Catalytic Asymmetric Bromination and Chlorination of β-Ketoesters

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Abstract: The first general catalytic asymmetric bromination and chlorination of β-ketoesters has been developed. The reactions proceed for both acyclic and cyclic β-ketoesters catalyzed by chiral bisoxazolinecopper(II) complexes giving the corresponding optically active α-bromo- and α-chloro-β-ketoesters in high yields and moderate to good enantioselectivities. For the optically active chlorinated products the isolated yields are in the range of 88–99% and the enantiomeric excesses up to 77% *ee*, while the optically active brominated adducts are formed in 70–99% isolated yield and up to 82% *ee*. Based on the absolute configuration of the optically active products, the face selectivity for the catalytic enantioselective halogenation is discussed based on a bidentate coordination of the β-ketoester to the chiral catalyst and a X-ray structure of chiral α,γ-diketoesterenolatebisoxazolinecopper(II) complex.

Keywords: asymmetric catalysis · bromination · chlorination · ketoesters

Introduction

The conversion of a C–H bond to a C–X bond is a formal oxidation of an organic molecule. Despite the importance of optically active halocarbon compounds, for example in organic synthesis, natural product chemistry, and in biomedical and pharmaceutical sciences, the catalytic enantioselective formation of halogenated chiral carbon stereocenters by C–X bond forming reactions remain very rare.[1]

Recently, the first catalytic, enantioselective fluorination of β-ketoesters with "Selectfluor" as the fluoro source catalyzed by chiral [$TiCl_2$(TADDOLato)] complexes was disclosed to give up to 90% *ee* for a substituted benzyl ester substrate by Togni et al.[2] Further developments by Sodeoka et al. lead to a catalytic, highly enantioselective fluorination reaction of acyclic and cyclic β-ketoesters by using a chiral BINAP–Pd complex as the catalyst and *N*-fluorobenzenesulfonimide as the fluorinating reagent.[3] Another example with chinchonine-derived quaternary ammonium salts was reported and the best selectivitity obtained was 69% *ee*.[4]

For the catalytic enantioselective chlorination and bromination reactions, Togni et al. have reported one example of a catalytic enantioselective chlorination reaction of an acyclic β-ketoester, which had a bulky benzyl-substituted ester functionality, with good enantioselectivity using chiral [$TiCl_2$(TADDOLato)] complexes as the catalyst.[5] However, the enantiomeric excesses of other acyclic compounds studied were generally only moderate. Application of the same reaction conditions for bromination reactions resulted unfortunately in low enantiomeric excess. Lectka et al. have developed a tandem asymmetric halogenation/esterification process of acyl halides using perhaloquinone-derived reagents as the halogen source.[6] The reactions were catalyzed by benzoylquinine. For both the chlorination and bromination reactions very high enantioselectivities, but moderate yields were obtained.

In this paper we disclose the first catalytic enantioselective chlorination and bromination reaction applicable to both acyclic- and cyclic β-ketoesters, and a β-diketone, producing the corresponding optically active α-halogenated compounds in excellent yields and moderate to good enantioselectivities using mainly *N*-chlorosuccinimide (NCS) and *N*-bromosuccinimide (NBS) as the halogen sources and chiral bisoxazolinecopper(II) complexes as the catalyst.[7–9]

Results and Discussion

A thorough series of screening experiments were performed in order to find general conditions for the catalytic enantioselective chlorination of β-ketoesters. The ethyl ester of 2-methyl-3-oxobutyric acid (**1a**) was chosen for this process with different chloro donors **2a–e**, chiral ligands **6a–j**, Lewis acids, such as copper(II) and magnesium(II), and reactions conditions [Eq. (1)]. Some representative results for the best combination of chiral ligands and Lewis acids under different reaction conditions are given in Table 1.

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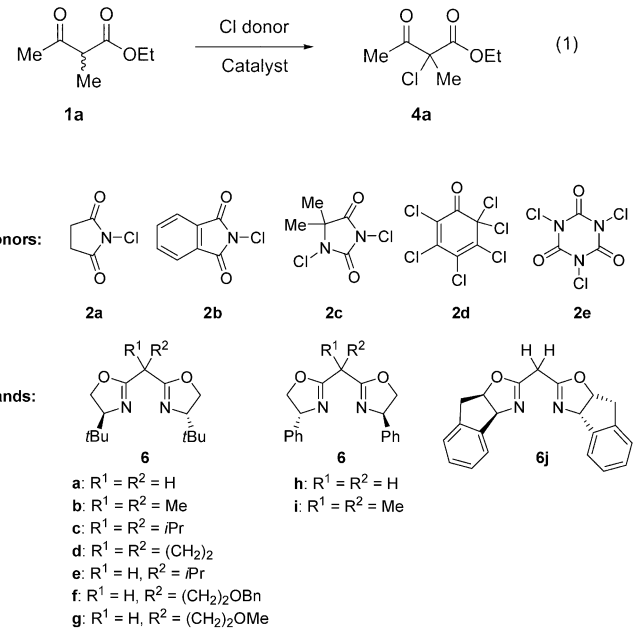

Table 1. Representative results from the screening of chiral ligands, copper(II) salts, reaction conditions for the catalytic asymmetric chlorination of the ethyl ester of 2-methyl-3-oxobutyric acid (**1a**) with various chlorination reagents **2a**–**e**.[a,b]

	Catalyst (10 mol%)	Chlorination reagent	Solvent	**4a** *ee*[c] [%]
1	[Cu(OTf)$_2$(**6b**)]	**2a**	Et_2O	77
2	[Cu(OTf)$_2$(**6b**)]	**2a**	CH_2Cl_2	30
3	[Cu(OTf)$_2$(**6b**)]	**2a**	dioxane	62
4	[Cu(OTf)$_2$(**6b**)]	**2a**	toluene	70
5	[Cu(OTf)$_2$(**6b**)]	**2a**	TBME	76
6	[Cu(SbF$_6$)$_2$(**6b**)]	**2a**	Et_2O	44
7	[Cu(OTf)$_2$(**6b**)]	**2b**	Et_2O	66
8	[Cu(OTf)$_2$(**6b**)]	**2c**	Et_2O	60
9	[Cu(OTf)$_2$(**6b**)]	**2d**	Et_2O	48
10	[Cu(OTf)$_2$(**6b**)]	**2e**	Et_2O	61
11	[Cu(OTf)$_2$(**6b**)]	**2e**[d]	Et_2O	61
12	[Cu(OTf)$_2$(**6i**)]	**2a**	Et_2O	32

[a] Experimental conditions: $Cu(OTf)_2$ (9 mg, 25 μmol) and (*S*)-(−)-2,2′-isopropylidene-bis(4-*tert*-butyl-2-oxazoline) (**6b**: 7.9 mg, 26 μmol) were mixed in an oven-dried Schlenk tube under vacuum for 2 h. The tube was then filled with N_2, distilled Et_2O (2 mL) was added, and the resulting solution was stirred for 1 h. Ethyl ester **1a** was added followed by the addition of *N*-chlorosuccinimide (**2a**) (39.9 mg, 0.30 mmol). After 16 h at room temperature the product was isolated by plug on silica using CH_2Cl_2 as eluent (see Experimental Section). [b] All reactions give full conversion. [c] Enantiomeric excess determined by GC or HPLC, see Experimental Section. [d] 33 mol% **2d**, not full conversion.

The investigation of combinations of chiral ligands and Lewis acids revealed that the [Cu(OTf)$_2${(*S*)-**6b**}] complex is the most promising catalyst. The catalytic enantioselective chlorination of **1a** proceeds in excellent yields and 77% *ee* of the ethyl ester of 2-chloro-2-methyl-3-oxobutyric acid (**4a**) was obtained by using NCS as the chlorination reagent with Et_2O as the solvent (Table 1, entry 1). The chlorination with NCS also proceeds well in different solvents (entries 2–5), but with lower enantioselectivity relative to Et_2O. The enantiomeric excess of **4a** is dependent on the copper(II) counterion as observed by comparing entry 1 with entry 6, as well as the chlorination reagent. We have found that the use of **2b**–**e** as the chloro source resulted in lower enantioselectivity of **4a** (entries 7–11) relative to NCS (entry 1). It is notable that the use of only 33 mol% of **2e** relative to **1a** gave the same enantiomeric excess (61% *ee*) of **4a**, as the use of one equimolar of **2e** (entry 11). The use of the [Cu(OTf)$_2${(*R*)-**6i**}] catalyst resulted in a drop in enantioselectivity of **4a** to 32% *ee* (entry 12). The drop in enantioselectivity with the latter catalyst is in contrast to the direct amination reactions of β-ketoesters, for which this catalyst gave the best results.[9e]

The addition of additives such as bases (e.g., Et_3N) and hexafluoroisopropanol (HFIP), did not improve the enantiomeric excess for reactions catalyzed by [Cu(OTf)$_2${(*S*)-**6b**}]. The chlorination of **1a** by **2a** catalyzed by [Cu(OTf)$_2${(*S*)-**6b**}] in Et_2O carried out at 0°C, 20°C and reflux afforded **4a** with identical optical purity; however, the reaction time was reduced significantly from 8 h at 0°C to 1 h at reflux.

The ester functionality of **1g** (ethyl ester) has been varied in order to investigate the influence of sterics of the ester on the enantioselectivity. Chlorination by NCS catalyzed by [Cu(OTf)$_2${(*S*)-**6b**}] at room temperature in Et_2O proceeds with full conversion, and for the corresponding methyl and *tert*-butyl esters 63% and 30% *ee*, respectively, were obtained, compared to 72% *ee* for the ethyl ester of 2-chloro-2-oxocyclopentancarboxylic acid (**4g**). It was found that the absolute configuration of the other chlorinated esters did not change relative to the absolute configuration of **4g** (see Experimental Section).

An important feature by the catalytic enantioselective chlorination applying NCS as the chloro source and [Cu(OTf)$_2${(*S*)-**6b**}] as the catalyst is that the reaction proceeds also well for other acyclic- and cyclic β-ketoesters, and a β-dicarbonyl compound, **1a**–**j** [Eq. (2) and Table 2].

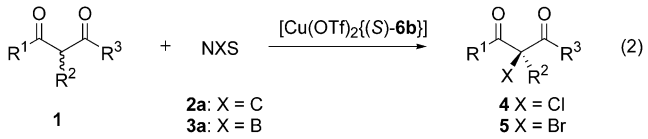

Table 2 shows the results for the chlorination of acyclic- and cyclic β-ketoesters, and a β-dicarbonyl compound, **1a**–**j** by NCS and with [Cu(OTf)$_2${(*S*)-**6b**}] (10 mol%) as the catalyst.

The catalytic enantioselective chlorination with **2a** at room temperature afforded the optically active α-chlorinated adducts **4a**–**j** in excellent yields; the products are isolated in 88–99% yield (Table 2, entries 1–10). For the optically active α-chlorinated acyclic β-ketoesters **4a**–**f**, up to 77% *ee* was obtained (entries 1–6), while the enantioselectivities for the optically active α-chlorinated cyclic β-ketoesters **4h**–**i** were in the range of 72–76% *ee* (entries 7–9). It should be noted that the enantiomeric excess of the optically active α-chlorinated β-ketoester adduct could be improved by recrystallization.[10] The β-diketone, 2-benzoyl-cyclohexanone (**1j**) was also chlorinated in an enantioselective manner by **2a** and optically active 2-chloro-2-benzoyl-cyclohexanone (**4j**)

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Table 2. Catalytic enantioselective chlorination and bromination of β-keto esters, and a β-diketone, **1a–j** with NCS (**2a**) and NBS (**3a**) catalyzed by [Cu(OTf)$_2$(**6b**)] (10 mol%) at room temperature in Et_2O and 1,4-dioxane, respectively [Eq. (2)].[a]

	β-Keto compound			Halogenation reagent	
	R^1	R^2	R^3	NCS **2a** Yield[b]/*ee*[c]	NBS **3a** Yield[b]/*ee*[c]
1	Me	Me	OEt (**1a**)	**4a** 98/77	**5a** 98/80
2	Et	Me	OEt (**1b**)	**4b** 96/57	**5b** 77/57
3	*i*Pr	Me	OEt (**1c**)	**4c** 88/48	**5c** 70/46
4[d]	Ph	Me	OEt (**1d**)	**4d** 98/53	**5d** 95/41
5	Me	Bn	OEt (**1e**)	**4e** 98/61	**5e** 99/66
6	Me	Et	OEt (**1f**)	**4f** 93/66	**5f** 90/70
7	$(CH_2)_3$		OEt (**1g**)	**4g** 96/72	–
8	$(CH_2)_4$		OEt (**1h**)	**4h** 99/76	**5h** 85/82
9	$(CH_2)_5$		OEt (**1i**)	**4i** 98/73	**5i** 80/71
10	$(CH_2)_4$		Ph (**1j**)	**4j** 99/32	–

[a] Experimental conditions: Cu(OTf)$_2$ (9 mg, 25 μmol) and (*S*)-(−)-2,2′-isopropylidene-bis(4-*tert*-butyl-2-oxazoline) (**6b**: 7.9 mg, 26 μmol) were mixed in an oven-dried Schlenk tube under vacuum for 2 h. The tube was then filled with N_2, distilled Et_2O (2 mL) was added, and the resulting solution was stirred for 1 h. The β-ketoester was added followed by the addition of *N*-chlorosuccinimide (39.9 mg, 0.30 mmol) or *N*-bromosuccinimide (50.0 mg, 0.29 mmol). After 16 h at room temperature the product was isolated by plug on silica using CH_2Cl_2 as eluent (see Experimental Section). [b] Isolated yields. [c] Determined by GC or HPLC, see Experimental Section. [d] Reaction time 40 h.

was obtained in excellent yields, but with lower enantioselectivitity relative to the β-ketoesters.

The absolute configuration of the optically active chlorination product was determined on the basis of optical rotation, which gave the *S* configuration for the ethyl ester of 1-phenyl-2-chloro-2-methyl-3-oxopropanoic acid (**4d**)[5] when [Cu(OTf)$_2${(*S*)-**6b**}] was the catalyst at room temperature in Et_2O and NCS as the chlorination reagent. The use of other chlorination reagents under the same reaction conditions gave the same absolute configuration of **4d**.

The [Cu(OTf)$_2${(*S*)-**6b**}] catalytic system was successfully applied for the bromination of acyclic- and cyclic β-ketoesters [Eq. (2)]. Different bromination reagents were studied and NBS was found to be an effective reagent both in terms of yield and enantiomeric excess of the optically active α-brominated β-ketoesters.

Table 2 also shows the results for the catalytic enantioselective bromination of the acyclic- and cyclic β-ketoesters **1a–f**,**h**,**i**. The results for the catalytic enantioselective bromination reactions are in many respects parallel to the chlorination reactions. The yields of the optically active α-bromo β-ketoesters **5a–f**,**h**,**i** are generally good with isolated yields in the range of 70–99%. Both the acyclic and cyclic β-ketoesters react with NBS and for the ethyl esters of 2-bromo-2-methyl-3-oxobutyric acid (**5a**) and 1-bromo-2-oxocyclohexanecarboxylic acid (**5h**), 80% and 82% *ee*, respectively, were obtained (entries 1 and 8). For the remaining α-bromo β-ketoesters formed the optically purity of the active bromo compounds ranges from moderate to good.

The formation of the *S*-enantiomer of **4d** by means of the catalyst [Cu(OTf)$_2${(*S*)-**6b**}] is in accordance with the coordination of the β-ketoester to the catalyst in a bidentate fashion. There is experimental and theoretical evidence that the molecular plane of the β-ketoester relative to the chiral bisoxazoline plane is approximately 45°.[11] The ligand (*S*)-**6b** in this intermediate will shield the *Re* face of the reactive enolate carbon atom of the β-ketoester leading to the observed absolute configuration. We have further support for such an intermediate, as we isolated and characterized the enolate form of an α,γ-diketoester coordinated to the [Cu^{II}{(*S*)-**6b**}] complex. The structure of this complex is depicted in Figure 1.[12]

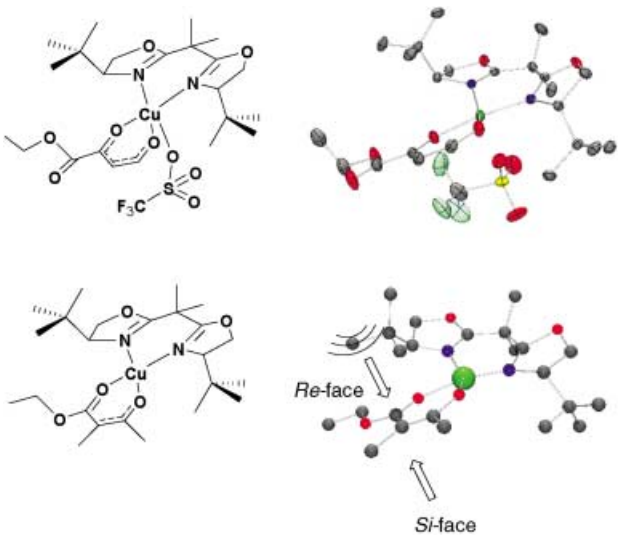

Figure 1. Top: X-ray structure of the enolate form of an α,γ-diketoester coordinated to the [Cu^{II}-(*S*)-**6b**] catalyst supporting the *Si*-face selectivity in the catalytic halogenation enantioselective reactions. Bottom: Proposed intermediate for the ethyl ester of 2-methyl-3-oxobutyric acid (**1a**) coordinated to the [Cu^{II}-(*S*)-**6b**] catalyst and suggested shielding of the *Re*-face of the enolate leaving the *Si*-face available for approach by the halogenation reagents.

The X-ray structure in Figure 1 (top) supports the face selectivity of the halogenation reaction. The ketoester coordinates to the [Cu^{II}{(*S*)-**6b**}] catalyst in its enolate form (C–C enolate bond length 1.391 Å); the *Re* face of the reacting carbon atom is shielded by the *tert*-butyl substituent of the chiral bisoxazoline ligand. Based on the absolute configuration of the *S* enantiomer of **4d** we proposed the intermediate shown in Figure 1 (bottom) for the reactions.[11] In this intermediate the chiral ligand of the [Cu^{II}{(*S*)-**6b**}] catalyst shields the *Re* face of the enolate leaving the *Si* face available for approach by the halogenation reagents

Conclusion

We have presented the first general catalytic asymmetric chlorination and bromination of both acyclic- and cyclic β-ketoesters using easy available halogenation reagents such as NCS and NBS, and [Cu(OTf)$_2${(*S*)-**6b**}] as the catalyst. The reactions proceeds in general in high yields for both the chlorination and bromination reactions and the corresponding optically active α-halogenated products are obtained

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with moderate to good enantioselectivities. The face-selectivity was accounted for by the β-ketoester coordinated to chiral catalyst in a bidentate fashion in its enolate form and with the *Re* face of the reacting carbon atom shielded by the *tert*-butyl substituent of the bisoxazoline ligand leaving the *Si* face open for approach of the halogenation reagent.

Experimental Section

General methods: The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to $CHCl_3$ ($\delta = 7.26$ ppm) for ^{1}H NMR spectra and relative to the central $CDCl_3$ resonance ($\delta = 77.0$ ppm) for ^{13}C NMR spectra. Coupling constants in ^{1}H NMR measurements are in Hz. Solvents were distilled according to standard procedures. Optical rotations were measured on a Perkin–Elmer 241 polarimeter and MeOH was used as solvent. The enantiomeric excess (*ee*) of the products was determined by HPLC using Chiralcel OJ or Daicel Chiralpack OB with *i*-PrOH/hexane as eluent, and by GC using a Chiraldex G-TA chiral stationary phase or a Chirasil Dex-CB chiral stationary phase.

Materials: Ligands **6h–j**, $Cu(OTf)_2$, β-ketoesters **1e–h,j** and *N*-chlorosuccinimide (**2a**) were purchased from Aldrich and used as received. The ethyl ester of 2-methyl-3-oxobutyric acid (**1a**) was purchased from Aldrich and used after purification. The ethyl ester of 2-methyl-3-oxopentanoic acid (**1b**) was prepared following literature procedure.[5] β-Ketoesters **1c,d,i** were prepared by *C*-alkoxycarbonylation of appropriate ketone following a literature procedure.[13] Ligands **6a–g** were prepared following a literature procedure.[14] *N*-bromosuccinimide **3a** was purified by recrystallization according to standard procedures.

General procedure for catalytic asymmetric chlorination of β-ketoesters: $Cu(OTf)_2$ (9 mg, 0.025 mmol) and (*S*)-(−)-2,2′-isopropylidene-bis(4-*tert*-butyl-2-oxazoline) (**6b**) (7.9 mg, 0.026 mmol) were added to an oven-dried Schlenk tube equipped with a magnetic stirrer bar. The mixture was stirred under vacuum for 2 h and filled with N_2. Distilled Et_2O (2 mL) was added and the solution was stirred for 1 h. The β-ketoester (0.25 mmol) was added at room temperature followed by the addition of *N*-chlorosuccinimide (**2a**) (39.9 mg, 0.30 mmol). After 16 h at room temperature the product was isolated by plug on silica using CH_2Cl_2 as eluent.

Ethyl ester of 2-chloro-2-methyl-3-oxobutyric acid (4a) The enantiomeric excess was determined by GC with use of a Chirasil Dex-CB chiral stationary phase. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.28$ (q, $J = 7.1$, 2H, OCH_2CH_3), 2.37 (s, 3H, CH_3CO), 1.82 (s, 3H, CCH_3), 1.30 ppm (t, 3H, $J = 7.1$, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 198.8$, 168.0, 70.7, 63.0, 25.2, 24.2, 13.8 ppm; HRMS: *m/z* calcd for $C_7H_{11}ClO_3$: calculated: 201.0294; found: 201.0325 $[M+Na]^+$; $[\alpha]_D = +3.6$ ($c = 10$ mg mL^{-1}, 77% *ee*).

Ethyl ester of 2-Chloro-2-methyl-3-oxopentanoic acid (4b) The enantiomeric excess was determined by GC with use of a Chirasil Dex-CB chiral stationary phase. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.25$ (q, $J = 7.1$, 2H, OCH_2CH_3), 2.83–2.63 (m, 2H, CH_3CH_2CO), 1.81 (s, 3H, CCH_3), 1.28 (t, 3H, $J = 7.1$, CH_2CH_3), 1.10 ppm (t, 3H, $J = 7.1$, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 202.2$, 188.2, 70.7, 62.9, 30.9, 13.8, 8.3 ppm; HRMS: *m/z* calcd for $C_8H_{13}ClO_3$: 215.0451; found: 215.0455 $[M+Na]^+$.

Ethyl ester of 2-chloro-2,4-dimethyl-3-oxopentanoic acid (4c): The enantiomeric excess was determined by GC with use of a Chiraldex G-TA chiral stationary phase. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.26$ (q, $J = 7.1$, 2H, OCH_2CH_3), 3.18 (m, 1H, $CH(CH_3)_2$), 1.82 (s, 3H, CCH_3), 1.30 (t, 3H, $J = 7.1$, CH_2CH_3), 1.20 (d, 3H, $J = 6.6$, $CHCH_3$), 1.14 ppm (d, 3H, $J = 6.6$, $CHCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 203.6$, 166.2, 70.2, 60.9, 34.5, 23.4, 18.9, 18.1, 11.9 ppm; HRMS: *m/z* calcd for $C_9H_{15}ClO_3$: 229.0670; found: 229.0597$[M+Na]^+$; $[\alpha]_D = -5.0$ ($c = 17$ mg mL^{-1}, 48% *ee*).

Ethyl ester of 1-henyl-2-chloro-2-methyl-3-oxopropanoic acid (4d): NMR data according to literature values,[5] $[\alpha]_D = -50.1$ ($c = 11$ mg mL^{-1}, 53% *ee*).

Ethyl ester of 2-chloro-2-benzyl-3-oxobutyric acid (4e): The enantiomeric excess was determined by HPLC using a Daicel Chiralpack OJ column (hexane/*i*PrOH (90:10): flow rate 1.0 mL min^{-1}: $\tau_{major} = 10.5$; $\tau_{minor} = 12.4$ min; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.23$ (m, 5H, ArH), 4.21 (m, 2H, OCH_2CH_3), 3.52 (d, $J = 14.4$, 1H, CCH_2Ph), 3.43 (d, $J = 14.4$, 1H, CCH_2Ph), 2.23 (s, 3H, CH_3), 1.23 ppm (t, 3H, $J = 7.3$, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 198.8$, 167.0, 133.9, 130.5, 128.1, 127.4, 75.2, 63.3, 42.1, 26.4, 13.8 ppm; HRMS: *m/z* calcd for $C_{13}H_{25}ClO_3$: 277.0607; found: 277.0609 $[M+Na]^+$.

Ethyl ester of 2-chloro-2-ethyl-3-oxobutyric acid (4f): The enantiomeric excess was determined by GC with use of a Chiraldex G-TA chiral stationary phase. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.27$ (q, $J = 7.1$, 2H, OCH_2CH_3), 2.33 (s, 3H, CH_3), 2.19 (m, 2H, CH_3CH_2C), 1.29 (t, 3H, $J = 7.1$, CH_2CH_3), 0.99 ppm (t, 3H, $J = 7.1$, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 198.4$, 167.3, 76.6, 62.9, 29.8, 25.9, 13.9, 8.5 ppm; HRMS: *m/z* calcd for $C_8H_{13}ClO_3$: 215.0451; found: 215.0445 $[M+Na]^+$; $[\alpha]_D = +1.3$ ($c = 12$ mg mL^{-1}, 66% *ee*).

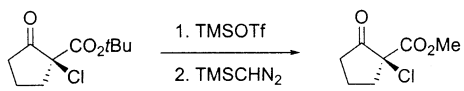
Ethyl ester of 2-chloro-2-oxocyclopentancarboxylic acid (4g): The enantiomeric excess was determined by GC with use of a Chirasil Dex-CB chiral stationary phase. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.27$ (q, $J = 7.1$, 2H, OCH_2CH_3), 2.74 (m, 1H, CH_2), 2.53 (m, 1H, CH_2), 2.39 (m, 2H, CH_2), 2.13 (m, 2H, CH_2), 1.30 ppm (t, 3H, $J = 7.1$, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 206.5$, 167.5, 69.9, 63.4, 38.6, 35.6, 19.3, 14.2 ppm; HRMS: *m/z* calcd for $C_8H_{11}ClO_3$: 213.0294; found: 213.0296 $[M+Na]^+$; $[\alpha]_D = -15.6$ ($c = 12$ mg mL^{-1}, 72% *ee*).

Ethyl ester of 2-chloro-2-oxocyclohexanecarboxylic acid (4h): The enantiomeric excess was determined by GC with use of a Chirasil Dex-CB chiral stationary phase. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.26$ (q, $J = 7.2$, 2H, OCH_2CH_3), 2.78 (m, 2H, CH_2), 2.40 (m, 1H, CH_2), 2.10 (m, 1H, CH_2), 1.88 (m, 2H, CH_2), 1.72 (m, 2H, CH_2), 1.27 ppm (t, 3H, $J = 7.3$, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 199.6$, 167.2, 73.5, 39.5, 38.8, 26.6, 22.1, 13.8 ppm; HRMS: *m/z* calcd for $C_9H_{13}ClO_3$: 227.0451; found: 227.0453 $[M+Na]^+$; $[\alpha]_D = -10.9$ ($c = 12$ mg mL^{-1}, 76% *ee*).

Ethyl ester of 2-chloro-2-oxocycloheptanecarboxylic acid (4i): The enantiomeric excess was determined by GC with use of a Chirasil Dex-CB chiral stationary phase. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.26$ (q, $J = 7.2$, 2H, OCH_2CH_3), 2.80 (m, 1H, CH_2), 2.66 (m, 1H, CH_2), 2.45 (m, 1H, CH_2), 2.29 (m, 1H, CH_2), 1.88–1.51 (m, 6H, CH_2), 1.29 ppm (t, 3H, $J = 7.2$, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 202.4$ 168.0, 66.2, 62.8, 40.6, 37.6, 29.1, 25.3, 24.6, 13.8 ppm; HRMS: *m/z* calcd for $C_{10}H_{15}ClO_3$: 241.0607; found: 241.0610 $[M+Na]^+$; $[\alpha]_D = -3.7$ ($c = 10.2$ mg mL^{-1}, 73% *ee*).

2-Chloro-2-benzoyl-cyclohexanone (4j): The enantiomeric excess was determined by HPLC using a Daicel Chiralpack OJ column (hexane/*i*PrOH (90:10)); flow rate 1.0 mL min^{-1}; $\tau_{major} = 9.9$; $\tau_{minor} = 9.0$; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.95$ (d, 2H, $J = 8.1$, ArH), 7.54 (t, 1H, $J = 7.4$, ArH), 7.40 (t, 2H, $J = 7.7$, ArH), 3.05 (m, 1H, CH_2), 2.77 (m, 1H, CH_2), 2.23–1.87 ppm (m, 6H, CH_2); ^{13}CNMR (100 MHz, $CDCl_3$): $\delta = 203.4$, 190.7, 134.1, 133.6, 130.0, 128.5, 41.3, 41.1, 28.3, 22.9 ppm; HRMS: *m/z* calcd for $C_{13}H_{13}ClO_3$: 259.0502; found: 259.0506 $[M+Na]^+$; $[\alpha]_D = +40.6$ ($c = 12$ mg mL^{-1}, 32% *ee*).

Compounds **7** and **8** were obtained from the appropriate β-ketoester, by using $[Cu(OTf)_2\{(S)$-**6b**$\}]$ and **2a** in Et_2O as solvent, with 30% and 63% *ee*, respectively. Transesterification of **7** to **8** (Scheme 1) confirmed the identical absolute configuration of the chlorinated adducts.



7 **8**

Scheme 1.

General procedure for catalytic asymmetric bromination of β-ketoesters: $Cu(OTf)_2$ (9 mg, 0.025 mmol) and (*S*)-**6b** (7.9 mg, 0.026 mmol) were added to an oven-dried Schlenk tube equipped with a magnetic stirrer bar. The mixture was stirred under vacuum for 2 h and filled with N_2.

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Distilled 1,4-dioxane (2 mL) was added and the solution was stirred for 1 h. 0.25 mmol of the β-ketoester was added at room temperature followed by the addition of *N*-bromosuccinimide (**3a**) (50 mg, 0.28 mmol). After 16 h at room temperature the product was isolated by flash chromatography.

Ethyl ester of 2-bromo-2-methyl-3-oxobutyric acid (5a): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.26$ (q, $J = 7.2$, 2H, $OC\mathbf{H_2}CH_3$), 2.42 (s, 3H, $\mathbf{CH_3}CO$), 1.96 (s, 3H, $CC\mathbf{H_3}$), 1.29 ppm (t, 3H, $J = 7.1$, $CH_2C\mathbf{H_3}$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 198.2$, 168.2, 70.7, 63.1, 63.1, 25.7, 25.2, 13.8 ppm; HRMS: *m*/*z* calcd for $C_7H_{11}BrO_3$: 244.9789; found: 244.9788 $[M+Na]^+$; $[\alpha]_D = +15.6$ ($c = 10$ mg mL^{-1}, 80% *ee*). The *ee* was determined after transformation to compound **5ap**.

Ethyl ester of 2-bromo-2-(2-methyl-[1,3]dioxolan-2-yl)propionic acid (5ap): The enantiomeric excess was determined by GC with use of a Chirasil Dex-CB chiral stationary phase. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.26$ (m, 2H, $OC\mathbf{H_2}CH_3$), 4.01 (m, 4H, $\mathbf{OCH_2CH_2O}$), 1.94 (s, 3H, $CC\mathbf{H_3}$), 1.57 (s, 3H, $CC\mathbf{H_3}$),1.30 ppm (t, 3H, $J = 7.1$, $CH_2C\mathbf{H_3}$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 169.4$, 110.5, 66.1, 66.0, 65.9, 62.3, 25.3, 21.7, 13.9 ppm; HRMS: *m*/*z* calcd for $C_9H_{15}BrO_4$: 289.0051; found: 289.0048 $[M+Na]^+$.

Ethyl ester of 2-bromo-2-methyl-3-oxopentanoic acid (5b): The enantiomeric excess was determined by GC with use of a Chirasil Dex-CB chiral stationary phase. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.25$ (q, $J = 7.1$, 2H, $OC\mathbf{H_2}CH_3$), 2.91–2.65 (m, 2H, $CH_3C\mathbf{H_2}CO$), 1.97 (s, 3H, $CC\mathbf{H_3}$), 1.28 (t, 3H, $J = 7.1$, $CH_2C\mathbf{H_3}$), 1.12 ppm (t, 3H, $J = 7.1$, $CH_2C\mathbf{H_3}$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 201.7$, 168.4, 63.0, 62.7, 31.5, 25.4, 13.8, 8.8 ppm; HRMS: *m*/*z* calcd for $C_8H_{13}BrO_3$: 258.9946; found: 258.9941 $[M+Na]^+$; $[\alpha]_D = +13.6$ ($c = 11$ mg mL^{-1}, 57% *ee*).

Ethyl ester of 2-bromo-2,4-dimethyl-3-oxopentanoic acid (5c): The enantiomeric excess was determined by GC with use of a Chiraldex G-TA chiral stationary phase. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.26$ (q, $J = 7.1$, 2H, $OC\mathbf{H_2}CH_3$), 3.17 (m, 1H, $CH_3(CH_3)_2$), 1.98 (s, 3H, $CC\mathbf{H_3}$), 1.30 (t, 3H, $J = 7.1$, $CH_2C\mathbf{H_3}$), 1.23 (d, 3H, $J = 6.6$, $CHC\mathbf{H_3}$), 1.14 ppm (d, 3H, $J = 6.6$, $CHC\mathbf{H_3}$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 205.2$, 168.3, 63.3, 63.1, 37.1, 25.4, 21.5, 20.5, 13.8 ppm; HRMS: *m*/*z* calcd for $C_9H_{15}BrO_3$: 273.0102; found: 273.0102 $[M+Na]^+$; $[\alpha]_D = +6.4$ ($c = 9$ mg mL^{-1}, 46% *ee*).

Ethyl ester of 1-phenyl-2-chloro-2-methyl-3-oxopropanoic acid (5d): NMR data according with literature values,[5] $[\alpha]_D = -44.6$ ($c = 12$ mg mL^{-1}, 41% *ee*).

Ethyl ester of 2-bromo-2-benzyl-3-oxobutyric acid (5e): The enantiomeric excess was determined by HPLC using a Daicel Chiralpack OJ column (hexane/*i*PrOH 90:10): flow rate 1.0 mL min^{-1}: $\tau_{major} = 9.2$; $\tau_{minor} = 11.1$ min; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.20$ (m, 5H, Ar**H**), 4.13 (m, 2H, $OC\mathbf{H_2}CH_3$), 3.49 (m, 2H, $CC\mathbf{H_2}Ph$), 2.27 (s, 3H, $C\mathbf{H_3}$) 1.15 ppm (t, 3H, $J = 7.1$, $CH_2C\mathbf{H_3}$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 197.7$, 167.0, 134.5, 130.4, 128.1, 127.4, 68.9, 63.1, 42.6, 26.8, 13.7 ppm; HRMS: *m*/*z* calcd for $C_{13}H_{25}BrO_3$: 321.0102; found: 321.0100 $[M+Na]^+$; $[\alpha]_D = +3.6$ ($c = 18$ mg mL^{-1}, 66% *ee*).

Ethyl ester of 2-bromo-2-ethyl-3-oxobutyric acid (5f): The enantiomeric excess was determined by GC with use of a Chiraldex G-TA chiral stationary phase. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.27$ (q, $J = 7.1$, 2H, $OC\mathbf{H_2}CH_3$), 2.38 (s, 3H, $COC\mathbf{H_3}$), 2.23–2.10 (m, 2H, $CH_3C\mathbf{H_2}C$), 1.29 (t, 3H, $J = 7.1$, $CH_2C\mathbf{H_3}$), 0.99 ppm (t, 3H, $J = 7.1$, $CH_2C\mathbf{H_3}$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 197.6$, 167.4, 70.6, 63.0, 30.4, 26.2, 13.9, 9.8 ppm; HRMS: *m*/*z* calcd for $C_8H_{13}ClO_3$: 258.9946; found: 258.9948 $[M+Na]^+$; $[\alpha]_D = +12.1$ ($c = 11$ mg mL^{-1}, 70% *ee*).

Ethyl ester of 1-bromo-2-oxocyclohexanecarboxylic acid (5h): The enantiomeric excess was determined by HPLC using a Daicel Chiralpack OB column (hexane/*i*PrOH 99.5:0.5): flow rate 0.5 mL min^{-1}: $\tau_{major} = 30.7$; $\tau_{minor} = 35.5$ min; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.23$ (q, $J = 7.2$, 2H, $OC\mathbf{H_2}CH_3$), 2.82 (m, 2H, $C\mathbf{H_2}$), 2.40 (m, 1H, $C\mathbf{H_2}$), 2.17 (m, 1H, $C\mathbf{H_2}$), 1.88–1.66 (m, 4H, $C\mathbf{H_2}$), 1.27 ppm (t, 3H, $J = 7.2$, $CH_2C\mathbf{H_3}$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 199.1$, 167.4, 67.5, 62.9, 40.5, 38.8, 26.7, 23.1, 13.8 ppm; HRMS: *m*/*z* calcd for $C_9H_{13}BrO_3$: 270.9946; found: 270.9939 $[M+Na]^+$.

Ethyl ester of 1-bromo-2-oxocycloheptanecarboxylic acid (5i): The enantiomeric excess was determined by GC with use of a Chirasil Dex-CB chiral stationary phase. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.26$ (q, $J = 7.2$, 2H, $OC\mathbf{H_2}CH_3$), 2.80 (m, 1H, $C\mathbf{H_2}$), 2.66 (m, 1H, $C\mathbf{H_2}$), 2.45 (m, 1H, $C\mathbf{H_2}$), 2.29 (m, 1H, $C\mathbf{H_2}$), 1.88–1.51 (m, 6H, $C\mathbf{H_2}$), 1.29 ppm(t, 3H, $J = 7.2$, $OCH_2C\mathbf{H_3}$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 202.4$ 168.0, 66.2, 62.8, 40.6, 37.6, 29.1, 25.3, 24.6, 13.8 ppm; HRMS: *m*/*z* calcd for $C_{10}H_{15}BrO_3$: 285.0102; found: 285.0099 $[M+Na]^+$; $[\alpha]_D = -30.6$ ($c = 16$ mg mL^{-1}, 71% *ee*).

Acknowledgements

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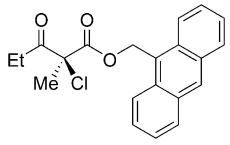

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