Cu(I)-Catalyzed Asymmetric Chlorination of β-Keto Esters in the Presence of Chiral Phosphine-Schiff Base Type Ligands

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ABSTRACT Chiral phosphine-Schiff base type ligand **L8** prepared from (*R*)-(−)-2-(diphenylphosphino)-1,1'-binaphthyl-2'-amine was found to be a fairly effective ligand for Cu(I)-promoted enantioselective chlorination of β-keto esters to give the corresponding products in high yields and with moderate enantioselectivities. *Chirality 23:272–276, 2011.*

KEY WORDS: enantioselective chlorination; β-keto esters; Cu(I)-catalyzed; phosphine-Schiff base type ligands

INTRODUCTION

The direct catalytic enantioselective functionalization of carbon–hydrogen bonds to carbon-heteroatom bonds is an important synthetic transformation.[1] In particular, the enantioselective electrophilic halogenation of dicarbonyl compounds represents one of the best established strategies for the construction of the chiral C—X bonds in organic chemistry.[2–5] The resulting chiral halogen-containing compounds have attracted much attention in various research fields such as biological and medicinal chemistry as well as material science.[6] The first enantioselective fluorination of β-keto esters was reported by Togni and coworkers[7–9] Following this pioneering work, Sodeoka and coworkers reported an efficient enantioselective fluorination of various acyclic and cyclic β-keto esters catalyzed by chiral BINAP-palladium complexes.[10–14] Other late transition metal complexes including Cu(II), Ni(II), and Zn(II), which are complementary to the palladium complexes, were also successfully applied to catalyze asymmetric halogenation reactions.[15–23] Moreover, organocatalytic asymmetric halogenation reactions have also proven to be useful protocols for the asymmetric halogenation of β-keto esters.[24–31] 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.

Previously, we reported the phosphine-Schiff base-Cu(I)-catalyzed enantioselective Henry reaction.[32] Herein, we will demonstrate that these catalysts can also be used to effect enantioselective chlorination of β-keto esters.

EXPERIMENTAL

General Methods

MP was obtained with a Yanagimoto micro melting point apparatus and is uncorrected. Optical rotations were determined in a solution of $CHCl_3$ at 20°C by using a Perkin–Elmer-241 MC polarimeter; $[\alpha]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1}. Infra-red spectra were measured on a spectrometer. ^1H NMR spectra and ^{31}P NMR spectra were recorded on a Bruker AM-400 spectrometer for solution in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded with a HP-5989 instrument and HRMS was measured by a Finnigan MA+ mass spectrometer. Organic solvents used were dried by standard methods when necessary. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with Huanghai GF_{254} silica gel coated plates. Flash column chromatography was carried out using 300–400 mesh silica gel at increased pressure. All reactions were performed under argon using standard Schlenk techniques. 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) and the absolute configuration of the major enantiomer was assigned according to the sign of the specific rotation.[33]

Chiral phosphine-Schiff base type ligands **L1-L6** were prepared according to our previously reported procedure.[32] Substrates **1a-1i** were prepared according to the literature.[34] SI is available from the website or from the authors.

Typical Procedure of the Preparation of Chiral Phosphine-Schiff Base Type Ligands L7 and L8

To a solution of (*R*)-(−)-2-(diphenylphosphino)-1,1'-binaphthyl-2'-amine (227 mg, 0.5 mmol) in absolute ethanol (4.0 mL) was added salicylaldehydes (0.5 mmol) at room temperature and the reaction mixture was stirred under reflux for 12 h. After cooling to room temperature, red precipitates settled out, which were filtered to give the corresponding phosphine-Schiff base type ligands **L7** and **L8** as red solids.

(R,E)-3-((2'-(Diphenylphosphino)-1,1'-Binaphthyl-2-ylimino)Methyl)Benzene-1,2-Diol L7

A red solid. Yield: 75%. Mp: 156–158°C; IR (CH_2Cl_2) ν 3533, 3044, 2911, 1611, 1582, 1462, 1218, 745 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 5.53 (s, 1H), 6.61-6.70 (m, 2H), 6.87-7.28 (m, 15H), 7.38-7.55 (m, 4H), 7.93-7.95 (m, 3H), 8.07 (d, J = 9.0 Hz, 1H), 8.29 (s, 1H), 12.39 (s, 1H); ^{31}P NMR ($CDCl_3$, 121 MHz, 85% H_3PO_4) δ -12.66; MS (ESI) *m/z* 574 (M^++1, 100); HRMS (ESI) Calcd. For $C_{39}H_{28}NO_2P$ ($M+H^+$): 574.1936, found: 574.1920; $[\alpha]_D^{20}$ = +108 (*c* 0.4, $CHCl_3$).

(R,E)-3-((2'-(Diphenylphosphino)-1,1'-Binaphthyl-2-ylimino)Methyl)-6-Nitrobenzene-1,2-Diol L8

A red solid. Yield: 55%. Mp: 165-167 °C; IR (CH_2Cl_2) ν 3054, 2333, 1741, 1601, 1509, 1280, 1217, 1089, 818, 745, 694 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 6.72 (d, J = 8.7 Hz, 1H), 6.89-6.99 (m, 5H), 7.04-7.33

Additional Supporting Information may be found in the online version of this article.

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(m, 9H), 7.44-7.54 (m, 4H), 7.67 (d, J = 9.0 Hz, 1H), 7.97-8.03 (m, 3H), 8.15 (d, J = 8.4 Hz, 1H), 9.17 (s, 1H), 15.22 (s, 1H); ^{31}P NMR ($CDCl_3$, 121 MHz, 85% H_3PO_4) δ -13.11; MS (ESI) *m/z* 619 (M^++1, 100); HRMS (ESI) Calcd. For $C_{39}H_{27}N_2O_4P$ ($M+H^+$): 619.1787, found: 619.1792; $[\alpha]_D^{20}$ = -221 (*c* 0.4, $CHCl_3$).

General Procedure for the Catalytic Enantioselective Chlorination of β-Keto Esters

To a Schlenk tube of ligand **L8** (12.4 mg, 0.02 mmol) and 4 Å molecular sieves (10 mg) in DCE (1.0 mL) was added $CuOTf{\cdot}1/2C_6H_6$ (5.0 mg, 0.02 mmol), the resulting solution was stirred at room temperature for 30 minutes. Then the reaction tube was allowed to cool down to 0°C followed by the addition of the β-keto esters **1** (0.2 mmol) and the reaction mixture was stirred for another 15 minutes. Finally, NCS (32 mg, 0.24 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 for quenching the reaction. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with 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 **2**. The ee of the product **2** was determined by chiral HPLC analysis.

(+)-2-Chloro-1-Oxo-Indan-2-Carboxylic Acid Methyl Ester (2a)

A pale yellow oil. Yield 99%. A known product.[33] $[\alpha]_D^{20}$ = +51 (*c* 1.05, $CHCl_3$, 75% ee). HPLC (DAICEL CHIRALPAK AD-H, hexane/iPrOH = 95/5, 0.75 ml/min, 230 nm) t_r (major) = 13.53 min, t_r (minor) = 14.57 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).

(+)-2-Chloro-1-Oxo-Indan-2-Carboxylic Acid Isopropyl Ester (2b)

A pale yellow oil. Yield 99%. A known product.[33] $[\alpha]_D^{20}$ = +36 (*c* 0.95, $CHCl_3$, 77% ee). HPLC (DAICEL CHIRALPAK OD-H, hexane/iPrOH = 95/5, 0.7 ml/min, 230 nm) t_r (minor) = 9.62 min, t_r (major) = 10.10 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).

(+)-2-Chloro-1-Oxo-Indan-2-Carboxylic Acid Benzyl Ester (2c)

A pale yellow oil. Yield 87%. A known product.[33] $[\alpha]_D^{20}$ = +33 (*c* 1.60, $CHCl_3$, 81% ee). HPLC (DAICEL CHIRALPAK AD-H, hexane/iPrOH = 70/30, 0.6 ml/min, 230 nm) t_r (minor) = 11.88 min, t_r (major) = 12.67 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).

(+)-2-Chloro-1-Oxo-Indan-2-Carboxylic Acid Tert*-Butyl Ester (2d)*

A white solid. Yield 92%. A known product.[33] $[\alpha]_D^{20}$ = +25 (*c* 0.70, $CHCl_3$, 67% ee). HPLC (DAICEL CHIRALPAK OJ-H, hexane/iPrOH = 70/30, 0.7 ml/min, 230 nm) t_r (major) = 8.90 min, t_r (minor) = 10.70 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).

(+)-5-Bromo-2-Chloro-1-Oxo-Indan-2-Carboxylic Acid Methyl Ester (2e)

A white solid. Yield 99%. A known product.[33] $[\alpha]_D^{20}$ = +32 (*c* 1.35, $CHCl_3$, 71% ee). HPLC (DAICEL CHIRALPAK OD-H, hexane/iPrOH = 90/10, 0.7 ml/min, 254 nm) t_r (minor) = 17.34 min, t_r (major) = 20.54 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).

(+)-5-Bromo-2-Chloro-1-Oxo-Indan-2-Carboxylic Acid Tert*-Butyl Ester (2f)*

A pale yellow solid. Yield 90%. A known product.[33] $[\alpha]_D^{20}$ = +16 (*c* 1.75, $CHCl_3$, 52% ee). HPLC (DAICEL CHIRALPAK OJ-H, hexane/iPrOH = 90/10, 0.7 ml/min, 254 nm) t_r (major) = 11.21 min, t_r (minor) = 12.12 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).

(+)-2,5-Dichloro-1-Oxo-Indan-2-Carboxylic Acid Methyl Ester (2g)

A white solid. Yield 99%. A known product.[33] $[\alpha]_D^{20}$ = +46 (*c* 1.35, $CHCl_3$, 82% ee). HPLC (DAICEL CHIRALPAK OD-H, hexane/iPrOH = 90/10, 0.65 ml/min, 254 nm) t_r (minor) = 14.44 min, t_r (major) = 16.25 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).

(+)-2,5-Dichloro-1-Oxo-Indan-2-Carboxylic Acid Tert*-Butyl Ester (2h)*

A pale yellow solid. Yield 99%. A known product.[33] $[\alpha]_D^{20}$ = +20 (*c* 1.70, $CHCl_3$, 58% ee). HPLC (DAICEL CHIRALPAK OJ-H, hexane/iPrOH = 90/10, 0.7 ml/min, 254 nm) t_r (major) = 10.15 min, t_r (minor) = 11.54 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).

(+)-2-Chloro-5,6-Dimethoxy-1-Oxo-Indan-2-Carboxylic Acid Methyl Ester (2i)

A pale yellow solid. Yield 78%. A known product.[33] $[\alpha]_D^{20}$ = +30 (*c* 1.15, $CHCl_3$, 67% ee). HPLC (DAICEL CHIRALPAK OD-H, hexane/iPrOH = 80/20, 0.7 ml/min, 254 nm) t_r (minor) = 20.00 min, t_r (major) = 22.32 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).

(+)-2-Chloro-5,6-Dimethoxy-1-Oxo-Indan-2-Carboxylic Acid Tert*-Butyl Ester (2j)*

A white solid. Yield 79%. A known product.[33] $[\alpha]_D^{20}$ = +11 (*c* 1.65, $CHCl_3$, 50% ee). HPLC (DAICEL CHIRALPAK OJ-H, hexane/iPrOH = 80/20, 0.7 ml/min, 254 nm) t_r (minor) = 29.34 min, t_r (major) = 34.97 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).

(+)-2-Chloro-1-Oxo-1,2,3,4-Tetrahydro-Naphthalene-2-Carboxylic Acid Methyl Ester (2k)

A pale yellow oil. Yield 99%. A known product.[33] $[\alpha]_D^{20}$ = +12 (*c* 1.35, $CHCl_3$, 34% ee). HPLC (DAICEL CHIRALPAK IC-H, hexane/iPrOH = 90/10, 0.8 ml/min, 230 nm) t_r (major) = 21.75 min, t_r (minor) = 26.85 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).

(+)-1-Chloro-2-Oxo-Cyclopentanecarboxylic Acid Tert*-Butyl Ester (2l)*

A pale yellow oil. Yield 63%. $[\alpha]_D^{20}$ = +0.6 (*c* 0.75, $CHCl_3$, 12% ee). HPLC (DAICEL CHIRALPAK OJ-H, hexane/iPrOH = 90/10, 0.6 ml/min, 230 nm) t_r (minor) = 8.36 min, t_r (major) = 8.69 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 (EI) 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 (EI) Calcd. for $C_{10}H_{15}ClO_3$: 218.0710, Found: 218.0715.

(+)-Methyl 5-Chloro-2-Fluoro-1-Oxo-2,3-Dihydro-1H-Indene-2-Carboxylate (2n)

A white solid. Yield 75%. $[\alpha]_D^{20}$ = +13 (*c* 0.25, $CHCl_3$, 17% ee). HPLC (DAICEL CHIRALPAK OD-H, hexane/iPrOH = 95/5, 0.9 ml/min, 254 nm) t_r (minor) = 15.38 min, t_r (major) = 18.09 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.42 (dd, *J* = 22.8, 17.6 Hz, 1H), 3.78 (dd, *J* = 17.6, 10.8 Hz, 1H), 3.82 (s, 3H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.51 (s, 1H), 7.78 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.9 (d, *J* = 24.1 Hz), 53.4, 94.5 (d, *J* = 200.7 Hz), 126.7, 126.9 (d, *J* = 1.6 Hz), 129.6, 131.6, 143.5, 152.1 (d, *J* = 3.4 Hz), 167.3 (d, *J* = 27.6 Hz), 193.6 (d, *J* = 18.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$, CF_3COOH) δ -164.0. IR ($CHCl_3$) ν 2954, 2924, 2855, 1776, 1732, 1600, 1456, 1377, 1209 cm^{-1}. MS (ESI) m/z 265 (M^++Na). HRMS (ESI) Calcd. for $C_{11}H_8O_3FClNa$: 265.0044, Found: 265.0044.

RESULTS AND DISCUSSION

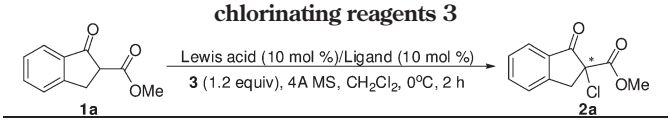
Synthesis of Chiral Phosphine-Schiff Base Type Ligands

Chiral phosphine-Schiff base type ligands **L1**-**L8** were synthesized from the reaction of salicylaldehydes as well as its analogues with (*R*)-(−)-2-(diphenylphosphino)-1,1'-binaphthyl-2'-amine[35,36] in absolute ethanol under reflux for 12 h, respectively. After usual workup, these ligands can be obtained in good yields (Scheme 1).

Cu(I)-catalyzed Asymmetric Chlorination of β-Keto Esters in the Presence of Chiral Phosphine-Schiff Base Type Ligands

Initial examinations using β-keto ester **1a** and *N*-chlorosuccinimide (NCS) as the substrates in the presence of a Lewis acid CuOTf·1/2C_6H_6 (10 mol %) combined with various chiral phosphine-Schiff base type ligands **L1**-**L8** (10 mol %) were aimed at determining the optimal conditions; the results of these experiments are summarized in Table 1. We found that using CH_2Cl_2 as a solvent and 4 Å MS (10 mg) as an additive, the corresponding product **2a** was obtained in high yields at 0°C and up to 68% ee was achieved using **L8** as the ligand (Table 1, entries 1-8). Another electrophilic chlorinating reagent **3b**[31] was also examined in this reaction, giving the corresponding product **2a** in very low ee (Table 1, entry 9). By screening various Lewis acids such as AgOAc, $Cu(OTf)_2$, and $Pd(OAc)_2$ in this asymmetric reaction, we found that using CuOTf.1/2C_6H_6 as a Lewis acid gave the best result, affording the product **2a** in 68% ee and 99% yield (Table 1, entries 9-12). It should be noted that chiral phosphine-salen type ligand **L8**, bearing a strong electron-withdrawing such as NO_2 substituent on the benzene ring, gave the best result under identical conditions (Table 1, entry 8). In addition, an electron-donating group or a weak electron-withdrawing group on the benzene ring such as chiral phosphine-Schiff base type ligands **L1**-**L7** gave the corresponding product **2a** in lower ees (5–35%) and good yields (Table 1, entries 1-7). These results suggested that the substituent on the benzene ring in the chiral phosphine-Schiff base type ligands played a very important role in chiral induction in this enantioselective chlorination of β-keto esters.

TABLE 1. Optimization of the reaction conditions in the asymmetric chlorination of β-keto ester 1a and electropjilic chlorinating reagents 3

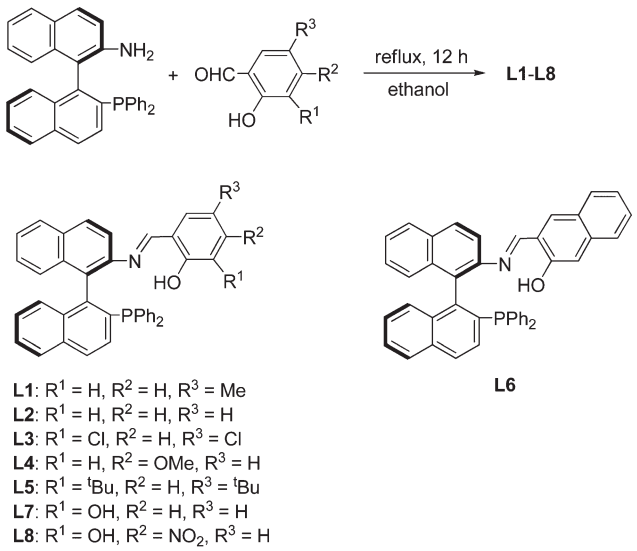


1a 2a

Entry[a]	Lewis acid	3	Ligand	Yield (%)[b]	ee (%)[c]
1	CuOTf·1/2C_6H_6	**NCS (3a)**	**L1**	99	10 (−)
2	CuOTf·1/2C_6H_6	**3a**	**L2**	99	5 (−)
3	CuOTf·1/2C_6H_6	**3a**	**L3**	99	18 (−)
4	CuOTf·1/2C_6H_6	**3a**	**L4**	99	33 (+)
5	CuOTf·1/2C_6H_6	**3a**	**L5**	99	16 (−)
6	CuOTf·1/2C_6H_6	**3a**	**L6**	99	30 (+)
7	CuOTf·1/2C_6H_6	**3a**	**L7**	99	35 (+)
8	CuOTf·1/2C_6H_6	**3a**	**L8**	99	68 (+)
9	CuOTf·1/2C_6H_6		**L8**	99	3 (+)
10	$Cu(OTf)_2$	**3a**	**L8**	99	30 (+)
11	AgOAc	**3a**	**L8**	99	0
12	$Pd(OAc)_2$	**3a**	**L8**	99	0

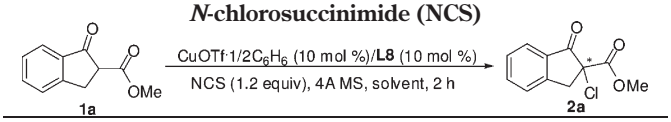
[a]Reaction conditions: **1a** (0.2 mmol), **3** (0.24 mmol), Lewis acid (10 mol %), Ligand (10 mol %), 4A MS (10 mg), CH_2Cl_2 (1.0 ml) and the reaction was carried out 0°C for 2 h.
[b]Isolated yield.
[c]Determined by chiral HPLC analysis. The absolute configuration of the products was assigned by comparison with literature compounds.

Using chiral phosphine-Schiff base type ligand **L8** under the standard conditions, we next examined the solvent and temperature effects in this asymmetric reaction. The results are summarized in Table 2. We found that DCE is the best solvent, affording product **2a** in 75% ee and 99% yield at 0°C (Table 2, entries 3 and 6-9). Lowering or elevating the reaction temperature resulted in a decrease of the ee of the product **2a** (Table 2, entries 1-5). It should be noted that molecular sieves 4 Å are crucial for this enantioselective chlorination of β-keto esters because in the absence of MS 4 Å, no ee could be observed under identical conditions (Table 2, entries 10). Using 100 mg of MS 4 Å as additives, no



Scheme 1. Preparation of phosphine-Schiff base type ligands **L1**-**L8**.

TABLE 2. Optimization of the reaction conditions in the asymmetric chlorination of β-keto ester 1a and *N*-chlorosuccinimide (NCS)



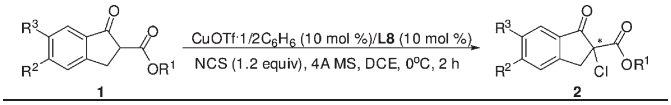
Entry[a]	Solvent	T (°C)	Yield (%)[b]	ee (%)[c]
1	CH_2Cl_2	20	99	25 (+)
2	CH_2Cl_2	10	99	30 (+)
3	CH_2Cl_2	0	99	68 (+)
4	CH_2Cl_2	−10	99	40 (+)
5	CH_2Cl_2	−20	99	37 (+)
6	CH_3CN	0	99	0
7	Toluene	0	99	0
8	DCE	0	99	75 (+)
9	$CHCl_3$	0	99	20 (+)
10[d]	DCE	0	99	0
11[e]	DCE	0	99	43 (+)

[a]Reaction conditions: **1a** (0.2 mmol), NCS (0.24 mmol), CuOTf·1/2C_6H_6 (10 mol %), **L8** (10 mol %), 4A MS (10 mg), solvent (1.0 ml) and the reaction was carried out for 2 h.
[b]Isolated yield.
[c]Determined by chiral HPLC analysis. The absolute configuration of the products was assigned by comparison with literature compounds.
[d]In the absence of 4A MS.
[e]4A MS (100 mg) was added.

significant improvement could be realized (Table 2, entry 11). The effect of MS 4 Å is not clear at the present stage. However, on the basis of previous investigation, it may be attributed to the ability of molecular sieves to serve as a Brϕnsted base and to improve the catalyst stability.[37]

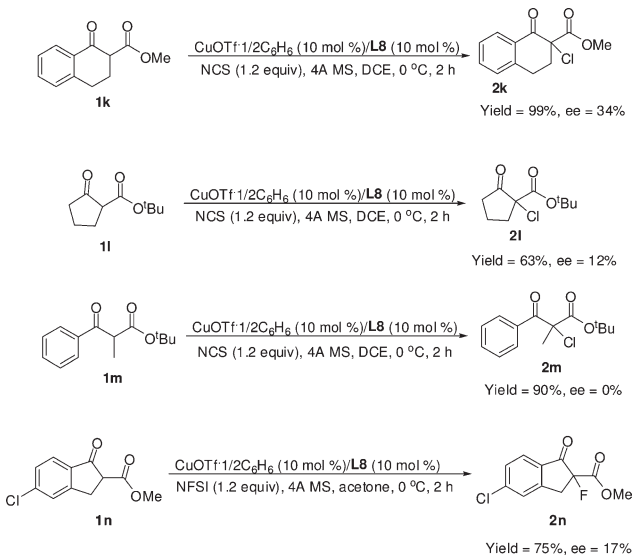
Therefore, the best reaction conditions are to carry out the reaction in DCE using CuOTf·1/2C_6H_6 (10 mol %) as a Lewis acid and 4 Å MS (10 mg) as an additive, as well as *N*-chlorosuccinimide (NCS) as the halogen source in the presence of phosphine-Schiff base type ligand **L8** (10 mol %) at 0°C.

TABLE 3. Asymmetric chlorination of β-keto esters 1 and *N*-chlorosuccinimide (NCS) under the optimal conditions



Entry[a]	Substrate	Yield (%)[b]	ee (%)[c]
1	**1a**, R^1 = Me, R^2 = R^3 = H	**2a**, 99	75 (+)
2	**1b**, R^1 = ^{i}Pr, R^2 = R^3 = H	**2b**, 99	77 (+)
3	**1c**, R^1 = Bn, R^2 = R^3 = H	**2c**, 87	81 (+)
4	**1d**, R^1 = ^{t}Bu, R^2 = R^3 = H	**2d**, 92	67 (+)
5	**1e**, R^1 = Me, R^2 = Br, R^3 = H	**2e**, 99	71 (+)
6	**1f**, R^1 = ^{t}Bu, R^2 = Br, R^3 = H	**2f**, 90	52 (+)
7	**1g**, R^1 = Me, R^2 = Cl, R^3 = H	**2g**, 99	82 (+)
8	**1h**, R^1 = ^{t}Bu, R^2 = Cl, R^3 = H	**2h**, 99	58 (+)
9[d]	**1i**, R^1 = Me, R^2 = R^3 = OMe	**2i**, 78	67 (+)
10[d]	**1j**, R^1 = ^{t}Bu, R^2 = R^3 = OMe	**2j**, 79	50 (+)

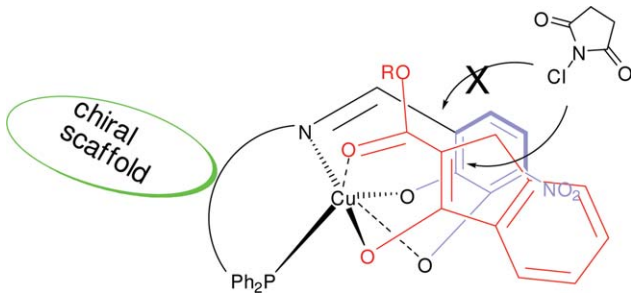
[a]Reaction conditions: **1** (0.2 mmol), NCS (0.24 mmol), CuOTf·1/2C_6H_6 (10 mol %), **L8** (10 mol %), 4A MS (10 mg), DCE (1.0 ml) and the reaction was carried out 0°C for 2 h.
[b]Isolated yield.
[c]Determined by chiral HPLC analysis. The absolute configuration of the products was assigned by comparison with the literature compounds.
[d]The reaction was performed for 24 h.



Scheme 2. Lewis acid catalyzed asymmetric halogenation of substrates **1k**, **1l**, **1m**, and **1n**.

With these optimal reaction conditions in hand, a series of β-keto esters **1a**-**1j** with various substituents in the ester group and on the aromatic scaffold were used to further explore the substrate scope (Table 3). It was found that for substrates **1a**-**1d** with different ester groups, the corresponding products **2a**-**2d** were obtained in moderate enantioselectivities (67–81% ee) and good yields (Table 3, entries 1-4). Substrates **1e**-**1h** bearing electron-withdrawing Cl or Br atom and substrates **1i** and **1j** having electron-donating such as MeO substituent on the benzene ring also produced the products **2e**-**2j** in 78–99% yields and 50–82% ees in this enantioselective chlorination of β-keto esters, indicating a wide substrate scope in this reaction (Table 3, entries 5-10). Furthermore, tetralone β-keto ester **1k** and cyclopentanone β-keto ester **1l** were also used as substrates in this enantioselective chlorination under the standard conditions. However, it was found that the corresponding products **2k** and **2l** were obtained in good yields but with 34% ee and 12% ee, respectively (Scheme 2). In the case of acyclic β-keto ester **1m**, the product **2m** was formed in high yield without any enantioselectivity (Scheme 2). On the other hand, the extension of the catalytic system to the Lewis acid catalyzed asymmetric fluorination of β-keto esters was also evaluated under the standard conditions. It was found that as for substrate **1n**, the corresponding product **2n** was obtained in 75% yield and 17% ee using *N*-fluorodibenzenesulfonimide (NFSI) as the fluorinating reagent. Further studies to improve the efficiency of the present catalytic system in enantioselective fluorination of β-keto esters are undergoing in our laboratories (Scheme 2).

Although the real active species has not yet been fully understood, we believe that Cu(I) can be potentially coordinated with the N, O, and P atoms in ligand **L8** as we proposed in our previous paper.[32] A plausible reaction mechanism for this asymmetric reaction is outlined in Scheme 3. These interactions control the stereochemical outcome of the reaction and subsequently accelerate the reaction rate.



Scheme 3. A plausible reaction mechanism. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

CONCLUSIONS

In conclusion, chiral phosphine-Schiff base type ligand **L8** prepared from (*R*)-2-(diphenylphosphino)-1,1'-binaphthyl-2'-amine was found to be a fairly effective ligand for Cu(I)-promoted enantioselective chlorination of β-keto esters to give the corresponding products with moderate enantioselectivities and in good yields under mild conditions. These results will promote us to design and synthesize more new effective chiral phosphine-Schiff base type ligands for asymmetric reactions. Efforts are underway to elucidate the mechanistic details of this asymmetric chlorination of β-keto esters and to disclose the exact structure of the active species in this catalytic system.

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