R*,2*S*)-*N*-pyrrolidinylephedrine **2** as the chiral ligand.[10–12] Recently, Feringa et al. reported a general asymmetric catalytic Reformatsky reaction of ketones based on the use of BINOL derivatives **3**.[13,14] They also extended this catalytic system to more challenging diarylketone substrates.[15] Subsequently Hayashi et al. examined the reaction of acetophenone with ethyl iodoacetate using chiral Schiff base **4** to afford the adduct in 63% ee.[16]

Chiral β-amino alcohols, especially pyrrolidine derivatives, have already been used in catalytic asymmetric Reformatsky reactions,[11,17–20] but the systems still need to be further improved upon since good enantioselectivities were only obtained for aldehyde substrates. On the other hand, we noticed that chiral indole-derived catalysts have recently been successfully applied in many reactions, such as diethylzinc addition to aldehydes,[21] ketone reduction,[22] ring openings of *meso*-epoxides,[23–25] desymmetrization of cyclic carbamates,[26] aldol reactions[27], and so on. Our group also reported the application of new dihydroindole and perhydroindole derivatives in the asymmetric Michael reaction of aldehydes to nitroalkenes and obtained good yields, high diastereoselectivities and enantioselectivities.[28] Compared with pyrrolidine analogs, indole derivatives possessing additional cyclohexane or phenyl rings in the backbone, may exert stronger influences on the orientation of substrates, hence improving the stereoselectivities for the asymmetric reaction. Herein, a series of chiral indolinylmethanol ligands were applied for the first time in the asymmetric Reformatsky reaction of α-bromoester with ketones.

2. Results and discussions

2.1. Effect of ligands

At first, experiments were carried out on the Reformatsky-type reaction of ethyl bromoacetate to acetophenone. Using an excess of Et_2Zn and 10 mol % of $NiBr_2$, with THF as solvent and dihydroindole derived amino alcohol as the chiral ligand, the desired product was isolated in low yield (25%) and 96% enantioselectivity (Fig. 2). The slow addition of Et_2Zn over several hours was crucial for high stereoselectivity, but was detrimental for good yield and repeatability due to the air-sensitive organozinc reagents.

To further simplify the reaction conditions, we reasoned that a controlled and mild formation of the zinc reagent using the less reactive Zn powder in the presence of a chiral zinc complex, should lead to considerable enantioselectivity but high yield. When zinc

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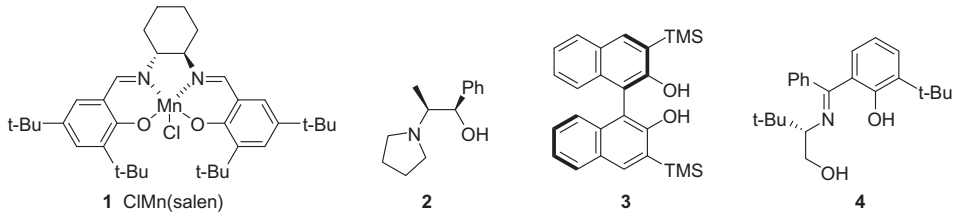


Figure 1. Some efficient catalysts for the asymmetric Reformatsky reaction of ketones.

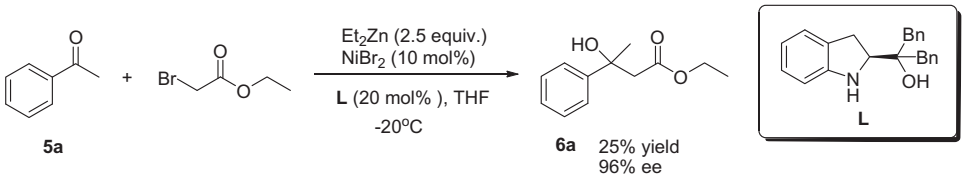
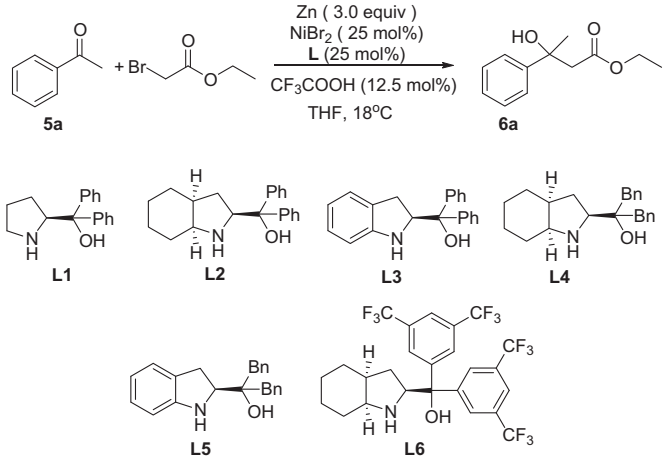


Figure 2. Homogeneous Ni-catalyzed Reformatsky reaction with Et_2Zn as the zinc source.

powder was used in the model reaction, we did observe a significant improvement in yield (Table 1 entry 5). Next, we turned our attention to the screening of various perhydroindole- and dihydroindole-derived amino alcohol ligands.

Table 1
Stereoselective Reformatsky reaction catalyzed by indole-derived chiral ligands[a]



Entry	Ligand	Time (h)	Yield[b] (%)	ee[c] (%)
1	**L1**	64	74	19
2	**L2**	64	71	31
3	**L3**	64	68	55
4	**L4**	64	67	33
5	**L5**	64	71	58
6	**L6**	64	20	23

[a] Reaction conditions: PhCOMe/Zn/ligand/$BrCH_2CO_2Et$ = 1.0:3.0:0.25:1.5.
[b] Isolated yield.
[c] Determined by HPLC analysis using a Daicel Chiralcel AS-H column.

With respect to the selectivity, monocyclic pyrrolidine derived amino alcohol **L1** showed poor enantioselectivity (19% ee) for the asymmetric Reformatsky reaction (Table 1 entry 1). When a rigid cyclohexane ring was attached to the pyrrolidine ring as in **L2**, the ee increased slightly to 31% (entry 2). Changing the cyclohexane ring to a planar benzene ring as in **L3** resulted in better ee (55%, entry 3). Chiral ligands with bulkier, less flexible phenyl substituents at the hydroxyl-bearing carbon atom **L1**–**L3** (see Fig. 3) showed little difference with regards to the enantioselectivity when compared with benzyl substituents **L4** and **L5** (Table 1 entries 2 vs 4, entries 3 vs 5). Compound **L6** provided low ee due to the large steric hindrance as well as the strong electron-withdrawing property of the 3,5-di(trifluoromethyl)phenyl substituent (entry 6). The highest enantioselectivity was observed for dihydroindoline derived **L5**, which may be due to its suitable steric structure, the nearly planar dihydroindoline moiety for the existence of the phenyl ring, and sp^2 hybridized nitrogen. We also obtained the crystal structures of **L3** and **L5**, which were quite similar to their molecular structures (Fig. 3 vs 4)

2.2. Influence of solvents

The effect of solvents on the catalytic Reformatsky reaction was examined in the presence of **L5** and the results are listed in Table 2. It seems that ether solvents (such as Et_2O, 1,4-dioxane and THF) were effective in terms of both reactivity and selectivity. For example 1,4-dioxane afforded up to 94% yield and 57% ee (entry 7), but its high melting point (12 °C) limited its application under low temperature. Thus we chose THF as the optimal solvent, which also afforded comparable ee but a slightly lower yield (entry 8).

In THF, when decreasing the amount of **L5** from 25 to 10 mol %, the enantioselectivity dropped significantly from 58% to 28%, albeit the yield rose from 71% to 93% (entries 8 vs 9). Normally a low temperature is helpful for stereoselectivity, hence we also carried out the reaction at 0 °C and observed a higher enantioselectivity (81% ee) and good yield (entry 10). Increasing the reaction time from 48 to 64 h did not influence the ee or yield (entries 10–11).

2.3. Influence of nickel salts[29–31]

Various nickel salts, such as $NiBr_2$, $NiCl_2(PPh_3)$, $NiBr_2$·diglyme, $NiCl_2$, and $Ni(acac)_2$ were examined for the Reformatsky reaction of bromoester to ketones and the results are summarized in Table 3. High yield (61%) and enantioselectivity (81% ee) were achieved with $NiBr_2$ (entry 3). When the catalyst loading was increased from 15 to 25 mol %, an increase in both yield and enantioselectivity were observed, but a further increase to 35 mol % only showed considerable reactivity and selectivity with the original 25 mol % (entries 2–4). In the absence of any nickel salt, the reaction also proceeded smoothly to give the corresponding β-hydroxyester in relative low yield but comparable ee under otherwise the same conditions (entry 1), which revealed that the nickel salt may act only as a Lewis acid in this process, and the chiral ligand that was able to coordinate with zinc was crucial for chirality transfer.

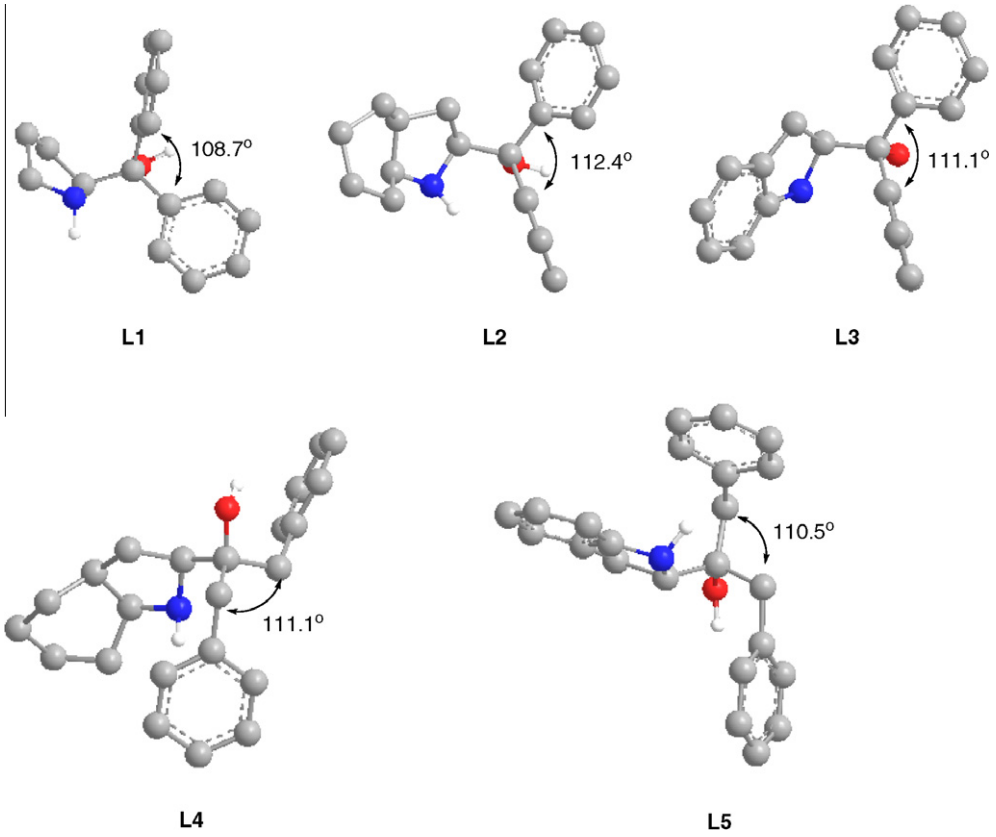


Figure 3. Molecular structures of **L1**–**L5**. The hydrogen atoms are omitted for the purpose of clarity. The indicated bond angles were estimated by Chem Draw 3D calculations (MM2).

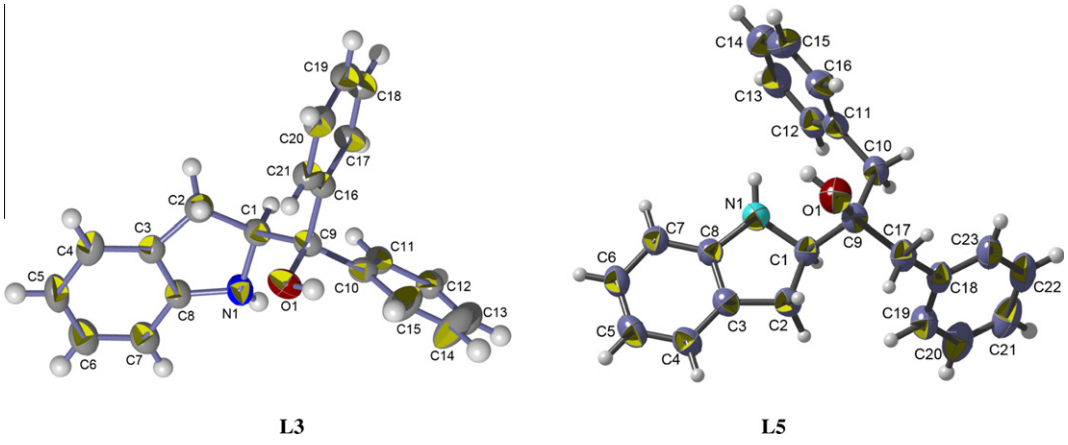


Figure 4. X-ray crystal structures of **L3** and **L5**.

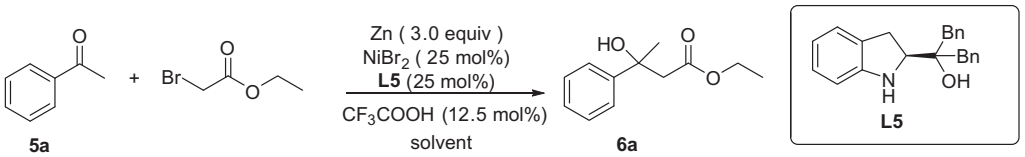
The most promising results were achieved with $Ni(acac)_2$, which gave up to 96% ee in the Reformatsky reaction of bromoester to acetophenone although the yield was low (18%, entry 8). The low yield can be explained by the relatively weaker Lewis acidity of $Ni(acac)_2$, which can be further improved upon by increasing the ratio of organic acid, such as CF_3COOH; however, high acidity was detrimental to the stereoselectivity (entries 8 vs 9). Other nickel salts, such as $NiBr_2$·diglyme, $NiCl_2$, and $NiCl_2(PPh_3)$ afforded 62–93% ees but low to moderate yields (entries 5–7). More experiments and results were still needed to establish the relationship between the sequence of Lewis acidity of the metal salts and the yields.

A high reaction temperature led to high yield but a significant decrease in enantioselectivity was also observed (entry 10). In view of both reactivity and selectivity, we chose $NiBr_2$ as the optimal nickel salt.

2.4. Scope and limitations of the catalytic system

Next, we investigated the scope of the reaction. A variety of aromatic and aliphatic ketones were used in this reaction, affording the desired β-hydroxyesters in good yields and stereoselectivities (Table 4). The enantioselectivity was not affected by the electronic properties of the substituents on the phenyl ring of the ketone. For

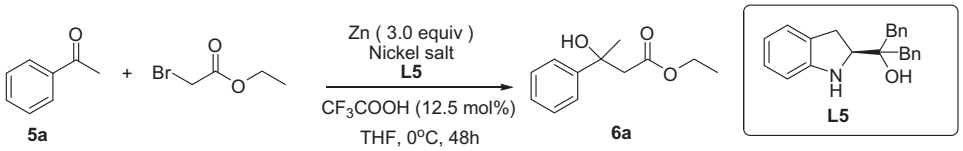
Table 2
Influences of solvents[a]



Entry	Solvent	*T* (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	DMF	22	24	59	10
2	Et_2O	22	36	59	45
3	Toluene	22	36	70	17
4	DCM	22	36	87	16
5	CH_3CN	18	45	70	36
6	Hexane	18	64	43	65
7	1,4-Dioxane	13	60	94	57
8	THF	22	36	71	58
9[d]	THF	22	36	93	28
10	THF	0	48	61	81
11	THF	0	64	60	81

[a] Reaction conditions: PhCOMe/Zn/ligand/$BrCH_2CO_2Et$ = 1.0:3.0:0.25:1.5.
[b] Isolated yield.
[c] Determined by HPLC analysis using a Daicel Chiralcel AS-H column.
[d] 10 mol % ligand.

Table 3
Influences of nickel salts[a]



Entry	Catalyst	Nickel salt (mol %)	**L5** (mol %)	Yield (%)[b]	ee[c] (%)
1	—	—	25	44	76
2	$NiBr_2$	15	15	52	77
3	$NiBr_2$	25	25	61	81
4	$NiBr_2$	35	35	59	80
5	$NiCl_2(PPh_3)$	25	25	43	62
6	$NiBr_2$·diglyme	25	25	26	89
7	$NiCl_2$	25	25	23	93
8	$Ni(acac)_2$	25	25	18	96
9[d]	$Ni(acac)_2$	25	25	38	81
10[e]	$Ni(acac)_2$	25	25	57	57

[a] Reaction conditions: PhCOMe/Zn/$BrCH_2CO_2Et$ = 1.0:3.0:1.5.
[b] Isolated yield.
[c] Determined by HPLC analysis using a Daicel Chiralcel AS-H column.
[d] 25 mol % CF_3COOH.
[e] Reaction was performed at 18 °C.

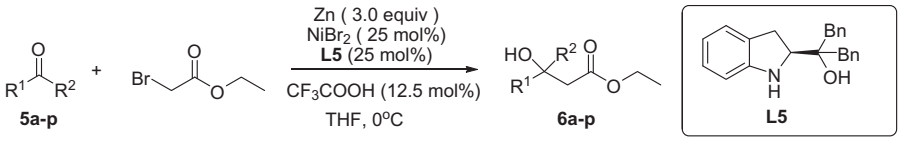
example, electron-donating *p*-methyl and *p*-methoxy substituted ketones afforded comparable ees with electron-withdrawing *p*-chloro, *p*-bromo, and *p*-fluoro substituted ketones (entries 2 and 3 vs entries 6–8). The steric effects of the aromatic rings of ketones were significant; the highly sterically hindered *o*-chloro substituted ketone afforded 87% ee for a preferable adduct, while *m*- and *p*-chloro substituted ketones gave 78% ee and 83% ee, respectively (entries 4–6). 1-Tetralone and 1-indanone were converted into the desired product in high enantioselective manner albeit with moderate yields (entries 11 and 12), presumably because their large steric hindrances retarded the addition of the active nucleophile. Compound **L5** was also used to catalyze the Reformatsky reaction of heterocyclic 2-furylacetone and 2-thienylacetone and provided the product with a bit low enantioselectivities (entries 13 and 14). The poor ee might be due to the strong coordination of the oxygen and sulfur atoms in the substrate to the organozinc reagents.

To further explore the scope of the substrates, we also investigated the effectiveness of the catalyst in the asymmetric addition to aliphatic ketones, including both saturated and unsaturated ketones (entries 15 and 16). The ee for the unsaturated ketone such as (*E*)-4-phenyl-3-buten-2-one was substantially higher than for the analogous saturated ketone, which can be attributed to the decreased steric discrimination within aliphatic ketones.

2.5. Possible mechanism for the $NiBr_2$–Zn catalyzed asymmetric Reformatsky reaction

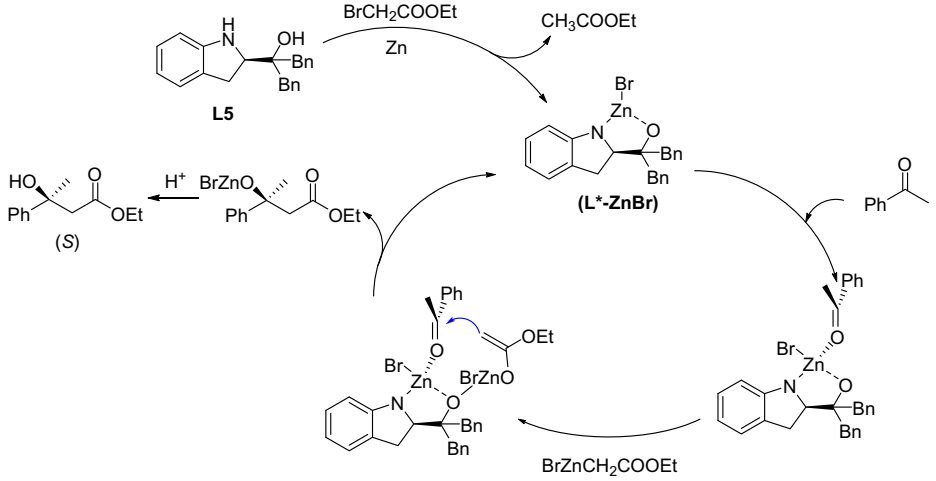
A possible mechanism is proposed in Scheme 1.[32,33] The bromoester reacted with zinc powder to form the Reformatsky reagent, which coordinated with the chiral ligand to liberate active catalyst **L∗-ZnBr** and ethyl acetate. Then **L∗-ZnBr** added to the acetophenone to form a tetra-coordinated zinc intermediate, where the orientation of ketone was regulated by the steric hindrance of the

Table 4
Catalytic enantioselective Reformatsky reaction with various ketones[a]



Entry	Ketone	Time (h)	Yield[b] (%)	ee[c] (%)	Config.
1	Acetophenone **5a**	48	61	81	(*S*)
2	4-Methylacetophenone **5b**	60	60	87	(+)
3	4-Methoxyacetophenone **5c**	60	56	81	(+)
4	2-Chloroacetophenone **5d**	48	73	87	(−)
5	3-Chloroacetophenone **5e**	48	67	78	(+)
6	4-Chloroacetophenone **5f**	48	68	83	(+)
7	4-Bromoacetophenone **5g**	48	65	86	(*S*)
8	4-Fluoroacetophenone **5h**	48	70	82	(+)
9	2-Acetonaphthone **5i**	48	50	81	(+)
10	Propiophenone **5j**	48	65	70	(+)
11	1-Tetralone **5k**	48	52	82	(−)
12	1-Indanone **5l**	48	57	71	(*S*)
13[d]	2-Furylacetone **5m**	60	53	51	(+)
14[d]	2-Thienylacetone **5n**	60	64	62	(+)
15	(*E*)-4-Phenyl-3-buten-2-one **5o**	48	72	42	(−)
16	4-Phenylbutan-2-one **5p**	48	75	28	(−)

[a] Reaction conditions: ketone/Zn/ligand/$BrCH_2CO_2Et$ = 1.0:3.0:0.0.25:1.5.
[b] Isolated yield.
[c] Determined by HPLC analysis using Daicel Chiralcel OD-H, AD-H or AS-H columns. The absolute configurations of the products were determined by comparison with the literature values.
[d] The reaction was performed at 15 °C.



Scheme 1. Possible mechanism for the asymmetric Reformatsky reaction.

chiral ligand. Direct attack of $BrZnCH_2COOEt$ to the ketone on the *Si*-face established the (*S*)-configuration of the organic product, which may be readily cleaved using an acid to provide the free alcohol. Next, **L*-ZnBr** was released from the catalytic system, regenerating the active species and completing the catalytic cycle. Here we postulate that the nickel salt worked only as a Lewis acid to activate zinc,[34] albeit the classical Ni^0/Ni^{II} catalytic cycles have been proposed.[5,31]

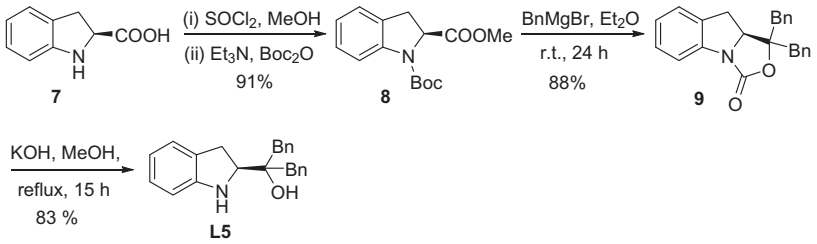
3. Conclusions

In conclusion, we have developed a highly enantioselective Reformatsky reaction of an α-bromoester with various ketones using a chiral indolinylmethanol ligand. In the presence of $NiBr_2$ and zinc powder, β-hydroxyesters were obtained in good yields and enantioselectivities. Changing the nickel salt to $Ni(acac)_2$ led to enantioselectivities as high as 96% ee although the corresponding yields were low. This process provided a convenient method to access synthetically useful chiral β-hydroxyesters. Modification of the ligand structure, as well as the development of other efficient catalytic systems for the asymmetric Reformatsky reaction is currently underway and will be reported in due course.

4. Experimental

4.1. General methods

All reactions were carried out in flame-dried glassware under a nitrogen atmosphere. All solvents were freshly distilled prior to use. Unless otherwise stated, commercial reagents purchased from Alfa Aesar, Acros, and Aldrich chemical companies were used without further purification. Purification of reaction products was



Scheme 2. Synthesis of **L5**.

carried out by flash chromatography using Qing Dao Sea Chemical Reagent silica gel (200–300 mesh). ^{1}H NMR spectra were recorded on a Bruker Advance III spectrometer (400 MHz) and the spectra were referenced internally to the residual proton resonance in $CDCl_3$ (δ = 7.26 ppm), or with tetramethylsilane (TMS, δ = 0.00 ppm) as the internal standard. Chemical shifts were reported as parts per million (ppm) in the δ scale downfield from TMS. ^{13}C NMR spectra were recorded on a Bruker Advance III spectrometer (400 MHz) with complete proton decoupling, and chemical shifts were reported in ppm from TMS with the solvent as the internal reference ($CDCl_3$, δ = 77.0 ppm). HPLC analyses were conducted on a Shimadzu 10A instrument using Daicel Chiralcel OD-H, AD-H, or AS-H columns (0.46 cm diameter × 25 cm length). Optical rotations were recorded on a Perkin–Elmer polarimeter (Model 341). Mass spectra were recorded on an ESI-ion trap Mass spectrometer (Shimadzu LC–MS-IT-TOF). Analytical TLC was performed using EM separations percolated silica gel 0.2 mm layer UV 254 fluorescent sheets.

4.2. Procedures for the preparation of ligands

Ligands **L1**[35] and **L2**–**L4**[28] were synthesized following the procedure described in the literatures.

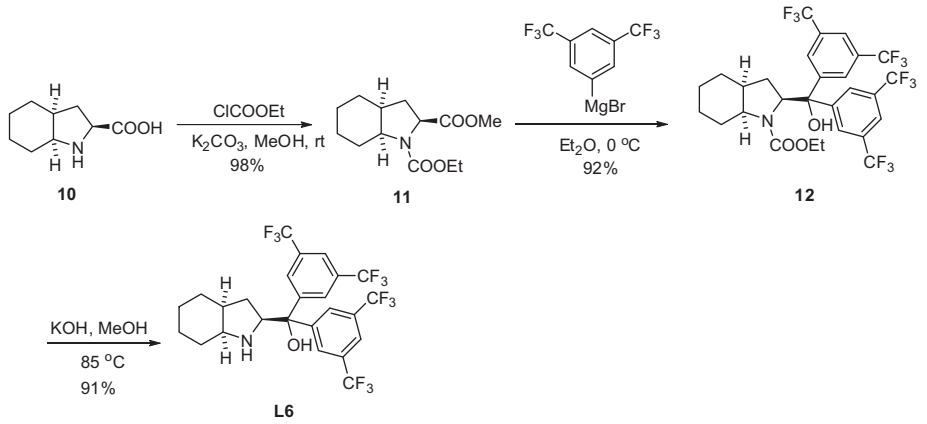
4.2.1. Synthesis of (*S*)-2-(indolin-2-yl)-1,3-diphenylpropan-2-ol L5

At first, BnMgBr (1 M in Et_2O, 60 mL, 60 mmol) was added dropwise at 0 °C to a solution of methyl ester **8**[28] (4.16 g, 15 mmol) in Et_2O (30 mL). The resulting mixture was warmed to room temperature and gradually heated at reflux overnight under a nitrogen atmosphere. The reaction was quenched with saturated NH_4Cl, and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography to afford (*S*)-1,1-dibenzyl-9,9a-dihydrooxazolo[3,4-a]indol-3(1*H*)-one **9** (4.67 g, 13.2 mmol, 88% yield) (Scheme 2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.91 (m, 3H), 3.18 (dd, *J* = 14.3, 23.4 Hz, 2H), 3.29 (dd, *J* = 9.2, 16.3 Hz, 1H), 4.85 (t, *J* = 9.5 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 7.12–7.30 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.84, 41.03, 42.33, 65.23, 86.77, 114.43, 124.25, 125.28, 127.10, 127.34, 128.10, 128.35, 128.70, 130.62, 131.10, 132.39, 134.42, 134.81, 139.97, 154.70. HRMS (ESI-TOF): *m/z* calcd for $C_{24}H_{21}NO_2Na$ $[M+Na]^+$ 378.1470; found: 378.1465.

KOH (14 g, 250 mmol) was added at 0 °C to a solution of the above residue (3.27 g, 10 mmol) in MeOH (50 mL). The reaction mixture was refluxed overnight. After cooling, the solvent was evaporated under reduced pressure, and then 50 mL H_2O was added. The aqueous phase was extracted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography to afford (*S*)-2-(indolin-2-yl)-1,3-diphenylpropan-2-ol **L5** (2.73 g, 8.3 mmol, 83% yield). $[\alpha]_D^{20} = -18.4$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 1H), 2.70 (d, *J* = 13.8 Hz, 1H), 2.78 (s, 2H), 3.10 (m, 3H), 3.56 (br s, 1H), 3.93 (t, *J* = 9.5 Hz, 1H), 6.49 (d, *J* = 7.7 Hz, 1H), 6.68 (t, *J* = 7.4 Hz, 1H), 6.97 (t, *J* = 7.6 Hz, 1H), 7.06 (d, *J* = 7.2 Hz, 1H), 7.20–7.32 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.55, 42.22, 44.10, 65.85, 75.36, 109.56, 119.03, 124.57, 126.56, 126.70, 127.34, 128.30, 128.46, 128.51, 130.31, 130.86, 137.21, 137.56, 150.63. HRMS (ESI-TOF): *m/z* calcd for $C_{23}H_{24}NO[M+H]^+$ 330.1858; found: 330.1850.

4.2.2. Synthesis of (*S*)-(3,5-bis(trifluoromethyl)phenyl)-((2*S*,3a*S*,7a*S*)-octahydro-1*H*-indol-2-yl) phenyl) methanol L6

At first, ClCOOEt (6.0 mL, 63 mmol) was added to a solution of **10** (4.89 g, 28.9 mmol) and K_2CO_3 (4.0 g, 28.9 mmol) in 40 mL of MeOH, then the reaction mixture was stirred at room temperature for 48 h. The solvent was evaporated and 50 mL of saturated Na_2CO_3 was added. The aqueous phase was extracted with CH_2Cl_2, and the combined organic extracts were dried with anhydrous



Scheme 3. Synthesis of **L6**.

Na_2SO_4 and concentrated under reduced pressure to afford product **11**[28] as an oil (7.23 g, 98% yield) (Scheme 3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05–1.27 (m, 5H), 1.31–1.43 (m, 2H), 1.54–1.67 (m, 3H), 1.91–2.05 (m, 3H), 2.25 (d, J = 4.2 Hz, 1H), 3.68 (s, 3H), 3.70–3.83 (m, 1H), 3.96–4.07 (m, 2H), 4.16–4.25 (m, 1H).

A solution of methyl ester **11** (3.0 g, 16.4 mmol) in Et_2O (10 mL) was added dropwise to a solution of 3,5-di-CF_3-PhMgBr (3 M in Et_2O, 22 mL, 65 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 3 h. The reaction was quenched with aqueous saturated NH_4Cl, and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography to afford product **12** as a white solid (9.8 g, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.74–0.89 (m, 2H), 1.14–1.29 (m, 7H), 1.38–1.67 (m, 3H), 1.84–1.91 (m, 1H), 2.13–2.21 (m, 1H), 3.67–3.74 (m, 1H), 3.97–4.05 (m, 1H), 4.12–4.20 (m, 1H), 4.87 (dd, J = 7.0, 11.0 Hz, 1H), 7.79 (s, 1H), 7.83 (d, J = 6.7 Hz, 3H), 7.89 (s, 2H), 8.22 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.37, 20.07, 23.47, 25.38, 27.11, 32.30, 35.29, 59.46, 62.77, 67.81, 80.84, 121.92, 124.50, 127.94, 128.98, 131.01, 131.34, 131.60, 131.93, 144.17, 146.36, 159.38.

KOH (21.12 g, 377 mmol) was added at 0 °C to a solution of **12** (9.8 g, 15.08 mmol) in MeOH (75 mL). The reaction mixture was refluxed overnight. After cooling, the solvent was evaporated under reduced pressure, 100 mL of H_2O was added. The aqueous phase was extracted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography to afford pure product **L6** as a white solid (13.7 g, 91% yield). $[\alpha]_D^{20} = -50.6$ (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23–1.36 (m, 3H), 1.46–1.69 (m, 8H), 2.05–2.13 (m, 1H), 3.31 (dd, J = 5.6, 11.3 Hz, 1H), 4.39 (t, J = 8.1 Hz, 1H), 5.24 (s, 1H), 7.76 (d, J = 6.7 Hz, 2H), 7.96 (s, 2H), 8.06 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.97, 23.35, 28.26, 30.34, 32.08, 36.98, 56.64, 63.91, 75.79, 121.25, 121.50, 121.84, 124.54, 125.57, 126.00, 131.62, 131.91, 131.95, 132.24, 146.53, 149.47. HRMS (ESI-TOF): m/z calcd for $C_{25}H_{20}NOF_{12}$ $[M-H]^+$ 578.1353; found: 578.1354.

4.3. Typical procedure for the Reformatsky reaction of ketones with ethyl bromoacetate

Under a nitrogen atmosphere, zinc powder (97.5 mg, 1.5 mmol), $NiBr_2$ (27.3 mg, 0.125 mmol), ligand **L5** (41.2 mg, 0.125 mmol), and anhydrous THF (1 mL) were added to a dried Schlenk flask. Then the mixture was stirred at 0 °C, after which the ketone (0.5 mmol) and ethyl bromoacetate (83 μL, 0.75 mmol) were added to the flask via syringe. The suspension was stirred for 10 min, and then CF_3COOH (5 μL, 0.0625 mmol) was added to activate the zinc powder. The reaction mixture was stirred at 0 °C for 48 h and quenched with 1 M hydrochloric acid (8 mL). Then 8 mL of diethyl ether were added. The aqueous layer was extracted with Et_2O (8 mL × 2) and the combined organic layers were washed with saturated brine (4 mL), and dried over Na_2SO_4. Evaporation of the solvent and flash chromatography (hexane/ethyl acetate 20:1) gave a colorless oil. The enantiomeric excess was determined by HPLC with Daicel Chiralcel OD-H, AD-H or AS-H columns.

4.3.1. (*S*)-(−)-Ethyl 3-hydroxy-3-phenylbutanoate 6a[9]

$[\alpha]_D^{20} = -12.1$ (c 1.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (t, J = 7.1 Hz, 3H), 1.54 (s, 3H), 2.79 (d, J = 15.9 Hz, 1H), 2.97 (d, J = 15.9 Hz, 1H), 4.06 (q, J = 7.1 Hz, 2H), 4.37 (s, 1H), 7.23 (dt, J = 4.0, 7.2 Hz, 1H), 7.33 (t, J = 7.3 Hz, 2H), 7.45 (d, J = 7.9 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.98, 30.63, 46.47, 60.71, 72.75, 124.46, 126.84, 128.22, 146.85, 172.68. HPLC conditions: Daicel Chiralcel AS-H column, hexane/*i*-PrOH 99:1, flow rate 1.0 mL/min, UV detection at 208 nm, t_{minor} = 7.67 min, t_{major} = 9.05 min, ee 81%.

4.3.2. (+)-Ethyl 3-hydroxy-3-*p*-tolylbutanoate 6b[36]

$[\alpha]_D^{20} = +7.1$ (c 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (t, J = 7.1 Hz, 3H), 1.52 (s, 3H), 2.32 (s, 3H), 2.77 (d, J = 15.9 Hz, 1H), 2.95 (d, J = 15.9 Hz, 1H), 4.06 (q, J = 7.1 Hz, 2H), 4.33 (s, 1H), 7.13 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.00, 20.93, 30.71, 46.45, 60.67, 72.62, 124.37, 128.91, 136.36, 143.97, 172.72. HPLC conditions: Daicel Chiralcel AS-H column, hexane/*i*-PrOH 99:1, flow rate 1.0 mL/min, UV detection at 214 nm, t_{minor} = 7.55 min, t_{major} = 8.72 min, ee 87%.

4.3.3. (+)-Ethyl 3-hydroxy-3-(4-methoxyphenyl)butanoate 6c[37]

$[\alpha]_D^{20} = +4.2$ (c 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (t, J = 7.1 Hz, 3H), 1.52 (s, 3H), 2.76 (d, J = 15.8 Hz, 1H), 2.94 (d, J = 15.8 Hz, 1H), 3.79 (s, 3H), 4.06 (q, J = 7.1 Hz, 2H), 4.34 (s, 1H), 6.86 (d, J = 8.9 Hz, 2H), 7.36 (d, J = 8.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.01, 30.73, 46.53, 55.22, 60.70, 72.48, 113.52, 125.65, 139.07, 158.40, 172.74. HPLC conditions: Daicel Chiralcel AS-H column, hexane/*i*-PrOH 99:1, flow rate 1.0 mL/min, UV detection at 234 nm, t_{minor} = 17.66 min, t_{major} = 21.48 min, ee 81%.

4.3.4. (−)-Ethyl 3-(2-chlorophenyl)-3-hydroxybutanoate 6d[9]

$[\alpha]_D^{20} = -5.6$ (c 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (t, J = 7.1 Hz, 3H), 1.72 (s, 3H), 2.94 (d, J = 16.0 Hz, 1H), 3.57 (d, J = 15.9 Hz, 1H), 4.02 (q, J = 7.1 Hz, 2H), 4.69 (s, 1H), 7.19 (t, J = 7.5 Hz, 1H), 7.30 (m, 2H), 7.86 (dd, J = 1.2, 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.91, 27.18, 43.77, 60.71, 73.08, 126.94, 128.02, 128.56, 130.43, 131.16, 142.92, 172.92. HPLC conditions: Daicel Chiralcel AS-H column, hexane/*i*-PrOH 99:1, flow rate 1.0 mL/min, UV detection at 214 nm, t_{minor} = 6.78 min, t_{major} = 7.48 min, ee 87%.

4.3.5. (+)-Ethyl 3-(3-chlorophenyl)-3-hydroxybutanoate 6e

$[\alpha]_D^{20} = +2.9$ (c 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (t, J = 7.1 Hz, 3H), 1.52 (s, 3H), 2.78 (d, J = 16.0 Hz, 1H), 2.94 (d, J = 16.0 Hz, 1H), 4.08 (q, J = 7.1 Hz, 2H), 4.47 (s, 1H), 7.25 (m, 3H), 7.47 (t, J = 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.98, 30.52, 46.14, 60.88, 72.50, 122.73, 125.03, 127.01, 129.54, 134.25, 149.10, 172.48. HRMS (ESI-TOF): m/z calcd for $C_{12}H_{15}O_3ClNa$ $[M+Na]^+$ 265.0607; found: 265.0586. HPLC conditions: Daicel Chiralcel OD-H column, hexane/*i*-PrOH 99:1, flow rate 0.5 mL/min, UV detection at 226 nm, t_{minor} = 17.12 min, t_{major} = 18.23 min, ee 78%.

4.3.6. (+)-Ethyl 3-(4-chlorophenyl)-3-hydroxybutanoate 6f[9]

$[\alpha]_D^{20} = +14.8$ (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (t, J = 7.1 Hz, 3H), 1.52 (s, 3H), 2.77 (d, J = 16.0 Hz, 1H), 2.93 (d, J = 16.0 Hz, 1H), 4.07 (q, J = 7.1 Hz, 2H), 4.43 (s, 1H), 7.30 (d, J = 8.7 Hz, 2H), 7.39 (d, J = 8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.99, 30.62, 46.20, 60.88, 126.04, 128.35, 132.69, 145.47, 172.55. HPLC conditions: Daicel Chiralcel AS-H column, hexane/*i*-PrOH 99:1, flow rate 1.0 mL/min, UV detection at 208 nm, t_{minor} = 10.06 min, t_{major} = 11.71 min, ee 83%.

4.3.7. (*S*)-(+)-Ethyl 3-(4-bromophenyl)-3-hydroxybutanoate 6g[9]

$[\alpha]_D^{20} = +13.9$ (c 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (t, J = 7.1 Hz, 3H), 1.51 (s, 3H), 2.77 (d, J = 16.0 Hz, 1H), 2.93 (d, J = 16.0 Hz, 1H), 4.06 (q, J = 7.1 Hz, 2H), 4.43 (s, 1H), 7.33 (d, J = 8.6 Hz, 2H), 7.45 (d, J = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.00, 30.56, 46.15, 60.87, 72.50, 120.82, 126.43, 131.29, 146.03, 172.50. HPLC conditions: Daicel Chiralcel OD-H column, hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, UV detection at 234 nm, t_{minor} = 5.56 min, t_{major} = 6.09 min, ee 86%.

4.3.8. (+)-Ethyl 3-(4-fluorophenyl)-3-hydroxybutanoate 6h

$[\alpha]_D^{20} = +7.5$ (*c* 0.7, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.14 (t, *J* = 7.1 Hz, 3H), 1.53 (s, 3H), 2.77 (d, *J* = 15.9 Hz, 1H), 2.94 (d, *J* = 15.9 Hz, 1H), 4.07 (q, *J* = 7.1 Hz, 2H), 4.44 (s, 1H), 7.01 (t, *J* = 8.7 Hz, 2H), 7.42 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.95, 29.65, 45.45, 59.77, 71.47, 113.79, 114.00, 125.22, 125.30, 141.70, 141.73, 159.50, 161.93, 171.56. HRMS (ESI-TOF): *m*/*z* calcd for $C_{12}H_{15}O_3FNa$ $[M+Na]^+$ 249.0903; found: 249.0889. HPLC conditions: Daicel Chiralcel OD-H column, hexane/*i*-PrOH 99:1, flow rate 0.5 mL/min, UV detection at 254 nm, t_{minor} = 15.34 min, t_{major} = 18.78 min, ee 82%.

4.3.9. (+)-Ethyl 3-hydroxy-3-(naphthalen-2-yl)butanoate 6i

$[\alpha]_D^{20} = +15.4$ (*c* 0.6, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.09 (t, *J* = 7.1 Hz, 3H), 1.62 (s, 3H), 2.87 (d, *J* = 15.9 Hz, 1H), 3.07 (d, *J* = 15.9 Hz, 1H), 3.99–4.05 (m, 2H), 4.54 (s, 1H), 7.42–7.47 (m, 2H), 7.54 (d, *J* = 8.9 Hz, 1H), 7.81 (t, *J* = 7.7 Hz, 3H), 7.93 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.99, 30.64, 46.36, 60.76, 72.93, 123.08, 123.17, 125.79, 126.08, 127.48, 128.01, 128.21, 132.40, 133.21, 144.29, 172.68. HRMS (ESI-TOF): *m*/*z* calcd for $C_{16}H_{18}O_3Na$ $[M+Na]^+$ 281.1154; found: 281.1163. HPLC conditions: Daicel Chiralcel AD-H column, hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, UV detection at 234 nm, t_{minor} = 8.31 min, t_{major} = 10.45 min, ee 81%.

4.3.10. (*S*)-(+)-Ethyl 3-hydroxy-3-phenylpentanoate 6j[9]

$[\alpha]_D^{20} = +11.8$ (*c* 0.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.77 (t, *J* = 7.4 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H), 1.81 (dq, *J* = 4.5, 7.2 Hz, 2H), 2.79 (d, *J* = 15.8 Hz, 1H), 2.96 (d, *J* = 15.8 Hz, 1H), 4.02 (q, *J* = 7.1 Hz, 2H), 4.33 (s, 1H), 7.23 (dd, *J* = 8.4, 15.6 Hz, 1H), 7.32 (t, *J* = 7.7 Hz, 2H), 7.39–7.41 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.74, 13.89, 35.85, 45.04, 60.55, 75.17, 125.16, 126.63, 127.99, 145.25, 172.83. HPLC conditions: Daicel Chiralcel OD-H column, hexane/*i*-PrOH 95:5, flow rate 0.8 mL/min, UV detection at 210 nm, t_{minor} = 13.83 min, t_{major} = 15.38 min, ee 70%.

4.3.11. (−)-Ethyl 2-(1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl) acetate 6k[9]

$[\alpha]_D^{20} = -10.2$ (*c* 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, *J* = 7.1 Hz, 3H), 1.75–1.83 (m, 1H), 1.89–2.00 (m, 2H), 2.06–2.12 (m, 1H), 2.74 (d, *J* = 15.5 Hz, 1H), 2.78–2.82 (m, 2H), 2.86 (d, *J* = 15.5 Hz, 1H), 4.00 (s, 1H), 4.18 (q, *J* = 14.1 Hz, 2H), 7.06 (d, *J* = 7.0 Hz, 1H), 7.14–7.21 (m, 2H), 7.54–7.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.17, 19.99, 29.46, 36.35, 46.14, 60.78, 71.12, 126.32, 126.38, 127.38, 128.86, 136.47, 140.65, 172.49. HPLC conditions: Daicel Chiralcel AD-H column, hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, UV detection at 208 nm, t_{minor} = 8.96 min, t_{major} = 11.02 min, ee 82%.

4.3.12. (*S*)-(−)-Ethyl 2-(1-hydroxy-2,3-dihydro-1*H*-inden-1-yl)-acetate 6l[9]

$[\alpha]_D^{20} = -6.1$ (*c* 0.6, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (t, *J* = 7.1 Hz, 3H), 2.28 (t, *J* = 6.8 Hz, 2H), 2.69 (d, *J* = 15.8 Hz, 1H), 2.81–2.85 (m, 1H), 2.88 (d, *J* = 15.8 Hz, 1H), 3.01–3.08 (m, 1H), 4.12 (s, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 7.20–7.27 (m, 3H), 7.33–7.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.15, 29.38, 40.31, 43.95, 60.86, 81.05, 122.86, 124.96, 126.80, 128.48, 142.73, 146.00, 172.72. HPLC conditions: Daicel Chiralcel OD-H column, hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, UV detection at 210 nm, t_{minor} = 8.66 min, t_{major} = 10.59 min, ee 71%.

4.3.13. (+)-Ethyl 3-(furan-2-yl)-3-hydroxybutanoate 6m[9]

$[\alpha]_D^{20} = +7.1$ (*c* 0.8, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.22 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 2.72 (d, *J* = 15.8 Hz, 1H), 2.98 (d, *J* = 15.8 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 4.35 (s, 1H), 6.24 (d, *J* = 3.2 Hz, 1H), 6.29–6.30 (m, 1H), 7.32 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.02, 27.63, 44.47, 60.79, 69.64, 104.56, 110.15, 141.52, 158.47, 172.30. HPLC conditions: Daicel Chiralcel OD-H column, hexane/*i*-PrOH 98:2, flow rate 1.0 mL/min, UV detection at 254 nm, t_{major} = 8.89 min, t_{minor} = 12.25 min, ee 51%.

4.3.14. (+)-Ethyl 3-hydroxy-3-(thiophen-2-yl)butanoate 6n[13]

$[\alpha]_D^{20} = +4.2$ (*c* 0.8, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.19 (t, *J* = 7.1 Hz, 3H), 1.63 (s, 3H), 2.81 (d, *J* = 15.9 Hz, 1H), 2.98 (d, *J* = 15.9 Hz, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 4.74 (s, 1H), 6.89 (dd, *J* = 1.2, 3.5 Hz, 1H), 6.92 (dd, *J* = 3.6, 5.0 Hz, 1H), 7.18 (dd, *J* = 1.1, 5.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.02, 31.40, 46.96, 60.91, 71.87, 122.01, 124.00, 126.68, 152.25, 172.38. HPLC conditions: Daicel Chiralcel OD-H column, hexane/*i*-PrOH 98:2, flow rate 1.0 mL/min, UV detection at 234 nm, t_{major} = 8.85 min, t_{minor} = 10.43 min, ee 62%.

4.3.15. (−)-(*E*)-Ethyl 3-hydroxy-3-methyl-5-phenylpent-4-enoate 6o[9]

$[\alpha]_D^{20} = -14.3$ (*c* 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.1 Hz, 3H), 1.42 (s, 3H), 2.65 (d, *J* = 15.5 Hz, 2H), 4.06 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 6.27 (d, *J* = 16.0 Hz, 1H), 6.64 (d, *J* = 16.0 Hz, 1H), 7.20–7.30 (m, 1H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.36 (d, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.16, 28.44, 45.67, 60.77, 71.28, 126.50, 127.51, 127.87, 128.53, 134.85, 136.76, 172.43. HPLC conditions: Daicel Chiralcel AS-H column, hexane/*i*-PrOH 99:1, flow rate 1.0 mL/min, UV detection at 226 nm, t_{minor} = 17.81 min, t_{major} = 22.68 min, ee 42%.

4.3.16. (−)-Ethyl 3-hydroxy-3-methyl-5-phenylpentanoate 6p[9]

$[\alpha]_D^{20} = -2.0$ (*c* 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.1 Hz, 3H), 1.31 (s, 3H), 1.81–1.89 (m, 2H), 2.49 (d, *J* = 15.6 Hz, 1H), 2.57 (d, *J* = 15.6 Hz, 1H), 2.68–2.75 (m, 2H), 3.65 (s, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 7.17–7.20 (m, 3H), 7.25–7.29 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.06, 14.20, 26.75, 30.32, 43.90, 45.07, 46.04, 60.67, 61.72, 70.83, 125.80, 128.35, 128.42, 142.29, 172.88. HPLC conditions: Daicel Chiralcel OD-H column, hexane/*i*-PrOH 95:5, flow rate 0.5 mL/min, UV detection at 210 nm, t_{minor} = 15.76 - min, t_{major} = 18.07 min, ee 28%.

4.4. Crystal structure determination

Diffraction data were collected on a Bruker Smart Apex CCD diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). All intensity data were corrected for Lorentz and polarization effects, and empirical absorption corrections based on equivalent reflections were applied (SADABS). The structures were solved with direct methods and refined with the full-matrix least-squares method on F^2 with SHELXTL program package.[38] All non-hydrogen atoms were refined with anisotropic displacement parameters. The hydrogen atoms were generated geometrically. CCDC-770575 (**L3**), 770576 (**L5**) contained the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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