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Chiral 2-Amino Alcohol Derivatives Catalyze the Enantioselective α-Chlorination of β-Ketoesters

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The enantioselective α-chlorination of cyclic β-ketoesters catalyzed by chiral 2-aminoalcohol derivatives (**2f**) has been developed. For the optically active α-chlorinated products, the isolated yields are in the range of 85-94% and the enantiomeric excesses are up to 84% ee.

Key Words : Enantioselective α-chlorination, 2-Aminoalcohol derivatives, β-Ketoesters

Introduction

The enantioselective construction of C-X stereogenicity has gained considerable momentum in modern organic synthesis, drug, discovery and sciences.[1-5] For the enantioselective α-chlorination of β-ketoesters, several metal-mediated approaches have been reported.[6-11] However, the organocatalytic enantioselective α-chlorination is still rare.

In 2005, the first enantioselective α-chlorination of β-ketoesters with polyhalogenated quinolinone as the halogen source catalyzed by *O*-benzoylquinine was achieved by Melchiorre *et al*.[12] Feng *et al.* reported further developments on a highly enantioselective α-chlorination of β-ketoesters by using (*S*)-pipecolic acid derived *N,N'*-dioxide as organocatalyst and *N*-chlorosuccinimide (NCS) as the chlorinating reagent at –20 °C.[13] Furthermore, Etayo *et al.* also reported the examples of highly enantioselective chlorination of cyclic β-ketoesters catalyzed by chiral amino diol derivatives using NCS as the chlorine Source.[14] However, multi-step synthesis and complex structure catalysts were the main drawbacks of these methods.

In this paper we disclose that the commercially available chiral 2-aminoalcohol derivatives catalyze the asymmetric chlorination applicable to cyclic β-ketoesters producing the corresponding optically active α-halogenated compounds in good yields and moderate to good enantioselectivities using NCS (**3a**) as the chlorine source.

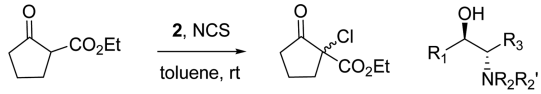
Results and Discussion

A series of screening experiments were performed in order to examine the catalytic efficiency of several commercially available chiral 2-aminoalcohol derivatives (**2a-i**). The ethyl-2-oxocyclopentane carboxylate (**1a**) was chosen as the model substrate with NCS (**3a**) as chlorine donor in toluene at room temperature. The results were shown in Table 1.

As shown in Table 1, all catalysts led to good yields. The size of R_3 played an important role in controlling the enantioselectivity. For example, catalyst **2b** containing the largest R_3 group gave better result (Table 1, entry 2), and the catalyst **2c** containing the smallest R_3 group showed the lowest catalytic selectivity with 13% ee (Table 1, entry 3). R_1 group has little influence on the enantioselectivity (Table 1, entries 1 and 5).

By comparing catalysts **2f** and **2b** or catalysts **2g** and **2a**, it was obvious that the introduction of a methyl group on the nitrogen atom has a beneficial effect on both conversion and enantioselectivity of products (Table 1, entries 1-2, 6 and 8). Nevertheless, the catalysts with two alkyl groups on the nitrogen atom only obtained mediate enantioselectivity (Table 1, entries 9-10). Lowering the temperature from room temperature to 0 °C in all cases led to an improvement in enantioselectivity (Table 1, entry 7).

Table 1. Screening of catalysts in the enantioselective α-chlorination of β-ketoesters (**1a**) with NCS[a]

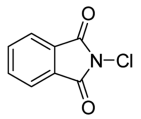
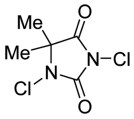
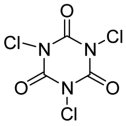


1a **4a** (**2**)

Entry	R_1	R_2, R_2'	R_3	Catalyst	Yield (%)[b]	ee (%)[c]
1	Ph	H, H	CH_3	**2a**	83	51
2	Ph	H, H	Ph	**2b**	85	59
3	1-naphth-OCH_2	H, H	H	**2c**	82	13
4	Ph_2CH	H, H	CH_2SEt	**2d**	82	53
5	2,5-$(MeO)_2Ph$	H, H	CH_3	**2e**	81	52
6	Ph	H, CH_3	Ph	**2f**	87	65
7	Ph	H, CH_3	Ph	**2f**	87	67[d]
8	Ph	H, CH_3	CH_3	**2g**	87	62
9	Ph	CH_3, $CHMe_2$	CH_3	**2h**	76	46
10	Ph	Bu, Bu	CH_3	**2i**	77	43

[a]**2a-i** (20 mol %), **1a** (1.0 mmol), NCS (**3a**, 1.2 mmol), toluene (5 mL) at room temperature. [b]Isolated yield. [c]Enantiomeric excess determined by GC using a chiraldex® G-TA column. [d]Reaction temperature at 0 °C

Table 2. Screening of the chlorine donors and solvents in **2f**-catalyzed α-chlorination of **1a**

Entry	Chlorine Donor	Solvent	Yield (%)[a]	ee (%)[b]
1	NCS (**3a**)	toluene	86	67
2	 (**3b**)	toluene	81	41
3	 (**3c**)	toluene	78	10
4	 (**3d**)	toluene	77	<5
5	CF_3SO_2Cl (**3e**)	toluene	77	0
6	NCS (**3a**)	cyclohexane	90	72
7	NCS (**3a**)	benzene	84	66
8	NCS (**3a**)	1,2-dichloroethane	84	45
9	NCS (**3a**)	tetrachloride	88	69

[a]Isolated yield. [b]Enantiomeric excess determined by GC using a Chiraldex® G-TA column

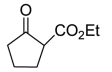
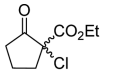
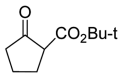
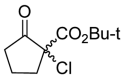
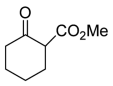
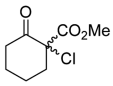
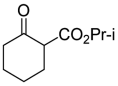
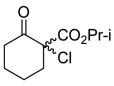
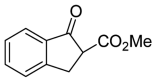
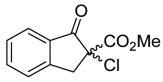
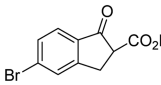
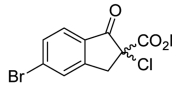
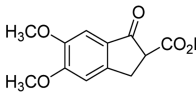
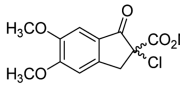
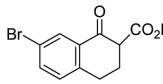
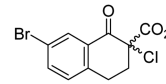
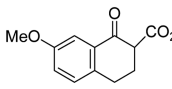
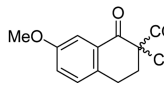
The effects of solvent and chlorine donor on the **2f**-catalyzed asymmetric α-chlorination of **1a** at 0 °C were studied. The results showed that NCS was the best choice (Table 2, entry 1). The use of reagents **3b-d**, which have nitrogen-chlorine bonds, afforded product **4a** with good yield but had a detrimental effect on the enantioselectivity (Table 2, entries 2-4). Using **3e** as chlorine donor, no enantiomeric excess product was obtained (Table 2, entry 5). The effects of solvent on the reaction were also studied. The best result was given when the reaction was performed in cyclohexane (Table 2, entry 6).

Under our optimized reaction conditions, we investigated **2f**-catalyzed enentioselective α-chlorination of various cyclic β-ketoesters with NCS (**3a**) in cyclohexane at 0 °C to afford the optically active α-chlorinated adducts **4a-i** in high yields (Table 3). The substrates with sterically more bulky ester groups gave the higher enantioselectivities (Table 3, entry 2). Substrates **1f** and **1h** bearing an electron withdrawing bromine atom and substrates **1g** and **1i** with electron donating groups such as MeO substituent on the benzene ring produced the similar enantioselectivities. Six-membered ring esters were less enantioselective than five-membered ring ones (Table 3, entries 5-9).

Conclusion

In summary, we have presented the enantioselective chlorination of cyclic β-ketoesters using inexpensive commercially available NCS as chlorine source and **2f** as the catalyst.

Table 3. 2f-Catalyzed enantioselective chlorination of β-ketoesters with NCS[a]

Entry	Substrate	Product	Yield (%)[b]	ee (%)[c]
1	 (**1a**)	 (**4a**)	90	72
2	 (**1b**)	 (**4b**)	87	75
3	 (**1c**)	 (**4c**)	87	69
4	 (**1d**)	 (**4d**)	85	72
5	 (**1e**)	 (**4e**)	91	81
6	 (**1f**)	 (**4f**)	92	81
7	 (**1g**)	 (**4g**)	94	84
8	 (**1h**)	 (**4h**)	86	77
9	 (**1i**)	 (**4i**)	85	78

[a]Reaction conditions: **2f** (20 mol %), **1a-i** (1.0 mmol.), NCS (1.2 mmol.), cyclohexane (5 mL) at 0 °C. [b]Isolated yield. [c]Enantiomeric excess determined by GC using a Chiraldex® G-TA column (**4a-d**), or by HPLC using a Chiralpak IB column (**4e**), AD-H column (**4h**), and Chiralpak OD-H column (**4f-g**, **i**).

The reactions proceeded smoothly to afford the corresponding optically active α-chlorinated products in high yields with moderate to good enantioselectivities.

Experimental

General Methods. The reagents were purchased from Merck, ^{1}H and ^{13}C spectra were recorded in $CDCl_3$ on a 400 MHz instrument at 400 MHz (^{1}H) and 100 MHz (^{13}C) with TMS as internal standard. High performance liquid chromatography (HPLC) was performed on an Agilent 1100 liquid chromatograph; HPLC analysis using Diacel chiralcel IB, OD or AD-H column. Gas chromatography analyses were performed using a Varian CP-3800 instrument equipped using an Astec Chiraldex® G-TA 30 m × 0.25 mm capillary column. Flash column chromatography was performed with 300- and 400-mesh silica gel.

General Procedure for Organocatalytic Asymmetric α-Chlorination of β-Ketoesters 4a-i. To a solution of chiral 2-amino alcohol derivatives (**2f**) (45.4 mg, 0.2 mmol) in the

cyclohexane (5 mL), the corresponding β-ketoester (1 mmol) was added and the mixture was stirred for 10 min at 0 °C. Then NCS (159.6 mg, 1.2 mmol) was added and stirring was continued for the indicated time. The crude reaction mixture was added to a silica gel column and eluted using dichloromethane/hexanes (1:1 or 2:1) as eluent depending on the product polarity. After evaporation of the solvent under vacuum the enantiomeric excess of the corresponding isolated α-chloro-β-ketoester was determined by GC or HPLC analysis using chiral stationary phases.

Ethyl of 2-Chloro-2-oxocyclopentanecarboxylic acid 4a: Colourless oil, GC conditions: Chiraldex® G-TA; T_1 = 50 °C, t_1 = 1 min, v_1 = 8 °C min^{-1}, T_2 = 150 °C, t_2 = 15 min, v_2 = 10 °C min^{-1}, T_3 = 50 °C, t_3 = 1 min; t_R = 20.0 [minor], t_R = 22.6 [major]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35 (t, 3H), 2.06–2.20 (m, 2H), 2.37–2.45 (m, 2H), 2.49–2.60 (m, 1H), 2.68–2.77 (m, 1H), 4.21 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 27.5, 35.8, 38.2, 60.9, 84.1, 166.1, 206.8; Elemental analysis found C, 50.40, H, 5.83, Cl, 18.63, $C_{13}H_{13}ClO_5$; Requires C, 50.41, H, 5.82, Cl, 18.60.

Tert-Butyl of 2-Chloro-2-oxocyclopentanecarboxylic acid 4b: Yellowish solid, GC conditions: Chiraldex® G-TA; T_1 = 50 °C, t_1 =1 min, v_1 = 8 °C min^{-1}, T_2 = 135 °C, t_2 = 25 min, v_2 = 10 °C min^{-1}, T_3 = 50 °C, t_3 = 1 min; t_R = 23.2 [major], t_R = 23.5 [minor]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48 (s, 9H), 2.06–2.19 (m, 2H), 2.35–2.46 (m, 2H), 2.47–2.59 (m, 1H), 2.67–2.77 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 27.7, 35.6, 38.5, 70.3, 84.1, 166.1, 206.8; Elemental analysis found C, 54.93, H, 6.93, Cl, 16.21, $C_{13}H_{13}ClO_5$; Requires C, 54.92, H, 6.91, Cl, 16.21.

Methyl of 2-Chloro-2-oxocyclohexanecarboxylic acid 4c: Colourless oil, GC conditions: Chiraldex® G-TA; T_1 = 50 °C, t_1 = 1 min, v_1 = 8 °C min^{-1}, T_2 = 150 °C, t_2 = 15 min, v_2 = 10 °C min^{-1}, T_3 = 50 °C, t_3 = 1 min; t_R = 21.7 [minor], t_R = 25.0 [major]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.65-1.78 (m, 1H), 1.84-2.01 (m, 3H), 2.14 (ddd, 14.0 Hz, 8.0 Hz, 3.2 Hz, 1H), 2.42 (ddd, *J* = 13.7 Hz, 6.6 Hz, 6.6 Hz, 1H), 2.72-2.89 (m, 2H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.9, 26.5, 38.6, 39.5, 53.3, 73.2, 166.8, 200.0; Elemental analysis found: C, 50.39, H, 5.80, Cl, 18.58 $C_8H_{11}ClO_3$; Requires C, 50.41, H, 5.82, Cl, 18.60.

Isopropyl of 2-Chloro-2-oxocyclohexanecarboxylic acid 4d: Colourless oil. GC conditions: Chiraldex® G-TA; T_1 = 50 °C, t_1 = 1 min, v_1 = 8 °C min^{-1}, T_2 = 150 °C, t_2 = 10 min, v_2 = 10 °C min^{-1}, T_3 = 50 °C, t_3 = 1 min; t_R = 20.9 [minor], t_R = 23.9 [major]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (d, *J* = 6.4 Hz, 3H), 1.27 (d, *J* = 6.4 Hz, 3H), 2.03–2.20 (m, 2H), 2.33–2.44 (m, 2H), 2.50–2.61 (m, 1H), 2.73 (ddd, *J* = 14.4 Hz, 9.2 Hz, 8.0 Hz, 1H), 5.11 (sept, *J* = 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.0, 21.5, 21.6, 35.5, 38.3, 69.9, 71.1, 166.8, 206.2; Elemental analysis found C, 54.91, H, 6.89, Cl, 16.19 $C_{10}H_{15}ClO_3$; Requires C, 54.92, H, 6.91, Cl, 16.21.

Methyl of 2-Chloro-1-oxo-indan-2-carboxylic acid 4e: Pale yellow oil. HPLC conditions: Daicel Chiralpak IB, hexane/*i*-PrOH = 96/4, 1.0 mL/min, 230 nm; t_R = 9.9 [major], t_R = 11.6 [minor]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.58 (d, *J* = 17.6 Hz, 1H), 3.83 (s, 3H), 4.11 (d, *J* = 17.6 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 2H), 7.70 (t, *J* = 7.2 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H); Elemental analysis found C, 58.80, H, 4.02, Cl, 15.77 $C_{11}H_9ClO_3$; Requires C, 58.81, H, 4.04, Cl, 15.78.

Methyl of 5-Bromo-2-chloro-1-oxo-indan-2-carboxylic acid 4f: White solid. HPLC conditions: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90/10, 0.7 mL/min, 254 nm; t_R = 16.9 [major], t_R = 20.6 [minor]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.54 (d, *J* = 18.0 Hz, 1H), 3.83 (s, 3H), 4.11 (d, *J* = 18.0 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.68 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 42.9, 54.0, 67.3, 127.0, 129.5, 131.0, 132.1, 132.3, 151.9, 167.5, 193.7; Elemental analysis found: C, 43.52, H, 2.64, Br, 26.34, Cl, 15.77 $C_{11}H_8BrClO_3$; Requires C, 43.53, H, 2.66, Br, 26.32, Cl, 15.76.

Methyl of 2-Chloro-5,6-dimethoxy-1-oxo-indan-2-carboxylic acid 4g: Pale yellow solid. HPLC conditions: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 80/20, 0.7 mL/min, 254 nm; t_R = 18.3 [major], t_R = 20.7 [minor]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.49 (d, *J* = 17.2 Hz, 1H), 3.82 (s, 3H), 3.92 (s, 3H), 4.01 (s, 3H), 4.04 (d, *J* = 17.2 Hz, 1H), 6.86 (s, 1H), 7.24 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 43.0, 54.0, 56.2, 56.5, 68.4, 105.6, 107.0, 125.0, 146.5, 150.3, 157.1, 167.8, 193.5; Elemental analysis found C, 54.82, H, 4.61, Cl, 12.45 $C_{13}H_{13}ClO_5$; Requires C, 54.84, H, 4.60, Cl, 12.45.

Methyl of 2-Chloro-7-bromo-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid 4h: White solid, HPLC conditions: Daicel Chiralpak AD-H; hexane/*i*-PrOH = 80/20, 1.0 mL/min, 254 nm; t_R = 12.0 [major], t_R = 13.1 [minor]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.49-2.55 (m, 1H), 2.93-3.10 (m, 2H), 3.17-3.26 (m, 1H), 3.85 (s, 3H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.65 (dd, *J* = 2.0 Hz, 8.4 Hz, 1H), 8.20 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.0, 29.8, 34.8, 54.0, 70.2, 121.5, 130.5, 131.5, 131.5, 137.1, 141.2, 167.5, 186.3; Elemental analysis found C, 45.36, H, 3.15, Br, 25.13, Cl, 11.14 $C_{12}H_{10}BrClO_3$; Requires C, 45.39, H, 3.17, Br, 25.16, Cl, 11.16.

Methyl of 2-Chloro-7-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid 4i: White solid. HPLC conditions: Daicel Chiralpak OD-H; hexane/*i*-PrOH = 98/2, 1.0 mL/min, 254 nm; t_R = 20.0 [major], t_R = 21.9 [minor]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.47-2.54 (m, 1H), 2.90-3.00 (m, 2H), 3.16-3.24 (m, 1H), 3.83 (s, 3H), 3.85 (s, 3H), 7.13 (dd, *J* = 8.4 Hz, 2.8 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.9, 35.5, 53.8, 55.5, 70.6, 110.5, 123.0, 130.0, 130.5, 135.3, 158.7, 168.0, 187.5; Elemental analysis found C, 58.08, H, 4.89, Cl, 13.20 $C_{13}H_{13}ClO_4$; Requires C, 58.11, H, 4.88, Cl, 13.19.

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