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Enantioselective α-chlorination of β-oxo esters catalyzed by chiral diterpenoid alkaloid derivatives

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ABSTRACT

Easily accessible diterpenoid alkaloid derivatives have been used as organocatalysts in the enantioselective α-chlorination of β-oxo esters. The treatment of β-oxo esters with *N*-chlorophthalimide (NCP) as a chlorine source under mild reaction conditions afforded the corresponding α-chlorinated β-oxo esters in excellent yields (up to 98%) and with moderate enantioselectivities (up to 68% ee) in 30 min.

1. Introduction

Alkaloids are a group of naturally occurring chemical compounds that contain mostly basic nitrogen atoms. They often have pharmacological effects and are used as medications.[1] Unique stereostructures, basic nitrogen groups, and other functionalities such as hydroxyl and carbonyl groups, render alkaloids a class of potential organocatalysts.[2] In the development of asymmetric organocatalysis with small chiral organic molecules as catalysts over the past decade, chiral alkaloids have played a significant role due to their special structures.[3] Although cinchona alkaloids and their derivatives have been widely used to promote a great variety of asymmetric reactions,[2,4] using other natural products as organocatalysts have rarely been reported on. Thus, it is very important to discover novel asymmetric frameworks from alkaloids.

Enantioenriched α-halo carbonyl compounds are valuable precursors for a variety of synthetic building blocks and also display a wide range of physiological activities.[5] As an important part of the asymmetric α-halogenation of carbonyl compounds, enantioselective α-chlorination of β-oxo esters has been reported not only using transition metal complexes[6] but also with organocatalysts such as cinchona alkaloid derivatives,[7] chiral *N*,*N*′-dioxides,[8] chiral amino diol derivatives,[9] and chiral phase-transfer catalysts.[10] Over the course of structural studies toward the organocatalysts used in the α-halogenation of carbonyl compounds, secondary and tertiary amine moieties attracted our interest since these structures can efficiently promote the formation of an enolate, which can then be chlorinated in a chiral environment to generate the desired product.[7,11] Inspired by these results, we started our investigation by selecting six commercially available chiral alkaloids (Scheme 1); lappaconitine **A1** (anti-arrhythmia), vincamine **A2** (vasodilator), vinpocetine **A3** (vasodilator), cytosine **A4** (smoking cessation drug), galantamine **A5** (cholinomimetic), and sinomenine **A6** (anti-rheumatic), and verified the feasibility of using them as organocatalysts for the asymmetric α-chlorination of β-oxo esters.

2. Results and discussion

Initially, we examined the reaction of methyl 1-indanone-2-carboxylate **1a** with *N*-chlorosuccinimide **3a** (NCS) as the halogen source in the presence of alkaloids **A1**–**A6** as the chiral-base catalyst. Representative results are listed in Table 1.

Some alkaloids proved to be useful in the asymmetric model reaction. Lappaconitine **A1**, which was used to catalyze the enantioselective α-hydroxylation of β-oxo esters in our previous work,[12] proved to be the most promising catalyst among the chiral alkaloids tested and afforded the (*R*)-chloro derivative **2a** with reasonable enantiomeric excess (Table 1, entry 1). However, vincamine **A2**, vinpocetine **A3**, and cytisine **A4** afforded **2a** with an (*S*)-configuration with decreased enantioselectivities (Table 1, entries 2–4). Nearly racemic **2a** was obtained when galantamine **A5** or sinomenine **A6** was employed as the organocatalyst (Table 1, entries 5 and 6).

Encouraged by these results, a series of different lappaconitine derivatives **L1**–**L6** were prepared and investigated. We found that the enantioselectivities were strongly influenced by substitution in the basic nitrogen group. A visible improvement in enantioselectivity, from 30% to 38% ee, was achieved by employing the secondary amine **L1** which was obtained from the N-deethylation of lappaconitine (Table 2, entry 1). Tertiary amine derivatives **L2** and **L3** reduced the selectivities (Table 2, entries 2 and 3), but

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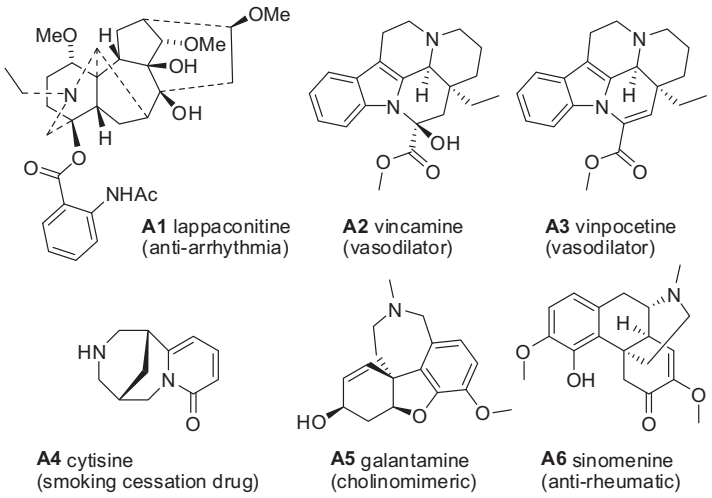
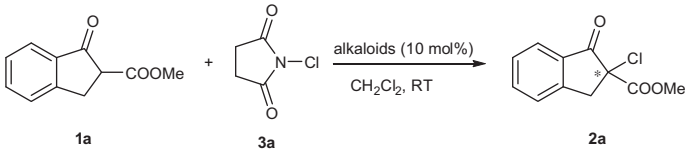


Scheme 1. Structures of chiral alkaloids **A1**–**A6**.

Table 1
Initial screening of chiral alkaloids **A1**–**A6** as organocatalysts for the asymmetric α-chlorination of β-oxo esters **1a**[a]



1a **3a** **2a**

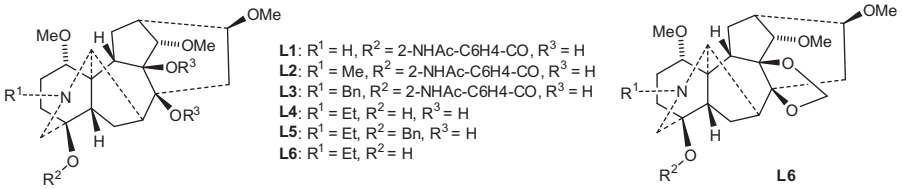
Entry	Catalyst	Conv.[b] (%)	ee[c,d] (%)
1	**A1**	>98	28 (*R*)
2	**A2**	>98	22 (*S*)
3	**A3**	>98	25 (*S*)
4	**A4**	>98	12 (*S*)
5	**A5**	>98	1 (*R*)
6	**A6**	>98	1 (*R*)

[a] Reactions were carried out with β-oxo ester **1a** (0.1 mmol), catalyst (0.01 mmol, 10 mol %), and *N*-chlorosuccinimide **3a** (0.11 mmol) in CH_2Cl_2 (2 mL) at room temperature.
[b] Determined by HPLC of the crude reaction mixture.
[c] The enantiomeric excess was determined by HPLC analysis of the product using a chiral column (DAICEL Chiralcel OD-H) with hexane/2-propanol (90:10) as the eluent.
[d] The configuration of **2a** was determined by comparison with the literature.[6e]

tertiary amine **L4**, which was obtained from the alkaline hydrolysis of lappaconitine **A1**, increased the enantiomeric excess to 33% (Table 2, entry 4). A slightly decreased enantioselectivity was observed when 4-benzyllappacinine **L5** was employed as the organocatalyst (Table 2, entry 5). 8,9-(Methylenedioxy)lappaconine **L6** afforded nearly racemic **2a** (Table 2, entry 6).

In order to establish the optimal reaction conditions for our novel organocatalyst **L1**, a solvent screen was attempted, and the results are summarized in Table 3 (entries 1–4). All of the reactions proceeded smoothly in the solvents tested, but the polar solvent THF was more successful with regard to high levels of enantiocontrol being achieved (Table 3, entry 4). The effect of commercially available electrophilic chlorinating agents was also investigated (Table 3, entries 5–9). Chlorinating agents **3a**–**3d** provided the desired product **2a** in excellent conversion (>98%), but only *N*-chlorophthalimide **3b** afforded **2a** with an increased enantiomeric excess (49% ee) (Table 3, entry 5). The use of **3e** and **3f** resulted in a significant reduction in yield and enantioselectivity, respectively (Table 3, entries 8 and 9). Catalyst loading was successfully reduced to 5 mol % in entry 10, while maintaining good conversion and enantioselectivity, but when decreased to 1 mol %, a reduction in both the yield and enantioselectivity was observed (Table 3, entry 11). Further improvements were found when using lower

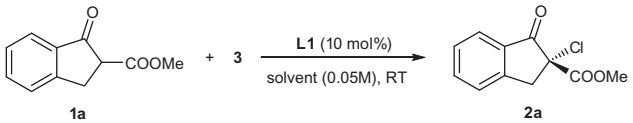
Table 2
The screening of lappaconitine derivatives **L1**–**L6** as organocatalysts for the asymmetric α-chlorination of β-oxo esters **1a**[a]



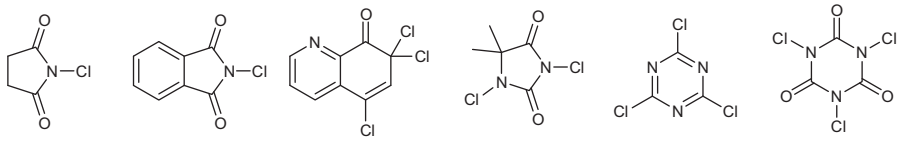
Entry	Catalyst	Conv.[b] (%)	ee[c] (%)
1	**L1**	>98	38
2	**L2**	>98	32
3	**L3**	>98	17
4	**L4**	>98	33
5	**L5**	>98	30
6	**L6**	>98	5

[a] Reactions were conducted with β-ketoester **1a** (0.1 mmol), catalyst (0.01 mmol, 10 mol %), and *N*-chlorosuccinimide **3a** (0.11 mmol) in CH_2Cl_2 (2 mL) at room temperature.
[b] Determined by HPLC of the crude reaction mixture.
[c] The enantiomeric excess was determined by HPLC analysis of the product using a chiral column (DAICEL Chiralcel OD-H) with hexane/2-propanol (90:10) as the eluent.

Table 3
Screening of the solvents, chlorinating agents, and reaction conditions for the organocatalytic α-chlorination of β-oxo esters **1a**[a]



1a **2a**



3a **3b** **3c** **3d** **3e** **3f**

Entry	3	solvent	*T* (°C)	Conv.[b] (%)	ee[c] (%)
1	**3a**	CH_2Cl_2	rt	>98	38
2	**3a**	$CHCl_3$	rt	>98	39
3	**3a**	toluene	rt	>98	37
4	**3a**	THF	rt	>98	42
5	**3b**	THF	rt	>98	49
6	**3c**	THF	rt	>98	35
7	**3d**	THF	rt	>98	26
8	**3e**	THF	rt	51	40
9	**3f**	THF	rt	92	7
10[d]	**3b**	THF	rt	>98	49
11[e]	**3b**	THF	rt	96	32
12[d]	**3b**	THF	0	>98	49
13[d]	**3b**	THF	−15	>98	57
14[d]	**3b**	THF	−30	>98	57
15[d]	**3b**	THF	−78	92	53

[a] Reactions were conducted with β-ketoester **1a** (0.1 mmol), catalyst (0.01 mmol, 10 mol %), and *N*-chlorosuccinimide **3a** (0.11 mmol) in CH_2Cl_2 (2 mL) at room temperature.
[b] Determined by HPLC of the crude reaction mixture.
[c] The enantiomeric excess was determined by HPLC analysis of the product using a chiral column (DAICEL Chiralcel OD-H) with hexane/2-propanol (90:10) as the eluent.
[d] Catalyst 5 mol %.
[e] Catalyst 1 mol %.

temperatures (Table 3, entries 12–15). Increased enantioselectivity was obtained when the reaction temperature was decreased to −15 °C (Table 3, entry 13). Lowering the reaction temperature to −78 °C led to a decrease in the ee and yield (Table 3, entry 15) which may be caused by the reduced solubility of **L1**. Finally, −15 °C was selected as the optimal reaction temperature. Therefore, the optimized reaction conditions were as follows: THF as the solvent with 5 mol % **L1** as the organocatalyst and **3b** as the electrophilic chlorinating agent at −15 °C.

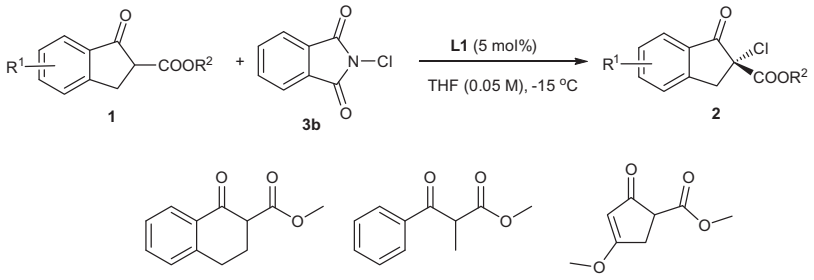
With the optimized reaction conditions established, a series of β-oxo esters **1a**–**1q** with various substituents on the ester group and aromatic scaffold were used to investigate the scope of the reaction, and the results are summarized in Table 4. Substrates bearing methyl or ethyl groups afforded products with similar enantioselectivities of 57 and 56% ee, respectively, (Table 4, entries 1 and 2). Carboxylates with more bulky ester groups, such as isopropyl **1c** or *tert*-butyl **1d** led to lower enantioselectivities (49% ee), meanwhile ^{1}Ad **1e** (1-adamantyl) provided similar selectivities to **1a** and **1b** (Table 4, entries 3–5). Even more noteworthy was that all of the β-oxo esters afforded the corresponding α-chlorination products in high yields. The same effect of ester groups was also observed in the α-chlorination of **1f**–**1i**, which bear –OMe substitution at the 4-position of the benzene ring. The –OMe substitution was found to be beneficial with regard to the enantioselectivity, especially **1i**, which increased the enantioselectivity to 68% ee (Table 4, entries 6–9). The influence of substituents on the benzene ring of the β-oxo ester was further investigated. The presence of electron-donating substituents, such as methyl or methoxyl, on the benzene ring led to a slight increase in enantioselectivity (Table 4, entries 6, 10, and 11). Halogenated substrates such as –Cl, –F, and –Br gave the desired products in high yield and with decreased enantioselectivity (Table 4, entries 12–14). These results indicate that electronegative substituents on the benzene ring of these substrates are relatively effective in the asymmetric induction. We hypothesized that the enolization process of β-oxo esters can be efficiently formed with electron-donating substituents, but impaired by electron-withdrawing substituents. Further investigation of the chlorination of six-membered ring **1o**, acyclic **1p**, and cyclopentenone ester **1q** was attempted. These substrates underwent chlorination with high yields, but unsatisfactory enantioselectivity (Table 4, entries 15–17).

The absolute configurations of **2a**–**2e** and **2l**–**2q** were tentatively determined to be (*R*) by comparison of their specific rotations with literature data,[6–10,15] and the stereochemistry of the other α-hydroxy-β-dicarbonyl compounds **2h**–**2k** was tentatively assigned by analogy.

3. Conclusion

In conclusion, proceeding from a comprehensive utilization of chiral alkaloids, twelve alkaloids and their derivatives bearing a secondary or tertiary amine moiety have been evaluated as chiral organocatalysts in the enantioselective α-chlorination of β-oxo esters. The use of *N*-deethyllappaconitine **L1** gave optically active α-chlorinated β-oxo esters in excellent yields and with moderate enantioselectivities (up to 68% ee) using commercially available *N*-chlorophthalimide as the chlorine source under mild reaction conditions. Relative to the abundant alkaloids in the natural world, the number of alkaloids that have been successfully used in organocatalysis are rare. We are currently searching for chiral alkaloids that can catalyze asymmetric reactions and make full use of the natural resource of alkaloids.

Table 4
Enantioselective α-chlorination of β-oxo esters **1a-q** using chiral alkaloid derivative **L1** as the organocatalyst[a]



Entry	2	R^1	R^2	Yield[b] (%)	ee[c] (%)
1	**2a**	H	Me	96	57
2	**2b**	H	Et	93	56
3	**2c**	H	*i*-Pr	95	49
4	**2d**	H	*t*-Bu	94	49
5	**2e**	H	^{1}Ad	98	54
6	**2f**	4-OMe	Me	96	65
7	**2g**	4-OMe	Et	94	63
8	**2h**	4-OMe	*i*-Pr	92	61
9	**2i**	4-OMe	^{1}Ad	98	68
10	**2j**	6-OMe	Me	96	60
11	**2k**	6-Me	Me	95	61
12	**2l**	5-Cl	Me	96	52
13	**2m**	6-Br	Me	94	49
14	**2n**	6-F	Me	93	47
15	**2o**	—	—	95	31
16	**2p**	—	—	96	2
17	**2q**	—	—	91	4

[a] Reactions were conducted with β-ketoester **1** (0.1 mmol), catalyst (0.005 mmol, 5 mol %), and *N*-chlorophthalimide **3b** (0.11 mmol) in THF (2 mL) at −15 °C.
[b] Isolated yield.
[c] The ee values were determined by chiral HPLC analysis.

4. Experimental

4.1. General

Unless otherwise stated, all commercial reagents and solvents were used without additional purification. Analytical TLC was visualized with UV light at 254 nm. Thin layer chromatography was carried out on TLC aluminum sheets with silica gel 60 F_{254}. Purification of the reaction products was carried out by chromatography using silica gel 60 (200–300 mesh) or flash chromatography, which was performed using Bonna-Agela Flash Column Silica-CS (12 g) with freshly distilled solvents. Columns were typically equilibrated with the appropriate solvent system prior to use. Optical rotations were measured on a digital polarimeter with a sodium lamp at 25 °C (10 cm cell, c given in g/100 mL). Optical rotations were reported as follows: $[\alpha]_D^T$ (*c* g/100 mL, solvent). All ^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) were recorded on a VARIAN INOVA-400M and AVANCE II 400 spectrometer at 25 °C. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26, for ^{1}H NMR and $CDCl_3$: δ 77.0 for ^{13}C NMR). High resolution mass spectrometry data were obtained with UPLC/Q-Tof Mass Spectrometer and determined by electrospray ionization (ESI). The enantiomeric excesses (ee) were determined by HPLC. Separation of stereoisomers was carried out with a Diacel Chiralpak AD-H, OD-H, and AS-H chiral column (0.46 cm × 25 cm). Retention times were reported at ambient temp (24 °C) with an injection volume of 20 μL at a flow rate of 1 mL/min, using mixtures of *n*-hexane/isopropyl alcohol as the mobile phase.

4.2. Preparation of chiral alkaloid derivatives

Lappaconitine **A1**, vincamine **A2**, vinpocetine **A3**, cytosine **A4**, galantamine **A5**, and sinomenine **A6** were obtained commercially and used as supplied. Compounds **L1**,[13] **L2**,[13] **L3**,[13] **L4**,[14] and **L6**[15] were prepared according to literature procedures, with data in agreement with those reported.

4.2.1. 4-Benzyloxylappaconine L5

Lappaconine **L4** (1.00 g, 2.36 mmol), benzyl bromide (0.61 g, 3.54 mmol), NaH (0.57 g, 9.44 mmol), and DMF (20 mL) were weighed into a 50 mL three-neck bottle and stirred overnight at 100 °C. The solvent was removed in vacuo and the crude mixture was redissolved in CH_2Cl_2 (100 mL). The solution was washed with water (3 × 20 mL), brine (3 × 20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc/TEA = 90:30:1) to afford **L5** (0.99 g, 82%) as white foam; $[\alpha]_D^{25}$ = +2.3 (*c* 0.49, MeOH); HRMS calcd for $[C_{30}H_{44}NO_6]^+$: 514.3169, found: 514.3158; δ_H (400 MHz, $CDCl_3$): 7.39 (2H, m), 7.33 (2H, m), 7.30–7.23 (1H, m), 4.57 (1H, d, *J* = 11 Hz), 4.46 (1H, d, *J* = 11 Hz), 3.97 (1H, s), 3.42 (3H, s), 3.41–3.33 (2H, m), 3.34 (3H, s), 3.28 (3H, s), 3.14 (1H, dd, *J* = 11, 7 Hz), 2.94 (1H, s), 2.76 (1H, d, *J* = 11 Hz), 2.65 (1H, dd, *J* = 15, 7 Hz), 2.55 (1H, m), 2.52 (1H, m), 2.48 (1H, m), 2.45 (1H, m), 2.35–2.30 (1H, m), 2.27 (1H, m), 2.24 (1H, m), 2.22–2.17 (1H, m), 2.07 (1H, m), 2.03 (1H, s), 2.02–1.94 (1H, m), 1.88 (1H, m), 1.82 (1H, d, *J* = 7 Hz), 1.52 (1H, m), 1.49 (1H, m), 1.09 (3H, t, *J* = 7 Hz); δ ^{13}C (101 MHz, $CDCl_3$): 138.95, 128.31, 128.27, 127.62, 127.34, 89.75, 85.23, 83.75, 79.37, 78.59, 71.00, 63.32, 61.21, 58.23, 57.86,

56.67, 56.32, 51.07, 50.52, 50.37, 49.00, 43.03, 38.29, 37.34, 36.76, 26.90, 23.12, 13.47.

4.3. General procedure for the catalytic enantioselective chlorination of β-oxo esters

β-Oxo ester **1** (0.1 mmol), catalyst **L1** (5 mol %), and THF (1 mL) were added to a stirring bar equipped test tube at −15 °C. After 15 min, **3b** (0.11 mmol) in THF (1 mL) was added, and the resulting mixture was stirred at −15 °C. After completion of the reaction, the reaction mixture was concentrated in vacuo. The residue was purified by flash chromatography to give pure product **2**. The ee of the product was determined by chiral HPLC. The specific rotation value corresponded to the enantioenriched mixtures of the two enantiomers of the chlorination products. Compounds **2a–2e** and **2l–2q** were known products with data in agreement with the literature.[6–10,16]

4.3.1. (*R*)-Methyl 4-methoxyl-2-chloro-1-indanone-2-carboxylate 2f

A pale yellow oil; 96% yield, 65% ee; $[\alpha]_D^{25} = -3.7$ (*c* 0.75, $CHCl_3$); HRMS calcd for $[C_{12}H_{11}O_4ClNa]^+$: 277.0244, found: 277.0246; δ_H (400 MHz, $CDCl_3$): 7.45–7.43 (2H, m), 7.17–7.10 (1H, m), 3.98 (1H, d, *J* = 18 Hz), 3.92 (3H, s), 3.81 (3H, s), 3.47 (1H, d, *J* = 18 Hz); δ ^{13}C (101 MHz, $CDCl_3$): 195.21, 167.70, 156.53, 139.47, 134.33, 130.21, 117.18, 116.54, 67.81, 55.63, 54.04, 40.47; HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane/*i*-PrOH = 90:10, 1 mL/min, 254 nm, τ_R(major) = 12.2 min, τ_R(minor) = 10.8 min.

4.3.2. (*R*)-Ethyl 4-methoxyl-2-chloro-1-indanone-2-carboxylate 2g

A yellow oil; 94% yield, 63% ee; $[\alpha]_D^{25} = -19.05$ (*c* 1.16, $CHCl_3$); HRMS calcd for $[C_{13}H_{13}O_4ClNa]^+$: 291.0400, found: 291.0403; δ_H (400 MHz, $CDCl_3$): 7.44 (2H, d, *J* = 4 Hz), 7.20–7.05 (1H, m), 4.27 (2H, q, *J* = 7 Hz), 3.96 (1H, d, *J* = 18 Hz), 3.92 (3H, s), 3.47 (1H, d, *J* = 18 Hz), 1.26 (3H, t, *J* = 7 Hz); δ ^{13}C (101 MHz, $CDCl_3$): 195.36, 167.17, 156.54, 139.50, 133.84, 130.16, 117.15, 116.47, 67.88, 63.36, 55.62, 40.47, 13.97; HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane/*i*-PrOH = 95:5, 1 mL/min, 254 nm, τ_R(major) = 12.7 min, τ_R(minor) = 10.6 min.

4.3.3. (*R*)-Isopropyl 4-methoxyl-2-chloro-1-indanone-2-carboxylate 2h

A yellow oil; 92% yield, 61% ee; $[\alpha]_D^{25} = -17.1$ (*c* 1.03, $CHCl_3$); HRMS calcd for $[C_{14}H_{15}O_4ClNa]^+$: 305.0557, found: 305.0555; δ_H (400 MHz, $CDCl_3$): 7.44 (2H, d, *J* = 4 Hz), 7.20–7.06 (1H, m), 5.13–5.07 (1H, m), 3.93 (1H, d, *J* = 18 Hz), 3.92 (3H, s), 3.46 (1H, d, *J* = 18 Hz), 1.24 (6H, dd, *J* = 6, 4 Hz); δ ^{13}C (101 MHz, $CDCl_3$): 195.43, 166.65, 156.54, 139.48, 134.32, 130.11, 117.13, 116.40, 71.40, 67.99, 55.61, 40.42, 21.48, 21.38; HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane/*i*-PrOH = 98:2, 1 mL/min, 254 nm, τ_R(major) = 7.3 min, τ_R(minor) = 6.8 min.

4.3.4. (*R*)-Adamantyl 4-methoxyl-2-chloro-1-indanone-2-carboxylate 2i

A pale yellow oil; 98% yield, 68% ee; $[\alpha]_D^{25} = -12.0$ (*c* 1.18, CH_2Cl_2); HRMS calcd for $[C_{21}H_{23}O_4ClNa]^+$: 397.1183, found: 397.1181; δ_H (400 MHz, $CDCl_3$): 7.49–7.38 (2H, m), 7.13–7.11 (1H, m), 3.97 (1H, d, *J* = 18 Hz), 3.92 (3H, s), 3.47 (1H, d, *J* = 18 Hz), 2.15 (3H, s), 2.05 (6H, d, *J* = 3 Hz), 1.62 (6H, t, *J* = 3 Hz); δ ^{13}C (101 MHz, $CDCl_3$): 195.50, 166.38, 156.50, 139.42, 134.33, 130.09, 117.03, 116.37, 80.30, 68.54, 55.64, 40.59, 37.17, 36.09, 31.58; HPLC conditions: Chiralcel AD-H column (250 × 4.6 mm), hexane/*i*-PrOH = 98:2, 1 mL/min, 254 nm, τ_R(major) = 16.9 min, τ_R(minor) = 15.0 min.

4.3.5. (*R*)-Methyl 6-methoxyl-2-chloro-1-indanone-2-carboxylate 2j

A yellow oil; 96% yield, 60% ee; $[\alpha]_D^{25} = -11.9$ (*c* 0.67, $CHCl_3$); HRMS calcd for $[C_{12}H_{11}O_4ClNa]^+$: 277.0244, found: 277.0241; δ_H (400 MHz, $CDCl_3$): 7.37 (1H, d, *J* = 8 Hz), 7.31–7.25 (2H, m), 4.03 (1H, d, *J* = 17 Hz), 3.86 (3H, s), 3.82 (3H, s), 3.49 (1H, d, *J* = 18 Hz); δ ^{13}C (101 MHz, $CDCl_3$): 194.96, 167.66, 160.20, 143.46, 134.32, 127.01, 126.09, 106.72, 68.57, 55.73, 54.08, 42.83; HPLC conditions: Chiralcel OD-H column (250 × 4.6 mm), hexane/*i*-PrOH = 90:10, 1 mL/min, 254 nm, τ_R(major) = 9.3 min, τ_R(minor) = 8.6 min.

4.3.6. (*R*)-Methyl 6-methyl-2-chloro-1-indanone-2-carboxylate 2k

A colorless oil; 95% yield, 61% ee; $[\alpha]_D^{25} = -18.0$ (*c* 0.95, $CHCl_3$); HRMS calcd for $[C_{12}H_{11}O_3ClNa]^+$: 261.0294, found: 261.0297; δ_H (400 MHz, $CDCl_3$): 7.66 (1H, s), 7.52 (1H, dd, *J* = 8, 1 Hz), 7.37 (1H, d, *J* = 8 Hz), 4.06 (1H, d, *J* = 18 Hz), 3.81 (3H, s), 3.52 (1H, d, *J* = 18 Hz), 2.55–2.34 (3H, m); δ ^{13}C (101 MHz, $CDCl_3$): 195.01, 167.73, 147.96, 138.82, 137.80, 134.33, 125.97, 125.79, 68.30, 54.07, 43.12, 21.10; HPLC conditions: Chiralcel OD-H column (250 × 4.6 mm), hexane/*i*-PrOH = 90:/10, 1 mL/min, 254 nm, τ_R(major) = 8.5 min, τ_R(minor) = 11.8 min.

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