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Access to Both Enantiomers of α-Chloro-β-keto Esters with a Single Chiral Ligand: Highly Efficient Enantioselective Chlorination of Cyclic β-Keto Esters Catalyzed by Chiral Copper(II) and Zinc(II) Complexes of a Spiro-2,2′-bischroman-Based Bisoxazoline Ligand

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Abstract: The spiro-2,2′-bichroman-based chiral bisoxazoline ligands (SPANbox) were found to be highly efficient in copper(II)- and zinc(II)-catalyzed asymmetric chlorinations of cyclic β-keto esters with *N*-chlorosuccinimide (NCS) as the chlorination reagent, to give the corresponding α-chloro-β-keto esters in excellent yields in 5–30 min with *ee* values up to 97%. The copper(II) triflate and zinc(II) triflate complexes of a single SPANbox ligand demonstrated complementary results to each other with respect to the enantioselection, affording both antipodes of the chlorinated product enantiomers with good to excellent optical purities.

Keywords: asymmetric catalysis; bisoxazolines; chlorination; α-chloro-β-keto esters; copper; zinc

Introduction

Chiral α-halo carbonyl compounds are versatile synthetic intermediates for further stereospecific transformations and important structural motifs in biologically active molecules.[1] Catalytic asymmetric electrophilic α-halogenation of carbonyl compounds can provide a direct access to enantioenriched α-halo carbonyl compounds, and thus has gained considerable interests in recent years.[2] Several strategies based on Lewis acid catalysis[3] or organocatalysis[4] have been successfully developed over the past decade for the stereocontrolled construction of carbon–halogen bonds adjacent to either one or two carbonyl groups, with the most significant progresses being made in the area of α-fluorination reactions.[5] On the other hand, the catalytic enantioselective α-chlorination reactions of carbonyl compounds have been relatively less explored, and catalytic systems with synthetically useful enantioselectivities (>90% *ee*) and general substrate adaptability are still rare. In this regard, Hintermann and Togni disclosed the first example of catalytic asymmetric α-chlorination (also involving fluorination and bromination) of β-keto esters in 2000, using isolated chiral Ti-TADDOLato complexes as the catalysts.[6] Following this pioneering work, a number of catalytic systems based on chiral Lewis acidic complexes of Cu(II),[7] Ni(II),[8] Cu(I),[9] Co(II),[10] or Zn(II)[11] have been found to be effective catalysts for asymmetric α-chlorination of 1,3-dicarbonyl compounds, which can form reactive enolates by chelation with the metal centers. The organocatalytic enantioselective α-chlorination of this type of substrates has also been recently developed by the groups of Bartoli, Feng, and Díaz-de-Villegas, respectively, using chiral amines,[12] *N*,*N*′-dioxides,[13] or amino diol derivatives[14] as the catalysts for the enolate generation. High enantioselectivities have been achieved for the α-chlorination of 1,3-dicarbonyl compounds in some cases, but the protocols incorporating cheap chlorinating reagents, mild conditions, and excellent yields remain scarce. Herein, we report a highly efficient α-chlorination of cyclic β-keto esters by *N*-chlorosuccinimide (NCS) using Cu(II) or Zn(II) complexes of chiral spiro-2,2′-bichroman-based[15,16] bisoxazoline ligands[17] (SPANbox **1**,[18] Figure 1) as the catalysts.

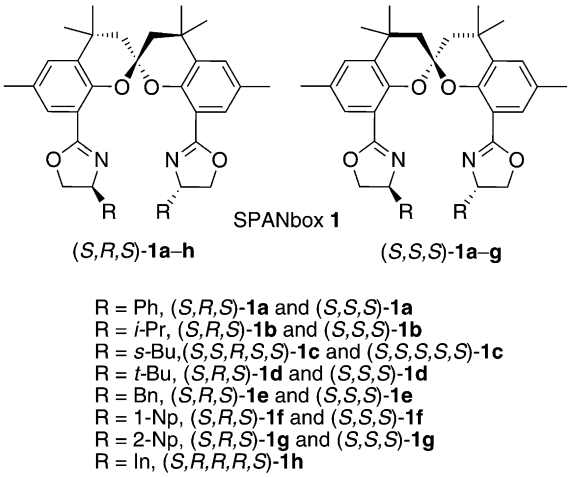
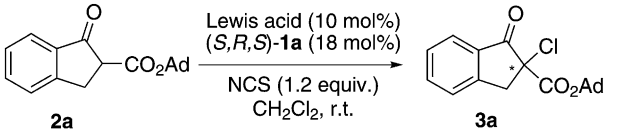


Figure 1. Chiral spiro bisoxazoline ligands (SPANbox **1**) used in this study.

Under mild conditions, most of the reactions were accomplished in 5 min to afford the α-chloro-β-keto esters in almost quantitative yields with good to high enantioselectivities. Notably, the SPANbox complexes of Cu(II) and Zn(II) are found to be complementary to each other in the sense of asymmetric induction, and both antipodes of the chlorinated product enantiomers can be readily accessed using a single chiral ligand simply by switching the metal salt from $Cu(OTf)_2$ to $Zn(OTf)_2$, or *vice versa*.

Table 1. Screening of Lewis acids in the catalytic enantioselective chlorination of β-keto ester **2a**.[a]



2a **3a**

Entry	Lewis acid	Time [min]	Yield [%][b]	*ee* [%][c]
1	None	20	70	*rac.*
2	$Sc(OTf)_3$	5	>99	*rac.*
3	$La(OTf)_3$	5	>99	*rac.*
4	$InCl_3$	5	>99	10 (−)
5	$InBr_3$	5	>99	10 (−)
6	$In(OTf)_3$	5	>99	3 (−)
7	$Mg(OAc)_2$	5	>99	*rac.*
8	$Fe(OAc)_2$	5	>99	2 (+)
9	$Ni(ClO_4)_2{\cdot}6H_2O$	5	>99	10 (+)
10	$CuOTf{\cdot}0.5C_6H_6$	5	>99	56 (−)
11	$Cu(OTf)_2$	5	99	86 (−)
12	$Cu(OAc)_2$	5	>99	21 (+)
13	$Cu(TFA)_2{\cdot}0.56H_2O$	5	>99	84 (−)
14	$Cu(ClO_4)_2{\cdot}6H_2O$	5	>99	33 (+)
15	$Zn(OTf)_2$	5	>99	85 (+)
16	$Zn(OAc)_2$	5	>99	rac.

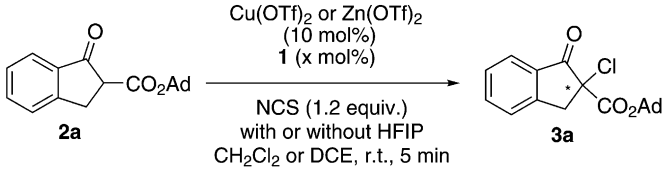
[a] *Reaction conditions:* **2a** (0.1 mmol), Lewis acid (10 mol%), **1a** (18 mol%), NCS (1.2 equiv.), dichloromethane solvent (0.75 mL), room temperature. Ad = 1-adamantyl.
[b] Yield of the isolated product.
[c] Determined by chiral HPLC.

Results and Discussion

The chiral spiro-bisoxazoline ligands SPANbox **1** (Figure 1) were synthesized by following our previously published procedure.[18] As an initial investigation of the reaction, a number of commercially available Lewis acidic metal salts in combination with SPANbox ligand (*S*,*R*,*S*)-**1a** were examined as the potential catalysts for the enantioselective chlorination of a cyclic β-keto ester, 1-adamantyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**2a**). The reactions were performed in dichloromethane at room temperature in the presence of a catalytic amount of Lewis acid (10 mol%) and the chiral ligand (*S*,*R*,*S*)-**1a** (18 mol%), using NCS (1.2 molar equiv.) as the chlorinating agents (Table 1). Clearly, **2a** is a highly enolizable substrate, which readily underwent an uncatalyzed background reaction in the absence of any Lewis acid to afford a racemic product **3a** (entry 1). In all cases, the presence of a catalytic amount of Lewis acid (10 mol%) was found to significantly accelerate the reactions, however, the enantioselectivities varied widely (0–86% *ee*) depending on the salt used. While the majority of the examined metal salts only gave **3a** in nil or modest *ee* values (entries 1–9 and 16), some cupric salts and $Zn(OTf)_2$ are exceptions (entries 10–15). The identity of the anions also plays a prominent role in the catalysis. For instance, the catalyst generated from $Cu(OTf)_2$ and (*S*,*R*,*S*)-**1a** gave the product (−)-**3a** with an *ee* value of 86% (entry 11), whereas changing the anion of the cupric salt to either acetate or perchlorate led to an erosion in enantioselectivity or even a change in stereochemistry (entries 12 and 14). Similar behaviors can also be found in Zn(II)-mediated reactions (entries 15 *vs.* 16). Most interestingly, the (*S*,*R*,*S*)-**1a**/$Zn(OTf)_2$ catalyst combination afforded the (+)-**3a** in 85% *ee*, but with a complete reversal of enantioselectivity with respect to that of (*S*,*R*,*S*)-**1a**/$Cu(OTf)_2$ under the otherwise identical conditions (entries 15 *vs.* 11). In consideration of their complementary nature in asymmetric inductions, both (*S*,*R*,*S*)-**1a**/$Cu(OTf)_2$ and (*S*,*R*,*S*)-**1a**/$Zn(OTf)_2$ catalyst combinations were employed in subsequent reaction studies.

A general survey of the reaction conditions was subsequently conducted for the enantioselective chlorination of **2a**, using the complexes generated *in situ* from (*S*,*R*,*S*)-**1a** and $Cu(OTf)_2$ or $Zn(OTf)_2$ as the catalyst, respectively. The reactions were typically performed by treatment of a solution of **2a** with an elec-

Table 2. Screening of ligands **1a–h** for $Cu(OTf)_2$- or $Zn(OTf)_2$-catalyzed enantioselective chlorination of β-keto ester **2a**.[a]



Entry	Ligand	**3a** [Cu(II)/**1**]		**3a** [Zn(II)/**1**]	
		Yield [%][b]	*ee* [%][c]	Yield [%][b]	ee [%][c]
1	(*S*,*R*,*S*)-**1a**	>99	90 (−)	>99	88 (+)
2	(*S*,*S*,*S*)-**1a**	99	15 (+)	>99	14 (−)
3	(*S*,*R*,*S*)-**1b**	91	73 (−)	>99	66 (+)
4	(*S*,*S*,*S*)-**1b**	>99	*rac.*	>99	*rac.*
5	(*S*,*S*,*R*,*S*,*S*)-**1c**	>99	71 (−)	>99	79 (+)
6	(*S*,*S*,*S*,*S*,*S*)-**1c**	>99	25 (−)	>99	*rac.*
7	(*S*,*R*,*S*)-**1d**	>99	*rac.*	>99	24 (+)
8	(*S*,*S*,*S*)-**1d**	>99	*rac.*	>99	29 (+)
9	(*S*,*R*,*S*)-**1e**	90	69 (−)	>99	10 (+)
10	(*S*,*S*,*S*)-**1e**	>99	9 (−)	>99	6 (+)
11	(*S*,*R*,*S*)-**1f**	99	43 (−)	>99	49 (+)
12	(*S*,*S*,*S*)-**1f**	>99	*rac.*	>99	7 (+)
13	(*S*,*R*,*S*)-**1g**	99	35 (−)	>99	29 (+)
14	(*S*,*S*,*S*)-**1g**	>99	*rac.*	>99	4 (+)
15	(*S*,*R*,*R*,*R*,*S*)-**1h**	>99	3 (−)	>99	2 (+)

[a] Unless otherwise noted, all reactions were performed at temperature for 5 min with **2a** (0.1 mmol) using NCS (1.2 equiv.) as the chlorinating agent, in the presence of the catalyst geneated *in situ* by mixing of $Cu(OTf)_2$ (10 mol%) with ligand **1** (18 mol%) in CH_2Cl_2 (0.75 mL), or $Zn(OTf)_2$ (10 mol%) with ligand **1** (22 mol%) in DCE (0.75 mL), respectively. HFIP (1.0 equiv.) was used as additive in $Cu(OTf)_2$-mediated reactions. Ad = 1-adamantyl.

[b] Yield of the isolated product.

[c] Determined by chiral HPLC.

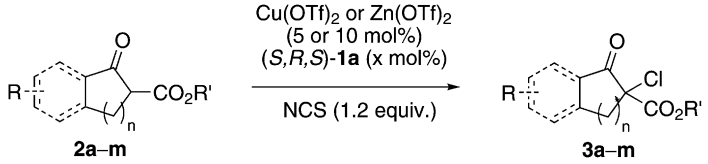
trophilc chlorinating agent (1.2 equiv.), generally NCS, in the presence of a catalytic amount of ligand (*S*,*R*,*S*)-**1a** together with $Cu(OTf)_2$ (10 mol%) or $Zn(OTf)_2$ (10 mol%). Many reaction parameters were found to have an influence on the reactivity and/or enantioselectivity of the catalysis, including the metal to ligand molar ratio, solvent, catalyst concentration, temperature, additive, as well as the chlorinating agent (for details, see Table S1–Table S11 in the Supporting Information). As a result, the reaction performed in dichloromethane at room temperature with a catalyst concentration of 0.13 mM and a metal to ligand molar ratio of 1:1.8 was found to be beneficial for the (*S*,*R*,*S*)-**1a**/$Cu(OTf)_2$-catalyzed chlorination of **2a**,[19] giving a quantitative yield of (−)-**3a** in 5 min with an *ee* value of 86% (entry 4, Table S1 in the Supporting Information). A deviation from these conditions led to some loss in enantioselectivity (Table S1–Table S4 in the Supporting Information). Further scrutiny of some electrophilic chlorinating agents revealed that NCS was still the best one in terms of both activity and enantioselectivity for the Cu(II)-catalyzed reaction (Table S5 in the Supporting Information). Some common additives were examined for (*S*,*R*,*S*)-**1a**/$Cu(OTf)_2$-catalyzed chlorination as well, among which the weak Brønsted acid hexafluoro-2-propanol (HFIP, 1.0 equiv.) was found to have a beneficial effect on the enantioselectivity, leading to an enhancement of *ee* value of **3a** to 90% (Table S6 in the Supporting Information). Finally, a screening of reaction conditions for (*S*,*R*,*S*)-**1a**/$Zn(OTf)_2$-catalyzed chlorinations of **2a** (Table S7–Table S11 in the Supporting Information) revealed a behavior somewhat parallel to that of **1a**/$Cu(OTf)_2$ catalysis. In this case, the reaction was found to be best conducted in 1,2-dichloroethane (DCE) at 60 °C for 5 min, using NCS as the chlorine source and with a metal to ligand molar ratio of 1:2.2, to give a quantitative yield of (+)-**3a** in 95% *ee* (entry 2, Table S11 in the Supporting Information).

In order to identify the optimal ligand(s), the library of chiral SPANbox ligands (*S*,*R*,*S*)- and (*S*,*S*,*S*)-**1** was screened for the chlorination of **2a** catalyzed by $Cu(OTf)_2$ or $Zn(OTf)_2$, respectively. The reactions were conducted at room temperature in CH_2Cl_2 [for Cu(II)] or DCE [for Zn(II)] using NCS as the chlorine source, and the results are summarized in Table 2. While almost all the catalyst combinations were highly active in this reaction (>99% yield in 5 min), the *ee* values of the chlorinated product **3a** varied widely (0–90%) depending on the ligand structure. It is noteworthy that for each SPANbox ligand, the

$Cu(OTf)_2$- and $Zn(OTf)_2$-mediated reaction demonstrated an enantioselectivity level parallel to each other, but always with the opposite sense of chiral induction (columns 4 *vs.* 6 in Table 2). In addition, the match or mismatch of the chiralities on the spiro backbone (axial) and oxazolinyl (central) moieties of **1** was found to have a considerable impact on the asymmetric induction of the catalysis. The reactions with (*S*,*R*,*S*)-**1** generally afforded the product **3a** with *ee* values higher than those obtained using their corresponding (*S*,*S*,*S*)-counterparts (entries 1 *vs.* 2, 3 *vs.* 4, 5 *vs.* 6, 9 *vs.* 10, 11 *vs.* 12, and 13 *vs.* 14, respectively), indicating that (*S*,*R*,*S*) should be the matched pair for both $Cu(OTf)_2$- and $Zn(OTf)_2$-catalyzed reactions. Finally, the substituents on the oxazolinyl moieties of the (*S*,*R*,*S*)-**1** were also found to have a significant effect on the enantioselectivity. For instance, the reactions involving phenyl-substituted ligand (*S*,*R*,*S*)-**1a** afforded **3a** with high *ee* values (entry 1), whereas sterically more bulky 1-naphthyl-, 2-naphthyl-, *cis*-1,2-indanyl, or *tert*-butyl-substituted ligands (*S*,*R*,*S*)-**1f–h** and (*S*,*R*,*S*)-**1d** only led to poor enantioselectivities (entries 7, 11, 13, and 15). In these cases the sterically encumbering oxazolyl substituents might hinder or inhibit the substrate coordination and hence prevent its activation, presumably as a result of steric congestion caused by their proximity to the catalytic metal center. Overall, (*S*,*R*,*S*)-**1a** was found to be optimal in terms of enantioselectivity for both $Cu(OTf)_2$- and $Zn(OTf)_2$-catalyzed chlorination of **2a**, providing (−)- or (+)-antipodes of **3a**, respectively, both in high *ee* values (entry 1).

Therefore, the enantioselective chlorination with NCS was extended to a variety of cyclic β-keto ester substrates **2a–m**, using $Cu(OTf)_2$/(*S*,*R*,*S*)-**1a** or $Zn(OTf)_2$/(*S*,*R*,*S*)-**1a** as the catalyst under their respective optimized reaction conditions. As shown in Table 3, most of the reactions were completed in 5–10 min under mild conditions, to afford the chlorinated products in good to excellent yields (82 to >99%).

Table 3. (*S*,*R*,*S*)-**1a** complex of $Cu(OTf)_2$- or $Zn(OTf)_2$-catalyzed asymmetric chlorination of β-oxo esters **2a–m**.[a]



2a–m **3a–m**

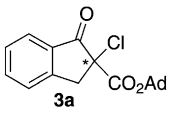
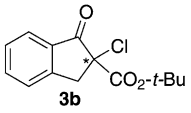
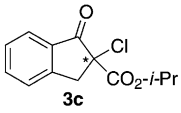
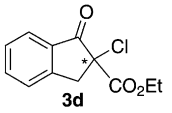
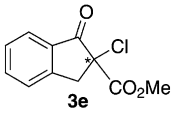
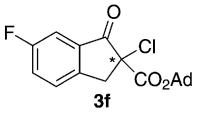
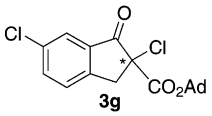
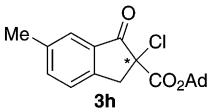
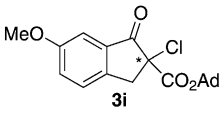
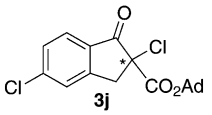
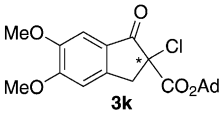
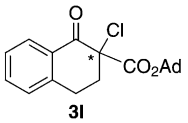
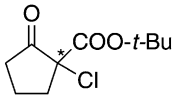
Entry	Product	**3** [Cu(II)/**1a**] Yield [%][b]	*ee* [%][c]	**3** [Zn(II)/**1a**] Yield [%][b]	*ee* [%][c]
1	 **3a**	>99	90 (−)	99[f]	94[f] (+)
2	 **3b**	>99[d]	90[d] (−)	>99[f]	83[f] (+)
3	 **3c**	>99	74 (−)	>99	28 (+)
4	 **3d**	82	64 (−)	–[g]	–[g]
5	 **3e**	99	63 (−)	–[g]	–[g]
6	 **3f**	89	81 (−)	>99	90 (+)
7	 **3g**	98	81 (−)	>99	89 (+)

Table 3. (Continued)

Entry	Product	**3** [Cu(II)/**1a**] Yield [%][b]	*ee* [%][c]	**3** [Zn(II)/**1a**] Yield [%][b]	*ee* [%][c]
8	 **3h**	98	92 (−)	>99	96 (+)
9	 **3i**	97	84 (−)	99	95 (+)
10	 **3j**	84	63 (−)	>99[f]	90[f] (+)
11	 **3k**	99	82 (−)	>99	92 (+)
12	 **3l**	98[e]	75[e] (−)	>99[f]	81[f] (+)
13[h]	 **3m**	85	97 (−)	80	92 (+)

[a] Unless otherwise specified, all reactions were performed for 5 min with **2a–l** (0.1 mmol) using NCS (1.2 equiv.) as the chlorinating agent, in the presence of the catalyst geneated *in situ* by mixing of $Cu(OTf)_2$ (10 mol%) with ligand **1** (18 mol%) in CH_2Cl_2 (0.75 mL), or $Zn(OTf)_2$ (10 mol%) with ligand **1** (22 mol%) in DCE (0.75 mL), respectively. The reactions with $Cu(OTf)_2$ were carried out at room temperature in the presence of HFIP (1.0 equiv.) as the additive, whereas the reactions involving $Zn(OTf)_2$ were performed at 60 °C.
[b] Yield of the isolated product.
[c] Determined by chiral HPLC.
[d] $Cu(OTf)_2$ (5 mol%) and (*S*,*R*,*S*)-**1a** (9 mol%).
[e] Reaction time: 10 min.
[f] $Zn(OTf)_2$ (5 mol%) and (*S*,*R*,*S*)-**1a** (11 mol%).
[g] Not examined.
[h] Reaction time: 30 min.

A general trend with respect to the enantioselectivity is clearly discernible for both Cu(II)- and Zn(II)-catalyzed chlorination of 2-carboxylate indanones **2a–e**, i.e., the sterically bulkier ester substituents (1-adamantyl or *t*-Bu) generally impart higher enantioselectivity in the chlorinated products **3a–e** (entries 1 and 2 *vs.* 3-5). Remarkably, $Cu(OTf)_2$/(*S*,*R*,*S*)-**1a** and $Zn(OTf)_2$/(*S*,*R*,*S*)-**1a** were found to afford the opposite enantiomers in the chlorination of of adamantyl β-keto esters **2a** and **2f–l**, with good to high *ee* values (63–96%) being attained in the chlorinated products (entries 1 and 6–12). Excellent results have also been obtained for the chlorination of cyclopentanone derivative **2m** (entry 13). In the case of *tert*-butyl 2-methyl-3-oxo-3-phenylpropanoate, a more challenging acyclic β-keto ester, the chlorination product was obtained in good yields after a prolonged time (12 h), but with only modest *ee* values (see the Supporting Information). These results suggested that the SPANbox (*S*,*R*,*S*)-**1a** complexes of $Cu(OTf)_2$ and $Zn(OTf)_2$ can show complementary results to each other in the chlorination reactions,[20] presumably as a result of a change in the coordination geometry in the copper and zinc catalysts.[21]

Conclusions

SPANbox complexes of $Cu(OTf)_2$ and $Zn(OTf)_2$ were found to be highly efficient catalysts for enantioselective chlorination of cyclic β-keto esters using the commercially available NCS as the cheap chlorinating agent, affording the chlorinated products in good to excellent yields (82 to >99%) with high enantioselec-

tivity (up to 97% *ee*) in 5–30 min under mild conditions. Intriguingly, Cu(II)- and Zn(II)-catalyzed reactions with a single SPANbox ligand produce the chlorinated products with opposite enantioselection in good to high enantiopurity, indicating that both antipodes of the chlorinated β-keto ester enantiomers can be readily accessed by simply switching the zinc(II) and copper(II) salts in the present system. These features suggest that the method can potentially be extended to asymmetric reactions involving the use of other nucleophiles.

Experimental Section

General Procedure for $Cu(OTf)_2$/SPANbox-Catalyzed Enantioselective Chlorination of β-Keto Esters

To an anhydrous dichloromethane solution (0.75 mL) of copper(II) triflate (3.6 mg, 0.01 mmol) and the SPANbox ligand **1a** (11.2 mg, 0.018 mmol) in a 5-mL Schlenk tube was added β-keto ester **2** (0.1 mmol), and the resulting mixture was stirred under argon at room temperature for 0.5 h. HFIP (11 μL, 0.1 mmol) was injected into the tube, and the mixture was stirred further for 10 min at room temperature before the chlorinating agent NCS (15.9 mg, 0.12 mmol) was added. After completion of the reaction as indicated by TLC analysis (5–10 min), the solvent was evaporated under vacuum and the residue was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (20:1) as the eluent. The *ee* value of the α-chloro-β-keto ester **3** was determined by chiral HPLC.

General Procedure for $Zn(OTf)_2$/SPANbox-Catalyzed Enantioselective Chlorination of β-Keto Esters

Zinc(II) triflate (1.8 mg, 0.005 mmol) and the SPANbox ligand **1a** (6.8 mg, 0.011 mmol) were dissolved in anhydrous 1,2-dichloroethane (0.37 mL) in a 5-mL Schlenk tube, and the solution was stirred at 60 °C under argon for 1 h. The β-keto ester **2** (0.1 mmol) was added, and the resulting mixture was stirred further at 60 °C for 0.5 h before the chlorinating agent NCS (15.9 mg, 0.12 mmol) was added. The reaction mixture was stirred at this temperature for a short period (*ca.* 5 min) until TLC indicated the completion of the reaction. The solvent was evaporated under vacuum and the residue was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (20:1) as the eluent. The *ee* value of the α-chloro-β-keto ester **3** was determined by chiral HPLC.

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References

[1] a) N. D. Kimpe, R. Verhé, *The Chemistry of α-Haloketones, α-Haloaldehydes, and α-Haloimines*, John Wiley & Sons, New York, **1988**; b) G. Thomas, *Medicinal Chemistry: An Introduction*, 2nd edn., John Wiley & Sons, Chichester, **2007**.

[2] For a highlight, see: a) M. Oestreich, *Angew. Chem.* **2005**, *117*, 2376–2379; *Angew. Chem. Int. Ed.* **2005**, *44*, 2324–2327. For reviews, see: b) H. Ibrahim, A. Togni, *Chem. Commun.* **2004**, 1147–1155; c) S. France, A. Weatherwax, T. Lectka, *Eur. J. Org. Chem.* **2005**, 475–479.

[3] For a review, see: A. M. R. Smith, K. K. Hii, *Chem. Rev.* **2011**, *111*, 1637–1656.

[4] For a review, see: G. Guillena, D. J. Ramon, *Tetrahedron: Asymmetry* **2006**, *17*, 1465–1492.

[5] For reviews: a) J. A. Ma, D. Cahard, *Chem. Rev.* **2004**, *104*, 6119–6146; b) S. Lectard, Y. Hamashima, M. Sodeoka, *Adv. Synth. Catal.* **2010**, *352*, 2708–2732; c) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470–477.

[6] a) L. Hintermann, A. Togni, *Helv. Chim. Acta* **2000**, *83*, 2425–2435; b) H. Ibrahim, F. Kleinbeck, A. Togni, *Helv. Chim. Acta* **2004**, *87*, 605–610; c) L. Hintermann, M. Perseghini, A. Togni, *Beilstein J. Org. Chem.* **2011**, *7*, 1421–1435.

[7] a) M. Marigo, N. Kumaragurubaran, K. A. Jørgensen, *Chem. Eur. J.* **2004**, *10*, 2133–2137; b) M. Frings, C. Bolm, *Eur. J. Org. Chem.* **2009**, 4085–4090. For an example of Cu(II)-catalyzed enantioselective *gem*-chlorofluorination of active methylene compounds, see: c) K. Shibatomi, A. Narayama, Y. Soga, T. Muto, S. Iwasa, *Org. Lett.* **2011**, *13*, 2944–2947.

[8] a) N. Shibata, J. Kohno, K. Takai, T. Ishimaru, S. Nakamura, T. Toru, S. Kanemasa, *Angew. Chem.* **2005**, *117*, 4276–4279; *Angew. Chem. Int. Ed.* **2005**, *44*, 4204–4207; b) K. Shibatomi, Y. Tsuzuki, S. Iwasa, *Chem. Lett.* **2008**, *37*, 1098–1099.

[9] a) M.-H. Qi, F.-J. Wang, M. Shi, *Tetrahedron: Asymmetry* **2010**, *21*, 247–253; b) J. J. Jiang, J. A. Huang, D. Wang, Z. L. Yuan, M. X. Zhao, F. J. Wang, M. Shi, *Chirality* **2011**, *23*, 272–276.

[10] M. Kawatsura, S. Hayashi, Y. Komatsu, S. Hayase, T. Itoh, *Chem. Lett.* **2010**, *39*, 466–467.

[11] Chiral bisoxazoline complexes of Zn(II) have been used in enantioselective chlorination and fluorination of β-keto phosphonates, a class of closely related chelating carbonyl substrates. See: L. Bernardi, K. A. Jørgensen, *Chem. Commun.* **2005**, 1324–1326.

[12] G. Bartoli, M. Bosco, A. Carlone, M. Locatelli, P. Melchiorre, L. Sambri, *Angew. Chem.* **2005**, *117*, 6375–6378; *Angew. Chem. Int. Ed.* **2005**, *44*, 6219–6222.

[13] Y. Cai, W. Wang, K. Shen, J. Wang, X. Hu, L. Lin, X. Liu, X. Feng, *Chem. Commun.* **2010**, 1250–1252.

[14] P. Etayo, R. Badorrey, M. D. Díaz-de-Villegas, J. A. Gálvez, *Adv. Synth. Catal.* **2010**, *352*, 3329–3338.

[15] The spiro-2,2′-bichroman motif has been used by van Leeuwen and co-workers for the construction of bisphosphine ligands (SPANphos) that are prone to *trans*-ligation as well as some modular diamine ligands, for leading works, see: a) Z. Freixa, M. S. Beentjes, G. D.

Batema, C. B. Dieleman, G. P. F. van Strijdonck, J. N. H. Reek, P. C. J. Kamer, J. Fraanje, K. Goubitz, P. W. N. M. van Leeuwen, *Angew. Chem.* **2003**, *115*, 1322–1325; *Angew. Chem. Int. Ed.* **2003**, *42*, 1284–1287; b) Z. Freixa, P. C. J. Kamer, M. Lutz, A. L. Spek, P. W. N. M. van Leeuwen, *Angew. Chem.* **2005**, *117*, 4459–4462; *Angew. Chem. Int. Ed.* **2005**, *44*, 4385–4388; c) C. Jiménez-Rodríguez, F. X. Roca, C. Bo, J. Benet-Buchholz, E. C. Escudero-Adán, Z. Freixa, P. W. N. M. van Leeuwen, *Dalton Trans.* **2006**, 268–278; d) X. Sala, E. J. García Suárez, Z. Freixa, J. Benet-Buchholz, P. W. N. M. van Leeuwen, *Eur. J. Org. Chem.* **2008**, 6197–6205. Very recently, we developed a catalytic asymmetric synthesis of aromatic spiroketals, which provided a facile synthesis of enantiopure analogous SPANphos: e) X. Wang, Z. Han, Z. Wang, K. Ding, *Angew. Chem.* **2012**, *124*, 960–964; *Angew. Chem. Int. Ed.* **2012**, *51*, 936–940.

[16] The spiro backbone has been recognized as one type of the privileged structures for chiral ligand construction: a) A. S. C. Chan, W. H. Hu, C. C. Pai, C. P. Lau, Y. Z. Jiang, A. Q. Mi, M. Yan, J. Sun, R. L. Lou, J. G. Deng, *J. Am. Chem. Soc.* 1997, ***119***, 9570–9571; b) M. A. Arai, M. Kuraishi, T. Arai, H. Sasai, *J. Am. Chem. Soc.* 2001, ***123***, 2907–2908; c) T. Tsujihara, K. Takenaka, K. Onitsuka, M. Hatanaka, H. Sasai, *J. Am. Chem. Soc.* 2009, ***131***, 3452–3453; d) Y. Fu, J.-H. Xie, A.-G. Hu, H. Zhou, L.-X. Wang, Q.-L. Zhou, *Chem. Commun.* **2002**, 480–481; e) S.-F. Zhu, Y. Cai, H. Mao, J.-H. Xie, Q.-L. Zhou, *Nat. Chem.* **2010**, *2*, 546–551; f) Z. Han, Z. Wang, X. Zhang, K. Ding, *Angew. Chem.* **2009**, *121*, 5449–5453; *Angew. Chem. Int. Ed.* **2009**, *48*, 5345–5349; g) K. Shibatomi, T. Muto, Y. Sumikawa, A. Narayama, S. Iwasa, *Synlett* **2009**, 241–244; h) K. Shibatomi, A. Narayama, Y. Soga, T. Muto, S. Iwasa, *Org. Lett.* **2011**, *13*, 2944–2947. For reviews, see: i) *Privileged Chiral Ligands and Catalysts*, (Ed.: Q.-L. Zhou), Wiley-VCH: Weinheim, **2011**; j) J.-H. Xie, Q.-L. Zhou, *Acc. Chem. Res.* 2008, **41**, 581–593; k) G. B. Bajracharya, M. A. Arai, P. S. Koranne, T. Suzuki, S. Takizawa, H. Sasai, *Bull. Chem. Soc. Jpn.* **2009**, *82*, 285–302; l) K. Ding, Z. Han, Z. Wang, *Chem. Asian J.* 2009, ***4***, 32–41.

[17] Bisoxazoline ligands (Box) are one type of the most versatile chiral inducers in various transition metal-catalyzed asymmetric reactions, for reviews, see: a) A. K. Ghosh, M. Packiarajan, J. Cappiello, *Tetrahedron: Asymmetry* **1998**, *9*, 1–45; b) H. A. McManus, P. J. Guiry, *Chem. Rev.* **2004**, *104*, 4151–4202; c) G. Desimoni, G. Faita, K. A. Jørgensen, *Chem. Rev.* **2006**, *106*, 3561–3651.

[18] Very recently, the Zn(II) complexes of this class of ligands have been shown to be highly efficient in the catalytic asymmetric hydroxylation of β-keto esters, see: J. Li, G. Chen, Z. Wang, R. Zhang, X. Zhang, K. Ding, *Chem. Sci.* **2011**, *2*, 1141–1144.

[19] The importance of metal/ligand ratios in copper-bisoxazoline catalysis has been demonstrated for other systems, for examples, see: a) R. Rasappan, M. Hager, A. Gissibl, O. Reiser, *Org. Lett.* **2006**, *8*, 6099–6102; b) A. Schätz, R. Rasappan, M. Hager, A. Gissibl, O. Reiser, *Chem. Eur. J.* **2008**, *14*, 7259–7265; c) M. Hager, S. Wittmann, A. Schätz, F. Pein, P. Kreitmeier, O. Reiser, *Tetrahedron: Asymmetry* **2010**, *21*, 1194–1198. In these studies, an excess of ligands was shown to have a detrimental effect on the catalysis. Even when an excess of ligand **1a** is used for the present catalysis using $Zn(OTf)_2$ or $Cu(OTf)_2$ salt, our previous study on a mechanistically related hydroxylation of keto esters using the same zinc catalyst (ref.[18]) suggested the catalytically active species in the chlorination reaction should be a 1:1 M/L species. The mass spectrum of $Cu(OTf)_2$/**1a** also indicated the presence of an 1:1 species along with a significant amount of free ligand **1a** (see the Supporting Information), indicating an equilibration of the species in the precatalyst solution. Presumably, an excess of ligand is required to suppress the background reaction promoted by ligand-free and unselective metal centers.

[20] Similar behavior has been observed in bisoxazoline complexes-catalyzed asymmetric fluorination of keto esters, where the choice of the metal salt Cu or Ni has been shown to afford opposite enantioselectivity, see: N. Shibata, T. Ishimaru, T. Nagai, J. Kohno, T. Toru, *Synlett* **2004**, 1703–1706.

[21] Assuming tetracoordinated modes adopted by SPANbox metal enolate intermediates for $Cu(OTf)_2$- or $Zn(OTf)_2$-mediated catalysis might account for their complementary nature in enantioselection. The reaction involving $Cu(OTf)_2$ is likely to proceed *via* a square-planar SPANbox-Cu-enolate intermediate, whereas the one with $Zn(OTf)_2$ should favor the formation of a tetrahedral SPANbox-Zn-enolate intermediate as a result of filled *d* orbitals (d^{10}) in Zn(II). Chiral bisoxazoline metal-bound substrates with these two geometries can afford opposite selectivity, since rotation of a coordinated substrate by 90° moves its accessible face from the shielded into the unshielded region, and *vice versa*. For an excellent review, see: R. Rasappan, D. Laventine, O. Reiser, *Coord. Chem. Rev.* **2008**, *252*, 702–714.

