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Copper(II)-mediated resolution of α-halo carboxylic acids with chiral *O*,*O*′-dibenzoyltartaric acid: spontaneous racemization and crystallization-induced dynamic resolution†

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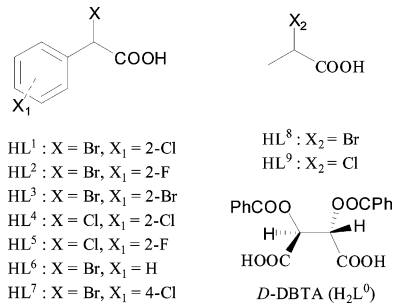
Herein we present a new example of coordination-mediated resolution of racemic acids by a chiral acid. The reaction of copper(II) acetate monohydrate, optically pure *O*,*O*′-dibenzoyltartaric acid (DBTA) and racemic α-bromo-2-chlorophenylacetic acid (HL^1) in acetonitrile solution afforded a binuclear copper(II) complex with D-DBTA dianion, α-bromo-2-chlorophenylacetate and acetate as ligands. After decomposition of the complex with acid, the optically active acid ((*R*)–HL^1) was obtained. Similarly, α-bromo-2-fluorophenylacetic acid (HL^2), α-bromo-2-bromophenylacetic acid (HL^3), α-chloro-2-chlorophenylacetic acid (HL^4), α-chloro-2-fluorophenylacetic acid (HL^5), α-bromophenylacetic acid (HL^6), α-bromo-4-chlorophenylacetic acid (HL^7), 2-bromopropionic acid (HL^8) and 2-chloropropionic acid (HL^9) were resolved by the same method. Satisfactory results were obtained for HL^2 to HL^5. For HL^6 and HL^7, only racemic acids were obtained. For the two α-halo aliphatic acids (HL^8 and HL^9), poor enantioselectivity was obtained. It is more interesting that three acids (HL^1, HL^2 and HL^3) could spontaneously racemize in acetonitrile solution, which resulted in crystallization-induced dynamic resolution (CIDR) with greater than 50% yield.

Introduction

Optically active molecules play important roles in both industrial and academic sectors. Methods of obtaining the enantiomerically enriched substances can be classified into two broad categories: optical resolution of racemates, and asymmetrization of prochiral or meso compounds. Although many traditional resolutions have already been well-established methods for the preparation of optically active compounds, they have an economic disadvantage in that the maximum yield for each of the two pure enantiomers is theoretically limited to 50%.[1] Crystallization-induced dynamic resolution (CIDR), which is a method utilizing the epimerization of the substrate and the solubility difference of the diastereomeric salts, is one of the most important recent developments in the preparation of optically pure compounds due to the greater than 50% yield of the obtained enantiomer.[2,3]

Racemic carboxylic acids are generally resolved by optically active bases. However, these bases are often extremely toxic and expensive.[1] For example, α-bromo-2-chlorophenylacetic acid, which is an important intermediate for some medicines,[4–6] was resolved by such bases in low yield (<25%).[6] Recently, the Mravik group applied optically active DBTA, which is usually used for the resolution of bases, as a new resolving reagent for the racemic carboxylic acids. Some new metal–mixed ligand complexes of DBTA can form with the corresponding acids and then optically active acids can be obtained by their decomposition.[7–9] In contrast to the bases, optically pure DBTA is a relatively cheap, nontoxic reagent. Therefore, this method is promising for the resolution of acids.

We report here a new example in which a series of racemic α-halo acids (Scheme 1) were resolved with a chiral acid. The reactions of $Cu(OAc)_2 \cdot H_2O$, optically pure *O*,*O*′-dibenzoyltartaric acid monohydrate and the corresponding racemic halo acid in acetonitrile solution afforded mixed ligand copper(II) complexes. After their decomposition with hydrogen chloride solution, optically active acids were obtained. Moreover, three acids (HL^1, HL^2, and HL^3) can spontaneously racemize in acetonitrile solution, and thus were resolved by crystallization-induced dynamic resolution.



Scheme 1 The structures of α-halo acids.

Results and discussion

Resolution of HL^1

To a solution of D-DBTA·H_2O ($H_2L^0 \cdot H_2O$, 1 equiv.) and racemic α-bromo-2-chlorophenylacetic acid (HL^1, 2 equiv.) in acetonitrile, was added copper(II) acetate monohydrate (1 equiv.) and the resulting mixture was stirred for several days at 25 °C. A green precipitate was collected by filtration and characterized as $[Cu_2(L^0)(L^1)(OAc)(H_2O)_2] \cdot 1.5$ MeCN (complex **1**) by elemental

† Electronic supplementary information (ESI) available: Experimental procedures, IR spectra, UV-vis spectra, thermograms. See DOI: 10.1039/b510170k

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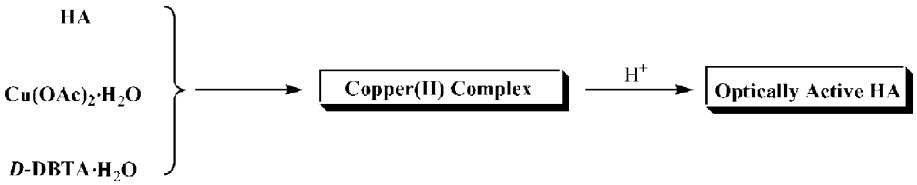
Table 1 Resolution of the α-halo acids



Entry	HA	Solvent	Ratio[a]	T (°C)	Time/d	Obtained complex	Ee of the acid (%)[b]	Yield of the acid (%)[c]
1	HL^1	MeCN	2 : 1 : 2	25	7	**1**	85.0 (*R*)	42.2
2	HL^1	MeCN	1 : 1 : 2	25	7	**1**	85.0 (*R*)	84.0
3	HL^1	MeCN	1 : 1 : 2	30	7	**1**	90.5 (*R*)	84.3
4	HL^1	MeCN	1 : 1 : 2	35	7	**1**	91.8 (*R*)	84.3
5	HL^1	MeCN	1 : 1 : 2	40	7	**1**	94.7 (*R*)	82.4
6	HL^1	MeCN	1 : 1 : 2	50	7	**1**	91.3 (*R*)	83.5
7	HL^1	MeCN–H_2O (16 : 1)	1 : 1 : 2	40	5	**1**	94.1 (*R*)	84.1
8	HL^1	EtOH–H_2O (3 : 1)	2 : 1 : 2	40	1[d]	**10**	25.7 (*S*)	20.2
9	HL^2	MeCN	2 : 1 : 2	40	7	**2**	92.0 (−)	43.3
10	HL^2	MeCN	1 : 1 : 2	40	7	**2**	91.5 (−)	83.5
11	HL^2	MeCN–H_2O (16 : 1)	1 : 1 : 2	40	5	**2**	89.9 (−)	83.3
12	HL^3	MeCN	2 : 1 : 2	40	7	—[e]	—	—
13	HL^3	MeCN–H_2O (16 : 1)	2 : 1 : 2	40	5	**3**	93.7 (+)	43.7
14	HL^3	MeCN–H_2O (16 : 1)	1 : 1 : 2	40	5	**3**	93.6 (+)	85.5
15	HL^4	MeCN	2 : 1 : 2	40	7	**4**	87.6 (−)	30.6
16	HL^4	MeCN	1 : 1 : 2	40	14[f]	**4**	94.8 (−)	37.2
17	HL^4	MeCN–H_2O (16 : 1)	1 : 1 : 2	40	5	—[e]	—	—
18	HL^5	MeCN	2 : 1 : 2	40	7	**5**	87.9 (−)	34.0
19	HL^5	MeCN	1 : 1 : 2	40	14[f]	**5**	80.5 (−)	38.6
20	HL^5	MeCN–H_2O (16 : 1)	1 : 1 : 2	40	5	—[e]	—	—
21	HL^6	MeCN	2 : 1 : 2	40	7	**6**	0	45.7
22	HL^6	MeCN	1 : 1 : 1	40	7	**6**	0	89.5
23	HL^7	MeCN	2 : 1 : 2	40	7	**7**	3.2	43.8
24	HL^7	MeCN	1 : 1 : 1	40	7	**7**	0	90.0
25	HL^8	MeCN	2 : 1 : 2	40	7	**8**	20.9 (*R*)	45.3
26	HL^8	MeCN	1 : 1 : 2	40	7	**8**	14.8 (*R*)	74.2
27	HL^8	MeCN–H_2O (16 : 1)	1 : 1 : 2	40	5	**8**	17.3 (*R*)	74.1
28	HL^9	MeCN	2 : 1 : 2	40	7	**9**	26.8 (*R*)	42.6
29	HL^9	MeCN	1 : 1 : 2	40	7	**9**	27.9 (*R*)	72.5
30	HL^9	MeCN–H_2O (16 : 1)	1 : 1 : 2	40	5	**9**	30.8 (*R*)	72.4

[a] The molar ratio of the reactants, HA, D-DBTA·H_2O and $Cu(OAc)_2·H_2O$. [b] Enantiomeric excesses of HL^1 to HL^5 were determined by HPLC analysis on Chiralcel AS Column with heptane-2-propanol-trifluoroacetic acid (90 : 10 : 0.1) as elute at 1 mL min^{-1} flow rate. The enantiomeric excess of HL^6 to HL^9 were determined by GC analysis on Chiralcel Dex 225 column after conversion to the corresponding ethyl esters. The configuration of HL^1, HL^8 and HL^9 were determined by comparing the sign of rotation to that of the literature. [c] Based on the racemic acid. [d] The complex was obtained by cooling the resulting solution to −10 °C. [e] Only the Cu(II) complex of DBTA was obtained. [f] The precipitate formed 8 d later.

and ICP analyses. The (*R*)-(+)-form[6] of HL^1 was obtained in good enantioselectivity (85.0% ee, Table 1, entry 1) by treatment of the solid complex with 10% hydrogen chloride.

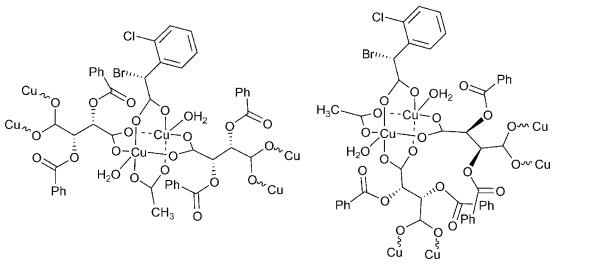
The thermogram of the complex (see the electronic supplementary information) displays a two-step decomposition profile from ambient temperature to 300 °C. The first continuous weight loss step was observed from ambient temperature to 140 °C. The observed weight loss corresponds to the loss of loosely bound acetonitrile and water molecules. This confirmed the result of the elemental analyses. The second step was observed from 148 to 225 °C, which should be attributed to the decomposition of the other organic ligands. After the complex was dried in vacuum for 5 h at 50 °C, the loss of acetonitrile was observed by microanalysis[10] and the result was identical with the thermogram of the dried solid (see the electronic supplementary information), in which only the loss of water molecules was observed. Moreover, after the sample was exposed to air for a long period, the partial loss of acetonitrile molecules in the complex was confirmed by microanalysis. Both the results indicate that the acetonitrile molecules only act as lattice solvent molecules, rather than the ligands of the complex.

The solid state UV-vis spectrum of the complex showed a broad absorption band (band I) in the visible region around 672 nm, which is assigned to a metal–ligand interaction.[11] Moreover, it also displays a shoulder around the 372 nm (band II). Although the origin of band II is controversial, it is believed to be indicative of a dimeric complex,[12] suggesting that the complex is binuclear, which also confirms the result of elemental analyses.

The IR spectrum of the complex exhibits strong absorptions at 1721 and 1271 cm^{-1} which is assigned to the DBTA ligands. It also shows a broad band at 3438 cm^{-1} which is assigned to water molecules.

A carboxylate, $RCOO^-$, can coordinate to metals in a number of ways, *viz.* as a unidentate ligand, as a chelating ligand, as a bridging bidentate ligand, or as a monatomic bridging ligand. The mode of coordination to the center copper ion can be determined from the value of Δ ($\Delta = \nu_{asym} - \nu_{sym}$) in the IR spectrum.[13] This criterion can also be used in this copper complex. The moderately strong band at 1401 cm^{-1} is assigned to the symmetric carboxyl stretching frequency (ν_{sym}). The analogous asymmetric stretching frequency (ν_{asym}) is 1602 cm^{-1}. The value of Δ (201 cm^{-1}) and the positions of these bands are comparable to those reported for other binuclear copper(II) complexes,[11–14] in which a bridging bidentate coordination mode of carboxylate groups exists.

TGA, UV-vis, IR spectra, elemental and ICP analyses of the complex suggest that it is a binuclear with the D-DBTA dianion, α-bromo-2-chlorophenylacetate and acetate as ligands. On the other hand, that DBTA often acts as bridging ligand because of the two carboxylate groups,[8,15] together with the fact that the complex is soluble only in DMF and DMSO, indicate that the complex is polymeric (Scheme 2). Unfortunately, the single



Scheme 2 The two possible structures for the binuclear copper(II) complex of α-bromo-2-chlorophenylacetic acid (HL^1).

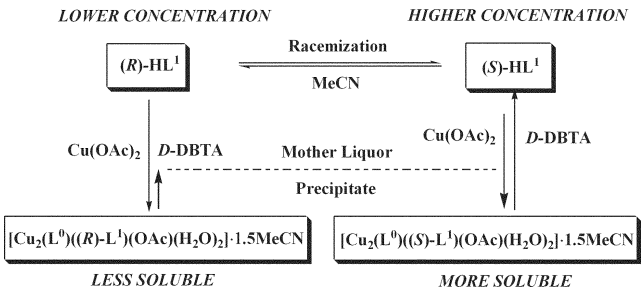
crystal of the complex was not obtained although many methods were tried. The definite structure can not be clarified by the present results.

Crystallization-induced dynamic resolution of HL^1

Initially, it was thought that the ratio of the three reactants (*rac*-HL^1, H_2L^0 and $Cu(OAc)_2{\cdot}H_2O$) should be 2 : 1 : 2 because the resulting complex was formulated as $[Cu_2(L^0)(L^1)(OAc)(H_2O)_2]{\cdot}1.5$ MeCN. However, after the mother liquid was concentrated to dryness, only racemic α-bromo-2-chlorophenylacetic acid was obtained by following the same procedure for the decomposition of the copper(II) complex. It showed that there was a process in which (*S*)-HL^1 was converted to racemic HL^1. Subsequent study showed that optically active HL^1 can racemize spontaneously in acetonitrile,[16] which indicated that the acid could be resolved by crystallization-induced dynamic resolution.

Thus, the experiment, in which the ratio of *rac*-HL^1, D-DBTA·H_2O and $Cu(OAc)_2{\cdot}H_2O$ was 1 : 1 : 2, was performed at room temperature. The resulting complex was also fomulated as $[Cu_2(L^0)((R)\text{-}L^1)(OAc)(H_2O)_2]{\cdot}1.5$ MeCN and the yield (84.0%) of the acid was almost doubled with a comparable diastereomeric excess (entry 2 *vs.* entry 1). So crystallization-induced dynamic resolution occurred.

As is shown in Scheme 3, after the mixtures of $Cu(OAc)_2{\cdot}H_2O$, optically pure D-DBTA·H_2O and racemic HL^1 in acetonitrile had been stirred for 2 d at 40 °C, the less soluble complex $[Cu_2(L^0)((R)\text{-}L^1)(OAc)(H_2O)_2]{\cdot}1.5$ MeCN deposited preferentially[17] with 79.8% diastereomeric excess.[18] The result was that the concentration of (*S*)-HL^1 was higher than that of (*R*)-HL^1 in the solution and the inversion of (*S*)-HL^1 to (*R*)-HL^1 occurred.[16,17] Therefore, more and more $[Cu_2(L^0)((R)\text{-}L^1)(OAc)(H_2O)_2]{\cdot}1.5$ MeCN accumulated as time went by.[18] At the same time, the fact that the more soluble complex dissolves more easily than the less soluble one can also cause a concentration difference between the two diastereomers in the mother liquid. At last, the diastereomeric excess was increased to 94.7%.



Scheme 3 Proposed mechanism for the crystallization-induced dynamic resolution of α-bromo-2-chlorophenylacetic acid (HL^1).

Investigation of the resolution conditions

(a) Temperatures. When the reaction was conducted at 0 °C, no precipitate was obtained even though it had been conducted for 7 d. With increasing reaction temperature, the diastereomeric excess increased, with the yield being almost unaffected and the best result was obtained at 40 °C (entries 2–5). However, when the reaction was conducted at more higher temperature (50 °C), the enantioselectivity and yield of acid obtained by decomposition of the solid complex declined (entry 6).

(b) Solvents. Interestingly, it was found that adding water to the reaction mixture can increase the reaction rate greatly. When the ratio of acetonitrile and water was 16 : 1, the best result was obtained. After 30 min, a green precipitate formed and after 5 d, the yield and the diastereomeric excess of the complex were close to those obtained from the same reaction in absolute acetonitrile (entry 7 *vs.* entry 5). The water molecules are auxiliary ligands of the resulting compound, and must be regarded as a kind of reactant. The addition of the water meant that the concentration of water was increased. Therefore, the reaction was speeded up.

When the experiment was performed in mixed solvents (EtOH : H_2O = 3 : 1), a green precipitate was obtained by cooling the resulting mixture to −10 °C. Microanalysis and ICP and TGA analyses showed that the complex was formulated as $Cu_2(L^0)(L^1)(OAc)(H_2O)_2$ (complex **10**) and the diastereomeric excess (25.7%) of the resulting complex was lower than that obtained from acetonitrile. In addition, the predominant form, (*S*)-HL^1, was different to that from acetonitrile (entry 8).[19] Both the results indicated the importance of solvents to the resolution of HL^1.

Furthermore, crystallization-induced dynamic resolution was not observed when mixed solvents (EtOH : H_2O = 3 : 1) were used, owing to the slow spontaneous racemization rate.[20,21]

When dichloromethane, methanol, anhydrous ethanol or dimethylformamide was used as the solvent, no precipitate was obtained even though the reaction was conducted over 7 d.

(c) Reagents. When $Ca(OH)_2$ was used, only calcium salt of DBTA was obtained. And when $Zn(OAc)_2$ was used, although a mixed ligand Zn(II) complex was obtained, only the racemic acid was obtained by decomposition of the solid complex.

On the other hand, when *O*,*O*′-di-*p*-toluoyltartaric acid (DTTA) as well as tartaric acid (TA) were used as the resolving agent, only the copper(II) salts of DTTA or TA were obtained.[15]

There are two kinds of free acids (DBTA and α-halo acid) in the reactants. However, the ligands in the resulting complex are D-DBTA dianion, α-bromo-2-chlorophenylacetate and acetate. It seems that using the salts in place of the corresponding acids (NaL^1 for example) might increase the reaction.[11] However, such an attempt was unsuccessful and only the copper(II) salt of *O*,*O*′-dibenzoyltartaric acid was obtained.

Resolution of the other α-halo acids

(a) HL^2 and HL^3. When racemic α-bromo-2-fluorophenylacetic acid (HL^2) was resolved in acetonitrile, satisfactory results (the acid with 91.5% ee and 83.5% yield) were obtained (entry 10). Similarly to the resolution of HL^1, water can accelerate the resolution rate (entry 11).

When racemic α-bromo-2-bromophenylacetic acid (HL^3) was resolved in absolute acetonitrile, only the copper(II) salt of DBTA was obtained (entry 12). However, when it was resolved in mixed solvents (MeCN : H_2O = 16 : 1), a mixed ligand complex (complex **3**), which was similar to complex **1**, was obtained in 93.6% ee and 85.5% yield (entry 14). The results showed the important roles of water and the substituents of the benzene ring in the formation of the complex.

(b) HL^4 and HL^5. Racemic α-chloro-2-chlorophenylacetic acid (HL^4) and α-chloro-2-fluorophenylacetic acid (HL^5) can be resolved by the same method, while the yields and selectivities were slightly lower than those in the resolution of HL^1 (entries 15 and 18). Moreover, when they were resolved in the mixed solvents (MeCN : H_2O = 16 : 1), only the copper(II) salt of DBTA was obtained (entries 17 and 20).

Crystallization-induced dynamic resolution was not observed in the resolution process of these two acids (entries 16 and 19) and these results may originate from that α-chloroarylacetic acid are more configurationally stable than α-bromoarylacetic acid in acetonitrile solution.

(c) HL⁶ and HL⁷. Reaction of D-DBTA·H_2O, racemic α-bromophenylacetic acid (HL^6) and $Cu(OAc)_2·H_2O$ in acetonitrile only afforded a mononuclear compound formulated as $Cu(HL^0)(L^6)·1.5H_2O$. The result can be confirmed from that the solid state UV-vis spectrum of the complex did not display the band II of the dimeric complexes. After decomposition of the solid complex, only racemic HL^6 was obtained (entries 21 and 22).

In the resolution of α-bromo-4-chlorophenylacetic acid (HL^7), although a binuclear mixed ligand complex, which is formulated as $Cu_2(L^0)(L^7)(OAc)(H_2O)_2$, was obtained by same method, the acid obtained by decomposition was nearly racemic (entries 23 and 24).

The poor diastereoselectivities for the two acids further confirmed that the *ortho*-substitute of the benzene ring of α-bromoarylacetic acid play an important role in chiral recognition of the copper(II) complexes.

(d) HL⁸ and HL⁹. It was reported by Mravik group that 2-bromopropionic acid and 2-chloropropionic acid can be resolved by forming two mixed ligand Cu(II) complexes in EtOH solution, which were formulated as $[Cu(A)_{n1}(H_2O)_{nw}](HL^0)(L)$ (L^0 is DBTA dianion, L is a α-halo acid anion and A stands for an alcohol molecule).[9] However, when we did the same experiments in acetonitrile solution, the obtained complexes were formulated as $[Cu_2(L^0)(L)(OAc)(H_2O)_2]·1.5$ MeCN. After decomposition of them with HCl solution, optically active acids (20.9 and 26.8% ee for HL^8 and HL^9, respectively) were obtained (entries 25 and 28). The poor enantioselectivities for the two acids, HL^8 and HL^9, indicate the important role of substitutes at α-position in the chiral recognition of the copper(II) complexes.

Interestingly, when the molar ratio of reactants changed to 1 : 1 : 2 (entries 26 and 27, and entries 29 and 30), high yield of the acids was obtained and resulted in that the optical purities (39.3% ee and 68.2% ee for (*S*)-HL^8 and (*S*)-HL^9, respectively) in the mother liquid were higher than those (14.8 and 27.9% ee for (*R*)-HL^8 and (*R*)-HL^9, respectively) in the crystals (entries 26 and 29). Moreover, these results showed that no racemization occurred during the resolution process and thus crystallization-induced dynamic resolution was not observed for these two acids.

Conclusions

We have described a successful example of coordination-mediated resolution of a series of α-halo acids using *O*,*O*′-dibenzoyltartaric acid and copper(II) acetate monohydrate as resolving reagents. Moreover, we also found that crystallization-induced dynamic resolution occurred in the resolution processes of HL^1, HL^2 and HL^3, because they can spontaneously racemize in acetonitrile solution. Finally, substituents at the α-position of the α-halo acids play important roles in the chiral recognition of the copper(II) complexes.

Experimental section

Material and reagents

HL^2 to HL^7 were prepared by the reported methods.[5,22] All the other reagents were purchased from commercial sources and were used without purification.

Physical measurements

Optical rotations were measured on a Perkin-Elmer 341 polarimeter. IR spectra were recorded on a Nicolet 200SXV FT-IR spectrophotometer over the range 4000–400 cm^{-1}, using KBr pellets. ^1H NMR spectra were measured on a Bruker (300 MHz) spectrometer in $CDCl_3$ or D_2O solutions with tetramethylsilane as the internal standard. The elemental (C, H, N) analyses of the powdered samples were performed on a Perkin-Elmer model 240 C automatic instrument. The concentrations of Cu in the complexes were determined using an IRIS Advantage ICP spectrophotometer after heating to 400 °C and treatment with acid. The thermograms of the complexes were conducted with a Perkin-Elmer TGA instrument. The UV-vis spectra of the solid complexes were recorded from 200–800 nm, using an UV-1000 spectrophotometer. Liquid chromatographic analyses were conducted on a Beckman 110 instrument equipped with a model 168 detector. Gas chromatographic analyses were conducted on a Varian 3380 instrument.

Resolution of the acids: syntheses and decomposition of the complexes

$[Cu_2(L^0)(L^1)(OAc)(H_2O)_2]·1.5$ MeCN (complex 1). To a solution of D-DBTA·H_2O (760 mg, 0.2 mmol) and racemic α-bromo-2-chlorophenylacetic acid (500 mg, 0.2 mmol) in 10 mL acetonitrile at 40 °C was added $Cu(OAc)_2·H_2O$ (800 mg, 0.4 mmol). After stirring for about 5 min, $Cu(OAc)_2$ was dissolved and the mixture became clear. 2 d later, a green precipitate formed, and the mixture was stirred for an additional 5 d. The complex was filtered, washed with 10 mL acetonitrile and air-dried overnight at room temperature. 1.581 g green solid were obtained. Anal. ($C_{31}H_{28.5}N_{1.5}O_{14}BrClCu_2$) C, H, N, Cu: calcd, 41.91%, 3.23%, 2.36%, 14.3%; found, 42.12%, 3.16%, 2.40%, 14.0%. IR absorption bands (cm^{-1}): 3438 (br), 3069 (w), 1721 (s), 1602 (vs), 1450 (w), 1401 (s), 1271 (s), 1178 (w), 1115 (m), 1070 (w), 1027 (w), 741 (m), 709 (m). UV-vis of the solid sample (λ/nm): 372, 672.

The complex **1** was suspended in 25 mL 10% hydrochloric acid and 5 mL toluene. The mixture was warmed to 50 °C for a short period with vigorous stirring, and then cooled to the room temperature. The precipitate (DBTA·H_2O) was filtered. The toluene layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic phases were combined, dried over sodium sulfate and concentrated in vacuum. To the residue was added 20 mL of toluene to dissolve the product and then the undissolved DBTA was filtered off. The filtrate was concentrated to give optically active (*R*)-α-bromo-2-chlorophenylacetic acid (412 mg). Yield: 82.4% (based on the racemic acid). Ee: 94.7%; $[a]_D^{28} = +102.7$ (*c* 1.0, EtOH), $[a]_D^{25} = +8.9$ (*c* 2.4, MeOH); the (*R*)-isomer reported in literature:[6] $[a]_D^{25} = +6.3$ in MeOH. ^1H NMR (300 MHz, $CDCl_3$), δ: 10.38 (br, 1H, COOH), 7.40–7.93 (m, 4H, Ar–H), 6.09 (s, 1H, CH) ppm.

$[Cu_2(L^0)(L^2)(OAc)(H_2O)_2]·1.5$ MeCN (complex 2). This compound was prepared with a similar method to the preparation of complex **1**. Anal. ($C_{31}H_{28.5}N_{1.5}O_{14}BrFCu_2$) C, H, N, Cu: calcd, 42.70%, 3.29%, 2.41%, 14.6%; found, 43.01%, 3.22%, 2.44%, 14.9%. IR absorption bands (cm^{-1}): 3443 (br), 3069 (w), 1719 (s), 1646 (vs), 1602 (*v*s), 1490 (m), 1451 (m), 1406 (s), 1316 (w), 1267 (s), 1178 (w), 1114 (m), 1096 (m), 1070 (m), 1026 (w), 750 (m), 712 (m). UV-vis of the solid sample (λ/nm): 364, 692.

Optically active α-bromo-2-fluorophenylacetic acid was obtained by the similar method for HL^1. Yield: 83.5% (based on the racemic acid). Ee: 91.5%; $[a]_D^{28} = -50.4$ (*c* 1.0, EtOH). ^1H NMR (300 MHz, $CDCl_3$), δ: 10.43 (br, 1H, COOH), 7.05–7.70 (m, 4H, Ar–H), 5.74 (s, 1H, CH) ppm.

$[Cu_2(L^0)(L^3)(OAc)(H_2O)_2]·2$ MeCN (complex 3). This compound was prepared with a similar method to the preparation of complex **1** in a solution of acetonitrile and H_2O (16 : 1). Anal. ($C_{32}H_{30}N_2O_{14}Br_2Cu_2$) C, H, N, Cu: calcd, 40.31%, 3.17%, 2.94%, 13.3%; found, 40.59%, 3.20%, 2.90%, 13.7%. IR absorption bands (cm^{-1}): 3443 (br), 3068 (w), 2942 (sh), 1720 (s), 1648 (vs), 1602 (vs), 1585 (sh), 1467 (w), 1450 (m), 1401 (s), 1316 (w), 1268

(s), 1177 (w), 1115 (m), 1099 (m), 1071 (m), 1026 (m), 738 (m), 713 (m), 686 (m), 623 (w). UV-vis of the solid sample (λ/nm): 373, 669.

Optically active α-bromo-2-bromophenylacetic acid was obtained by the similar method for HL[1]. Yield: 85.5% (based on the racemic acid). Ee: 93.6%; $[\alpha]_D^{28} = +12.3$ (*c* 1.0, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 11.40 (br, 1H, COOH), 7.22–7.80 (m, 4H, Ar–H), 5.96 (s, 1H, CH) ppm.

$[Cu_2(L^0)(L^4)(OAc)(H_2O)_2]\cdot 1.5MeCN$ (complex 4). This compound was prepared with a similar method to the preparation of complex **1** except that 2 equiv. racemic HL[4] was used. Anal. ($C_{31}H_{28.5}N_{1.5}O_{14}Cl_2Cu_2$) C, H, N, Cu: calcd, 44.11%, 3.40%, 2.49%, 15.1%; found, 44.39%, 3.31%, 2.43%, 14.7%. IR absorption bands (cm^{-1}): 3440 (br), 3070 (w), 1720 (s), 1648 (vs), 1602 (vs), 1491 (w), 1451 (m), 1404 (s), 1317 (w), 1268 (s), 1177 (w), 1114 (m), 1098 (m), 1026 (w), 754 (m), 711 (m), 686 (m). UV-vis of the solid sample (λ/nm): 362, 692.

Optically active α-chloro-2-chlorophenylacetic acid was obtained by the similar method for HL[1]. Yield: 30.6% (based on the racemic acid). Ee: 87.6%; $[\alpha]_D^{28} = -87.6$ (*c* 1.0, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 10.58 (br, 1H, COOH), 7.32–7.67 (m, 4H, Ar–H), 5.86 (s, 1H, CH) ppm.

$[Cu_2(L^0)(L^5)(OAc)(H_2O)_2]\cdot 1.5$ MeCN (complex 5). This compound was prepared with a similar method to the preparation of complex **4**. Anal. ($C_{31}H_{28.5}N_{1.5}O_{14}ClFCu_2$) C, H, N, Cu: calcd, 44.99%, 3.47%, 2.54%, 15.6%; found, 44.85%, 3.41%, 2.63%, 16.0%. IR absorption bands (cm^{-1}): 3425 (br), 3069 (w), 1719 (s), 1642 (vs), 1602 (vs), 1492 (w), 1451 (m), 1404 (s), 1317 (w), 1268 (s), 1177 (w), 1115 (m), 1096 (m), 1071 (m), 1026 (w), 754 (m), 711 (m), 686 (m). UV-vis of the solid sample (λ/nm): 362, 677.

Optically active α-chloro-2-fluorophenylacetic acid was obtained by the similar method for HL[1]. Yield: 34.0% (based on the racemic acid). Ee: 87.9%; $[\alpha]_D^{28} = -60.2$ (*c* 1.0, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.81 (br, 1H, COOH), 7.08–7.60 (m, 4H, Ar–H), 5.76 (s, 1H, CH) ppm.

$Cu(HL^0)(L^6)\cdot 1.5H_2O$ (complex 6). This compound was prepared with a similar method to the preparation of complex **4**. Anal. ($C_{26}H_{22}O_{11.5}BrCu$) C, H, N, Cu: calcd, 47.18%, 3.35%, 0, 9.6%; found, 47.19%, 3.29%, 0, 9.4%. IR absorption bands (cm^{-1}): 3439 (br), 3244 (sh), 3158 (sh), 3064 (sh), 1718 (s), 1640 (vs), 1603 (vs), 1493 (w), 1451 (m), 1400 (m), 1337 (m), 1318 (w), 1268 (s), 1178 (w), 1115 (m), 1097 (m), 1070 (m), 1026 (m), 997 (w), 943 (w), 799 (w), 754 (m), 712 (m), 695 (m). UV-vis of the solid sample (λ/nm): 683.

α-Bromophenylacetic acid was obtained by the similar method for HL[1]. Yield: 45.7% (based on the racemic acid). Ee: 0. ^{1}H NMR (300 MHz, D_2O), δ: 7.42 (brs, 5H, Ar–H), 5.26 (s, 1H, CH) ppm.

$Cu_2(L^0)(L^7)(OAc)(H_2O)_2$ (complex 7). This compound was prepared with a similar method to the preparation of complex **4**. Anal. ($C_{28}H_{24}O_{14}ClBrCu_2$) C, H, N, Cu: calcd, 40.67%, 2.93%, 0, 15.4%; found, 40.40%, 3.10%, 0, 15.7%. IR absorption bands (cm^{-1}): 3436 (br), 1717 (s), 1638 (vs), 1601 (vs), 1492 (w), 1451 (m), 1404 (m), 1268 (s), 1178 (w), 1115 (m), 1096 (m), 1070 (w), 1027 (w), 792 (m), 710 (m), 685 (w). UV-vis of the solid sample (λ/nm): 352, 683.

α-Bromo-4-chlorophenylacetic acid was obtained by the similar method for HL[1]. Yield: 43.8% (based on the racemic acid). Ee: 3.2%. ^{1}H NMR (300 MHz, D_2O), δ: 7.42 (brs, 4H, Ar–H), 5.27 (s, 1H, CH) ppm.

$[Cu_2(L^0)(L^8)(OAc)(H_2O)_2]\cdot 1.5$ MeCN (complex 8). This compound was prepared with a similar method to the preparation of complex **4**. Anal. ($C_{26}H_{28.5}N_{1.5}O_{14}BrCu_2$) C, H, N, Cu: calcd, 39.38%, 3.62%, 2.65%, 16.0%; found, 39.45%, 3.55%, 2.64%, 16.3%. Major IR absorption bands (cm^{-1}): 3444 (br), 3051 (w), 2929 (w), 2277 (w), 1723 (s), 1641 (vs), 1601 (vs), 1492 (w), 1451 (m), 1412 (s), 1319 (w), 1265 (s), 1177 (w), 1117 (m), 1071 (m), 711 (m), 686 (m). UV-vis of the solid sample (λ/nm): 361, 676.

Optically active (*R*)-2-bromopropionic acid was obtained by the decomposition of the complex and distillation of the residue. Yield: 45.3% (based on the racemic acid). Ee: 20.9%; $[\alpha]_D^{22} = +6.2$ (*c* 1.0, MeOH); the (*S*)-isomer reported in literature:[23] $[\alpha]_D^{22} = -29.8$ in methanol. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 11.78 (br, 1H, COOH), 4.40 (q, $J = 6.96$ Hz, 1H, CH), 1.83 (d, $J = 6.96$ Hz, 3H, CH_3) ppm.

$[Cu_2(L^0)(L^9)(OAc)(H_2O)_2]\cdot 1.5$ MeCN (complex 9). This compound was prepared with a similar method to the preparation of complex **4**. Anal. ($C_{26}H_{28.5}N_{1.5}O_{14}ClCu_2$) C, H, N, Cu: calcd, 41.72%, 3.84%, 2.81%, 17.0%; found, 41.65%, 3.74%, 2.80%, 17.4%. Major IR absorption bands (cm^{-1}): 3435 (br), 3075 (w), 2929 (w), 2275 (vw), 1723 (s), 1641 (vs), 1602 (vs), 1585 (sh), 1491 (w), 1451 (m), 1413 (s), 1328 (w), 1267 (s), 1177 (w), 1117 (m), 1071 (m), 1026 (w), 711 (m), 686 (m). UV-vis of the solid sample (λ/nm): 360, 685.

Optically active (*R*)-2-chloropropionic acid was obtained by the similar method for HL[8]. Yield: 42.6% (based on the racemic acid). Ee: 26.8%; $[\alpha]_D^{25} = +4.3$ (*c* 1.0, $CHCl_3$); the (*S*)-isomer reported in literature:[24] $[\alpha]_D^{25} = -15.1$ in $CHCl_3$. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 11.54 (br, 1H, COOH), 4.46 (q, $J = 9.78$ Hz, 1H, CH), 1.72 (d, $J = 9.78$ Hz, 3H, CH_3) ppm.

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16 This was confirmed by the following experiment. After (*R*)-HL^1 (93.6% ee) was stirred for 20 h in acetonitrile at 40 °C, HPLC analysis showed that racemic HL^1 was obtained.
17 To verify our hypothesis further, we did the following experiments. Reaction of (*R*)-HL^1 (93.6% ee), D-DBTA·H_2O and $Cu(OAc)_2·H_2O$ (1 : 1 : 2 molar ratio) in acetonitrile solution afforded [Cu_2(D-DBTA)((*R*)-L^1)(OAc) $(H_2O)_2$]·1.5 MeCN in 30 min and (*R*)-HL^1 with 90.1% ee was obtained after the treatment of the complex with HCl. While L-DBTA was used in place of D-DBTA, green precipitate formed only after 2 d. Moreover, microanalysis and ICP analysis of the complex and HPLC analysis of the acid (85.6% ee) obtained by decomposition of the complex showed that it was formulated as [Cu_2(L-DBTA)((*S*)-L^1)(OAc)$(H_2O)_2$]·1.5 MeCN, rather than [Cu_2(L-DBTA)((*R*)-L^1)(OAc)$(H_2O)_2$]·1.5 MeCN.
18 This can be confirmed by the following experiment. The complex with 79.8% diastereomeric excess, which was obtained by filtration when the reaction had been conducted for 2 d, was suspended in acetonitrile, and stirred at 40 °C for 5 d. HPLC analysis showed that the diastereomic excess was increased to 85.2%.
19 The phenomenon that different enantiomer was obtained when different solvents were used can also be observed in the coordination-mediated resolution of mandelic acid ester (see reference 8).
20 After (*R*)-HL^1 (93.6% ee) was stirred in ethanol for 2 d at 40 °C, HPLC analysis showed that there was only slight racemization (88.7% ee) and also no racemization was observed in ethyl acetate and toluene.
21 Reaction of (*R*)-HL^1 (93.3% ee), L-DBTA·H_2O and $Cu(OAc)_2·H_2O$ (1 : 1 : 2 molar ratio) in EtOH–H_2O (3 : 1) afforded Cu_2(L-DBTA)((*R*)-L^1)(OAc) $(H_2O)_2$ and (*R*)-HL^1 with 92.6% ee was obtained after the treatment of the complex with HCl. When D-DBTA was used in place of L-DBTA, Cu_2(D-DBTA)((*R*)-L^1)(OAc)$(H_2O)_2$ was obtained and (*R*)-HL^1 with 87.7% ee was obtained after the treatment of the complex with HCl.
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