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Resolution of chiral metal tetrahedral compounds through transamidation or transacetylation using lipase as a catalyst

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ABSTRACT

Highly enantiomerically pure tetrahedral metal compounds were obtained by transamidation catalyzed by a lipase. Meanwhile another tetrahedral type compound with high enantiomeric excess (92.62%) was also obtained by transacetylation catalyzed by lipase.

1. Introduction

The first optically active tetrahedral metal cluster was synthesized by Richer in 1980.[1] Since then many chemists have made great efforts to study this molecular model's synthesis and properties.[2] It is hoped for it to become a new type of catalyst which could be applied to asymmetric catalytic reactions. However, it is difficult to obtain highly enantiomerically pure metal framework clusters as catalysts. Although many methods have been attempted, none have provided satisfactory results due to limitations. A single pure enantiomer of the cluster may be obtained either by a spontaneous resolution (which occurs in some of fortuitous instances) or by a series of diastereomer separations. Although Vahrenkamp had obtained some pioneering results in this field before 1990, only a few racemic chiral clusters have been separated into pure enantiomers at present.[3] Moreover, it has been shown that such tetrahedral molecules can easily racemize during the removal of the chiral auxiliary.[1] In 1998, Shulin et al. obtained some optically active clusters based on framework chirality through a metal exchange reaction in the presence of chiral phase-transfer-catalyst,[4] but ee values of the compounds (which were got latter) is low; in the same year, he resolved successfully the chiral tetrahedral complex by HPLC with amylopectin-tris-phenylcarbamate as chiral stationary phase, but it was too little to be used as catalyst.[5] In recent years, our group has always been attempting to get pure chiral tetrahedral clusters by asymmetric hydrolysis catalyzed by lipase, some results were obtained presently.[6] Here, we report a new strategy for syntheses of the optically active compounds by transamidation and transacetylation using lipases as catalyst.

2. Results and discussion

2.1. Resolution of $ERuCoM(CO)_8CpCOOCH_3$ (E = S, Se; M = W, Mo) through transamination

Tetrahedral metal clusters cannot make lipase denature or be inactive.[6] In order to obtain better enantioselective lipases, we screened 30 lipases and got 6 kinds of lipases which show distinct enantioselectivity.[7] Meanwhile we optimized solvent system from THF, cyclohexane, toluene, DIPE, we found that DIPE is suitable for reactions. The transamidation of the tetrahedral metal clusters is fast at 60–70 °C. Under these conditions, not only the reactants and products are very stable, but also there are no byproducts resulting from CO ligand displaced by the N ligand. The reactions are shown in Scheme 1.

When $SRuCoW(CO)_8CpCOOCH_3$ **a** was used, we obtained two products, **1a** and **2a**. Products **1a** and **2a** can be easily separated by silica gel column chromatography with CH_2Cl_2/petroleum-ether (bp 60–90 °C) (v/v = 2:1) as eluent. Compound **1a** is a part of material which did not react; **2a** is $SRuCoW(CO)_8CpCONHC_3H_7$ and its R_f is much less than that of the former **1a**. For **b** and **c**, we obtained the similar compounds as those of compound **a**. The characteristic data for **2a**, **2b** and **2c** are in good agreement with their proposed structures. In the IR spectra of **2a**, **2b** and **2c**, the very strong absorption bands at 2100–1950 cm^{-1} are the signals of the terminal carbonyl, which shows that the framework is still intact; other strong absorption bands at 3324–3321 m, 1719–1631 m cm^{-1} show that a CONH unit exists. In the ^1H NMR spectra of **2a**, **2b** and **2c**, the chemical shifts of the four protons in the Cp were observed at 5.955–5.419 ppm as a multiplet, and that of the three protons in the CH_3 appeared at 0.871–0.905 ppm as a triplet. The signals at 3.724–3.786 ppm as triplet and at 1.668–1.258 ppm as a multiplet are the chemical shift of the two protons in NCH_2 and CH_2, respectively; the wide singlet at 3.872–3.849 ppm is the chemical shift of the proton in the NH.

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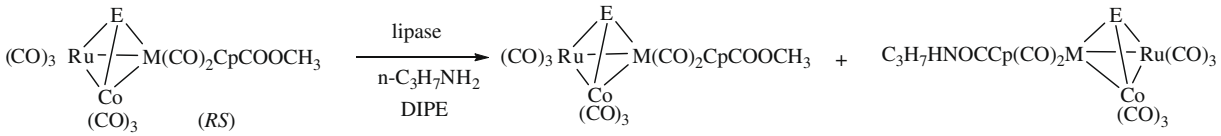


a E=S, M=W
b E=Se, M=W
c E=Se, M=Mo

Scheme 1.

Compared with the characterization of the structure of the tetrahedral metal cluster, measuring exactly the specific rotations and enantiomeric excess values proved to be difficult. Metal clusters are deeper dark-red compounds through which light almost passes. Vahrenkamp used 10^{-4}–10^{-3} M concentrations to measure cluster rotations which led to 20% error at most.[8] Secondly, there is no chiral stationary phase which is suitable to separate metal clusters. To reduce the error from too dilute a concentration and contamination, we increased the cluster concentration to about 10^{-2}. Their molar rotations are: **1a**, $[\Phi]_D^{19} = -154.4$ (*c* 0.03, CH_2Cl_2), and **2a**, $[\Phi]_D^{19} = +2483.0$ (*c* 0.025, CH_2Cl_2). In order to confirm asymmetric transamidation reaction feasible, we use **b** and **c** to repeat the same procedure, the cases are the same as the above. The ORD curves of **1b** and **2b** are shown in Figure 1. As the SeRuCoW(CO)$_8$CpCOOCH$_3$ and SeRuCoW(CO)$_8$CpCONHC$_3$H$_7$ are different compounds, and not pure clusters, their ORD curves are not as symmetric as pure enantiomers.[8] However, we can conclude that both of them have different configurations as their chirality stems from the same framework.

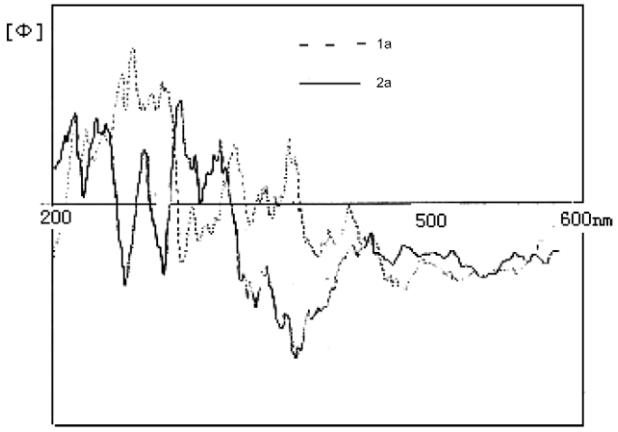


Figure 1. ORD of the compounds **1a** and **2a**.

The ee value of **1a** was obtained through HPLC with chiralcel OD as a chiral stationary phase and with hexane/isopropanol (99/1) as a flow phase, and it is about 73.54%. Compounds **1b**, **1c**, **2a**, **2b** and **2c** could not be separated at base line using the same chiral stationary phase.

2.2. Resolution of HC≡CCH$_2$OHCoW(CO)$_5$CpCOCH$_3$ through transacetylation

In order to obtain better enantiomeric excess values, we used another kind of compound in the transacetylation under the same conditions. The reaction route is shown in Scheme 2. The characterization data of the products are identical to those we expected. Compounds **1d** and **2d** can be easily separated by silica gel column chromatography with CH_2Cl_2/diethyl ether/petroleum-ether (bp 60–90 °C) (v/v = 2:1:1) as eluent. For compound **2d**, in the IR spectrum, 2055–1880 cm^{-1} are terminal carbonyl absorption bands, which shows that the tetrahedral metal compound framework is still intact. The signal at 1738 cm^{-1} is the carbonyl absorption band in –OCOCH$_3$ which does not appear in that of **1d**, and the signal at 1685 cm^{-1} is the absorption band of the carbonyl in the –COCH$_3$. In ^{1}H NMR spectrum of **2d**, the chemical shift of the three protons in the –COCH$_3$ appears at 2.337 ppm as a singlet; the signal of the three protons in the –OCOCH$_3$ was observed at 2.079 ppm as a singlet, which does not appear in that of **1d**. For **1d**, its IR and ^{1}H NMR spectra are the same as the reactant.

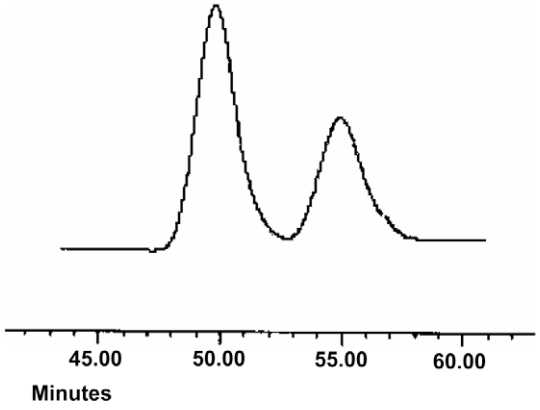
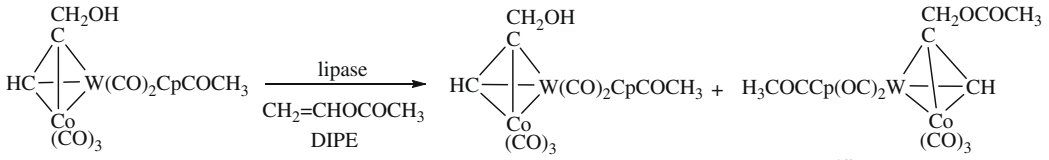


Figure 2. Chromatogram of the enantiomer-separation of **1d**.



d **1d** **2d**

Scheme 2.

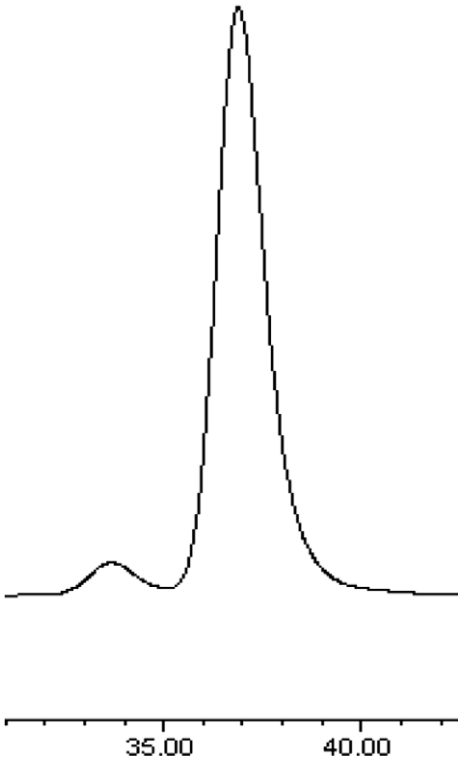


Figure 3. Chromatogram of the enantiomer-separation of **2d**.

The ee values of **1d** and **2d** were obtained with the same chiral column as described above, but the flow phase was adjusted to hexane/isopropanol 95/5, they are shown, respectively, in Figures 2 and 3. Ee values of **1d** and **2b** are 31.54% and 92.62%, respectively.

3. Conclusion

In conclusion, the kinetic resolution of a racemic tetrahedral metal compound using lipase through transamidation and transacetylation is possible, by which highly enantiomerically pure tetrahedral compounds were obtained. This will provide good foundations for a study on asymmetric catalytic reactions using the chiral tetrahedral framework as the chiral source.

4. Experimental

All reactions were carried under nitrogen. Commercial *n*-propylamine and isopropyl ether (DIPE) were dried using 4 Å molecular sieve before use. Three clusters were prepared according to the literature methods. All lipases that were screened, were provided by Zhejiang university, *Novozym* 435 (immobilized lipase from *Candida antarctica*) is registered trademark from Novo Nordisk. Column chromatography was carried out using 160–200 mesh silica gel. IR spectra were recorded on a Nicolet 10 DX spectrophotometer, ^{1}H NMR spectra on a Bruker AM-400 MHz spectrometer and elemental analysis (C,H) was performed on a Carlo Erba 1106-type analyzer. The enantiomeric excess value determination was performed by LC-6A(shimadzu, Japan) chromatograph, which SPD-6AV violet-visible inspector, wavelength $\lambda = 254$ nm, room temperature, flow rate 0.5 ml/min. Chromatographic column was prepared by our co-workers, with length 25 cm, i.d. = 4.6 mm, cellulose-tris(3.5-dimethylphenylcarbamate) upon absorbed over silica gel (called chiralcel OD) as a chiral stationary phase. Molar rotations and ORD were determined on J-20(Japan) circular dichroism spectrometer.

Compounds $SRuCoW(CO)_8CpCOOCH_3$ **a**, $SeRuCoW(CO)_8CpCOOCH_3$ **b** and $SeRuCoMo(CO)_8CpCOOCH_3$ **c**,[6a] $HC{\equiv}CCH_2OHCoW(CO)_5CpCOCH_3$ **d**[9] were synthesized according to the modified literature.

4.1. Transamination of $ERuCoM(CO)_8CpCOOCH_3$ (E = S, Se; M = W, Mo)

A solution of cluster **a** (100 mg) in CH_2Cl_2 (0.5 ml) was added to DIPE (30 ml) at room temperature. After stirring for 10 min, *n*-propylamine (20 μl) was injected to the mixture; 10 min later, *Novozym* 435 (50 mg) was added to the mixture solution. The reaction mixture was stirred slowly at 60–70 °C for 8 h. The solvent was removed in vacuo and the residue extracted by a small amount of CH_2Cl_2, and the extract was subjected to 2.5 × 25 cm silica gel column chromatography. CH_2Cl_2/petroleum-ether (bp 60–90 °C) (v/v = 2:1) eluted the main red band, from which **1a** 50 mg (50% yield, 73.54% ee) and **2a** (40 mg, 38.5% yield) as a black solid were obtained. Compound **1a** is unreacted material, $[\Phi]_D^{19} = -154.4$ (*c* 0.03, CH_2Cl_2). Compound **2a**: Anal. Calcd for $C_{17}H_{12}O_9NCoRuSW$: C, 26.0; H, 1.5. Found: C, 26.1; H, 1.6. IR (KBr disc, cm^{-1}): 2100vs, 2080vs, 2042vs, 2003vs, 1998s, 1950s, 3324m, 1723m, 1631m, 1587w. ^{1}H NMR ($CDCl_3$, ppm): δ 5.552–5.955 (m, 4H, C_5H_4), 0.871 (t, 3H, CH_3), 3.735 (t, 2H, $-NCH_2-$), 1.668 (m, 2H, $-CH_2$), 3.872 (br, 1H, NH). $[\Phi]_D^{19} = +2482.96$ (*c* 0.025, CH_2Cl_2).

As for compounds **b** and **c**, the procedures and workup were similar to those of compound **a**; both **1b**, **1c** are unreacted materials.

For **1b**: 50 mg (50% yield); $[\Phi]_D^{19} = -1003.4$ (*c* 0.05, CH_2Cl_2). Compound **2b**: 40 mg (37.5% yield). Anal. Calcd for $C_{17}H_{12}O_9NCoRuSeW$: C, 24.4; H, 1.4. Found: C, 24.1; H, 1.6. IR (KBr disc, cm^{-1}): 2078s, 2038vs, 2000vs, 1966vs, 1945s, 3322m, 1721m, 1583w. ^{1}H NMR ($CDCl_3$, ppm): δ 5.497–5.861 (m, 4H, C_5H_4), 0.905 (t, 3H, CH_3), 3.786 (t, 2H, $-NCH_2-$), 1.258 (m, 2H, $-CH_2$), 3.868 (br, 1H, NH). $[\Phi]_D^{19} = -1086.6$ (*c* 0.05, CH_2Cl_2).

Compound **1d**: 50 mg (50% yield); $[\Phi]_D^{19} = -1014.7$ (*c* 0.05,CH_2Cl_2). Compound **2c**: 45 mg (42.5% yield). Anal. Calcd for $C_{17}H_{12}O_9CoNMoRuSe$: C, 28.8; H, 1.7. Found: C, 28.1; H, 1.6. IR (KBr disc, cm^{-1}): 2074s, 2035vs, 2003vs, 1998s, 1950s, 3321m, 1719m, 1582w. ^{1}H NMR ($CDCl_3$, ppm): δ 5.419–5.873 (m, 4H, C_5H_4), 0.879 (t, 3H, CH_3), 3.724 (t, 2H, $-NCH_2$), 1.430 (m, 2H, $-CH_2$), 3.849 (br, 1H, NH). $[\Phi]_D^{19} = +282.5$ (*c* 0.05, CH_2Cl_2).

4.2. Transacetylation of $HC{\equiv}CCH_2OHCoW(CO)_5CpCOCH_3$

Compound $HC{\equiv}CCH_2OHCoW(CO)_5CpCOCH_3$ **d** (1.2 g) was dissolved in CH_2Cl_2 (0.5 ml) under nitrogen, and DIPE (50 ml) was added. The mixture was stirred for 10 min at room temperature, and 100 μl vinyl acetate was added. Ten minutes later, *Novozym* 435 (100 mg) was added to the mixture. The reaction mixture was stirred slowly at 60–70 °C for 8 h. The solvent was removed in vacuo and the residue was extracted by a small amount of CH_2Cl_2, and the extract was subjected to 2.5 × 25 cm silica gel column chromatography. CH_2Cl_2/diethyl ether/petroleum-ether (b.p 60–90 °C) (v/v = 2:1:1) eluted the main red band, from which **1d** and **2d** as brown-red oils were obtained.

Compound **1d**: (0.6 g, 50% yield, ee% 31.54). Anal. Calcd for $C_{15}H_{11}O_7CoW$: C, 32.96; H, 2.01. Found: C, 32.85; H, 1.99. IR (KBr, cm^{-1}) 2053s, 2000vs, 1941vs, 1876s, 1680s. ^{1}H NMR ($CDCl_3$, ppm): δ 2.352 (s, 3H, $COCH_3$), 4.798 (s, 1H, OH), 5.059 (s, 1H, CH), 5.673 (m, 4H, Cp), 5.876 (s, 2H, CH_2). $[\Phi]_D^{19} = +1048.3$ (*c* 0.05, CH_2Cl_2).

Compound **2d**: (0.5 g, 41.7% yield, ee% 92.62). Anal. Calcd for $C_{17}H_{13}O_8CoW$: C. 34.70; H, 2.21. Found: C, 34.65, H, 2.14. IR (KBr, cm^{-1}): 2055s, 2005vs, 1988vs, 1945s, 1880s, 1738s, 1685s. ^{1}H NMR ($CDCl_3$, ppm): δ 2.337 (s, 3H, $COCH_3$), 2.079 (s, 3H, $OCOCH_3$),

5.064 (s, 1H, CH), 5.673 (m, 4H, Cp), 5.879 (s, 2H, CH_2). $[\Phi]_D^{19} = -68.2$ (c 0.05, CH_2Cl_2).

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