

Communication

Catalytic Asymmetric Chlorination of β -Ketoesters Using *N*-PFB-PyBidine-Zn(OAc)₂

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Abstract: A PyBidine-Zn(OAc)₂ complex catalyzed asymmetric chlorination of β -ketoesters. With assistance of NaHCO₃, a newly developed *N*-pentafluorobenzyl-PyBidine (*N*-PFB-PyBidine)-Zn(OAc)₂ catalyst promoted the reaction of α -benzyl- β -ketoesters with *N*-chlorosuccinimide (NCS) to give the chlorinated products with up to 82% ee. Results of a mechanistic study suggested that zinc-enolate of β -ketoesters was formed on the basic (*N*-PFB-PyBidine)-Zn(OAc)₂ catalyst. The α -chlorinated- β -ketoester was successfully transformed into the chiral epoxide through sequential asymmetric chlorination/cyano-epoxidation in a one-pot synthesis.

Keywords: chlorination; β -ketoester; asymmetric reaction; catalyst

1. Introduction

Halogenation is an important transformation for producing highly functionalized organic compounds. Characteristics of chlorinated compounds have been evaluated for application in material science, medicinal chemistry, and agrochemistry [1]. Halogenated compounds also are valuable as synthetic intermediates in cross-coupling reactions. Among the wide range of synthetic methods for introducing halogens to the organic compounds, the most reliable is chlorination of the α -position of carbonyl compounds, which has been applied to the catalytic asymmetric version [2].

Asymmetric chlorination of β -ketoesters was described by Togni et al. using a Lewis acid catalyst TiCl₂(TADDOLato) in 2000 [3,4]. After seminal work by Jørgensen's bisoxazoline-copper catalysis [5], various metal-catalyzed enantioselective chlorinations of β -ketoesters have been developed using Cu [6–13], Ni [14], Co [15], Zn [10], Pd [16], and Fe [17]. The use of Cu and Zn salts for a single chiral ligand allows a switch in enantioselectivity [10]. Organocatalyzed reactions also have been reported [18–29]. In these reports, formation of enolates from the β -ketoesters has been proposed. Though previously reported metal-catalyzed reactions have involved relatively strong Lewis acids with stable counter anions (e.g., TfO[−]), increasing the basicity of the metal catalyst should promote formation of the enolate and smooth nucleophilic reaction of the enolate to the chlorinating reagent.

As part of a program for developing advanced halogenated compounds, a series of chiral metal catalysts for iodolactonization were developed [30–33]. Catalytic asymmetric iodolactonization was achieved using a newly developed chiral bis(imidazolidine)pyridine ligand (PyBidine)-metal complex [30]. The formation of an Ni-carboxylate intermediate from the alkenyl carboxylic acid plays a key role in promoting the iodolactonization. The PyBidine-metal complexes also have been applied successfully to metal enolate chemistry [34–36]. For example, generation of metal-enolates from β -ketoesters was achieved with a bis(imidazolidine)pyridine (PyBidine)-CoCl₂ complex [36].

The conjugation of the iodolactonization and enolate formation on the PyBidine-metal complex promoted an examination of the asymmetric chlorination of β -ketoesters using basic catalysts.

2. Results

Initially, a study was done to determine the appropriate catalyst for asymmetric chlorination of β -ketoesters.

For asymmetric chlorination of β -ketoester **1a** using *N*-chlorosuccinimide (NCS), various PyBidine(L1)-metal salt complexes possessed catalytic activity to give the α -chlorinated β -ketoester **2a** in an enantioselective manner (Table 1). Although L1-Co(II), Ni(II), and Cu(II) complexes, which had been examined previously, were catalytically active, **2a** was obtained in low enantiomeric excess. Among the fourth period metal salts examined, the (*S,S*)-diphenyldiamine-derived PyBidine (L1)-Zn(OAc)₂ complex gave (*S*)-enriched **2a** in 60% yield with 60% ee (entry 7). Typically, the weakly basic metal acetate complexes showed greater catalyst activity than those complexes prepared from neutral metal chlorides or Lewis acidic metal salts. Other chiral ligands were also examined for applicability to the Zn(OAc)₂-catalyzed reaction (entries 11–14). The trinuclear-aminoiminoBINOL (L2)-Zn₃(OAc)₄ complex, which possessed outstanding catalytic activity for the iodolactonization reaction, gave **2a** in 41% yield with 21% ee (entry 11) [31,32]. Reaction using PyBim (L3)-Zn(OAc)₂ gave **2a** with low ee (entry 12) [37].

Table 1. First screening of metal catalysts for asymmetric chlorination of β -ketoester.

PyBidine (L1)

Bis(aminoimino)BINOL (L2)

PyBim (L3)

Half-PyBidine (L4)

PyBodine (L5)

Entry	Ligand	Metal Salt	Yield (%)	ee (%)
1	L1	FeCl ₂	9	44
2	L1	Co(OAc) ₂ ¹	54	42
3	L1	CoCl ₂	34	27
4	L1	Ni(OAc) ₂ ¹	64	28
5	L1	Cu(OAc) ₂	57	10
6	L1	Cu(OTf) ₂	23	22
7	L1	Zn(OAc) ₂	60	60
8	L1	Zn(OBz) ₂	85	56
9	L1	ZnCl ₂	13	−21
10	L1	Zn(OTf) ₂	22	21
11	L2	Zn(OAc) ₂	41	21
12	L3	Zn(OAc) ₂	90	−6
13	L4	Zn(OAc) ₂	98	13
14	L5	Zn(OAc) ₂	52	15

¹ Tetrahydrate was used.

Based on the first screening of catalysts for asymmetric chlorination, the PyBidine-Zn(OAc)₂ catalyst system was chosen for further optimization (Table 2).

Table 2. Optimization of asymmetric chlorination of β -ketoester catalyzed by PyBidine-Zn(OAc)₂.

Reaction scheme: $\text{rac. } \mathbf{1a}$ (1 eq) + NCS (1.1 eq) $\xrightarrow[\text{Solvent, r.t., 24h}]{\text{Ligand (11 mol \%), Zn(OAc)}_2 \text{ (10 mol \%)}}$ $\mathbf{2a}$

R =

L1 **L6** **L7** **L8** **L9** **L10**

Chlorinating reagent

NCS **NCP** **TCC** **DCH** **Chloramine-T**

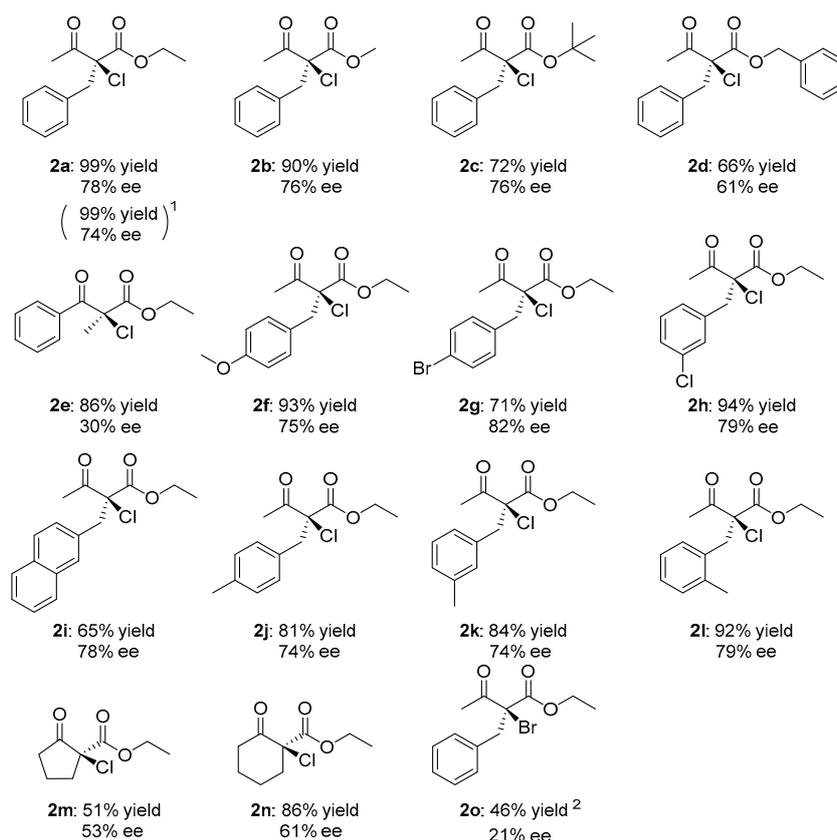
Entry	Ligand	Solvent	Chlorinating Reagent	Additive ¹	Yield (%)	Ee (%)
1	L1	toluene	NCS	-	60	60
2	L6	toluene	NCS	-	62	41
3	L7	toluene	NCS	-	92	66
4	L8	toluene	NCS	-	69	68
5	L9	toluene	NCS	-	25	65
6	L10	toluene	NCS	-	86	70
7	L10	EtOAc	NCS	-	88	35
8	L10	Et ₂ O	NCS	-	67	57
9	L10	CH ₂ Cl ₂	NCS	-	38	53
10	L10	CCl ₄	NCS	-	78	77
11	L10	cyclohexane	NCS	-	85	79
12	L10	cyclohexane	NCP	-	92	75
13	L10	cyclohexane	TCC	-	42	26
14	L10	cyclohexane	DCH	-	47	23
15	L10	cyclohexane	Chloramine-T	-	95	9
16	L10	cyclohexane	NCS	K ₂ CO ₃	96	59
17	L10	cyclohexane	NCS	TEA	95	65
18	L10	cyclohexane	NCS	NaHCO ₃	99	78

¹ 10 mol % were added.

The substitution effect on the imidazolidine ring of the PyBidine ligand (R-group) was examined (Table 2, entries 1–6). Although the bulky *N*-trimethylbenzyl-PyBidine (**L6**)-Zn(OAc)₂ catalyst resulted in lower asymmetric induction to give **2a**, the catalysts prepared from *N*-cyclohexylmethyl-PyBidine (**L7**) and *N*-1-naphthylmethyl-PyBidine (**L8**) slightly improved asymmetric induction (entries 3–4). By introducing an electron-withdrawing substituent directly onto the imidazolidine-ring, *N*-tosyl-PyBidine (**L9**) reduced the catalytic activity to give **2a** in 25% yield, which can be explained by a reduction in basicity of the PyBidine-Zn(OAc)₂ complex (entry 5). Finally, the *N*-pentafluorobenzyl-PyBidine (**L10**), referred to as *N*-PFB-PyBidine, improved the Zn(OAc)₂-catalyzed reaction to give **2a** in 86% yield with 70% ee. For *N*-PFB-PyBidine (**L10**)-Zn(OAc)₂ catalysis, additional reaction optimization was conducted in entries 7–18. Reactions conducted in a polar solvent tended to reduce asymmetric induction, while the use of cyclohexane improved the

asymmetric induction of **2a** with up to 79% ee (entry 11). Although other chlorinating reagents were investigated (entries 12–15), reaction using the original NCS provided **2a** with the greatest ee value. Based on the weaker basic character of the PyBidine-Zn(OAc)₂ complex, some basic additives were also examined (entries 16–18). The best reaction conditions were the addition of 1 equivalent NaHCO₃ to the *N*-PFB-PyBidine (**L10**)-Zn(OAc)₂ catalyst (10 mol%), which gave **2a** in 99% yield while maintaining the asymmetric induction of 78% ee (entry 18).

With the optimized reaction conditions in hand, the generality of β -ketoesters was examined in Scheme 1.

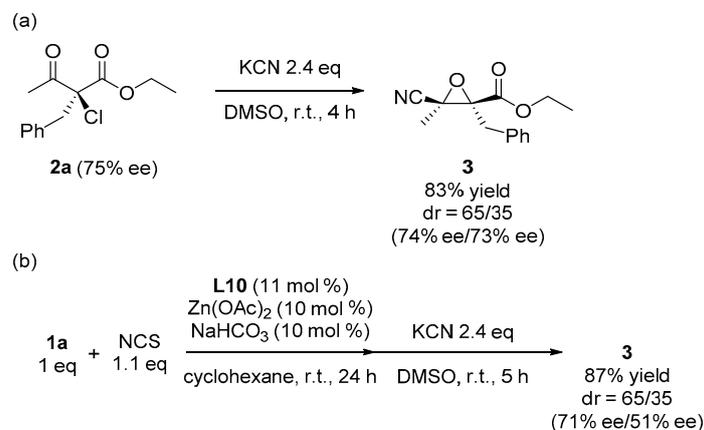


Scheme 1. General applicability of β -ketoesters. ¹5 mol % of catalyst were used. ²*N*-bromosuccinimide (NBS) was used instead of *N*-chlorosuccinimide (NCS).

The methyl ester **2b** and *tert*-butyl ester **2c** were obtained with 76% ee. For the benzyl substituent of β -ketoesters, both electron-donating and -withdrawing substituents on the benzene ring were tolerated to give products ranging from 74% ee to 82% ee. Similarly, the 2-naphthylmethyl substituted product **2i** was obtained with 78% ee. However, the simple methyl substituent of the β -ketoester reduced the asymmetric induction to 30% ee in generating **2e**. Cyclic β -ketoesters could be used and gave **2m** and **2n** with 53% ee and 61% ee, respectively. When *N*-bromosuccinimide (NBS) was used instead of NCS, α -bromo- β -ketoester **2o** was obtained in 46% yield and 21% ee. Even in the decreased catalyst loading (5 mol %), **2a** was obtained in quantitative yield with 74% ee.

For synthetic application of chiral α -chloro- β -ketoesters, Shibatomi et al. reported the S_N2 substitution reaction using azide and thiol nucleophiles [9]. In contrast, when KCN was applied to the chiral α -chloro- β -ketoester **2a**, epoxide **3** was obtained in 83% yield, which was generated by 1,2-addition of cyanide to the α -chloro- β -ketoester **2a** and subsequent intramolecular epoxide formation (Scheme 2). Although **3** was obtained as a diastereo-mixture, both isomers retained their

optical purity of the α -position. Epoxide formation also was possible from sequential asymmetric chlorination/cyano-epoxidation in a one-pot synthesis.



Scheme 2. Synthesis of chiral epoxide **3**: (a) stepwise synthesis; (b) one-pot synthesis.

3. Discussion

Figure 1a presents a proposed reaction mechanism. The β -ketoesters coordinate to the PyBidine-Zn complex to form intermediate **A**. The Zn-enolate **B** then is generated with assistance of base (e.g., NaHCO₃). Enolate **B** reacts with the chlorinating reagent (NCS) to give the product along with regeneration of the catalyst.

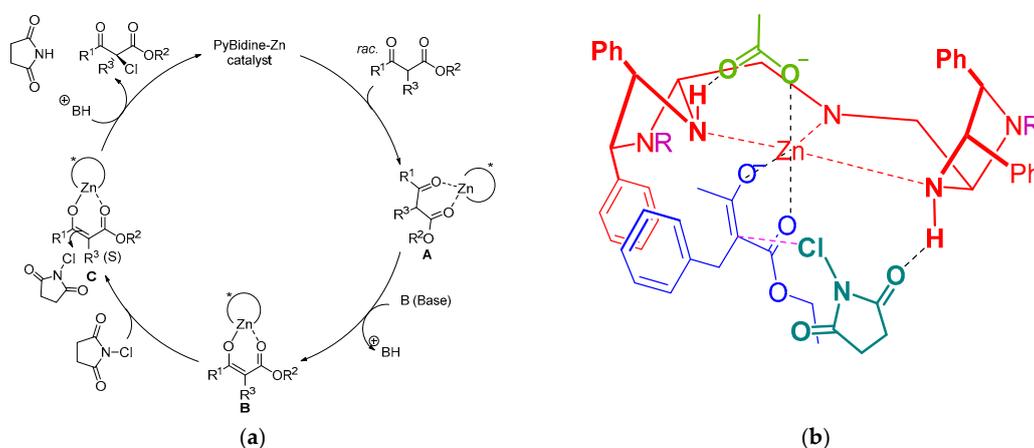
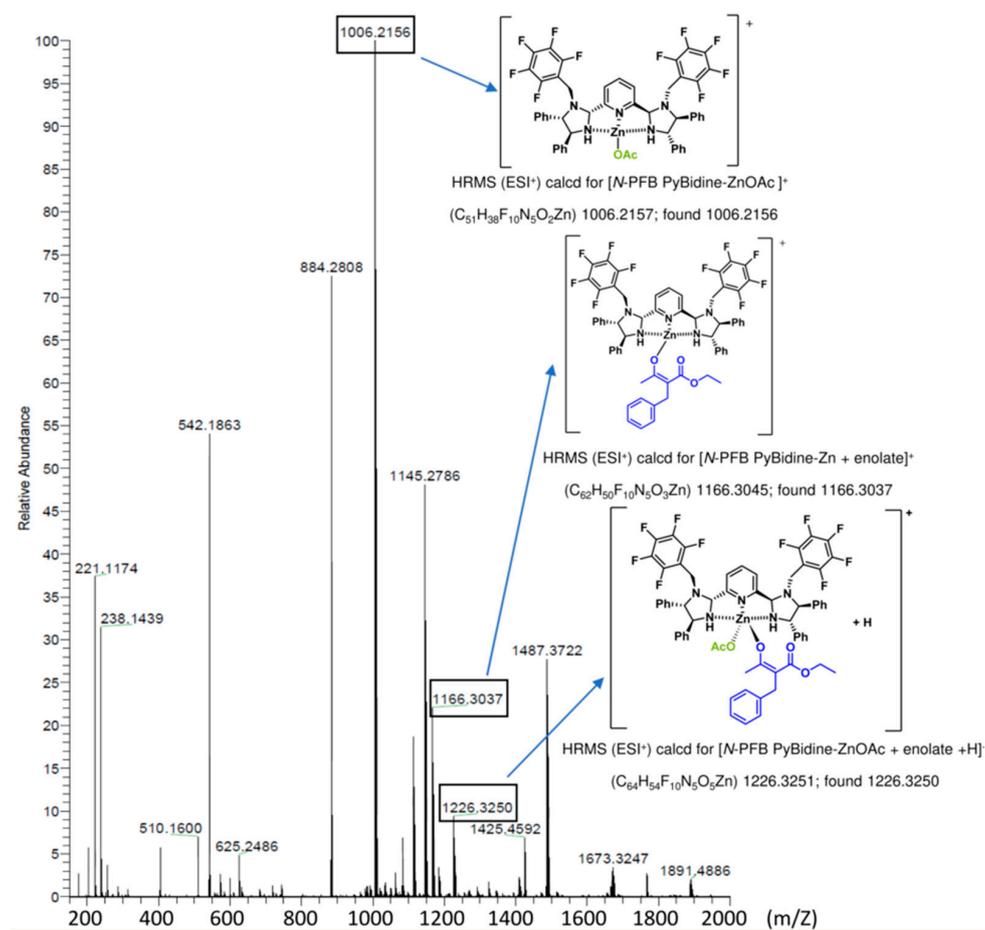
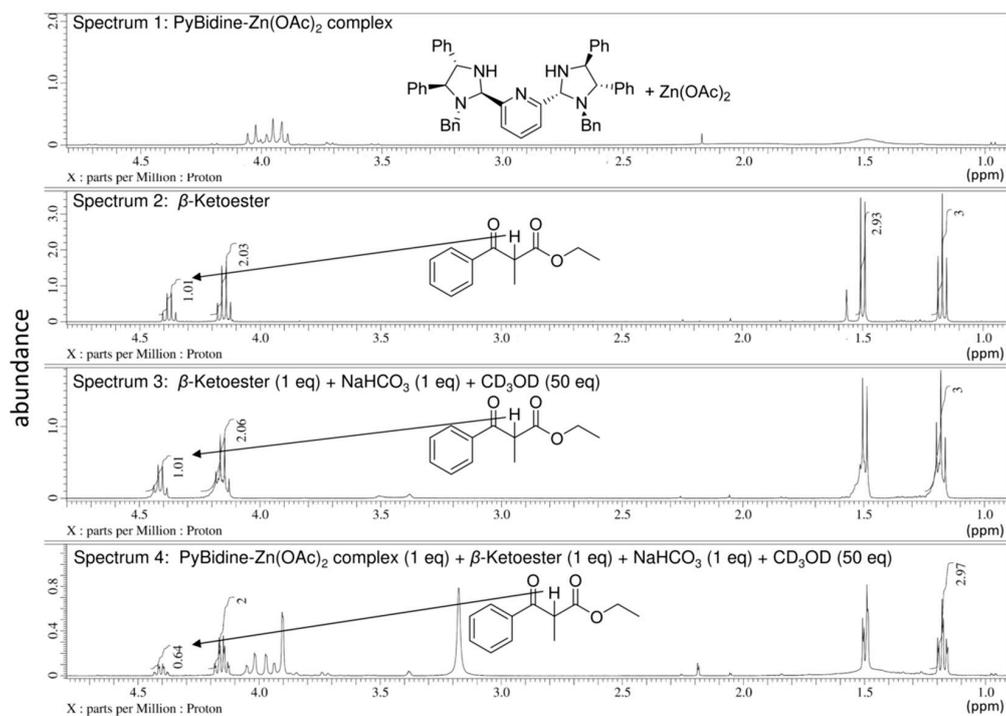


Figure 1. Proposed reaction mechanism of asymmetric chlorination of β -ketoesters catalyzed by *N*-PFB-PyBidine (**L10**)-Zn(OAc)₂ complex: (a) catalytic cycle; (b) reaction model.

Formation of Zn-enolate **B** was suggested by ¹H-NMR and ESI-MS results. When the *N*-PFB-PyBidine (**L10**)-Zn(OAc)₂ complex was treated with **1a** (1 eq) and NaHCO₃ (1 eq) in CH₂Cl₂, new peaks were observed in the ESI-MS spectrum at 1166.3037 and 1226.3250, corresponding to the [**L10**-Zn + enolate (**1a** - H)]⁺ and [**L10**-ZnOAc + enolate (**1a** - H) + H]⁺, respectively (Figure 2a). Furthermore, in the ¹H-NMR study, mixing **L10**-Zn(OAc)₂ complex, **1a** (1 eq), NaHCO₃ (1 eq), and CD₃OD (50 eq) in CDCl₃, reduced the intensity of the α -proton of **1a** to 0.64 proton, which suggests smooth formation of the enolate **1a** under the reaction conditions (Figure 2b).



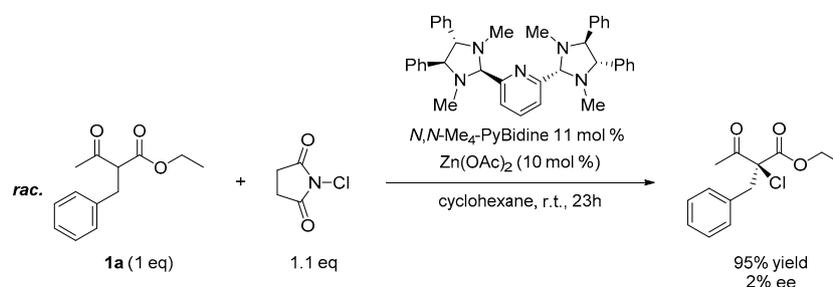
(a)



(b)

Figure 2. (a) ESI-MS analysis and (b) ¹H-NMR study in CDCl₃.

The PyBim (**L3**)-Zn(OAc)₂ gave (*R*)-**2a** with only 6% ee (Table 1, entry 11), and an *N,N*-Me₄-PyBidine)-Zn(OAc)₂ resulted in poor asymmetric induction under the optimized reaction conditions (Scheme 3) [36]. These results suggest that the NH-proton of the imidazolidine ring in the *N*-PFB-PyBidine (**L10**)-Zn(OAc)₂ complex apparently plays a significant role in organizing the appropriate reaction sphere [35].



Scheme 3. Reaction using *N,N*-Me₄-PyBidine-Zn(OAc)₂.

The reaction model described in Figure 1b explains the formation of (*S*)-enriched **2a** using (*S,S*)-diphenyldiamine-derived *N*-PFB-PyBidine (**L10**)-Zn(OAc)₂ catalyst, in which the formation of hydrogen bonding between NCS and the NH-proton of imidazolidine ring is involved.

4. Materials and Methods

N-PFB PyBidine (**L10**) (0.022 mmol) and Zn(OAc)₂ (0.02 mmol) were added to a glass tube equipped with a magnetic stirrer bar under Ar. Then, DCM (1.0 mL) was added to the glass tube and the mixture stirred overnight. After removal of the solvent under reduced pressure, cyclohexane (2.0 mL) was added, followed by the addition of the β-ketoesters (0.2 mmol) at 25 °C and then the addition of NaHCO₃ (0.02 mmol) and *N*-chlorosuccinimide (0.22 mmol). After stirring for 24 h, the reaction mixture was directly purified by silica-gel column chromatography to afford the product. The enantiomeric excess of the products was determined using chiral stationary phase HPLC with Daicel Chiralcel OJ-H and Chiralpak AS-H and IC-3 columns.

The detailed experimental procedure and analytical data are available in the Supporting Information.

5. Conclusions

In conclusion, an efficient Zn-catalyzed enantioselective chlorination reaction of β-ketoesters was developed. The *N*-PFB-PyBidine (**L10**)-Zn(OAc)₂ complex acts as a basic catalyst to generate the enolate of the β-ketoesters, and to promote α-chlorination in high yield with moderate to good enantioselectivity. Transformation of the α-chlorinated product into chiral epoxide by one-pot sequential asymmetric chlorination/cyano-epoxidation reaction was also achieved.

Supplementary Materials: The following are available online at <http://www.mdpi.com/2073-4344/10/10/1177/s1>, Detailed experimental procedure, analytical data, Figure S1: nOe experiment of major epoxide **3**, Figure S2: ESI-MS analysis of a mixture of *N*-PFB-PyBidine (**L10**)-Zn(OAc)₂ complex, **1a** (1 eq) and NaHCO₃ (1 eq) in CH₂Cl₂, Figure S3: ¹H-NMR study of **L10**-Zn(OAc)₂ complex, **1a** (1 eq), NaHCO₃ (1 eq), and CD₃OD (50 eq) in CDCl₃.

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Conflicts of Interest: The authors declare no conflict of interest.

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