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# Asymmetric Hydrogenation Catalyzed by Rhodium Complex with a New Chiral Bisphosphine Derived from L-Threonine

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A new chiral bisphosphine, (2*R*,3*S*)-1,2-bis(diphenylphosphino)-3-$^t$Boc-aminobutane (*RS*-**5**), was prepared from L-threonine. Mesylation of $^t$Boc-L-threonine methyl ester (**2**) and subsequent reduction with sodium borohydride gave the alcohol (**10**), which was treated with potassium carbonate to afford a key intermediate, (2*S*,3*S*)-1-$^t$Boc-3-methyl-2-aziridinemethanol (*SS*-**7b**). Mesylation of *SS*-**7b**, followed by treatment with sodium diphenylphosphide afforded the new chiral bisphosphine (*RS*-**5**). The structure of *RS*-**5** was confirmed by the X-ray analysis of its crystalline CuCl complex (*RS*-**12**). The cationic rhodium (I) complexes prepared from *RS*-**5** and *RS*-**12** are efficient asymmetric hydrogenation catalysts for *N*-acyldehydroamino acids, giving (*S*)-*N*-acylamino acids in high optical yields (83—94% ee).

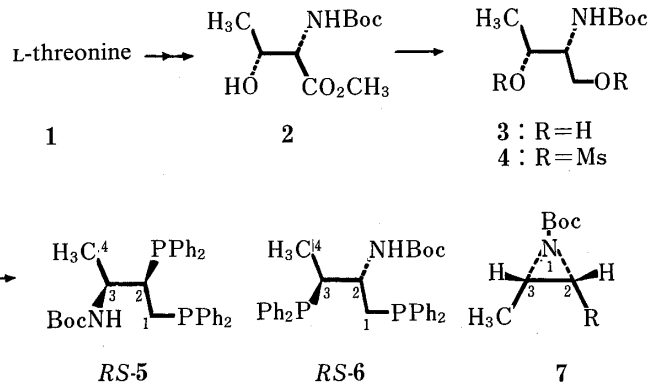
**Keywords**——asymmetric hydrogenation; L-threonine; (2*S*,3*S*)-1-$^t$Boc-3-methyl-2-aziridinemethanol; (2*R*,3*S*)-1,2-bis(diphenylphosphino)-3-$^t$Boc-aminobutane; (2*R*,3*S*)-1,3-bis(diphenylphosphino)-2-$^t$Boc-aminobutane

In recent years, a large number of catalytic asymmetric syntheses, such as homogeneous hydrogenations,[1] hydrosilylations,[2] hydroformylations,[3] olefin isomerizations,[4] *etc.* have been developed. Among them, homogeneous asymmetric hydrogenation of various prochiral olefins, catalyzed by rhodium complexes with chiral phosphine ligands, gives high enantioselectivity. As effective ligands, a number of chiral phosphines such as DIPAMP,[5] BPPM,[6] Chiraphos,[7] Prophos,[8] Phephos,[9] *etc.* have been synthesized.

We report herein the synthesis of a new chiral bisphosphine (2*R*,3*S*)-1,2-bis(diphenylphosphino)-3-$^t$Boc[10]-aminobutane (*RS*-**5**) and its cuprous chloride complex (*RS*-**12**),[11] and the homogeneous asymmetric hydrogenation of dehydro-α-amino acids catalyzed by the cationic rhodium complexes prepared from *RS*-**5** and *RS*-**12**.

## Synthesis of the Chiral 1,2-Bisphosphines

Reduction of $^t$Boc-L-threonine methyl ester (**2**), prepared from L-threonine (**1**), with




1 2 *RS*-**5** *RS*-**6** 7

Chart 1

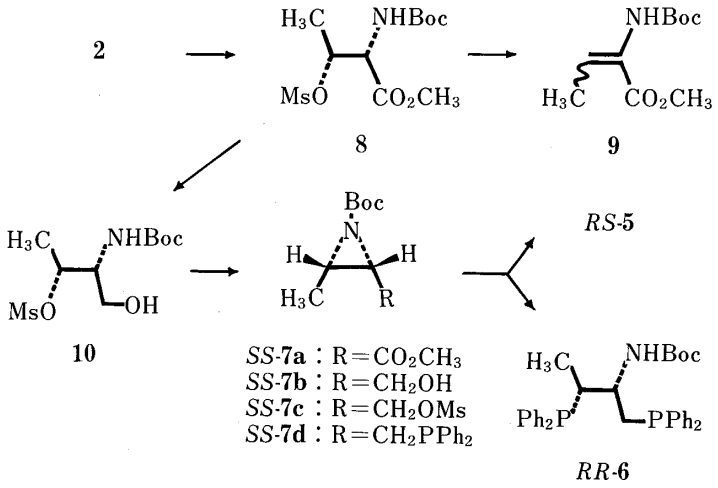



Chart 2

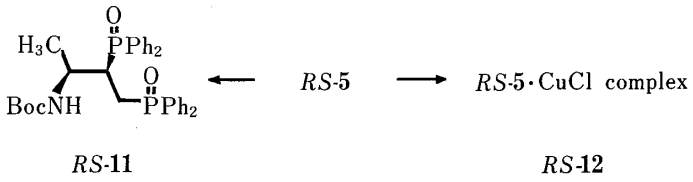



Chart 3

sodium borohydride in aqueous ethanol, followed by treatment with methanesulfonyl chloride and triethylamine in methylene chloride gave the corresponding dimesylate (**4**) in 75% yield from **1**. Treatment of **4** with sodium diphenylphosphide[12] in a mixture of 1,4-dioxane and tetrahydrofuran did not afford the expected bisphosphine, (2*R*,3*S*)-1,3-bis(diphenylphosphino)-2-$^t$Boc-aminobutane (*RS*-**6**). The product, obtained in 9% yield, was *RS*-**5** (Chart 1).

This result led us to speculate the involvement of the aziridine intermediate (**7**) in this reaction, and an investigation was undertaken to isolate **7** and to obtain *RS*-**5** in reasonable yield (Chart 2).

Mesylation of **2** with methanesulfonyl chloride in the presence of diisopropylethylamine in methylene chloride gave the mesylate (**8**)[13] as an unstable oil. Reduction of **8** with sodium borohydride in ethanol gave the oily alcohol (**10**) in 65% yield based on **1**. Cyclization of **10** with potassium carbonate in acetonitrile gave the key intermediate (*SS*-**7b**) in a moderate yield. Prior to this reaction, **8** was treated with a base such as potassium hydroxide, sodium hydride or sodium methoxide, but the product, obtained in 93% yield, was **9** and no aziridine compound (*SS*-**7a**) was isolated. Mesylation of *SS*-**7b** with methanesulfonyl chloride in the presence of triethylamine in methylene chloride gave the crystalline aziridine mesylate (*SS*-**7c**) (mp 43.5—45 °C, $[\alpha]_D^{20}$ −32.0° ($c$=1.0, $CHCl_3$)) in 71% yield. When *SS*-**7c** thus obtained was reacted with lithium diphenylphosphide in THF, the sole product was the monophosphine, still having the aziridine ring (*SS*-**7d**) (mp 50.5—52.5 °C, $[\alpha]_D^{20}$ −46.4° ($c$=1.0, $CHCl_3$), 21% yield). On the other hand, treatment of *SS*-**7c** with sodium diphenylphosphide[12] gave the desired bisphosphine (*RS*-**5**) as an amorphous powder ($[\alpha]_D^{22}$ +103.4° ($c$=1.0, $CHCl_3$), 60% yield), accompanied by its isomer, *RR*-**6**, as an amorphous powder ($[\alpha]_D^{20}$ +76.6° ($c$=1.0, $CHCl_3$), 5% yield). The air-sensitive bisphosphines, *RS*-**5** and *RR*-**6**, were isolated by flash column chromatography on silica gel. The major product (*RS*-**5**) was converted to the crystalline phosphine oxide (*RS*-**11**, mp 176—178 °C, 94% yield) by treatment with *m*-chloroperbenzoic acid in methylene chloride (Chart 3), and this was characterized by

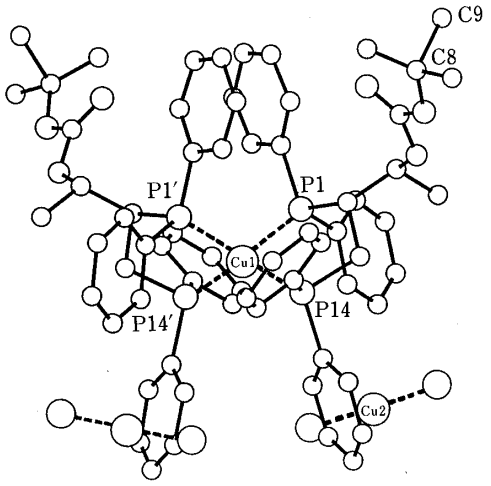
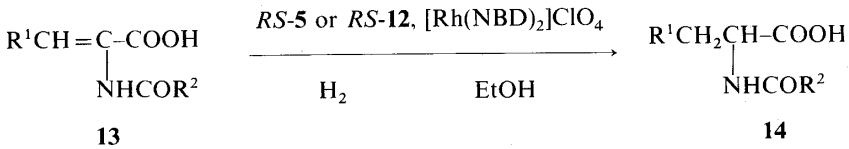
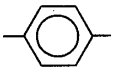
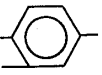



Fig. 1. The Structure of *RS*-**12**

TABLE I. Asymmetric Hydrogenation of *N*-Acyldehydroamino Acids




| Substrate | $R^1$ | $R^2$ | Chiral reagent | Chemical[a] yield (%) | Optical[b] yield (%) | Configuration |
|---|---|---|---|---|---|---|
| **13a** | H | $CH_3$ | *RS*-**5** | 99 | 86 | *S* |
| | | | *RS*-**12** | 92 | 89 | *S* |
| **13b** | $(CH_3)_2CH$ | $CH_3$ | *RS*-**5** | 90 | 89 | *S* |
| | | | *RS*-**12** | 95 | 89 | *S* |
| **13c** |  | $CH_3$ | *RS*-**5** | 92 | 88 | *S* |
| | | | *RS*-**12** | 92 | 89 | *S* |
| **13d** |  |  | *RS*-**5** | 93 | 91 | *S* |
| | | | *RS*-**12** | 92 | 94 | *S* |
| **13e** | AcO–  | $CH_3$ | *RS*-**5** | 99 | 84 | *S* |
| | | | *RS*-**12** | 98 | 83 | *S* |
| **13f** | AcO–  $CH_3O$ | $CH_3$ | *RS*-**5** | 93 | 85 | *S* |

*a*) Yield of isolated product. *b*) Calculated on the basis of reported values[7] for the optically pure compounds: (*R*)-**14a**, $[\alpha]_D^{26}$ +66.3° (*c*=2.0, $H_2O$); (*S*)-**14b**, $[\alpha]_D^{26}$ −23.2° (*c*=1.0, EtOH); (*S*)-**14c**, $[\alpha]_D^{26}$ +46.0° (*c*=1.0, EtOH); (*S*)-**14d**, $[\alpha]_D^{27}$ −40.3° (*c*=1.0, MeOH); (*S*)-**14e**, $[\alpha]_D^{27}$ +45.4° (*c*=1.5, MeOH); (*S*)-**14f**, $[\alpha]_D^{20}$ +40.7° (*c*=1.0, MeOH).

elemental analysis and spectroscopy. Further, the absolute configurations of two asymmetric centers of *RS*-**5** were confirmed by the results of X-ray analysis of its cuprous chloride complex[11] (*RS*-**12**, mp 223—225 °C (dec.), 61% yield); the result is shown in Fig. 1.

**Asymmetric Hydrogenation**

The cationic rhodium complex was prepared from *RS*-**5** or *RS*-**12** by treatment with rhodium norbornadiene perchlorate ($[Rh(NBD)_2]ClO_4$).[7] By use of these complexes as the catalyst, asymmetric hydrogenation of various dehydro-α-amino acids was attempted. All hydrogenations proceeded quantitatively in ethanol under 1 atm of hydrogen pressure for a period of 18—22 h at room temperature. The optical yields obtained were high in all cases

(83—94% ee), and the *S*-isomers were predominant as shown in Table I.

## X-Ray Study of *RS*-12

A colorless prismatic crystal ($0.3 \times 0.3 \times 0.2$ mm) was used for the X-ray study. The crystal is orthorhombic, space group $P2_12_12$, with cell dimensions of $a = 17.211$ (1), $b = 14.481$

TABLE II. Comparison of Observed and Calculated Values of Bijvoet's Pair Ratio [$|F(hkl)|/|F(\bar{h}\bar{k}\bar{l})|$] to Determine the Correct Configuration

| $(h, k, l)$ | $\|F(hkl)\|/\|F(\bar{h}\bar{k}\bar{l})\|$ Obsd | Calcd | $(h, k, l)$ | $\|F(hkl)\|/\|F(\bar{h}\bar{k}\bar{l})\|$ Obsd | Calcd |
|---|---|---|---|---|---|
| 4, 4, 1 | 1.042 | 1.072 | 5, 2, 2 | 1.053 | 1.065 |
| 4, 7, 1 | 1.057 | 1.061 | 5, 2, 3 | 1.061 | 1.063 |
| 4, 7, 2 | 0.916 | 0.908 | 5, 6, 3 | 0.951 | 0.950 |
| 4, 1, 3 | 1.058 | 1.075 | 5, 7, 3 | 1.306 | 1.131 |
| 4, 2, 3 | 0.831 | 0.925 | 5, 2, 4 | 1.133 | 1.112 |
| 4, 6, 3 | 0.921 | 0.931 | 5, 6, 5 | 0.928 | 0.945 |
| 4, 8, 3 | 0.929 | 0.930 | 5, 3, 6 | 0.930 | 0.940 |
| 4, 1, 4 | 1.053 | 1.052 | 6, 5, 1 | 1.044 | 1.054 |
| 4, 3, 4 | 1.404 | 1.064 | 6, 4, 3 | 0.938 | 0.940 |
| 4, 7, 4 | 1.062 | 1.067 | 6, 5, 3 | 0.910 | 0.913 |
| 4, 3, 5 | 0.949 | 0.941 | 6, 3, 4 | 1.040 | 1.060 |
| 4, 4, 5 | 1.071 | 1.062 | 6, 5, 4 | 1.049 | 1.077 |
| 4, 5, 5 | 1.048 | 1.056 | 6, 6, 4 | 0.938 | 0.944 |
| 4, 4, 7 | 0.888 | 0.896 | 6, 1, 6 | 1.163 | 1.199 |
| 5, 5, 1 | 0.926 | 0.893 | 6, 2, 7 | 0.761 | 0.835 |

TABLE III. Final Atomic Parameters with e.s.d.s[a] in Parentheses

| Atom | $x$[b] | $y$[b] | $z$[b] | $B_{eq}$[c] | Atom | $x$[b] | $y$[b] | $z$[b] | $B_{eq}$[c] |
|---|---|---|---|---|---|---|---|---|---|
| Cu1 | 0000 | 0000 | 8843 (1) | 3.1 | C18 | 1687 (4) | −0196 (4) | 12851 (4) | 5.8 |
| Cu2 | −0130 (1) | 4368 (2) | 11966 (2) | 9.6 | C19 | 2151 (4) | 0404 (4) | 12325 (4) | 6.1 |
| C11 | 0418 (3) | 3132 (5) | 12240 (4) | 12.2 | C20 | 2032 (3) | 0579 (3) | 11305 (4) | 4.6 |
| C12 | −0700 (3) | 5597 (4) | 11569 (3) | 11.4 | C21 | 1571 (3) | 1461 (3) | 9259 (4) | 4.3 |
| P1 | 1184 (1) | 0330 (1) | 9528 (1) | 3.3 | C22 | 2147 (4) | 1591 (5) | 8543 (5) | 6.8 |
| P14 | 0542 (1) | −1148 (1) | 7932 (1) | 3.4 | C23 | 2382 (5) | 2529 (6) | 8320 (6) | 9.7 |
| C2 | 1840 (3) | −0494 (3) | 8901 (4) | 3.8 | C24 | 2049 (6) | 3247 (5) | 8831 (7) | 9.9 |
| C3 | 1563 (3) | −0719 (3) | 7831 (3) | 3.4 | C25 | 1487 (5) | 3099 (4) | 9527 (6) | 7.9 |
| C4 | 2172 (3) | −1305 (4) | 7245 (4) | 4.3 | C26 | 1237 (4) | 2201 (4) | 9745 (5) | 6.0 |
| N5 | 2823 (3) | −0701 (3) | 6980 (4) | 5.1 | C27 | 0160 (3) | −1322 (4) | 6685 (3) | 4.2 |
| C6 | 2803 (4) | −0178 (6) | 6170 (5) | 7.6 | C28 | 0508 (4) | −1001 (6) | 5837 (4) | 5.7 |
| O7 | 3471 (3) | 0325 (3) | 6129 (4) | 8.3 | C29 | 0148 (5) | −1132 (6) | 4922 (4) | 7.8 |
| C8 | 3650 (5) | 0926 (7) | 5300 (10) | 14.6 | C30 | −0548 (5) | −1595 (6) | 4877 (6) | 9.1 |
| C9 | 3756 (6) | 0099 (11) | 4335 (7) | 14.3 | C31 | −0908 (4) | −1895 (6) | 5731 (6) | 7.9 |
| C10 | 3050 (6) | 1466 (9) | 4836 (11) | 17.1 | C32 | −0554 (4) | −1752 (5) | 6632 (5) | 6.2 |
| C11 | 4429 (5) | 1260 (7) | 5475 (9) | 12.5 | C33 | 0610 (3) | −2316 (3) | 8426 (4) | 4.4 |
| O12 | 2271 (3) | −0137 (6) | 5596 (5) | 13.4 | C34 | 0596 (4) | −3106 (4) | 7856 (5) | 5.6 |
| C13 | 2495 (4) | −2136 (4) | 7800 (5) | 5.6 | C35 | 0681 (4) | −3973 (4) | 8313 (7) | 7.8 |
| C15 | 1408 (3) | 0154 (3) | 10838 (3) | 3.6 | C36 | 0789 (4) | −4051 (4) | 9339 (7) | 8.1 |
| C16 | 0926 (3) | −0440 (4) | 11367 (4) | 5.0 | C37 | 0811 (4) | −3272 (5) | 9904 (6) | 7.4 |
| C17 | 1076 (4) | −0604 (5) | 12377 (4) | 6.5 | C38 | 0708 (4) | −2396 (4) | 9474 (4) | 5.5 |

*a*) Estimated standard deviations. *b*) Positional parameters are multiplied by $10^4$. *c*) $B_{eq} = \frac{4}{3} \sum_i \sum_j \beta_{ij} \boldsymbol{a}_i^* \boldsymbol{a}_j^*$.

(1), $c=13.501$ (1) Å and $Z=4$. Cell parameters were determined by the least-squares method using $2\theta$ values of 20 reflections. Intensity data for 3224 independent reflections were collected on a Rotar-AFC (Rigaku) with graphite-monochromated Cu$K_\alpha$ radiation using the $2\theta/\omega$ scan mode up to $2\theta=130°$. Of these, 3158 reflections [$|F_{obs}| \geqq 2\sigma(|F_{obs}|)$] were used for the structure analysis. No absorption and extinction corrections were applied.

The structure was solved by the heavy-atom method and refined by the block-diagonal matrix least-squares method assuming anisotropic temperature factors for all the non-H atoms and isotropic ones for H atoms except in the *tert*-butyl group. Unit weights were given to all reflections. The final $R$ and $R_w$ values were 0.047 and 0.049, respectively.

TABLE IV. Bond Lengths with the e.s.d.s in Parentheses (in Å Unit)

| Atom–atom | Bond length | Atom–atom | Bond length | Atom–atom | Bond length |
|---|---|---|---|---|---|
| Cu1–P1 | 2.266 (1) | O7–C8 | 1.450 (13) | C23–C24 | 1.372 (12) |
| Cu1–P14 | 2.300 (1) | C8–C9 | 1.779 (17) | C24–C25 | 1.366 (12) |
| Cu2–C11 | 2.081 (6) | C8–C10 | 1.440 (16) | C25–C26 | 1.400 (9) |
| Cu2–C12 | 2.079 (6) | C8–C11 | 1.444 (13) | C27–C28 | 1.373 (7) |
| P1–C2 | 1.848 (5) | P14–C27 | 1.825 (5) | C27–C32 | 1.379 (8) |
| P1–C15 | 1.827 (4) | P14–C33 | 1.821 (5) | C28–C29 | 1.395 (8) |
| P1–C21 | 1.805 (5) | C15–C16 | 1.391 (7) | C29–C30 | 1.373 (12) |
| C2–C3 | 1.555 (7) | C15–C20 | 1.390 (7) | C30–C31 | 1.379 (11) |
| C3–P14 | 1.868 (5) | C16–C17 | 1.408 (8) | C31–C32 | 1.376 (10) |
| C3–C4 | 1.564 (7) | C17–C18 | 1.366 (9) | C33–C34 | 1.380 (8) |
| C4–N5 | 1.465 (7) | C18–C19 | 1.377 (9) | C33–C38 | 1.429 (8) |
| C4–C13 | 1.523 (8) | C19–C20 | 1.415 (8) | C34–C35 | 1.407 (9) |
| N5–C6 | 1.330 (9) | C21–C22 | 1.397 (9) | C35–C36 | 1.402 (12) |
| C6–O7 | 1.363 (8) | C21–C26 | 1.382 (8) | C36–C37 | 1.362 (10) |
| C6–O12 | 1.202 (9) | C22–C23 | 1.448 (11) | C37–C38 | 1.406 (9) |

TABLE V. Bond Angles with e.s.d.s in Parentheses (in Degree Unit)

| | | | | | |
|---|---|---|---|---|---|
| P1–Cu1–P1′ | 134.9 (6) | O7–C8–C10 | 120.6 (8) | C21–C22–C23 | 118.0 (6) |
| P1–Cu1–P14 | 90.1 (4) | O7–C8–C11 | 105.8 (9) | C22–C23–C24 | 119.3 (8) |
| P1–Cu1–P14′ | 115.3 (4) | C9–C8–C10 | 97.0 (9) | C23–C24–C25 | 121.5 (7) |
| C11–Cu2–C12 | 175.0 (2) | C9–C8–C11 | 104.5 (8) | C24–C25–C26 | 120.5 (6) |
| C2–P1–C15 | 103.0 (2) | C10–C8–C11 | 123.7 (10) | C25–C26–C21 | 119.5 (6) |
| C2–P1–C21 | 105.5 (2) | C3–P14–C27 | 108.5 (2) | P14–C27–C28 | 124.4 (4) |
| C15–P1–C21 | 104.1 (2) | C3–P14–C33 | 106.0 (2) | P14–C27–C32 | 115.5 (4) |
| P1–C2–C3 | 112.0 (3) | C27–P14–C33 | 103.5 (2) | C28–C27–C32 | 119.9 (5) |
| C2–C3–C4 | 112.2 (4) | P1–C15–C16 | 117.2 (4) | C27–C28–C29 | 119.9 (6) |
| C2–C3–P14 | 106.9 (3) | P1–C15–C20 | 122.7 (4) | C28–C29–C30 | 119.5 (6) |
| C4–C3–P14 | 119.1 (3) | C16–C15–C20 | 120.1 (4) | C29–C30–C31 | 120.6 (7) |
| C3–C4–N5 | 108.2 (4) | C15–C16–C17 | 119.5 (5) | C30–C31–C32 | 119.5 (7) |
| C3–C4–C13 | 115.1 (4) | C16–C17–C18 | 121.5 (6) | C31–C32–C27 | 120.5 (6) |
| N5–C4–C13 | 108.3 (4) | C17–C18–C19 | 118.6 (5) | P14–C33–C34 | 124.3 (4) |
| C4–N5–C6 | 121.4 (5) | C18–C19–C20 | 122.1 (6) | P14–C33–C38 | 116.5 (4) |
| N5–C6–O7 | 108.5 (5) | C19–C20–C15 | 118.3 (5) | C34–C33–C38 | 119.2 (5) |
| N5–C6–O12 | 125.3 (7) | P1–C21–C22 | 121.6 (4) | C33–C34–C35 | 119.5 (6) |
| O7–C6–O12 | 126.2 (7) | P1–C21–C26 | 117.0 (4) | C34–C35–C36 | 121.3 (6) |
| C6–O7–C8 | 122.1 (6) | C22–C21–C26 | 121.2 (5) | C35–C36–C37 | 119.3 (6) |
| O7–C8–C9 | 100.6 (8) | | | C36–C37–C38 | 120.9 (7) |
| | | | | C37–C38–C33 | 119.8 (5) |

The absolute configuration was determined by the Bijvoet method. The structure was independently refined with atoms in both enantiomorphic configurations. The $R_w$ values were 0.063 for the correct configuration and 0.080 for the antipodal structure. In these calculations, H atoms were not included. The $f'$ and $f''$ values were taken from "International Tables for X-ray Crystallography."[14] Thirty reflections with $F_c$ differing significantly at the end of the two refinements were remeasured accurately. Table II compares the observed and calculated values of Bijvoet's pair ratio $[|F(hkl)|/|F(\bar{h}\bar{k}\bar{l})|]$ for the correct absolute configuration, where $|F(hkl)|$ was taken as the mean value of $|F(hkl)|$, $|F(\bar{h}\bar{k}l)|$, $|F(h\bar{k}\bar{l})|$, $|F(\bar{h}k\bar{l})|$ and $|F(\bar{h}\bar{k}\bar{l})|$ as the mean value of the other four reflections.

Figure 1 shows the molecular structure of *RS*-**12** in the correct configuration, drawn using the final atomic coordinates listed in Table III. Bound lengths and angles are shown in Tables IV and V, respectively.

Cu atoms occupy two sites. At site 1, the Cu atom is coordinated in a distorted tetrahedron by four P atoms of two molecules which are related by the 2-fold rotation axis of the crystal. Site 2 reveals a disordered structure; two Cu atoms, separated by 1.83 Å, and four Cl atoms are observed. From stoichiometric and symmetric considerations, these two atoms should exist on the 2-fold rotation axis. Recrystallizations, intensity measurements and refinements were repeated several times, but the positional parameters of these Cu atoms converged to almost the same values as given in Table III. A disordered structure was also observed for the *tert*-butyl group. $C_8$–$C_9$ (1.778 Å) is significantly longer, and $C_8$–$C_{10}$ (1.440 Å) and $C_8$–$C_{11}$ (1.444 Å) are shorter than the usual $C_{sp^3}$–$C_{sp^3}$ bond. The large thermal vibration factors of this group may suggest the co-existence of a rotational isomer.

## Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded with a Hitachi 260—10 spectrophotometer. Proton nuclear magnetic resonance ($^1$H-NMR) spectra were measured with a JEOL JNM-PMX 60 or a JEOL FX-100 spectrometer using tetramethylsilane as an internal standard. Abbreviations: s=singlet, d=doublet, q=quartet, and m=multiplet. Mass spectral (MS) measurements were performed with a Hitachi RMU-6M mass spectrometer. Optical rotations were recorded with an automatic digital polarimeter (PM-201, Union Giken).

**Preparation of 2**——A solution of *S*-$^t$Boc-4,6-dimethyl-2-mercaptopyrimidine (54.5 g, 227 mmol) in dioxane (300 ml) was added to an ice-cooled mixture of L-threonine methyl ester hydrochloride[15] (35.0 g, 206 mmol) and $Et_3N$ (31.3 g, 309 mmol) in $H_2O$ (120 ml). The reaction mixture was stirred for 21 h at room temperature, then concentrated and saturated with NaCl to separate out 4,6-dimethyl-2-mercaptopyrimidine. The yellow crystals were removed by filtration and the filtrate was extracted with AcOEt. The AcOEt extract was washed with small amounts of 10% HCl and brine and then dried. Evaporation gave **2** (49.0 g) as a yellow oil, which was used for the preparation of **3** and **8** without further purification.

**Preparation of 3**——A solution of **2** (31.5 g, nominally 135 mmol) in 90% EtOH (140 ml) was added dropwise to a stirred suspension of powdered $NaBH_4$ (10.2 g, 269 mmol) in 90% EtOH (270 ml) at 5 °C. After 15 min at 5 °C and then 70 min at room temperature, the reaction was quenched by the addition of acetone (88 ml) under ice-cooling. The reaction mixture was evaporated, taken up in AcOEt, washed with brine and dried. Evaporation gave an oily residue, which was chromatographed on silica gel (acetone : benzene = 1 : 3 as an eluent) to give **3** as a pale yellow oil. The oil was dissolved in iso-$Pr_2O$ and treated with activated charcoal to give pure **3** (23.6 g, 85% yield from L-threonine methyl ester hydrochloride) as a pale yellow oil. IR $\nu_{max}^{liq.}$ cm$^{-1}$: 3380, 1690, 1510. NMR ($CDCl_3$) $\delta$: 1.21 (3H, d, $J$=7 Hz, $CH_3$), 1.45 (9H, s, $C(CH_3)_3$), 3.20—4.35 (6H, m, 2×CH, $CH_2$, 2×OH), 5.33 (1H, d, $J$=8 Hz, NH). MS *m/e*: 206 ($M^+$+1). $[\alpha]_D^{20}$ −18.5° ($c$=1.24, $CHCl_3$). *Anal.* Calcd for $C_{19}H_{19}NO_4$: C, 52.66; H, 9.33; N, 6.82. Found: C, 52.39; H, 8.94; N, 6.59.

**Preparation of 4**——A solution of MsCl[10] (16.7 g, 146 mmol) in $CH_2Cl_2$ (50 ml) was added to a stirred solution of **3** (10.0 g, 48.7 mmol) and $Et_3N$ (16.3 g, 161 mmol) in $CH_2Cl_2$ (75 ml) at 5 °C under an argon atmosphere. After 20 min at 5 °C and then 25 min at room temperature, the reaction mixture was diluted with $CH_2Cl_2$, washed with brine and dried. Evaporation gave an oily residue, which was chromatographed on silica gel (AcOEt : hexane = 2 : 1 as an eluent) to give **4** (16.4 g, 93% yield) as a pale yellow oil. IR $\nu_{max}^{liq.}$ cm$^{-1}$: 3380, 1710, 1510, 1360, 1170. NMR ($CDCl_3$) $\delta$: 1.45 (9H, s, $C(CH_3)_3$), 1.50 (3H, d, $J$=6 Hz, $CH_3$), 3.05 (6H, s, 2×$SO_2CH_3$), 4.0—4.35 (3H, m, N–CH, $CH_2$), 4.7—5.2 (2H, m, O–CH, NH). MS *m/e*: 288 ($M^+$ − *tert*-BuO).

**Preparation of *RS*-5 from 4**[16]——A solution of **4** (1.81 g, 5.00 mmol) in THF[10] (5 ml) was added to a stirred suspension of $NaP(C_6H_5)_2$ (13.0 mmol, prepared according to the method reported by Kagan[12]) in a mixture of 1,4-dioxane (17 ml) and THF (12 ml) at 5 °C, and the mixture was stirred for 1 h at 5 °C and then 0.5 h at room temperature. Insoluble materials were removed by filtration through Celite and were washed with benzene. After concentration of the filtrate and washings, the residue was subjected to preparative thin layer chromatography (TLC) (silica gel, AcOEt : hexane = 1 : 15) to give *RS*-**5** (250 mg, 9% yield) as a colorless amorphous powder, whose IR, NMR and mass spectra were identical with those of an authentic sample prepared from *SS*-**7c**.

**Preparation of 8**——A solution of MsCl (20.6 g, 180 mmol) in $CH_2Cl_2$ (60 ml) was added to a stirred solution of **2** (23.3 g, nominally 100 mmol) and $(iso\text{-}Pr)_2NEt$ (23.3 g, 180 mmol) in $CH_2Cl_2$ (100 ml) at 0 °C. After 40 min at 0 °C, the reaction mixture was poured into ice-water (200 g) and extracted with $CH_2Cl_2$. The $CH_2Cl_2$ solution was washed with brine and dried. Evaporation gave **8** (35.6 g) as a pale brown oil. IR $\nu_{max}^{liq.}$ $cm^{-1}$: 3360, 1750, 1710, 1510, 1360 (sh.), 1170. NMR ($CDCl_3$) $\delta$: 1.45 (9H, s, $C(CH_3)_3$), 1.50 (3H, d, $J$ = 7 Hz, C–$CH_3$), 3.00 (3H, s, $SO_2CH_3$), 3.80 (3H, s, O–$CH_3$), 4.4—4.7 (1H, m, N–CH), 5.05—5.55 (2H, m, O–CH, NH). MS *m/e*: 311 ($M^+$). This oil was used for the preparation of **10** without further purification.

**Conversion of 8 into 9**——An aqueous 0.1 N KOH solution (22.0 ml, 2.20 mmol) was added to a stirred solution of **8** (625 mg, 2.00 mmol) in MeOH (10 ml) under ice-cooling. The reaction mixture was stirred for 40 min at 0 °C, concentrated to remove MeOH and extracted with AcOEt. The extract was washed with brine and dried. Evaporation of the solvent gave **9** (400 mg, 93% yield) as colorless crystals, mp 68—73 °C. An analytically pure sample, mp 75—77 °C, was obtained by recrystallization from hexane. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3230, 3100, 1720, 1690, 1650, 1260, 1160. NMR ($CDCl_3$) $\delta$: 1.48 (9H, s, $C(CH_3)_3$), 1.80 (3H, d, $J$ = 7 Hz, $CH_3$), 3.77 (3H, s, $OCH_3$), 6.05 (1H, br s, NH), 6.65 (1H, q, $J$ = 7 Hz, $CH_3CH$=). MS *m/e*: 215 ($M^+$). *Anal.* Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.64; H, 7.69; N, 6.74.

**Preparation of 10**——Powdered $NaBH_4$ (8.33 g, 220 mmol) was added portionwise to a stirred solution of **8** (35.6 g, nominally 114 mmol) in EtOH (250 ml) under ice-cooling. The reaction mixture was stirred for 2.5 h at 0 °C and for an additional 1 h at room temperature. Acetone (70 ml) and AcOH (10 ml) were added to destroy the excess hydride under ice-cooling, and the whole mixture was concentrated and taken up in AcOEt. The AcOEt solution was washed with cold water, dried and evaporated to give an oily residue, which was chromatographed on silica gel (acetone : benzene = 1 : 5 as an eluent) to give **10** (19.0 g, 68% yield from L-threonine methyl ester hydrochloride) as a pale yellow oil. IR $\nu_{max}^{liq.}$ $cm^{-1}$: 3360, 1700, 1510, 1340, 1170. NMR ($CDCl_3$) $\delta$: 1.45 (9H, s, $C(CH_3)_3$), 1.48 (3H, d, $J$ = 7 Hz, $CH_3$), 2.65 (1H, br s, OH), 3.05 (3H, s, $SO_2CH_3$), 3.5—4.0 (3H, m, N–CH, $OCH_2$), 4.7—5.25 (2H, m, NH, O–CH). MS *m/e*: 252 ($M^+ - CH_2OH$), 210 ($M^+ - tert$-BuO).

**Preparation of *SS*-7b**——A mixture of **10** (19.8 g, 69.9 mmol) and powdered $K_2CO_3$ (19.3 g, 140 mmol) in $CH_3CN$ (310 ml) was stirred for 6.5 h at 75 °C. The reaction mixture was cooled to room temperature and the insoluble materials were removed by filtration. The filtrate and washings were evaporated and taken up in $Et_2O$. The ethereal solution was concentrated and subjected to flash column chromatography on silica gel (acetone : benzene = 1 : 15 as an eluent) to give *SS*-**7b** (7.94 g, 61% yield) as a colorless oil. IR $\nu_{max}^{liq.}$ $cm^{-1}$: 3400, 1720. NMR ($CDCl_3$) $\delta$: 1.25 (3H, d, $J$ = 5 Hz, $CH_3$), 1.45 (9H, s, $C(CH_3)_3$), 2.35—2.85 (3H, m, 2 × CH, OH), 3.67 (2H, dd, $J$ = 5 Hz, 5 Hz, $CH_2$). MS *m/e*: 114 ($M^+ - tert$-BuO). $[\alpha]_D^{20}$ −7.05° ($c$ = 1.022, $CHCl_3$). *Anal.* Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.31; H, 8.75; N, 7.29.

**Preparation of *SS*-7c**——A solution of MsCl (4.37 g, 38.1 mmol) in $CH_2Cl_2$ (30 ml) was added to a stirred solution of *SS*-**7b** (6.50 g, 34.7 mmol) and $Et_3N$ (3.86 g, 38.1 mmol) in $CH_2Cl_2$ (50 ml) under ice-cooling. After 40 min at 0 °C and an additional 20 min at room temperature, the reaction mixture was washed with cold water and brine and dried. Evaporation of the solvent gave a colorless oil, which was triturated with petroleum ether to give *SS*-**7c** (8.20 g, 89% yield). Recrystallization from $Et_2O$–petroleum ether gave analytically pure *SS*-**7c** (6.60 g, 71% yield) as colorless needles, mp 43.5—45 °C. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1710, 1360, 1160. NMR ($CDCl_3$) $\delta$: 1.30 (3H, d, $J$ = 5 Hz, $CH_3$), 1.45 (9H, s, $C(CH_3)_3$), 2.4—3.0 (2H, m, 2 × CH), 3.10 (3H, s, $SO_2CH_3$), 4.2—4.4 (2H, m, $CH_2$). MS *m/e*: 266 ($M^+ + 1$), 192 ($M^+ - tert$-BuO). $[\alpha]_D^{20}$ −32.0° ($c$ = 1.0, $CHCl_3$). *Anal.* Calcd for $C_{10}H_{19}NO_5S$: C, 45.26; H, 7.23; N, 5.28; S, 12.08. Found: C, 45.55; H, 7.36; N, 5.32; S, 11.96.

**Preparation of *RS*-5 and *RR*-6 from *SS*-7c**[16]——A solution of *SS*-**7c** (1.08 g, 4.07 mmol) in THF (5 ml) was added to a stirred suspension of $NaP(C_6H_5)_2$[12] (12.2 mmol) in THF (15 ml) at −40 °C. The reaction mixture was stirred for 1.5 h at −40 °C and then for an additional 1.5 h at −40—0 °C. Silica gel (8 g) and THF (10 ml) were added to the reaction mixture at 0 °C, and the mixture was stirred for a few minutes at room temperature. Insoluble materials were filtered off through Celite under an argon atmosphere. Evaporation of the filtrate and washings gave an oil, which was quickly purified on a silica gel flash column (AcOEt : hexane = 1 : 30 as an eluent) to give *RS*-**5** (1.32 g, 60% yield) as a colorless amorphous powder. The powder was again subjected to flash column chromatography ($SiO_2$, AcOEt : hexane = 1 : 5 as an eluent) to give an analytically pure sample. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3420, 1700, 1490. NMR ($CDCl_3$) $\delta$: 1.24 (3H, d, $J$ = 8 Hz, $CH_3$), 1.41 (9H, s, $C(CH_3)_3$, 1.94—2.20 (2H, m, P–$CH_2$), 2.36—2.80 (1H, br, P–CH), 3.85—4.5 (1H, br, N–CH), 5.0—5.45 (1H, br, NH), 6.7—7.8 (20H, m, aromatic H). MS *m/e*: 541 ($M^+$). $[\alpha]_D^{22}$ +103.4° ($c$ = 1.0, $CHCl_3$). *Anal.* Calcd for $C_{33}H_{37}NO_2P_2$: C, 73.18; H, 6.89: N, 2.59; P, 11.44. Found: C, 73.01; H, 6.97; N, 2.73; P, 10.97. Further elution of the flash column gave *RR*-**6** (0.110 g, 5% yield) as

a colorless amorphous powder. The powder was again subjected to flash column chromatography ($SiO_2$, AcOEt : hexane = 1 : 30 as an eluent) to give an analytically pure sample. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3430, 1700, 1490. NMR ($CDCl_3$) $\delta$: 0.93 (3H, dd, $J_{H-P}$ = 13 Hz, $J_{H-H}$ = 8 Hz, $CH_3$), 1.36 (9H, s, $OC(CH_3)_3$), 1.8—2.25 (2H, m, P–$CH_2$), 2.75—3.1 (1H, m, P–CH), 3.64—4.0 (1H, br, N–CH), 4.65 (1H, d, $J$ = 8 Hz, NH), 6.9—7.7 (20H, m, aromatic H). $[\alpha]_D^{20}$ +76.6° ($c$ = 1.0, $CHCl_3$). *Anal.* Calcd for $C_{33}H_{37}NO_2P_2$: C, 73.18; H, 6.89; N, 2.59; P, 11.44. Found: C, 72.81; H, 6.93; N, 2.61; P, 11.11.

**Preparation of *SS*-7d**[16]——A mixture of $HP(C_6H_5)_2$ (940 mg, 5.05 mmol) and lithium strips (50.0 mg, 7.20 mmol) in THF (3 ml) was stirred for 3 h at room temperature. The mixture thus obtained was added to a stirred solution of *SS*-**7c** (557 mg, 2.10 mmol) in THF (3 ml) at 5 °C. The reaction mixture was stirred for 4 h at room temperature, quenched with a solution of AcOH (180 mg, 3.00 mmol) in THF (3 ml) under ice-cooling, and filtered under an argon atmosphere. The filtrate and washings were evaporated and then subjected to flash column chromatography on silica gel (AcOEt : hexane = 1 : 30 as an eluent) to give *SS*-**7d** (155 mg, 21% yield) as colorless crystals, mp 50.5—52.5 °C. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1700. NMR ($CDCl_3$) $\delta$: 1.10 (3H, d, $J$ = 5 Hz, $CH_3$), 1.40 (9H, s, $C(CH_3)_3$), 1.95—2.65 (4H, br m, 2 × CH, $CH_2$), 7.15—7.65 (10H, m, aromatic H). MS *m/e*: 355 ($M^+$). $[\alpha]_D^{20}$ −46.4° ($c$ = 1.0, $CHCl_3$). *Anal.* Calcd for $C_{21}H_{26}NO_2P$: C, 70.97; H, 7.37; N, 3.94; P, 8.71. Found: C, 70.75; H, 7.25; N, 4.04; P, 8.83.

**Preparation of *RS*-11**——A solution of *m*-chloroperbenzoic acid (414 mg, 2.40 mmol) in $Et_2O$ (3 ml) was added to a stirred solution of *RS*-**5** (300 mg, 0.554 mmol) in $Et_2O$ (2 ml) at −30 °C under an argon atmosphere. The reaction mixture was stirred for 1 h at −30——10 °C and for an additional 0.5 h at 0 °C, then diluted with $Et_2O$, washed successively with saturated $NaHCO_3$, 1 N NaOH, and brine, and dried. Evaporation of the solvent gave colorless crystals, which were triturated with hexane to afford *RS*-**11** (297 mg, 94% yield) as colorless crystals, mp 176—178 °C. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3300, 1700, 1500, 1250. NMR ($CDCl_3$) $\delta$: 1.24 (3H, d, $J$ = 8 Hz, $CH_3$), 1.40 (9H, s, $C(CH_3)_3$), 2.3—3.0 (3H, m, P–$CH_2$, P–CH), 3.88—4.44 (1H, br, N–CH), 6.92—8.0 (21H, m, NH, aromatic H), MS *m/e*: 573 ($M^+$). *Anal.* Calcd for $C_{33}H_{37}NO_4P_2$: C, 69.09; H, 6.51; N, 2.44; P. 10.80. Found: C, 69.37; H, 6.80; N, 2.43; P. 10.74.

**Preparation of *RS*-12**[16]——A mixture of *RS*-**5** (784 mg, 1.45 mmol) and CuCl (158 mg, 1.60 mmol) in $CH_2Cl_2$ (15 ml) was refluxed for 1.5 h.[11] After removal of the solvent, the residue was dissolved in benzene. This solution was treated with activated charcoal, and evaporated. The residue was triturated with $Et_2O$ to give *RS*-**12** (570 mg, 61% yield) as a colorless powder, mp 207—209 °C (dec.). Recrystallization from $CH_2Cl_2$–$Et_2O$ afforded an analytically pure sample, mp 223—225 °C (dec.). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3280, 1700, 1500. MS *m/e*: 541 ($M^+$ of *RS*-**5**). $[\alpha]_D^{20}$ −135.0° ($c$ = 0.4, $CHCl_3$). *Anal.* Calcd for $C_{33}H_{37}NO_2P_2 \cdot CuCl$: C, 61.87; H, 5.82; N, 2.19; P. 9.67; Cl, 5.53. Found: C, 61.88; H, 6.05; N, 2.01; P, 9.78; Cl, 5.38.

**Asymmetric Homogeneous Hydrogenation of *N*-Acyldehydroamino Acids**——A. Substrates: 2-Acetamidoacrylic acid was purchased from Nakarai Chemicals, Ltd. The other substrates were prepared according to the method reported by Fryzuk.[7]

B. General Procedure: The hydrogenation flask containing a solution of substrate (2 mmol) in deoxygenated EtOH was purged of oxygen and filled with oxygen-free hydrogen. In another flask a mixture of *RS*-**5** or *RS*-**12** (0.04—0.044 mmol) and $[Rh(NBD)_2]ClO_4$[7] (0.04 mmol) in deoxygenated EtOH (4—5 ml) was stirred for 15 min at room temperature under an argon atmosphere. The resulting suspension was injected into the above hydrogenation flask. The reaction mixture was stirred for 18—22 h at room temperature under an atmospheric pressure of hydrogen. *O*,*N*-Diacetyltyrosine (**14e**) and *N*-acetyl-3-(4-acetoxy-3-methoxyphenyl)alanine (**14f**) were isolated as follows. The hydrogenation solution was treated with dry Dowex 50W-X2 cation ($H^+$ form) exchange resin for 1 h and then filtered. The filtrate was evaporated to dryness to give the desired products. Other *N*-acylamino acids were obtained according to the method reported by Riley.[17]

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## References and Notes

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