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Synthesis of novel chiral oxazoline-Schiff base ligands for the catalytic asymmetric chlorination of β-keto esters

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ABSTRACT

A series of novel monooxazoline-Schiff base ligands **1** has been successfully synthesized. The Cu(I)–**1a** complex showed excellent catalytic activities with up to 83% ee for the asymmetric α-chlorination of β-keto esters.

1. Introduction

Chiral halogen-containing compounds have attracted much attention in various research fields such as biological and medicinal chemistry as well as materials science.[1] The effective construction of carbon–halogen stereogenicity by electrophilic halogenation of carbonyl compounds has recently become the focus of intense research efforts in synthetic organic chemistry.[2]

Since the initial reports by Togni et al.,[3] catalytic enantioselective halogenation reactions have attracted much attention.[4] With the development of Pd-catalyzed fluorination reactions of β-keto esters with high enantioselectivities on the basis of palladium enolate chemistry,[5] other late transition metal complexes including Cu(II), Ni(II), and Zn(II) were also successfully applied to catalyze asymmetric halogenation reactions.[6] Moreover, organocatalyst-catalyzed asymmetric halogenation reactions have also proven to be useful protocols for the asymmetric α-halogenation of β-keto esters.[7] However, in some cases, these methods still suffer from some drawbacks including poor substrate-generality and low enantioselectivity. Thus, the development of more general and practical methods is still highly challenging. On the basis of a literature survey, we found that oxazoline ligands have been successfully applied in the Cu-catalyzed enantioselective aldol-type addition of the enolate formed from keto esters with a variety of electrophiles including a keto ester itself,[6a,b,8] and has also recently been used in the transition metal-catalyzed asymmetric halogenation.[9] Herein, we report the synthesis of a type of novel chiral oxazoline-Schiff base ligands (Fig. 1) and their applications in the Cu-catalyzed asymmetric α-chlorination reaction of β-keto esters under mild conditions.

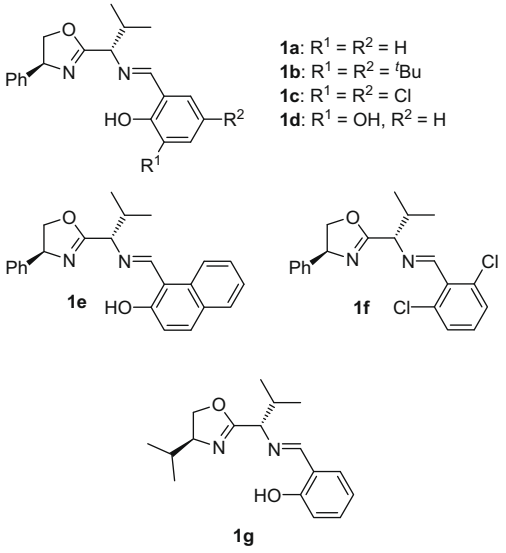

Figure 1. Novel oxazoline-Schiff base ligands.

2. Results and discussion

Chiral oxazoline-Schiff base ligand **1a** was synthesized according to the procedure shown in Scheme 1. First, Fmoc-oxazoline amine **2a** was prepared in 92% yield from commercially available *N*-Fmoc-L-valine with (*S*)-2-amino-2-phenylethanol under standard conditions. Then, removal of the Fmoc-protecting group afforded oxazoline amine **3a** in 95% yield.[10] Finally, compound **3a** was converted into the desired oxazoline-Schiff base ligand **1a** in moderate yield by reaction with salicylaldehyde under basic conditions (45% total yield for three steps).

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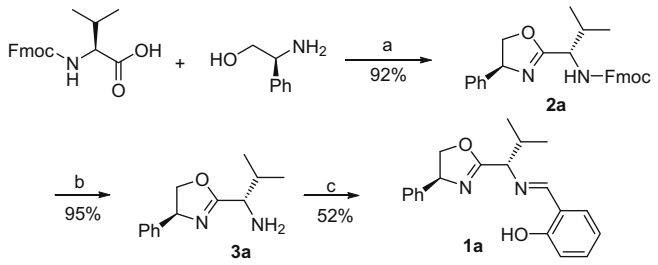
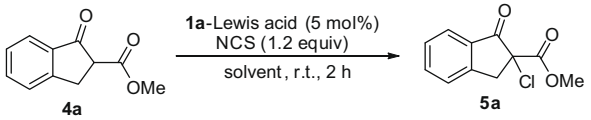


Scheme 1. Reagents and conditions: (a) PPh_3 (3.0 equiv), $^iPr_2NEt$ (3.0 equiv), CCl_4 (5.0 equiv), CH_2Cl_2, 0 °C to rt, 12 h; (b) Et_2NH/CH_3OH = 1:1 (v/v), 0 °C to rt, 12 h; (c) salicylaldehyde (1.0 equiv), anhydrous $MgSO_4$, C_2H_5OH, reflux, 12 h.

To evaluate the chiral-inducing ability of ligand **1a** in the Cu-catalyzed asymmetric α-chlorination reaction of β-keto esters, **1a** and various metal Lewis acids were initially used to catalyze the asymmetric chlorination of methyl-1-indanone-2-carboxylate **4a** with *N*-chlorosuccinimide (NCS); the results of these experiments are summarized in Table 1. As shown in Table 1, with the screening of metal Lewis acids (Table 1, entries 1–8) and solvent effect (Table 1, entries 9–13), it was found that using CuOTf·1/2C_6H_6 as a Lewis acid in dichloromethane gave the best catalytic results, affording methyl-2-chloro-1-indanone-2-carbonxylate **5a** in quantitative yield and good enantioselectivity (78% ee) (Table 1, entry 8). We also attempted the slow addition of a DCM solution of NCS within 15 min, but the addition procedure did not show any significant effect on the enantioselectivity.

Table 1
Optimization of the reaction conditions: Lewis acid and solvent[a]



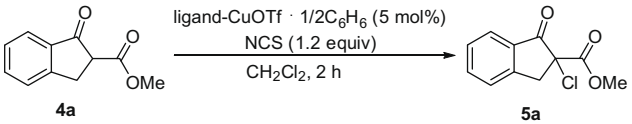
4a 5a

Entry	Solvent	Lewis acid	Yield[b] (%)	% ee[c] (config.)
1	CH_2Cl_2	$Cu(OTf)_2$	99	53 (*R*)
2	CH_2Cl_2	$Zn(OTf)_2$	99	2 (S)
3	CH_2Cl_2	$Ni(ClO_4)_2$ $6H_2O$	91	5 (S)
4	CH_2Cl_2	$Sc(OTf)_3$	99	0
5	CH_2Cl_2	$Cu(CH_3CN)_4ClO_4$	99	39 (R)
6	CH_2Cl_2	$Cu(OAc)_2·H_2O$	87	72 (R)
7	CH_2Cl_2	CuBr	99	28 (R)
8	CH_2Cl_2	CuOTf 1/2C_6H_6	99	78 (R)
9	THF	CuOTf 1/2C_6H_6	99	53 (R)
10	Et_2O	CuOTf 1/2C_6H_6	99	50 (R)
11	MeOH	CuOTf 1/2C_6H_6	99	64 (R)
12	DMF	CuOTf 1/2C_6H_6	99	16 (R)
13	Toluene	CuOTf 1/2C_6H_6	99	54 (R)

[a] All reactions were carried out at room temperature in the presence of 5 mol % of catalyst.
[b] Isolated yield.
[c] The ee values were determined by chiral HPLC analysis and the absolute configuration was determined according to the literature.[7j]

In order to further improve the enantioselectivity of this reaction, the optimization of the structure of oxazoline-Schiff base ligand **1** was carried out and a series of oxazoline-Schiff base ligands **1b–g** (Fig. 1) was synthesized according to the same procedure shown in Scheme 1 using the corresponding reagents. Next, these ligands were also applied to catalyze the asymmetric chlorination of methyl-1-indanone-2-carboxylate. The results are summarized in Table 2. Ligands **1d** and **1e** showed high catalytic activities to give **5a** in higher enantioselectivities (Table 2, entries 1, 4, and 5). However, using either ligand **1b** with sterically bulky/electron-donating groups on the benzene ring or ligand **1c** with

Table 2
Optimization of the reaction conditions: ligand and temperature[a]



4a 5a

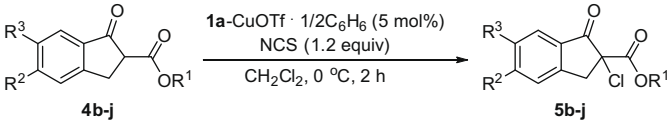
Entry	Ligand	*T* (°C)	Yield[b] (%)	% ee[c] (config.)
1	1a	rt	99	78 (*R*)
2	1b	rt	95	50 (*R*)
3	1c	rt	99	54 (*R*)
4	1d	rt	99	68 (*R*)
5	1e	rt	99	78 (*R*)
6	1f	rt	99	14 (*R*)
7	1g	rt	99	47 (*R*)
8	1a	0	99	83 (*R*)
9	1a	−20	99	72 (*R*)
10	1a	−78	99	6 (*R*)

[a] All reactions were carried out in the presence of 5 mol % of catalyst.
[b] Isolated yield.
[c] The ee values were determined by chiral HPLC analysis and the absolute configuration was determined according to the literature.[7j]

electron-withdrawing groups on the benzene ring in this reaction resulted in lower ee values (Table 2, entries 2 and 3). In addition, using ligand **1g** which has a bulky *i*-Pr substituent on the oxazoline moiety in this reaction produced **5a** in 99% yield with 47% ee (Table 2, entry 7). It should also be noted that the use of ligand **1f**, which has two chlorine atoms at the *ortho*-positions instead of hydroxyl groups gave product **5a** in poor enantioselectivity (Table 2, entry 6). These results suggest that the hydroxyl group at the *ortho*-positions of the benzene ring in ligands **1a**–**1e** and **1g** plays an important role in achieving higher enantioselectivity. The influence of the reaction temperature was also investigated using **1a** as the ligand and it was found that at 0 °C, **5a** could be obtained in 83% ee and 99% yield (Table 2, entry 8). Lowering the reaction temperatures further led to **5a** in lower enantioselectivities under otherwise identical conditions, presumably due to the inefficient coordination between the substrate and the catalytically active species at such low temperatures (Table 2, entries 9 and 10).

With the optimal reaction conditions in hand, a series of β-keto esters **4b–4j** with varying substituents in the ester group and on the aromatic scaffold was used to further explore the substrate scope (Table 3). It was found that for substrates **4b–d** with differ-

Table 3
Lewis acid catalyzed asymmetric chlorination of substituted *p*-keto esters[a]

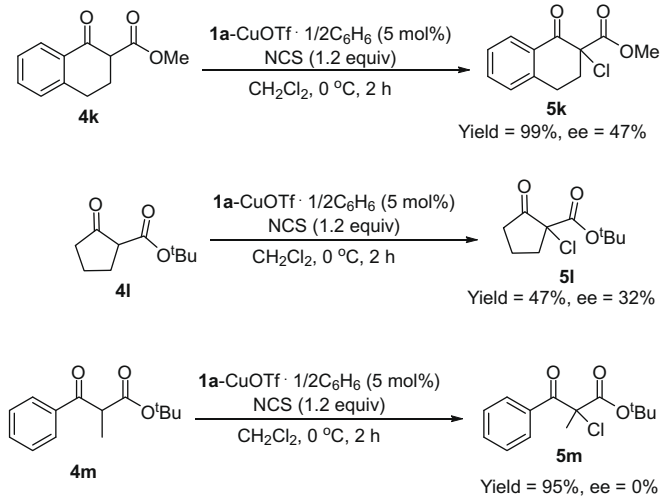


4b-j 5b-j

Entry	Substrate	Yield[b] (%)	% ee[c,d] (config.)
1	**4b**, R^1 = ^{t}Pr, R^2 = R^3 = H	95	**5b**, 83 (−)
2	**4c**, R^1 = ^{t}Bu, R^2 = R^3 = H	99	**5c**, 82 (−)
3	**4d**, R^1 = Bn, R^2 = R^3 = H	99	**5d**, 80 (−)
4	**4e**, R^1 = Me, R^2 = Cl, R^3 = H	99	**5e**, 74 (−)
5	**4f**, R^1 = ^{t}Bu, R^2 = Cl, R^3 = H	99	**5f**, 70 (−)
6	**4g**, R^1 = Me, R^2 = Br, R^3 = H	96	**5g**, 76 (−)
7	**4h**, R^1 = ^{t}Bu, R^2 = Br, R^3 = H	98	**5h**, 77 (−)
8	**4i**, R^1 = Me, R^2 = R^3 = MeO	95	**5i**, 74 (−)
9	**4j**, R^1 = ^{t}Bu, R^2 = R^3 = MeO	99	**5j**, 60 (−)

[a] All reactions were carried out at 0 °C in the presence of 5 mol % of catalyst.
[b] Isolated yield.
[c] The ee values were determined by chiral HPLC analysis.
[d] The configurations were not determined, but the sign of optical rotation was indicated in each case.

ent ester groups, the corresponding products **5b**–**5d** were obtained with similar enantioselectivities (80–83% ee) in high yields (Table 3, entries 1–3). Substrates **4e**–**4h** bearing an electron-withdrawing Cl or Br atom and substrates **4i** and **4j** with electron-donating groups such as an MeO substituent on the benzene ring also produced the products **5i** and **5j** in 95–99% yields and 60–77% ee's in this enantioselective chlorination reaction, indicating a wide substrate scope (Table 3, entries 4–9). Furthermore, tetralone β-keto ester **4k** and cyclopentanone β-keto ester **4l** were also used as substrates in this chlorination reaction under the standard conditions; however, the corresponding products **5k** and **5l** were obtained in 47% and 32% ee, respectively (Scheme 2). In the case of acyclic β-keto ester **4m**, product **5m** was formed in high yield but with no ee (Scheme 2).



Scheme 2. Lewis acid catalyzed asymmetric chlorination of substrates **4k**, **4l,** and **4m**.

3. Conclusion

In conclusion, a series of novel chiral oxazoline-Schiff base ligands **1a**–**g** was synthesized and applied to the Cu(I)-catalyzed asymmetric direct α-chlorination of β-keto esters, leading to the chlorination adducts in excellent yields with moderate to good enantioselectivities under mild conditions. Further efforts to apply the catalytic systems to other processes as well as to optimize the structure of the catalysts are currently underway.

4. Experimental

4.1. General

^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Bruker AM-300 and AM-400 spectrometer for solution in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard. Infrared spectra were measured on a PERKIN-ELMER 983 spectrometer. Mass spectra were recorded with a HP-5989 instrument. Commercially obtained reagents were used without further purification. Melting points were measured on a Yanagimoto micromelting apparatus and are uncorrected. Optical rotations were determined at 589 nm (sodium D line) using a Perkin Elmer 341 MC Polarimeter and $[\alpha]_D$ values are given with units of 10 cm^2 deg^{-1} g^{-1}. Chiral HPLC was performed by using a SHIMADZU SPD-10A *vp* series instrument with chiral columns (Chiralpak OJ-H, OD-H, and AD-H columns, φ 4.6 × 250 mm, Daicel Chemical Co. Ltd). Organic solvents used were dried by standard methods when necessary. All reactions were monitored by TLC with Huanghai GF254 silica gel-coated plates. Flash column chromatography was carried out using 300–400 mesh silica gel at increased pressure.

4.2. General procedure for the synthesis of Fmoc protecting oxazoline amine 2

At first, *N*-Fmoc-L-valine (6.79 g, 20 mmol), (*S*)-α-amino alcohol (20 mmol) and PPh_3 (15.74 g, 60 mmol) were weighed into a flame-dried 250 mL three-neck bottle equipped with a constant dropping funnel. The bottle was flushed with argon and 100 mL of CH_2Cl_2 were added followed by the addition of DIPEA (10.2 mL, 60 mmol). The bottle was cooled down to 0 °C with an ice bath. Next, CCl_4 (9.66 mL, 100 mmol) in another 50 mL of CH_2Cl_2 was added through a funnel over one hour, during this period the bottle was allowed to warm up to ambient temperature. The reaction was stirred for 12 h. The solvent was removed under reduced pressure and then about 100 mL of EtOAc was added into the residue. After 1–2 h of quiescence, colorless precipitates were generated and the suspensions were subjected to filtration. The filtrate was concentrated in vacuo. Further purification was performed by flash column chromatography on SiO_2 (PE/EtOAc = 4/1) to give product **2**.

4.2.1. [(*S*)-2-Methyl-1-((*S*)-4-phenyl-4,5-dihydro-oxazol-2-yl) propyl]carbamic acid 9*H*-fluoren-9-ylmethyl ester 2a

A white solid. Yield 92%. A known product:[10] Mp: 119.2–121.3 °C. $[\alpha]_D^{20} = -38.2$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 2.16–2.24 (m, 1H), 4.16 (t, *J* = 8.4 Hz, 1H), 4.25 (t, *J* = 6.8 Hz, 1H), 4.41 (d, *J* = 6.8 Hz, 2H), 4.50 (dd, *J* = 4.8 Hz, 8.4 Hz, 1H), 4.68 (t, *J* = 9.6 Hz, 1H), 5.22 (t, *J* = 9.6 Hz, 1H), 5.49 (d, *J* = 8.8 Hz, 1H), 7.23–7.41 (m, 9H), 7.60 (d, *J* = 6.8 Hz, 2H), 7.76 (d, *J* = 7.6 Hz, 2H).

4.2.2. [1-((*S*)-4-Isopropyl-4,5-dihydro-oxazol-2-yl)-(*S*)-2-methyl-propyl]-carbamic acid 9*H*-fluoren-9-ylmethyl ester 2b

A white solid. Yield 90%. A known product:[10] Mp: 111.5–112.5 °C. $[\alpha]_D^{20} = -47.3$ (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88–0.98 (m, 12H), 1.70–1.78 (m, 1H), 2.08–2.16 (m, 1H), 3.88–3.94 (m, 1H), 4.02 (t, *J* = 8.0 Hz, 1H), 4.23–4.30 (m, 2H), 4.34–4.40 (m, 3H), 5.44 (d, *J* = 8.4 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.58–7.61 (m, 2H), 7.76 (d, *J* = 7.6 Hz, 2H).

4.3. General procedure for the synthesis of oxazoline amine 3

Fmoc-protected oxazoline **2** (6.51 mmol) was dissolved in 15 mL of MeOH and cooled down to 0 °C with an ice bath. Then, 15 mL of Et_2NH were added over 30 min. After completion of the reaction, the solvent was removed under reduced pressure and the residue was purified by a short path silica gel column chromatography (EtOAc/EtOH = 10/1) to give product **3**

4.3.1. (*S*)-2-Methyl-1-((*S*)-4-phenyl-4,5-dihydro-oxazol-2-yl) propylamine 3a

A yellow oil. Yield 90%. $[\alpha]_D^{20} = -2.1$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, *J* = 6.8 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H), 1.76 (br, 2H), 2.01–2.09 (m, 1H), 3.47 (d, *J* = 5.6 Hz, 1H), 4.14 (t, *J* = 8.4 Hz, 1H), 4.66 (dd, *J* = 8.4 Hz, 10.0 Hz, 1H), 5.20 (t, *J* = 10.0 Hz, 1H), 7.25–7.37 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 19.2, 32.1, 55.4, 69.0, 74.7, 126.4, 127.4, 128.6, 142.0, 170.9. IR ($CHCl_3$) ν 3350, 2962, 2872, 1755, 1660, 1495, 1454, 1365, 1223, 1030, 988 cm^{-1}. MS (%) *m*/*z* 218.1 (M^+, 1), 176.1 (11), 175.1 (100), 120.1 (15), 91.1 (50). HRMS calcd for $C_{13}H_{18}N_2O$: 218.1419. Found: 218.1421.

4.3.2. 1-((*S*)-4-Isopropyl-4,5-dihydro-oxazol-2-yl)-(*S*)-2-methyl-propylamine 3b

A yellow oil. Yield 88%. $[\alpha]_D^{20} = -77.2$ (*c* 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 6H), 1.65 (br, 2H), 1.71–1.79 (m, 1H), 1.91–1.99 (m, 1H), 3.34 (d, *J* = 6.0 Hz, 1H), 3.87–3.93 (m, 1H), 3.98 (t, *J* = 8.0 Hz, 1H), 4.25 (t, *J* = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 18.2, 18.8, 19.4, 32.2, 32.6, 55.7, 70.1, 71.8, 169.4. IR ($CHCl_3$) ν 3327, 2959, 2926, 2872, 1750, 1664, 1467, 1386, 1368, 1241, 1088, 987 cm^{-1}. MS (%) *m*/*z* 184.2 (M^+, 0.4), 142.1 (7), 141.1 (100), 69.1 (12), 55.0 (8). HRMS calcd for $C_{10}H_{20}N_2O$: 184.1576. Found: 184.1572.

4.4. General procedure for the synthesis of oxazoline-Schiff base ligands 1

To a solution of the oxazoline amine **3** (436.6 mg, 2.0 mmol) in 15 mL of EtOH was added the corresponding aldehyde (2.0 mmol), then anhydrous $MgSO_4$ (400 mg) was added into the resulting solution. The reaction mixture was heated at reflux and stirred for 12 h. Next, $MgSO_4$ was removed by filtration, and the filtrate was concentrated under vacuum and the residue was purified by a short path silica gel column chromatography (PE/EtOAc = 10/1 with a few drops of Et_3N) to give the pure product **1**.

4.4.1. 2-{[(*S*)-2-Methyl-1-((*S*)-4-phenyl-4,5-dihydro-oxazol-2-yl)propylimino]methyl}phenol 1a

A yellow solid. Yield 52%. Mp: 106.2–107.3 °C. $[\alpha]_D^{20} = -34.8$ (*c* 0.90, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (d, *J* = 6.8 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 2.38–2.46 (m, 1H), 3.90 (d, *J* = 7.6 Hz, 1H), 4.16 (t, *J* = 8.4 Hz, 1H), 4.68 (t, *J* = 9.6 Hz, 1H), 5.21 (t, *J* = 9.6 Hz, 1H), 6.90 (t, *J* = 7.6 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 7.24–7.37 (m, 7H), 8.42 (s, 1H), 13.14 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 19.6, 31.6, 69.3, 73.7, 74.9, 117.1, 118.6, 118.7, 126.5, 127.6, 128.8, 131.7, 132.7, 142.0, 161.1, 166.5, 167.2. IR ($CHCl_3$) ν 2964, 1743, 1662, 1630, 1494, 1460, 1279, 1206, 1151, 978 cm^{-1}. MS (%) *m*/*z* 322.2 (M^+, 83), 307.1 (21), 203.1 (28), 188.1 (100), 175.1 (56), 132.0 (37), 120.1 (17), 69.0 (12). HRMS calcd for $C_{20}H_{22}N_2O_2$: 322.1681. Found: 322.1680.

4.4.2. 2,4-Di-*tert*-butyl-6-{[(*S*)-2-methyl-1-((*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)propylimino]methyl}phenol 1b

A yellow oil. Yield 47%. $[\alpha]_D^{20} = -11.5$ (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (d, *J* = 6.8 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.31 (s, 9H), 1.47 (s, 9H), 2.38–2.46 (m, 1H), 3.87 (d, *J* = 8.0 Hz, 1H), 4.10 (t, *J* = 8.4 Hz, 1H), 4.61 (t, *J* = 9.6 Hz, 1H), 5.17 (t, *J* = 9.6 Hz, 1H), 7.13 (s, 1H), 7.23 (d, *J* = 7.6 Hz, 3H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.43 (s, 1H), 8.44 (s, 1H), 13.5 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 19.5, 29.4, 31.4, 31.5, 34.0, 34.9, 69.1, 73.6, 74.7, 117.6, 126.2, 126.4, 127.3, 127.4, 128.6, 136.7, 140.0, 142.0, 158.1, 167.3, 167.6; IR ($CHCl_3$) ν 2961, 1743, 1659, 1629, 1467, 1362, 1273, 1250, 1173, 975 cm^{-1}; MS (%) *m*/*z* 434.3 (M^+, 100), 419.3 (48), 315.2 (78), 287.2 (63), 188.1 (96), 175.1 (42), 120.1 (24), 91.1 (32); HRMS calcd for $C_{28}H_{38}N_2O_2$: 434.2933. Found: 434.2934.

4.4.3. 2,4-Dichloro-6-{[(*S*)-2-methyl-1-((*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)propylimino]methyl}phenol 1c[12]

A yellow oil. Yield 41%. $[\alpha]_D^{20} = -39.8$ (*c* 1.05, $CHCl_3$). (*Z*- or *E*-isomer) ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (d, *J* = 6.8 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 2.37–2.46 (m, 1H), 3.98 (d, *J* = 6.8 Hz, 1H), 4.14 (t, *J* = 8.4 Hz, 1H), 4.68 (t, *J* = 9.6 Hz, 1H), 5.21 (t, *J* = 9.6 Hz, 1H), 7.19–7.37 (m, 6H), 7.42 (s, 1H), 8.35 (s, 1H), 14.19 (br, 1H). (*E*- or *Z*-isomer) ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (d, *J* = 6.8 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 2.38–2.46 (m, 1H), 3.98 (d, *J* = 6.8 Hz, 1H), 4.16 (t, *J* = 8.4 Hz, 1H), 4.68 (t, *J* = 9.6 Hz, 1H), 5.24 (t, *J* = 9.6 Hz, 1H), 7.19–7.37 (m, 6H), 7.42 (s, 1H), 8.35 (s, 1H), 14.19 (br, 1H). (*Z*- or *E*-isomer) ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5, 19.4, 31.6, 69.3, 72.4, 74.7, 119.4, 122.7, 122.8, 126.4, 127.6, 128.7, 129.3, 132.4, 141.5, 156.2, 164.8, 166.3. (*E*- or *Z*-isomer) ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 19.4, 31.7, 69.3, 72.9, 74.9, 119.4, 122.7, 122.8, 126.5, 127.6, 128.7, 129.3, 132.4, 141.7, 156.3, 164.8, 166.3. IR ($CHCl_3$) ν 2965, 1744, 1663, 1632, 1453, 1370, 1292, 1215, 1180, 976 cm^{-1}. MS (%) *m*/*z* 390.1 (M^+, 51), 375.1 (30), 271.0 (50), 243.0 (56), 200.0 (57), 188.1 (100), 126.1 (37), 104.1 (42). HRMS calcd for $C_{20}H_{20}Cl_2N_2O_2$: 390.0902. Found: 390.0904.

4.4.4. 3-{[(*S*)-2-Methyl-1-((*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)propylimino]methyl}benzene-1,2-diol 1d[12]

A yellow oil. Yield 46%. $[\alpha]_D^{20} = -37.5$ (*c* 1.05, $CHCl_3$). (*Z*- or *E*-isomer) ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (d, *J* = 6.8 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 2.37–2.45 (m, 1H), 3.97 (d, *J* = 6.8 Hz, 1H), 4.18 (t, *J* = 9.2 Hz, 1H), 4.69 (t, *J* = 9.2 Hz, 1H), 5.25 (t, *J* = 9.2 Hz, 1H), 6.73 (t, *J* = 7.6 Hz, 1H), 6.82 (t, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 7.21–7.36 (m, 5H), 8.35 (d, *J* = 7.6 Hz, 1H). (*E*- or *Z*-isomer) ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (d, *J* = 6.8 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 2.37–2.45 (m, 1H), 3.97 (d, *J* = 6.8 Hz, 1H), 4.18 (t, *J* = 9.2 Hz, 1H), 4.69 (t, *J* = 9.2 Hz, 1H), 5.25 (t, *J* = 9.2 Hz, 1H), 6.73 (t, *J* = 7.6 Hz, 1H), 6.82 (t, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 7.21–7.36 (m, 5H), 8.35 (d, *J* = 7.6 Hz, 1H). (*Z*- or *E*-isomer) ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6, 19.4, 31.7, 69.1, 72.0, 74.8, 117.2, 117.4, 118.2, 122.3, 126.5, 127.6, 128.7, 141.6, 145.4, 150.7, 166.2, 166.9. (*E*- or *Z*-isomer) ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 19.4, 31.8, 69.2, 72.5, 75.0, 117.3, 117.5, 118.2, 122.3, 126.5, 127.6, 128.7, 141.8, 145.5, 150.9, 166.3, 167.0. IR ($CHCl_3$) ν 2965, 1743, 1659, 1630, 1466, 1364, 1273, 1233, 977 cm^{-1}. MS (%) *m*/*z* 338.2 (M^+, 100), 323.1 (22), 234.1 (11), 219.1 (49), 190.1 (54), 148.0 (36). HRMS calcd for $C_{20}H_{22}N_2O_3$: 338.1630. Found: 338.1629.

4.4.5. 1-{[(*S*)-2-Methyl-1-((*S*)-4-phenyl-4,5-dihydro-oxazol-2-yl)propylimino]methyl}naphthalen-2-ol 1e[12]

A yellow oil. Yield 41%. $[\alpha]_D^{20} = -26.4$ (*c* 1.65, $CHCl_3$). (*Z*- or *E*-isomer) ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 (d, *J* = 6.8 Hz, 3H), 1.12 (d, *J* = 6.8 Hz, 3H), 2.40–2.48 (m, 1H), 4.08 (d, *J* = 7.2 Hz, 1H), 4.17 (t, *J* = 8.4 Hz, 1H), 4.70 (t, *J* = 9.6 Hz, 1H), 5.25 (t, *J* = 9.2 Hz, 1H), 7.03 (d, *J* = 9.2 Hz, 1H), 7.22–7.31 (m, 5H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 9.2 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 9.02 (d, *J* = 8.0 Hz, 1H), 14.88 (s, 1H). (*E*- or *Z*-isomer) ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 (d, *J* = 6.8 Hz, 3H), 1.12 (d, *J* = 6.8 Hz, 3H), 2.40–2.49 (m, 1H), 4.11 (d, *J* = 7.2 Hz, 1H), 4.19 (t, *J* = 8.4 Hz, 1H), 4.70 (t, *J* = 9.6 Hz, 1H), 5.26 (t, *J* = 9.2 Hz, 1H), 7.04 (d, *J* = 9.2 Hz, 1H), 7.22–7.31 (m, 5H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 9.2 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 9.02 (d, *J* = 8.0 Hz, 1H), 14.88 (s, 1H). (*Z*- or *E*-isomer) ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 19.2, 31.6, 69.2, 69.7, 74.7, 107.4, 118.3, 122.4, 122.8, 126.3, 126.6, 127.4, 128.5, 128.9, 133.0, 136.0, 141.5, 159.5, 166.2, 170.5, 170.9. (*E*- or *Z*-isomer) ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4, 19.2, 31.6, 69.3, 69.7, 74.7, 107.5, 118.3, 122.6, 122.8, 126.3, 126.6, 127.6, 128.5, 128.9, 133.0, 136.1, 141.6, 159.8, 166.2, 170.5, 171.0. IR ($CHCl_3$) ν 2964, 1743, 1662, 1627, 1354, 1186, 979 cm^{-1}. MS (%) *m*/*z* 372.2 (M^+, 60), 253.1 (21), 225.1 (19), 188.1 (100), 182.1 (43), 127.1 (10). HRMS calcd for $C_{24}H_{24}N_2O_2$: 372.1838. Found: 372.1836.

4.4.6. (2,6-Dichlorobenzylidene)-[(*S*)-2-methyl-1-((*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)propyl]amine 1f

A yellow oil. Yield 43%. $[\alpha]_D^{20} = -61.2$ (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, *J* = 6.8 Hz, 3H), 1.13 (d, *J* = 6.8 Hz, 3H), 2.45–2.54 (m, 1H), 3.98 (d, *J* = 8.0 Hz, 1H), 4.16 (t, *J* = 8.4 Hz, 1H), 4.69 (dd, *J* = 8.4 Hz, 10.4 Hz, 1H), 5.24 (dd, *J* = 8.4 Hz, 10.4 Hz, 1H),

7.19–7.36 (m, 8H), 8.52 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 19.6, 31.3, 69.2, 74.8, 76.3, 126.5, 127.4, 128.4, 128.6, 130.3, 132.9, 134.5, 142.1, 159.2, 167.3. IR ($CHCl_3$) ν 2963, 2872, 1745, 1660, 1580, 1559, 1431, 1192, 1094, 991, 957 cm^{-1}. MS (%) m/z 374.1 (M^+, 0.3), 331.0 (6), 203.1 (23), 188.1 (100), 120.1 (5), 69.0 (7). HRMS calcd for $C_{20}H_{20}Cl_2N_2O$: 374.0953. Found: 374.0934.

4.4.7. 2-(((*S*)-1-((*S*)-4-Isopropyl-4,5-dihydrooxazol-2-yl)-2-methylpropylimino)methyl)phenol 1g[12]

A yellow solid. Yield 42%. Mp: 71.5–72.2 °C. $[\alpha]_D^{20} = -54.1$ (c 1.05, $CHCl_3$). (*Z*- or *E*-isomer) ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85–1.01 (m, 12H), 1.71–1.81 (m, 1H), 2.27–2.37 (m, 1H), 3.79 (d, J = 7.6 Hz, 1H), 3.89–4.03 (m, 2H), 4.25–4.29 (m, 1H), 6.88 (t, J = 7.6 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 7.26–7.29 (m, 1H), 7.32 (t, J = 8.0 Hz, 1H), 8.37 (s, 1H), 13.18 (s, 1H). (*E*- or *Z*-isomer) ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85–1.01 (m, 12H), 1.71–1.81 (m, 1H), 2.27–2.37 (m, 1H), 3.80 (d, J = 7.6 Hz, 1H), 3.89–4.03 (m, 2H), 4.25–4.29 (m, 1H), 6.88 (t, J = 7.6 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 7.26–7.29 (m, 1H), 7.32 (t, J = 8.0 Hz, 1H), 8.37 (s, 1H), 13.20 (s, 1H). (*Z*- or *E*-isomer) ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1, 18.3, 18.7, 18.9, 19.4, 31.6, 32.5, 70.1, 71.7, 73.4, 117.1, 118.6, 131.6, 132.6, 161.1, 165.7, 166.0. (*E*- or *Z*-isomer) ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1, 18.3, 18.8, 18.9, 19.4, 31.6, 32.5, 70.2, 71.7, 73.8, 117.1, 118.6, 131.6, 132.6, 161.1, 165.8, 166.1. IR ($CHCl_3$) ν 2962, 2930, 2873, 1665, 1630, 1580, 1497, 1461, 1279, 1151, 978 cm^{-1}. MS (%) m/z 288.2 (M^+, 54), 273.2 (33), 245.1 (15), 175.1 (20), 154.1 (100), 132.0 (43). HRMS calcd for $C_{17}H_{24}N_2O_2$: 288.1838. Found: 288.1837.

4.5. General procedure for the catalytic enantioselective chlorination of β-keto esters

To a Schlenk tube with ligand **1a** (3.2 mg, 0.01 mmol) in CH_2Cl_2 (1.0 mL) was added CuOTf·1/2C_6H_6 (2.5 mg, 0.01 mmol). The resulting solution was stirred at room temperature for 15 min. Then the reaction tube was allowed to cool down to 0 °C followed by the addition of the β-keto ester **4** (0.2 mmol) and the reaction mixture was stirred for another 15 min. Finally, NCS (32 mg, 0.28 mmol) was added to the solution and the resulting mixture was stirred for 2 h. After completion of the reaction, saturated aqueous NH_4Cl solution was added to quench the reaction. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with water and brine. After drying over anhydrous Na_2SO_4, the solvent was removed under reduced pressure. Further purification of the residue was performed by flash column chromatography on SiO_2 (PE/EtOAc = 10/1) to give the pure product **5**. The ee of the product **5** was determined by chiral HPLC analysis.

4.5.1. (*R*)-2-Chloro-1-oxo-indan-2-carboxylic acid methyl ester 5a

A pale yellow oil. Yield 99%. A known product:[7j] $[\alpha]_D^{20} = -55.7$ (c 1.05, $CHCl_3$, 83% ee). HPLC (DAICEL CHIRALPAK AD-H, hexane/IPA = 95/5, 0.75 mL/min, 230 nm) t_r (minor) = 13.44 min, t_r (major) = 14.61 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.57 (d, J = 17.6 Hz, 1H), 3.82 (s, 3H), 4.11 (d, J = 17.6 Hz, 1H), 7.48 (t, J = 8.0 Hz, 2H), 7.71 (t, J = 7.2 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H).

4.5.2. 2-Chloro-1-oxo-indan-2-carboxylic acid isopropyl ester 5b

A pale yellow oil. Yield 95%. $[\alpha]_D^{20} = -41.0$ (c 0.95, $CHCl_3$, 83% ee). HPLC (DAICEL CHIRALPAK OD-H, hexane/IPA = 95/5, 0.7 mL/min, 230 nm) t_r (major) = 11.24 min, t_r (minor) = 11.86 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 3H), 1.26 (s, 3H), 3.56 (d, J = 17.7 Hz, 1H), 4.07 (d, J = 17.7 Hz, 1H), 5.04–5.16 (m, 1H), 7.48 (t, J = 7.5 Hz, 2H), 7.71 (t, J = 7.5 Hz, 1H), 7.86 (d, J = 7.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 21.4, 43.3, 68.1, 71.5, 125.9, 126.3, 128.5, 132.5, 136.3, 150.6. IR ($CHCl_3$) ν 2925, 2856, 1758, 1737, 1606, 1465, 1376, 1275, 1180, 1104, 1006, 922 cm^{-1}. MS (%) m/z 217.1 (M^+−Cl, 68), 175.0 (74), 165.0 (47), 157.0 (100), 147.0 (66), 131.0 (43), 102.0 (21), 101.0 (21). HRMS calcd for $C_{13}H_{13}O_3$ (M^+−Cl): 217.0865. Found: 217.0865.

4.5.3. 2-Chloro-1-oxo-indan-2-carboxylic acid *tert*-butyl ester 5c

A white solid. Yield 99%. A known product:[9b] Mp: 62.9–64.5 °C. $[\alpha]_D^{20} = -38.4$ (c 0.70, $CHCl_3$, 82% ee). HPLC (DAICEL CHIRALPAK OJ-H, hexane/IPA = 70/30, 0.7 mL/min, 230 nm) t_r (minor) = 7.76 min, t_r (major) = 9.38 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H), 3.54 (d, J = 18.0 Hz, 1H), 4.02 (d, J = 18.0 Hz, 1H), 7.47 (t, J = 7.8 Hz, 2H), 7.70 (t, J = 7.8 Hz, 1H), 7.86 (d, J = 7.8 Hz, 1H).

4.5.4. 2-Chloro-1-oxo-indan-2-carboxylic acid benzyl ester 5d

A pale yellow oil. Yield 99%. $[\alpha]_D^{20} = -32.8$ (c 1.60, $CHCl_3$, 80% ee). HPLC (DAICEL CHIRALPAK OD-H, hexane/IPA = 70/30, 0.7 mL/min, 230 nm) t_r (major) = 9.88 min, t_r (minor) = 10.55 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.56 (d, J = 18.0 Hz, 1H), 4.07 (d, J = 18.0 Hz, 1H), 5.21 (d, J = 12.6 Hz, 1H), 5.27 (d, J = 12.6 Hz, 1H), 7.26–7.34 (m, 5H), 7.45–7.49 (m, 2H), 7.69 (t, J = 7.5 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.3, 68.0, 68.6, 125.9, 126.3, 127.9, 128.5, 128.6, 132.4, 134.6, 136.4, 150.4. IR ($CHCl_3$) ν 2984, 2663, 1752, 1731, 1605, 1465, 1379, 1275, 1214, 1176, 1078, 1009, 940 cm^{-1}. MS (%) m/z 265.1 (M^+−Cl, 4), 194.0 (13), 159.0 (24), 91.1 (100), 65.0 (6). HRMS calcd for $C_{17}H_{13}O_3$ (M^+−Cl): 265.0865. Found: 265.0860.

4.5.5. 2,5-Dichloro-1-oxo-indan-2-carboxylic acid methyl ester 5e

A white solid. Yield 99%. A known product:[11] Mp: 119.1–120.0 °C. $[\alpha]_D^{20} = -43.9$ (c 1.35, $CHCl_3$, 74% ee). HPLC (DAICEL CHIRALPAK OD-H, hexane/IPA = 90/10, 0.65 mL/min, 230 nm) t_r (major) = 14.05 min, t_r (minor) = 16.05 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.54 (d, J = 18.0 Hz, 1H), 3.83 (s, 3H), 4.09 (d, J = 18.0 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.49 (s, 1H), 7.80 (d, J = 8.0 Hz, 1H).

4.5.6. 2,5-Dichloro-1-oxo-indan-2-carboxylic acid *tert*-butyl ester 5f

A pale yellow solid. Yield 99%. Mp: 101.6–103.1 °C. $[\alpha]_D^{20} = -24.4$ (c 1.70, $CHCl_3$, 70% ee). HPLC (DAICEL CHIRALPAK OJ-H, hexane/IPA = 90/10, 0.7 mL/min, 254 nm) t_r (minor) = 10.16 - min, t_r (major) = 11.21 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 9H), 3.51 (d, J = 18.0 Hz, 1H), 4.00 (d, J = 18.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.48 (s, 1H), 7.79 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 43.1, 68.6, 84.7, 126.5, 126.8, 129.3, 131.2, 142.9, 152.0, 165.4, 194.1. IR ($CHCl_3$) ν 2978, 2933, 1756, 1732, 1599, 1416, 1370, 1261, 1151, 1070, 1005 cm^{-1}. MS (%) m/z 300.0 (M^+, 0.2), 244.0 (87), 227.0 (38), 216.0 (55), 209.0 (61), 199.0 (100), 181.0 (89), 165.0 (34), 136.0 (29), 57.1 (90), 41.0 (16). HRMS calcd for $C_{14}H_{14}Cl_2O_3$: 300.0320. Found: 300.0330.

4.5.7. 5-Bromo-2-chloro-1-oxo-indan-2-carboxylic acid methyl ester 5g

A white solid. Yield 96%. Mp: 121.6–122.5 °C. $[\alpha]_D^{20} = -36.3$ (c 1.35, $CHCl_3$, 76% ee). HPLC (DAICEL CHIRALPAK OD-H, hexane/IPA = 90/10, 0.7 mL/min, 254 nm) t_r (major) = 16.92 min, t_r (minor) = 20.68 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.54 (d, J = 18.0 Hz, 1H), 3.82 (s, 3H), 4.10 (d, J = 18.0 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.68 (s, 1H), 7.72 (d, J = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.9, 54.2, 67.6, 127.0, 129.6, 131.2, 132.1, 132.3, 151.9, 167.2, 193.7. IR ($CHCl_3$) ν 2955, 2844, 1765, 1741, 1593, 1435, 1317, 1263, 1210, 1178, 1058, 1030, 958 cm^{-1}. MS (%) m/z 301.9 (M^+, 2), 269.0 (76), 267.0 (81), 236.9 (90), 234.9 (100), 208.9 (18),

206.9 (16), 136.0 (21). HRMS calcd for $C_{11}H_8BrClO_3$: 301.9345. Found: 301.9352.

4.5.8. 5-Bromo-2-chloro-1-oxo-indan-2-carboxylic acid *tert*-butyl ester 5h

A pale yellow solid. Yield 98%. Mp: 99.9–100.4 °C. $[\alpha]_D^{20} = -26.5$ (*c* 1.75, $CHCl_3$, 77% ee). HPLC (DAICEL CHIRALPAK OJ-H, hexane/IPA = 90/10, 0.7 mL/min, 254 nm) t_r (minor) = 11.35 min, t_r (major) = 12.18 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 9H), 3.51 (d, J = 18.0 Hz, 1H), 4.00 (d, J = 18.0 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.66 (s, 1H), 7.71 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 43.0, 68.5, 84.7, 126.8, 129.5, 131.6, 131.8, 132.2, 152.1, 165.4, 194.3. IR ($CHCl_3$) ν 2980, 2932, 1757, 1737, 1593, 1458, 1415, 1370, 1317, 1261, 1151, 1059, 1005 cm^{-1}. MS (%) m/z 344.0 (M^+, 3), 289.9 (99), 287.9 (77), 261.9 (66), 259.9 (49), 244.9 (100), 242.9 (75), 227.0 (64), 225.0 (69), 211.0 (26), 209.0 (34), 136.0 (26), 57.1 (63). HRMS calcd for $C_{14}H_{14}BrClO_3$: 343.9815. Found: 343.9823.

4.5.9. 2-Chloro-5,6-dimethoxy-1-oxo-indan-2-carboxylic acid methyl ester 5i

A pale yellow solid. Yield 95%. Mp: 136.9–138.2 °C. $[\alpha]_D^{20} = -32.5$ (*c* 1.15, $CHCl_3$, 74% ee). HPLC (DAICEL CHIRALPAK OD-H, hexane/IPA = 80/20, 0.7 mL/min, 254 nm) t_r (major) = 18.32 min, t_r (minor) = 20.73 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48 (d, J = 17.2 Hz, 1H), 3.82 (s, 3H), 3.93 (s, 3H), 4.00 (s, 3H), 4.03 (d, J = 17.2 Hz, 1H), 6.88 (s, 1H), 7.24 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.1, 54.0, 56.2, 56.4, 68.4, 105.7, 107.0, 125.0, 146.4, 150.3, 157.0, 167.8, 193.4. IR ($CHCl_3$) ν 2956, 2838, 1762, 1712, 1591, 1504, 1464, 1438, 1316, 1271, 1175, 1124, 1026 cm^{-1}. MS (%) m/z 284.0 (M^+, 9), 248.1 (24), 225.0 (7), 217.0 (100), 190.1 (6), 175.0 (4), 147.0 (3), 119.1 (2). HRMS calcd for $C_{13}H_{13}ClO_5$: 284.0452. Found: 284.0454.

4.5.10. 2-Chloro-5,6-dimethoxy-1-oxo-indan-2-carboxylic acid *tert*-butyl ester 5j

A white solid. Yield 99%. Mp: 73.1–74.8 °C. $[\alpha]_D^{20} = -15.0$ (*c* 1.65, $CHCl_3$, 60% ee). HPLC (DAICEL CHIRALPAK OJ-H, hexane/IPA = 80/20, 0.7 mL/min, 254 nm) t_r (major) = 24.20 min, t_r (minor) = 29.33 - min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 9H), 3.45 (d, J = 17.6 Hz, 1H), 3.931 (s, 3H), 3.934 (d, J = 17.6 Hz, 1H), 4.00 (s, 3H), 6.88 (s, 1H), 7.24 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 43.2, 56.1, 56.4, 69.2, 84.2, 105.6, 106.9, 125.4, 146.5, 150.1, 156.7, 166.1, 194.1. IR ($CHCl_3$) ν 2978, 2931, 2874, 1754, 1713, 1591, 1504, 1463, 1370, 1315, 1271, 1153, 1123, 1009, 984 cm^{-1}. MS (%) m/z 326.1 (M^+, 2), 270.0 (25), 252.0 (13), 234.1 (31), 217.0 (100), 191.1 (22), 175.0 (4), 147.0 (5), 119.1 (3). HRMS calcd for $C_{16}H_{19}ClO_5$: 326.0921. Found: 326.0923.

4.5.11. 2-Chloro-1-oxo-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid methyl ester 5k

A pale yellow oil. Yield 99%. A known product:[11] $[\alpha]_D^{20} = -13.9$ (*c* 1.35, $CHCl_3$, 47% ee). HPLC (DAICEL CHIRALPAK IC-H, hexane/IPA = 90/10, 0.8 mL/min, 230 nm) t_r (minor) = 20.46 min, t_r (major) = 24.69 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.51–2.57 (m, 1H), 2.97–3.05 (m, 2H), 3.25–3.32 (m, 1H), 3.86 (s, 3H), 7.28 (d, J = 7.2 Hz, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H).

4.5.12. 1-Chloro-2-oxo-cyclopentanecarboxylic acid *tert*-butyl ester 5l

A pale yellow oil. Yield 47%. $[\alpha]_D^{20} = -2.2$ (*c* 0.55, $CHCl_3$, 32% ee). HPLC (DAICEL CHIRALPAK OJ-H, hexane/IPA = 90/10, 0.6 mL/min, 230 nm) t_r (major) = 8.42 min, t_r (minor) = 8.78 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 9H), 2.06–2.17 (m, 2H), 2.33–2.45 (m, 2H), 2.48–2.59 (m, 1H), 2.66–2.76 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 27.7, 35.4, 38.4, 70.3, 84.1, 166.0, 206.6. IR ($CHCl_3$) ν 2981, 2936, 1748, 1719, 1591, 1459, 1396, 1371, 1256, 1143, 1003, 970 cm^{-1}. MS (%) m/z 218.1 (M^+, 4), 162.0 (67), 145.0 (45), 134.0 (60), 117.0 (39), 89.0 (27), 57.1 (100), 41.0 (18). HRMS calcd for $C_{10}H_{15}ClO_3$: 218.0710. Found: 218.0715.

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12. Compounds **1c**–**1e** and **1g** were isolated as two isomeric mixtures (*E*- and *Z*-isomer), which can be identified by NMR spectra, but we cannot separate them from each other by column chromatography on SiO_2.