PREPARATION OF OPTICALLY PURE DINUCLEAR COBALT(III)
COMPLEX WITH Λ-CONFIGURATION AS A DIANIONIC CHIRAL
CATALYST

Mohamed S. H. Salem, Ankit Kumar, Makoto Sako, Tsukasa Abe, Shinobu
Takizawa,* and Hiroaki Sasai*

The Institute of Scientific and Industrial Research, Osaka University, Mihogaoka,
Ibaraki-shi, Osaka 567-0047, Japan
Fax: (+81) 6-6879-8469
E-mail: taki@sanken.osaka-u.ac.jp, sasai@sanken.osaka-u.ac.jp

This manuscript is dedicated to Professor Dr. Yasuyuki Kita on the occasion of
his 77th birthday.

Abstract – The disodium salt of enantiomerically pure dimeric Λ-cobalt(III)
complex 1 was prepared in one-pot from sodium triscarbonatocobaltate(III) and
Schiff base ligand (R,S,S)-2 formed by the condensation of
(R)-3,3ʹ-diformyl-2,2ʹ-dihydroxy-1,1ʹ-binaphthyl 3 with (S)-tert-leucine 4.
Preliminary screening of 1 as a chiral catalyst was conducted for the
bromocyclization of a tryptamine derivative.

Enzymes often show high chemo-, regio-, and stereoselectivities that are difficult to achieve even with the
latest organic synthetic methods. In an enzyme-catalyzed process, two or more reaction-promoting units
in the active site increase the reaction rate by their synergistic cooperation, leading to efficient product
formation. Inspired by the enzymatic activation of substrates, many researchers have attempted the
development of catalysts mimicking their characteristic functionalities, toward the preparation of
optically enriched chemicals. Chiral hetero- and homo-bimetallic catalysts such as
lanthanum-lithium-tris(binaphthoxide) (LLB), aluminum-lithium-bis(binaphthoxide) (ALB),
and dinuclear vanadium complexes are representative examples in this regard. In 1977, Belokon first
introduced a series of chiral octahedral cobalt(III) complexes with a rigid framework and a unique chiral
environment (Λ and Δ configurations of a metal center). These anionic cobalt complexes are easily
prepared through the self-assembly of sodium triscarbonatocobaltate(III) and Schiff base ligands derived
from the condensation of salicylaldehydes and chiral amino acids. However, the potential of anionic cobalt(III) complexes in asymmetric catalysis has been much less recognized because of their saturation in coordination as well as the difficulty in the highly stereocontrolled complexation of the \( \Lambda \) or \( \Delta \) stereoisomer.\(^2\) As part of our continuous effort to develop optically pure bimetallic complexes as chiral catalysts,\(^4,8\) we herein report the stereoselective preparation of disodium salt of the dimeric \( \Lambda \)-cobalt(III) complex 1 and its application as a chiral dianionic catalyst for the enantioselective bromocyclization of a tryptamine derivative.

For designing the dinuclear cobalt(III) complex, a multidentate ligand (L) of \((R_a,S,S)\)-2\(^9\) obtained from the condensation of \((R)-3,3’\)-diformyl-2,2’-dihydroxy-1,1’-binaphthyl (3) and \((S)\)-tert-leucine (4) \textit{in situ} was selected for the one-pot complexation with sodium triscarbonatocobaltate(III) (Figure 1). We assumed that the dinuclear cobalt(III) complex 1, which is composed of the ligand and metal in the 2:2 ratio, would be generated to form a stable 18-electron Co complex. If the 2:1 complex 5 could work as an efficient template for the next intramolecular complexation, the sterically favored dinuclear cobalt complex \( \text{Na}_2\text{[LCo]}_2 \) 1 could be isolated as a single diastereomer.\(^10\)

\[
\text{Na}_2\text{[LCo]}_2 \xrightarrow{(R)-3} 1\text{ (}2.2 \text{ equiv), EtOH, 70 °C, 10 h} \xrightarrow{2) \text{Na}_3\text{[Co(CO}_3\text{)]}_3 \text{ (1.1 equiv), reflux, overnight}} \text{Na}_2\text{[LCo]}_2 \ 67\% \ yield
\]

**Figure 1.** Expected complexation of disodium salt of the dianionic dinuclear cobalt(III) complex 1

**Figure 2.** ORTEP drawing of the dimeric \( \Lambda \)-cobalt(III) complex 1 showing 50% probability thermal ellipsoids. \( \text{Na}^+ \) ions and hydrogen atoms are omitted for clarity.
As expected, the dimeric complex 1 was isolated in 67% yield (Figure 2). An immeasurable amount of oligomeric complexes was formed when using diastereomeric ligand \( (S_a,S,S) - 2 \), indicating that \( (R_a,S,S) - 2 \) constitutes the matched pair and \( (S_a,S,S) - 2 \) would be the mismatched pair for this complexation. The characteristic optical rotation of optically pure 1 showed the value \([\alpha]_D^{23} \) −7274 (c 0.021, MeOH). The cobalt(III) centers in 1 adopt \( \Lambda \) - or \( \Delta \) -helical mutual orientations of their tridentate ligands relative to the \( C_2 \) symmetry axis. The absolute configuration of the cobalt metal centers is determined to be \( \Lambda \) based on the starting materials \( (R) - 3 \), \( (S) - 4 \), and the Flack parameter \([0.015(5)] \) obtained via the X-ray crystallographic analysis (Figure 2).

Recently, chiral cobalt(III) complexes have been recognized as highly enantioselective anionic catalysts for Michael reaction, halocyclization, Mannich reaction, and Povarov reaction. We also carried out preliminary screening for the catalytic activity of the dimeric \( \Lambda \)-cobalt(III) complex 1 in the enantioselective bromocyclization of tryptamine derivative 6. Although the complex 1 afforded tricyclic product \( (S,S) - 7 \) in excellent chemical yield (91%), the enantioselectivity (9% ee) is still challenging at this stage (Scheme 1).

**Scheme 1.** Enantioselective bromocyclization of tryptamine derivative 6 catalyzed by the chiral dinuclear cobalt(III) complex 1

In summary, we prepared the chiral dinuclear \( \Lambda \)-cobalt(III) complex 1 for the first time and conducted preliminary screening of its chiral catalytic activity. Further studies aimed to improve the catalytic activity and enantioselectivity of this cobalt complex are in progress.

**ACKNOWLEDGMENTS**

This study was performed in part at Artificial Intelligence Research Center (AIRC-ISIR). This work was supported by JSPS Kakenhi Grant Numbers JP18KK0154 in Promotion of Joint International Research (Fostering Joint International Research(B)), Daiichi Sankyo Foundation of Life Science, and Hoansha Foundation. M.S.H.S. is grateful to Japanese government (MEXT) scholarship for their magnanimous financial support. A.K. is deeply indebted to Ninety-nine Asia student scholarship for their generous
financial support. We acknowledge the technical staff of the Comprehensive Analysis Center of ISIR, Osaka University (Japan).

REFERENCES AND NOTES


11. In a 50 mL round-bottom flask were placed (R)-3,3’-diformyl-2,2’-dihydroxy-1,1’-binaphthyl (3) (5.0 mmol, 1.71 g) and (S)-tert-leucine (4) (11 mmol, 1.44 g) in EtOH (25 mL) under N₂ atmosphere. The reaction mixture was heated at 70 °C for 10 h to afford ligand (Rₙ,S,S)-2 in situ. Then, freshly prepared Na₃[Co(CO₃)₃]₂²² (5.5 mmol, 1.69 g) was added and the mixture was refluxed overnight.
After being cooled to room temperature, the mixture was filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography first on silica gel (MeOH/CH$_2$Cl$_2$ = 1/4), then on neutral Al$_2$O$_3$ (MeOH as eluent) to afford the disodium salt of dimeric Λ-cobalt(III) complex 1 (2.17 g) in 67% yield as a dark red crystal.

$^1$H-NMR (700 MHz, DMSO-$d_6$) $\delta$ 7.65 (d, $J = 8.3$ Hz, 4H), 7.38 (s, 4H), 7.28 (s, 4H), 6.89 (t, $J = 7.0$ Hz, 4H), 6.80 (t, $J = 7.0$ Hz, 4H), 6.58 (d, $J = 8.3$ Hz, 4H), 3.24 (s, 4H), 0.99 (s, 36H); $^{13}$C-NMR (175 MHz, DMSO-$d_6$): $\delta$ 180.5, 167.5, 157.4, 138.2, 135.1, 128.5, 128.2, 125.4, 123.4, 122.3, 120.2, 119.3, 80.4, 36.2, 28.8; HRMS (ESI): calcd for C$_{68}$H$_{64}$Co$_2$N$_4$O$_{12}$ m/z 623.1593 [M–2Na]$^2$–, found 623.1560; $[\alpha]_D^{23}$ –7274 (c 0.021, MeOH); IR (KBr): 3434, 2956, 2873, 1643, 1616, 1481, 1398, 1350, 1178, 1080 cm$^{-1}$.


13. X-Ray crystallographic data of the dimeric Λ-cobalt(III) complex 1 has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 2036038.


21. A 10 mL oven-dried vial was charged with tryptamine derivative 6 (0.10 mmol, 36.0 mg), the dimeric Λ-cobalt(III) complex 1 (0.0050 mmol, 6.47 mg), activated molecular sieves 4A (microwave 600 w, 1 min x 3, 100 mg) and dry CH$_2$Cl$_2$ (1 mL) at room temperature in the absence of light. The mixture was cooled to –30 °C and stirred for 15 min. N-Bromosuccinimide (0.12 mmol, 21.4 mg) was added portionwise and the resulting solution was stirred vigorously under air for 24 h. The reaction was then quenched with NEt$_3$ (1.0 mmol, 140 μL) and saturated aqueous Na$_2$S$_2$O$_3$ (0.2 mL). The mixture was purified by flash column chromatography (silica gel, n-hexane/EtOAc = 6:1) to give the tricyclic product 7 (40.0 mg) in 91% yield. The $^1$H-NMR and $^{13}$C-NMR spectra of compound 7 were perfectly matched with the reported spectra.$^{17,23}$ $^1$H-NMR (600 MHz, CDCl$_3$) $\delta$ 7.56 (brs, 1H), 7.34 (dd, $J = 7.6$, 1.4 Hz, 1H), 7.27 (td, $J = 7.6$, 1.4 Hz, 1H), 7.08 (t, $J = 7.6$ Hz, 1H), 6.41 (s, 1H), 3.71 (dd, $J = 10.3$, 7.6 Hz, 1H), 2.81-2.67 (m, 3H), 1.56 (s, 9H), 1.46 (s, 9H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 153.5, 152.2, 142.1, 132.8, 130.3, 124.1, 123.8, 117.4, 83.9, 82.1, 80.8, 62.2,
46.2, 41.6, 28.3, 28.2; Enantiomeric excess 9% determined by HPLC (Daicel Chiralpak IC, 
n-hexane/i-PrOH = 50:1, flow rate 1.0 mL/min, 315 nm, t_{(R,R)-7} = 4.17 min, t_{(S,S)-7} = 5.68 min).

22. Y. N. Belokon, V. I. Maleev, D. A. Kataev, T. F. Saveleva, T. V. Skrupskaya, Y. V. Nelyubina, and  

Ed.*, 2013, 52, 12924.