Thermomorphic System with Non-Fluorous Phase-Tagged Ru(BINAP) Catalyst: Facile Liquid/Solid Catalyst Separation and Application in Asymmetric Hydrogenation

Yi-Yong Huang^{†,‡}, Yan-Mei, He[†], Hai-Feng Zhou[†], Lei Wu[†], Bao-Lin Li[†], Qing-Hua Fan^{†*}

[†] *Laboratory of Chemical Biology, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100080, P. R. China.*

[‡] *Graduate School of Chinese Academy of Sciences, Beijing 100080, P. R. China*

fanqh@iccas.ac.cn

Supporting Information

Table of Contents

1. General experimental	S2
2. Synthesis of 2 and (S)- 3	S2
2. Synthesis of ligand (S)- 1	S3
2. NMR data and GC conditions for the reduced products	S4
3. Spectra of ligand (S)- 1	S6
4. Manipulation for investigation the solubility of ligand	S10
5. References	S10

General experimental

All reactions were carried out under dry nitrogen atmosphere. Commercial reagents were used as received without further purification unless otherwise stated. All solvents used were dried using standard, published methods and were distilled under nitrogen atmosphere before use.

Preparation of **2**

Compound **2** was synthesized by alkylation of methyl 3,4,5-trihydroxybenzoate with 1-bromooctadecane in DMF at 100°C followed by hydrolysis in 80% total yield.¹ ¹H NMR (300 MHz, CDCl₃) δ: 0.88 (t, *J* = 6.6 Hz, 9 H), 1.20-1.49 (overlapped peaks, 90 H), 1.70-1.86 (m, 6 H), 4.00-4.06 (overlapped t, 6H), 7.32 (s, 2 H).

Preparation of (*S*)-**3**

(*S*)-**3** was prepared according to our previously reported method.² ¹H NMR (400 MHz, CDCl₃): δ 4.00 (s, 4 H), 6.29 (d, *J* = 8.4 Hz, 2 H), 6.56 (d, *J* = 7.3 Hz, 2 H), 6.69 (t, *J* = 7.8 Hz, 2 H), 7.12-6.99 (m, 20 H), 7.30 (dd, *J*₁ = 2.3 Hz, *J*₂ = 8.8 Hz, 2 H), 7.76 (d, *J* = 8.7 Hz, 2 H); ¹³C NMR (100.6 MHz, CDCl₃): δ 110.7, 119.2, 120.9, 123.3, 126.2, 127.5, 127.9, 128.2, 129.6, 132.8, 132.9, 133.0, 133.9, 134.0, 134.1, 134.2, 134.3, 134.4, 135.1, 135.2, 137.8, 137.8, 137.9, 137.9, 138.0, 141.8, 146.2, 146.3, 146.6, 146.7; ³¹P NMR (162.0 MHz, CDCl₃): δ -16.79.

Synthesis of ligand (S)-1

Under N_2 atmosphere, to a mixture of 3,4,5-trioctadecyloxybenzoic acid **2** (0.33 g, 0.36 mmol), (*R*)-5,5'-diamino BINAP **3** (0.1 g, 0.15 mmol) and calcium chloride (0.1 g) in 6 mL of NMP was added triphenyl phosphite (0.2 mL, 0.76 mmol) and pyridine (0.2 mL, 2.4 mmol). The mixture was stirred at 100°C for 6 h under nitrogen atmosphere and then poured into cool methanol. The precipitate was collected by centrifugation and was further purified by flash chromatography on silica gel (elution with 200:1 (v/v) dichloromethane/ethanol): 0.26 g, 70%; white solid; mp $86\text{--}87^\circ\text{C}$. $[\alpha]_{\text{D}}^{25} = -58$ (c, 0.48, CH_2Cl_2). ^1H NMR (600 MHz, CDCl_3): δ 0.87-0.89 (overlapped t, 18H), 1.22-1.37 (overlapped peaks, 168H), 1.47-1.50 (m, 12H), 1.76-1.86 (m, 12H), 4.04-4.08 (overlapped t, 12H), 6.74 (d, $J = 8.6$ Hz, 2H), 7.05 (t, $J = 8.3$ Hz, 2H), 6.95-7.26 (m, 24H), 7.51 (d, $J = 7.4$ Hz, 2H), 7.85 (d, $J = 7.1$ Hz, 2H), 8.00 (d, $J = 8.9$ Hz, 2H), 8.08 (s, 2H); ^{13}C NMR (150.9 MHz, CDCl_3): δ 14.1, 22.7, 26.1, 29.3, 29.4, 29.6, 29.7, 30.4, 31.9, 69.5, 73.6, 105.9, 121.1, 122.3, 125.8, 127.4, 127.7, 128.2, 128.7, 129.6, 131.1, 132.3, 132.7, 132.8, 132.9, 134.1, 134.2, 134.3, 136.1, 136.2, 136.8, 137.6, 141.7, 145.9, 153.4, 153.4, 166.1; ^{31}P NMR (121 MHz, CDCl_3): δ -16.00; IR (KBr, cm^{-1}): 3127, 2919, 2850, 1644, 1582, 1401, 1116; MS (MALDI-TOF) Calcd for $\text{C}_{166}\text{H}_{258}\text{N}_2\text{O}_8\text{P}_2$ 2469.9 $[\text{M}]^+$, 2285.9 $[(\text{M}-\text{PPh}_2)+\text{H}]^+$, found 2469.5, 2285.5. Anal. Calcd for $\text{C}_{166}\text{H}_{258}\text{N}_2\text{O}_8\text{P}_2$: C, 80.66; H, 10.52; N, 1.13. Found: C, 80.33; H, 10.69; N, 1.08.

NMR data and GC conditions for the reduced products

3-hydroxy-butyl ester (5a): ^1H NMR (300 MHz, CDCl_3): δ 1.22

(d, J = 6.3 Hz, 3 H), 1.45 (s, 9 H), 2.28-2.44 (m, 2 H), 4.11-4.18 (m, 1 H); ^{13}C NMR (75.4 MHz, CDCl_3): δ 22.3, 28.1, 43.8, 54.3, 81.2, 172.4. GC: Chirasil-Dex CP 7502 (30 m x 0.25 mm) column, 90°C, 10 psi, t_S = 22.1 min (major isomer), t_R = 23.6 min (minor isomer), t = 19.5 min (starting material).

3-Hydroxy-Butyric Acid Methyl Ester (5b): ^1H NMR (300 MHz, CDCl_3): δ 1.21 (d, J

= 6.9 Hz, 3 H), 2.35-2.50 (m, 2 H), 3.00 (br, 1 H), 3.67 (s, 3 H), 4.13-4.20 (m, 1 H); ^{13}C NMR (75.4 MHz, CDCl_3): δ 22.4, 42.6, 51.6, 64.2, 173.2. GC: **5b** was first transferred to its ester derivative by reaction with acetic anhydride before ee determination. Chirasil-Dex CP 7502 (30 m x 0.25 mm) column, 100 °C, 10 psi, t_S = 7.9 min (major isomer), t_R = 8.4 min (minor isomer), t = 4.5 min (starting material).

3-Hydroxy-3-Phenyl-Propionic acid Methyl Ester (5c): ^1H NMR (300 MHz, CDCl_3):

δ 2.58-2.73 (m, 2 H), 3.23 (br, 1 H), 3.63 (s, 3 H), 5.03-5.07 (m, 1 H), 7.18-7.31 (m, 5 H); ^{13}C NMR (75.4 MHz, CDCl_3): δ 43.2, 51.9, 70.3, 125.7, 127.8, 128.3, 142.6, 172.8. GC: **5c** was first transferred to its ester derivative by reaction with acetic anhydride before ee determination. Chiraldex G-TA CA 73035 (50 m x 0.25 mm) column, 140 °C, 10 psi, t_S = 40.4 min (major isomer), t_R = 41.1 min (minor isomer), t = 20.0 min (starting material).

3-Hydroxy-3-Phenyl-Propionic acid Ethyl Ester (5d): ^1H NMR (300 MHz,

CDCl_3): δ 1.25 (t, J = 7.1 Hz, 3 H), 2.65-2.80 (m, 2 H), 3.23 (br, 1 H), 4.17 (q, J = 7.1 Hz, 2 H), 5.10-5.15 (m, 1 H), 7.26-7.39 (m, 5 H); ^{13}C NMR (75.4 MHz, CDCl_3): δ 14.1, 43.3, 60.8, 70.3, 125.7, 127.8,

128.5, 142.5, 172.4. GC: **5d** was first transferred to its ester derivative by reaction with acetic anhydride before ee determination. Chirasil-Dex CP 7502 (30 m x 0.25 mm) column, 110 °C (60 min) and then programmed increasing (1 °C/min) to 120 °C and holding, 12 psi, t_S = 99.7 min (major isomer), t_R = 101.3 min (minor isomer), t = 64.0 min (starting material).

3-Hydroxy-3-(4-Chlorophenyl)-Propionic Acid Methyl Ester (5e): ^1H NMR (300

MHz, CDCl_3): δ 2.56-2.68 (m, 2 H), 3.33 (br, 1 H), 3.63 (s, 3 H), 4.99-5.03 (m, 1 H), 7.18-7.25 (m, 4 H); ^{13}C NMR (75.4 MHz, CDCl_3): δ 43.1, 52.0, 69.5, 127.1, 128.7, 133.5, 141.0, 172.6. GC: Chirasil-Dex CP 7502 (30 m x 0.25 mm) column, 165 °C, 14 psi, t_S = 18.7 min (major isomer), t_R = 19.5 min (minor isomer), t = 10.0 min (starting material).

3-Hydroxy-3-(4-Fluorophenyl)-Propionic Acid Ethyl Ester (5f): ^1H NMR (300

MHz, CDCl_3): δ 2.65-2.77 (m, 2 H), 3.43 (br, 1 H), 3.72 (s, 3 H), 5.10-5.13 (m, 1 H), 7.01-7.05 (m, 2 H), 7.32-7.36 (m, 2 H); ^{13}C NMR (75.4 MHz, CDCl_3): δ 43.1, 51.9, 69.7, 115.3, 127.3, 138.2, 163.9, 172.7. GC: Chirasil-Dex CP 7502 (30 m x 0.25 mm) column, 130 °C, 12 psi, t_S = 27.6 min (major isomer), t_R = 29.4 min (minor isomer), t = 12.0 min (starting material).

3-Hydroxy-3-(4-Methoxyphenyl)-Propionic Acid Methyl Ester (5g): ^1H NMR

(300 MHz, CDCl_3): δ 2.62-2.79 (m, 2 H), 3.26 (br, 1 H), 3.59 (s, 3 H), 3.77 (s, 3 H), 5.04-5.08 (m, 1 H), 6.87 (d, J = 8.69 Hz, 2 H), 7.26 (d, J = 8.69 Hz, 2 H); ^{13}C NMR (75.4 MHz, CDCl_3): δ 43.2, 51.8, 55.26, 70.0, 113.9, 127.0, 134.8, 159.2, 172.7. GC: Chirasil-Dex CP 7502 (30 m x 0.25 mm) column, 165 °C, 14 psi, t_S = 20.7 min (major isomer), t_R = 21.3 min (minor isomer), t = 10.0 min (starting material).

Spectra of ligand (S)-1

¹H NMR:

¹³C NMR:

www

IR:

MALDI-TOF MS:

Manipulation for investigation the solubility of ligand (S)-**1**

(S)-**1** (100 mg) was dissolved in solvent of 1, 4-dioxane (8 mL), or ethanol/1, 4-dioxane (32 mL, 3:1, v/v) at 60 °C. After being cooled down to 0 °C, the precipitated **1** was filtrated and weighted after being dried. The quantity of **1** in the filtrate could be obtained after evaporating the solvent. Based on these results, the solubility of **1** at low temperature and the ligand recovery could be calculated out.

References

1. Percec, V.; Tomazos, D.; Heck, J.; Blackwell, H.; Ungar, G. *J. Chem. Soc. Perkin Trans. 2*. **1994**, *1*, 34.
2. Huang, Y. Y.; Deng, G. J.; Wang, X. Y.; Fan, Q. H. *Chinese J. Chem.* **2004**, *22*, 891.