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RESEARCH ARTICLE

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# Investigation of Taniaphos as a chiral selector in chiral extraction of amino acid enantiomers

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**Abstract**

Finding chiral selector with high stereoselectivity to a variety of amino acid enantiomers remains a challenge and warrants further research. In this work, Taniaphos, a chiral ligand with rotatable spatial configuration, was employed as a chiral extractant to enantioseparate various amino acid enantiomers. Phenylalanine (Phe), homophenylalanine (Hphe), 4-nitrophenylalanine (Nphe), and 3-chloro-phenylglycine (Cpheg) were used as substrates to evaluate the extraction efficiency. The results revealed that Taniaphos-Cu exhibited good abilities to enantioseparate Phe, Hphe, Nphe, and Cpheg with the highest separation factors ($\alpha$) of 3.13, 2.10, 2.32, and 2.14, respectively. Taniaphos-Cu is more conducive to combine with D-amino acid in extraction. The influences of pH, Taniaphos-Cu, and concentration and extraction temperature on extraction were comprehensively evaluated. The highest performance factors (*pf*) for Phe, Hphe, Nphe, and Cpheg at optimal extraction conditions were 0.08892, 0.1250, 0.09621, and 0.08021, respectively. The recognition mechanism between Taniaphos-Cu and amino acid enantiomers was discussed. The coordination interaction between Taniaphos-Cu and —$COO^-$, π-π interaction between Taniaphos-Cu and amino acid enantiomers are important acting forces in chiral extraction. The steric-hindrance between —$NH_2$ and —OH lead to Taniaphos-Cu-D-Phe is more stable than Taniaphos-Cu-L-Phe. This work provided a chiral extractant that has good abilities to enantioseparate various amino acid enantiomers.

**KEYWORDS**

amino acid enantiomers, chiral extraction, recognition mechanism, Taniaphos

## 1 | INTRODUCTION

Enantiomers are chiral molecules that are non-superimposable mirror images of each other. In general, one enantiomer of chiral drugs is safe and effective, while the other is maybe ineffective or even toxic.[1] There are many examples of chiral medicines whose enantiomers vary drastically in their properties. For instance, the antimicrobial activity of (*S*)-ofloxacin is 9.3 times that of (*R*)-ofloxacin.[2] Consequently, much effort had been made to obtain optically pure enantiomers in the past decades.[3–6] Asymmetric synthesis, raceme separation, and isolation from natural sources are the main pathway to prepare pure enantiomers. Isolation of enantiomers from natural sources is not broadly used because of its low yield and the limited types of enantiomers. Thus, asymmetric synthesis and raceme separation are the most promising methods to obtain pure enantiomers. And numerous

  

efforts have been made in the past several decades to develop efficient chiral catalysts and selectors. For instance, BINAP was discovered by Miyashita et al.[7] And this ligand has been successfully applied in asymmetric catalysis with high efficiency and economic.[8,9] Recently, BINAP has also been confirmed to be an efficient chiral selector in the enantioseparation of racemic amino acids. Verkuijl et al.[10] reported that BINAP-Pd was a good chiral selector in enantioseparation of tryptophan with separation factor ($\alpha$) of 2.4. Tang et al.[11,12] and Liu et al.[13] also reported that BINAP-Cu complex was a good chiral selector for enantioseparation of phenylalanine, phenylglycine, and 4-Nitrophenylalanine with separation factor ($\alpha$) of 5.20, 2.15, and 3.37, respectively. Furthermore, the enantioseparation abilities of several BINAP derivatives had also been detected in our previous work. The results indicated that BINAP derivatives, such as (*S*)-SEGPHOS and (*S*)-MeO-BIPHEP, have good separation capabilities toward amino acid enantiomers.[14,15] More importantly, some other chiral diphosphine ligands used in asymmetric catalytic also exhibited considerable abilities to enantioseparate racemic amino acids. For instance, (*S*, *S*)-DIOP is a proper extractant to enantioseparate 3-chloro-phenylglycine enantiomers with $\alpha$ of 1.84.[16] (*S*)-SDP is a spiro ligand that could be used as chiral selector in chiral extraction of 4-Nitrophenylalanine with $\alpha$ of 3.32.[17] However, all these non-biphenyl (binaphthalene) diphosphine ligands only showed separation ability to one kind of amino acid enantiomers. Finding chiral selector with high stereoselectivity to a variety of amino acid enantiomers remains a challenge and warrants further research.

As shown in Figure 1, it is obvious that the benzene rings in the chemical structures of BINAP, MeO-BIPHEP, and SEGPHOS can rotate properly. Thus, these types of chiral extractants could enantioseparate various amino acid enantiomers by adjusting their stereochemical structures. However, (*S*)-SDP and (*S*, *S*)-DIOP are conformationally rigid ligands. Consequently, (*S*)-SDP only showed good ability to separate 4-Nitrophenylalanine enantiomers, and (*S*, *S*)-DIOP only showed good ability to separate 3-chloro-phenylglycine enantiomers. These features bring inspiration to us that chiral ligand with rotatable spatial configuration may be a versatile host in separation of an entire class of racemates.

Taniaphos((SP)-1-[(S)-α-(Dimethylamino)-2-(diphenylphosphino)benzyl]-2-diphenylphosphinoferrocene) is a famous Ferrocene ligand that is often used as catalyst in asymmetric synthesis.[18,19] The chemical structure of Taniaphos is shown in Figure 1. Compared with BINAP, MeO-BIPHEP, and SEGPHOS, benzene rings in Taniaphos also can rotate properly. Accordingly, we hypothesized that Taniaphos might be another chiral diphosphine ligand that has considerable abilities to enantioseparate various racemic amino acids. In this work, Taniaphos metal was applied as chiral extractant in chiral extraction for the first time. Phenylalanine (Phe), homophenylalanine (Hphe), 4-nitrophenylalanine (Nphe), and 3-chloro-phenylglycine (Cpheg) were used as substrates to evaluate the enantioselectivity of Taniaphos metal. The influences of metal precursor, organic solvent, pH, extractant concentration, and extraction temperature on extraction efficiency were investigated. Also, the possible recognition mechanism had been discussed.

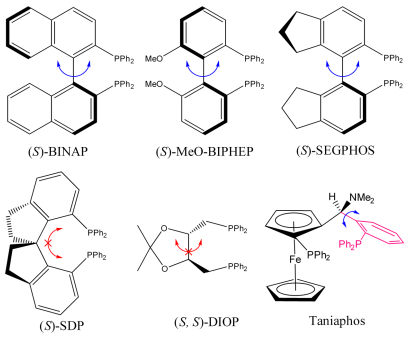


**FIGURE 1** Chiral diphosphine ligands investigated in previous work and this work

## 2 | MATERIALS AND METHODS

### 2.1 | Materials and reagents

Taniaphos (>99%) was purchased from Bide Pharmatech Ltd. Amino acid enantiomers and racemates were purchase from Adamas Reagent Co, Ltd. Metal precursors, such as $[(CH_3CN)_4Cu]PF_6$ (>98%), $(CH_3CN)_2PdCl_2$ (>99%) and $[(C_6H_5)_3P]_2NiCl_2$ (>98%), were purchased from J&K Scientific Ltd. Organic solvents (analytic grade) and inorganic salts (analytic grade) were purchased from Adamas Reagent Co, Ltd.

### 2.2 | Extraction of amino acid enantiomers

The organic phase was prepared as follows. Briefly, Taniaphos (0.1 mmol) and metal precursor (0.1 mmol) were dissolved in 100 ml organic solvent. After mixed for 12 h, the Taniaphos-metal complex was obtained with a concentration of 1.0 mmol/L. The water phase was prepared as follows. Briefly, amino acid racemates (0.2 mmol) were dissolved in 100 ml PBS solution (pH = 5–12) with concentration of 2.0 mmol/L.

Extraction of amino acid enantiomers was carried out as follows. Briefly, 2.0 ml Taniaphos-metal solution and 2.0 ml amino acid racemates were placed in a 10 ml centrifuge tube. The organic phase and water phase were shaken for 12 h at 120 rpm by a constant temperature shaker. Then, the extraction system stood for 12 h to make organic-water phases stratified. The water phase was filtered by a 0.45 μm filter membrane. The obtained filtrate was then analyzed by the HPLC method described in our previous work.[14,15]

## 2.3 | Calculations

Distribution coefficient is defined as the ratio of the total concentration of solute in the organic phase to the total concentration of solute in the aqueous phase. The distribution coefficients of L- and D-amino acid in extraction were calculated by Equations 1 and 2, respectively. $C_{L,org}$ and $C_{D,org}$ represent L- and D-amino acid in organic phase after extraction. $C_{L,w}$ and $C_{D,w}$ represent L- and D-amino acid in water phase after extraction. Separation factor ($\alpha$) can be employed to evaluate the degree of separation of L- and D-amino acid in single-stage extraction. And it could be calculated by Equation 3. In chiral extraction, the purity of enantiomer is an important indicator to evaluate the enantioselectivity of chiral extractant. The enantiomeric excess (*ee*) of amino acid enantiomers in organic phase was calculated by Equation 4. Fraction of enantiomer (*f*) is defined as the rate of substance that is extracted into the organic phase. It is often adopted to evaluate the yield of extraction. Fraction of enantiomer (*f*) can be calculated by Equation 5. Performance factor (*pf*) is always used to comprehensively evaluate the efficiency of enantioseparation. High value of *pf* implied that enantiomers are extracted with high purity and high yield simultaneously. The value of *pf* can be calculated according to Equation 6.[20,21]

$$k_L = C_{L,org}/C_{L,w}, \quad (1)$$

$$k_D = C_{D,org}/C_{D,w}, \quad (2)$$

$$\alpha = k_D/k_L, \quad (3)$$

$$ee_{org} = \frac{C_{D,org} - C_{L,org}}{C_{D,org} + C_{L,org}}, \quad (4)$$

$$f = C_{D,org}/\left(C_{D,org} + C_{D,w}\right), \quad (5)$$

$$pf = f \times ee_{org}. \quad (6)$$

## 2.4 | OPTIMIZATION OF EXTRACTION PROCESS

In this work, the extraction conditions were optimized through single-factor test and Response Surface Methodology. Based on the results obtained in single-factor experiments, the optimal conditions for extraction of amino acid enantiomers by Taniaphos-Cu were investigated with a central composite design (CCD). There were 13 runs carried out in CCD. The extraction models were obtained by a quadratic polynomial stepwise regression method. And the mathematical model can be given as Equation 7.

$$pf = b_0 + b_1A + b_2B + b_{12}AB + b_{11}A^2 + b_{22}B^2, \quad (7)$$

where *pf* is response, *A* is pH of water phase, *B* is Taniaphos-Cu concentration, $b_0$ is intercept, $b_1$ and $b_2$ are linear, $b_{11}$ and $b_{22}$ are quadratic, and $b_{12}$ is interaction regression coefficient term.[22]

# 3 | RESULTS AND DISCUSSION

## 3.1 | Extraction of amino acid enantiomers using different Taniaphos-metal complexes

In extraction, Taniaphos ligand should combine with metal ions to form an organometallic complex that has the ability to recognize amino acid enantiomers. According to previous reports, Cu(I), Pd (II), and Ni (II) are always used as metal precursors in chiral extraction of racemic amino acids.[12,23] Thus, the enantioselectivities of Taniaphos-Cu, Taniaphos-Pd, and Taniaphos-Ni had been detected, and the results were tabulated in Table 1. Obviously, Taniaphos-Ni showed little ability to recognize all racemic amino acids with $\alpha$ values were all below 1.20. Taniaphos-Pd exhibited moderate abilities to enantioseparate Phe, Hphe, Nphe, and Cpheg with $\alpha$ values were 1.26, 1.10, 1.61, and 1.44, respectively. Taniaphos-Cu showed the highest abilities to enantioseparate Phe, Hphe, Nphe, and Cpheg with $\alpha$ values were 2.17, 1.28, 1.81, and 1.54, respectively. Thus, Cu(I) is the most suitable metal precursor for Taniaphos in enantioseparation. The enantioselectivity of Taniaphos-Cu is higher than Taniaphos-Pd. This is probably because that 4-coordinated Cu has a tetrahedral structure while 4-coordinated Pd has a plane quadrilateral structure.[24,25] The difference of the spatial configurations makes Taniaphos-Cu more efficient in chiral extraction of amino acid enantiomers.[26] The values of $k_D$ were bigger than $k_L$, which indicated that D-amino acids

**TABLE 1** Enantioselectivities of Taniaphos-metal complexes in chiral extraction

| | $(CH_3CN)_2PdCl_2$[a] | | | $[(CH_3CN)_4Cu]PF_6$[a] | | | $[(C_6H_5)_3P]_2NiCl_2$[a] | | |
|---|---|---|---|---|---|---|---|---|---|
| **Amino acids** | $k_D$ | $k_L$ | α | $k_D$ | $k_L$ | α | $k_D$ | $k_L$ | α |
| Phe | 0.519 | 0.413 | 1.26 | 0.254 | 0.117 | 2.17 | 0.211 | 0.187 | 1.13 |
| Hphe | 0.824 | 0.751 | 1.10 | 1.701 | 1.325 | 1.28 | 0.674 | 0.631 | 1.07 |
| Nphe | 0.385 | 0.239 | 1.61 | 0.220 | 0.121 | 1.81 | 0.158 | 0.136 | 1.16 |
| Cpheg | 1.176 | 0.816 | 1.44 | 0.553 | 0.358 | 1.54 | 0.391 | 0.375 | 1.04 |

[a]The organic solvent is 1,2-Dichloroethane; pH is 8.0.

were the main enantiomers in organic phase after extraction. Consequently, Taniaphos-metal complexes tend to combine with D-amino acid enantiomers in enantioseparation.

## 3.2 | Extraction of amino acid enantiomers using different organic solvents

The spatial configuration of Taniaphos-Cu might be influenced by organic solvent.[15] Thus, the enantioselectivities of Taniaphos-Cu in four different organic solvents were evaluated, and the results were shown in Table 2. Taniaphos-Cu showed good abilities to enantioseparate amino acid enantiomers when Dichloromethane, Chloroform, and 1,2-Dichloroethane were used as organic solvent. The $\alpha$ values of Taniaphos-Cu in 1,2-Dichloroethane are much bigger than that in other solvents. And 1,2-Dichloroethane has lower volatility compared with Dichloromethane and Chloroform. Therefore, 1,2-Dichloroethane is the suitable organic solvent in this work. When Chlorobenzene was used as organic solvent, Taniaphos-Cu exhibited low enantioselectivities to amino acid enantiomers. This result is very similar to other chiral diphosphine ligands that were reported in previous works. The precious works suggested that Chlorobenzene would disturb the π-π interaction of phenyl groups between chiral extractants and substrates.[15–17] Accordingly, π-π interaction between Taniaphos-Cu and amino acid enantiomers might be an important acting force in chiral extraction.

## 3.3 | Enantioselectivities of Taniaphos-Cu at different Ph

The enantioselectivities of Taniaphos-Cu at different pH were determined and the curves of $k$, $\alpha$, $ee$, and $pf$ were demonstrated in Figure 2. Obviously, $k_D$ and $k_L$ were both increased with pH of water phase increased. This is probably due to the reason that Taniaphos-Cu is conducive to combine with anionic amino acid.[10,27] This result suggested that the complexation between —$COO^-$ and Taniaphos-Cu plays an important role in enantioseparation. With the increase of the pH of water phase, the $\alpha$ values increased at first and then achieved an equilibrium at pH above 10.0. And $\alpha$ values slightly decreased at pH of 12.0. This trend revealed that excessively high pH would weaken the enantioselectivity of Taniaphos-Cu complex.[10] As reported in previous work, high $\alpha$ values of chiral diphosphine ligands, such as BINAP, DIOP, and SDP, were always obtained at pH above 7.0. Which were lower than 10.0 reported in this work. This difference suggested that —OH may play an important role between Taniaphos-Cu and amino acid enantiomers. The $ee$ values of D-amino acid enantiomers in organic solvent increased at first and then decreased with pH above 9.0. In chiral extraction, performance factor ($pf$) is often used to comprehensively evaluate the efficiency of chiral extraction. High value of $pf$ implied that D-amino acid enantiomers are extracted into organic phase with high purity and high yield simultaneously.[28] The curves of $pf$ in Figure 2 revealed that high $pf$ were obtained at pH around 10.0. Thus, the following experiments were carried out at pH 10.0.

**TABLE 2** Enantioselectivities of Taniaphos-cu at different organic solvents

| | Dichloromethane | | | Chloroform | | | 1,2-Dichloroethane | | | Chlorobenzene | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Amino acids** | $k_D$ | $k_L$ | α | $k_D$ | $k_L$ | α | $k_D$ | $k_L$ | α | $k_D$ | $k_L$ | α |
| Phe | 0.251 | 0.137 | 1.83 | 0.253 | 0.168 | 1.50 | 0.254 | 0.117 | 2.17 | 0.230 | 0.173 | 1.33 |
| Hphe | 1.401 | 1.171 | 1.20 | 1.663 | 1.293 | 1.28 | 1.701 | 1.325 | 1.28 | 1.303 | 0.881 | 1.13 |
| Nphe | 0.271 | 0.195 | 1.40 | 0.309 | 0.208 | 1.49 | 0.220 | 0.121 | 1.81 | 0.225 | 0.197 | 1.14 |
| Cpheg | 0.209 | 0.151 | 1.38 | 0.280 | 0.214 | 1.31 | 0.553 | 0.358 | 1.54 | 0.183 | 0.136 | 1.35 |

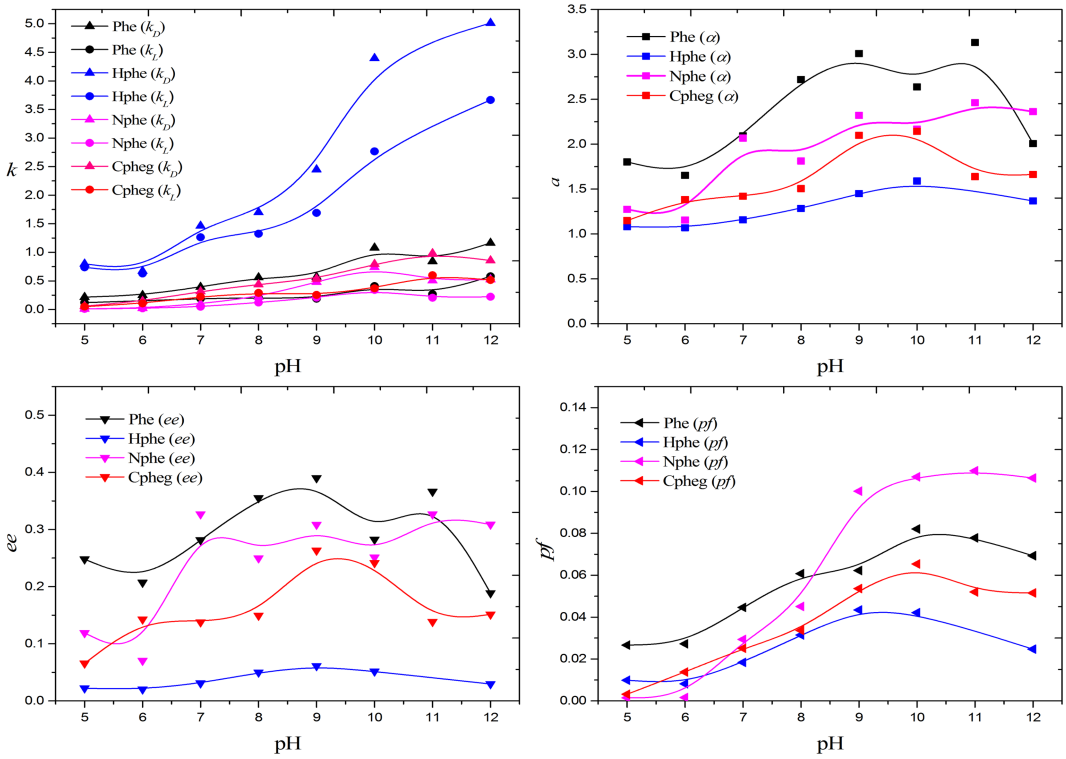


**FIGURE 2** Enantioselectivities of Taniaphos-Cu at different pH

## 3.4 | Enantioselectivities of Taniaphos-Cu at different concentration

Finding the optimal concentration range of Taniaphos-Cu is important for improving extraction efficiency and reducing extraction cost. The enantioselectivities of Taniaphos-Cu at concentration of 0.25–3.0 mmol/L were detected, and the results were depicted in Figure 3. With increasing of Taniaphos-Cu concentration, there were more extractants in organic phase that could combine with amino acid enantiomers. Thus, the values of $k_D$ and $k_L$ were both deservedly increased with increasing extractants concentration. The values of $\alpha$ were all increased with increasing Taniaphos-Cu concentration and then became stable with Taniaphos-Cu concentrations around 1.5 mmol/L. Generally, there was a small amount of racemic amino acid in organic phase that was extracted by physical dissolution with non-stereoselectivity.[29] This phenomenon would decrease the *ee* values when Taniaphos-Cu concentration was low. Thus, the curves of *ee* in Figure 3 were positively correlated with Taniaphos-Cu concentration in the range of 0.25–1.0 mmol/L. With the Taniaphos-Cu concentration further increased, *ee* values were slightly decreased. This is probably because that the competition between D- and L-enantiomers decreased with there was too much Taniaphos-Cu in organic phase that could combine with them.[30] The curves of *pf* indicated that the optimal Taniaphos-Cu concentrations for Phe, Hphe, Nphe, and Cpheg were 2.0, 1.5, 1.5, and 2.0 mmol/L, respectively.

## 3.5 | Enantioselectivities OF Taniaphos-Cu at different temperature

The enantioselectivities of Taniaphos-Cu at temperature in the range of 5–25°C were detected. As shown in Figure 4, the values of $k_D$ and $k_L$ for Nphe were both increased with increasing temperature. Generally, physical solubility of amino acid in organic phase increased with increasing extraction temperature.[31] Thus, *k* values were always increased with increasing extraction temperature. For the same reason, the value of $\alpha$ for Nphe was negatively correlated with extraction temperature. This phenomenon was similar to other diphosphine ligands reported in previous studies.[13,17] However, $k_D$ and $k_L$ for other amino acid enantiomers were both decreased with increasing temperature. And the values of $\alpha$ remained stable with increasing temperature. This phenomenon suggested that the structure of the substrate also has a significant influence on the extraction. The nitro in amino acid may play an important role in chiral extraction. The curves in Figure 4 revealed that the values of *ee* for Nphe slightly decreased with increasing temperature while the

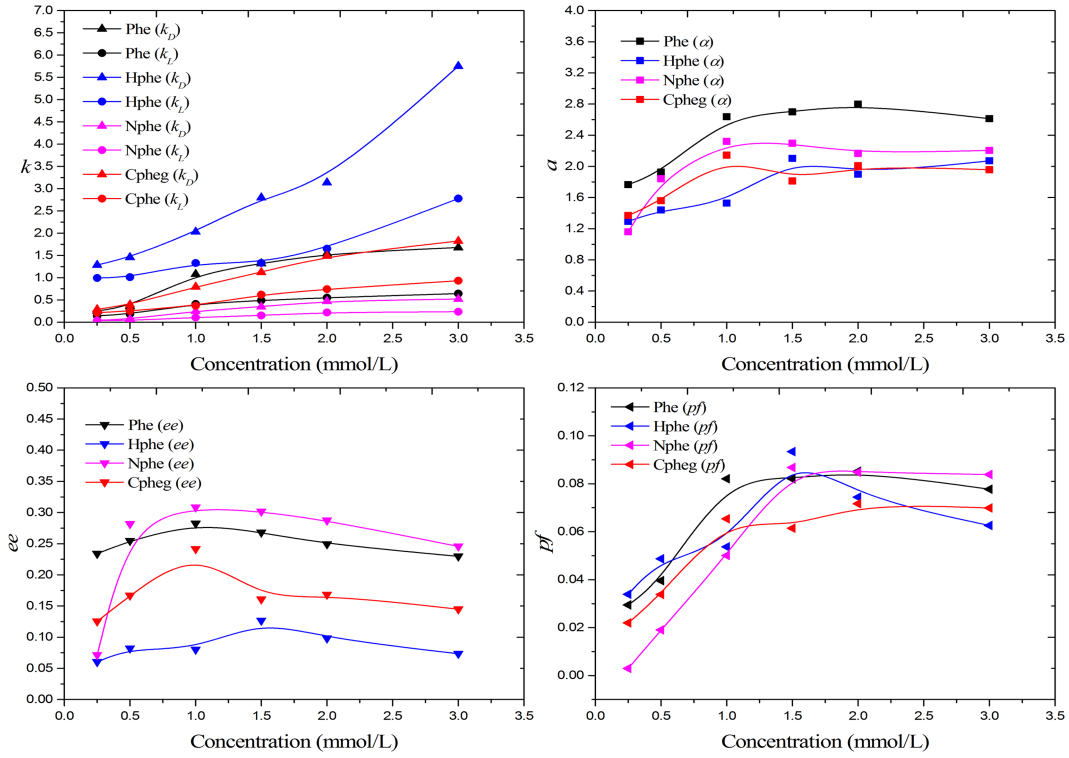


**FIGURE 3** Enantioselectivities of Taniaphos-Cu at different concentration

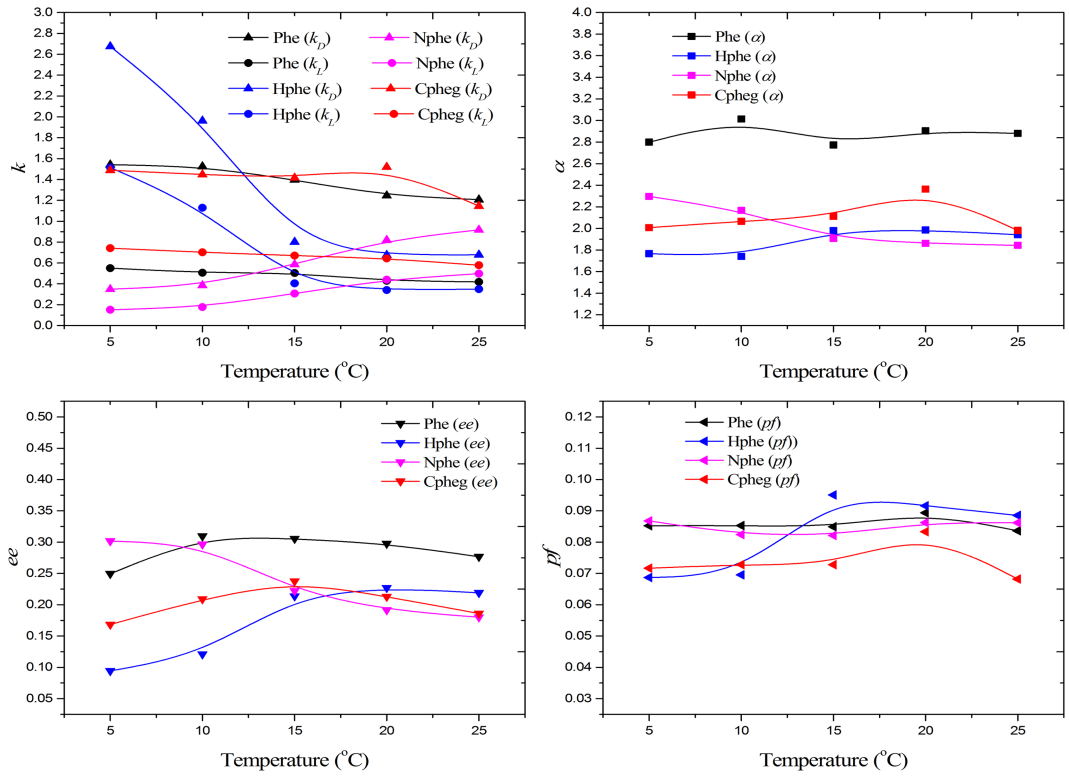


**FIGURE 4** Enantioselectivities of Taniaphos-Cu at different temperature

values of *ee* for Phe, Hphe, and Cpheg slightly increased with increasing temperature. The high values of *pf* were obtained at temperature around 20°C. The above results indicated that extraction temperature had no significant effect on extraction. Therefore, the chiral extraction could be carried out at room temperature. Compared with other diphosphine ligands, Taniaphos-Cu had the advantage of energy conservation in chiral extraction.

## 3.6 | Optimization of the extraction conditions

Response surface methodology design was always used to design and evaluate the extraction conditions.[22,32] Based on the results obtained in the above single factor experiments, the ranges of pH and Taniaphos-Cu concentration evaluated in optimization experiments were tabulated in Table S1. The optimal conditions for extraction of amino acid enantiomers by Taniaphos-Cu were investigated with a central composite design (CCD). There were 13 runs carried out in CCD, and the results were tabulated in Table 3. The extraction models were obtained by a quadratic polynomial stepwise regression method. And the mathematical models for Phe, Hphe, Nphe, and Cpheg were shown in Equations 8–11, respectively.

$$pf_{\text{Phe}} = -1.24712 + 0.24515A + 0.080011B + 0.004605AB - 0.012433A^2 - 0.031422B^2, \quad (8)$$

$$pf_{\text{Hphe}} = -1.48246 + 0.2746A + 0.19023B - 0.01671AB - 0.011868A^2 + 0.0002785B^2, \quad (9)$$

$$pf_{\text{Nphe}} = -0.75743 + 0.16194A + 0.13312B + 0.013425AB - 0.010019A^2 - 0.078175B^2, \quad (10)$$

$$pf_{\text{Cpheg}} = -0.79918 + 0.1571A + 0.08563B + 0.00409AB - 0.00828625A^2 - 0.029525B^2. \quad (11)$$

In this work, the influences of pH and Taniaphos-Cu concentration on *pf* and the statistical significance of the mathematical models were investigated by analysis of variance. The analyzed data for Phe, Hphe, Nphe, and Cpheg were shown in Tables S2–S5, respectively. The values of *P* for the fitted quadratic polynomial models were all below 0.05, which indicated that the obtained models fitted well with the experimental data in Table 3. Also, the values of *P* for "lack of fit" were all greater than 0.05, indicating that the actual experimental data and values predicted from models had no significant differences. *P* values also could be used to evaluate factors that affected extraction significantly. For instance, *P* values for *A*, $A^2$, and $B^2$ were all below 0.05 indicating that pH, quadratic levels of pH, and Taniaphos-Cu concentration showed significant influence on *pf* in extraction of Phe. After removing the nonsignificant influence parameters, the simplified models for Phe, Hphe, Nphe, and Cpheg were shown in Equations 12–15, respectively.

$$pf_{\text{Phe}} = -1.24712 + 0.24515A - 0.012433A^2 - 0.031422B^2, \quad (12)$$

$$pf_{\text{Hphe}} = -1.48246 + 0.2746A + 0.19023B - 0.011868A^2, \quad (13)$$

**TABLE 3** The *pf* values obtained in CCD experiments

| Run | $X_1$ | $X_2$ | *pf* (Phe) | *pf* (Hphe) | *pf* (Nphe) | *pf* (Cpheg) |
|---|---|---|---|---|---|---|
| 1 | 0 | 0 | 0.08461 | 0.1173 | 0.09106 | 0.07821 |
| 2 | −1 | −1 | 0.06023 | 0.07023 | 0.05762 | 0.06298 |
| 3 | 0 | 0 | 0.08877 | 0.1038 | 0.09504 | 0.07739 |
| 4 | 0 | 1.41 | 0.07055 | 0.1171 | 0.07365 | 0.06993 |
| 5 | 1 | 1 | 0.07555 | 0.1254 | 0.07773 | 0.06482 |
| 6 | 0 | 0 | 0.08826 | 0.1147 | 0.09609 | 0.07662 |
| 7 | 0 | 0 | 0.08647 | 0.1146 | 0.09479 | 0.07701 |
| 8 | 0 | −1.41 | 0.07646 | 0.09543 | 0.04121 | 0.05822 |
| 9 | 0 | 0 | 0.08962 | 0.1098 | 0.09063 | 0.08167 |
| 10 | −1 | 1 | 0.06055 | 0.1196 | 0.06010 | 0.06747 |
| 11 | 1.41 | 0 | 0.07313 | 0.1009 | 0.07842 | 0.06578 |
| 12 | 1 | −1 | 0.06602 | 0.1095 | 0.04840 | 0.05215 |
| 13 | −1.41 | 0 | 0.05557 | 0.06389 | 0.07454 | 0.05875 |

$$pf_{\text{Nphe}} = -0.75743 + 0.13312B + 0.013425AB - 0.010019A^2 - 0.078175B^2, \quad (14)$$

$$pf_{\text{Cpheg}} = -0.79918 + 0.08563B - 0.00828625A^2 - 0.029525B^2. \quad (15)$$

The three-dimensional response surface graphs of *pf* at different pH and Taniaphos-Cu concentration were shown in Figure 5. For Phe, the curve of *pf* is similar to a parabola with increasing pH or Taniaphos-Cu. The highest *pf* was obtained at pH around 10.0 and Taniaphos-Cu concentration around 2.0 mmol/L. For Hphe, *pf* values sharply increased with increasing pH and then slightly decreased with pH above 10.5. When pH was below 10.5, *pf* values increased with increasing Taniaphos-Cu concentration. However, *pf* values decreased with increasing Taniaphos-Cu concentration at pH above 10.5. For Nphe, *pf* values slightly increased with increasing pH and then significantly decreased with pH above 8.5. The *pf* values significantly increased with Taniaphos-Cu concentration in the range of 0.8–1.8 mmol/L and then slightly decreased with Taniaphos-Cu concentration further increased. For Cpheg, the curve of *pf* is similar to a parabola with increasing pH or Taniaphos-Cu. The highest *pf* was obtained at pH around 10.0 and Taniaphos-Cu concentration around 2.2 mmol/L.

The optimal extraction conditions for Phe, Hphe, Nphe, and Cpheg could be predicted by mathematical models in Equations 12–15. The optimal extraction conditions and the predicted highest *pf* were shown in Table S6. For instance, the optimal extraction condition for Phe is at pH of 10.20, and Taniaphos-Cu concentration of 2.0 mmol/L with the predicted *pf* is 0.08822. At these optimal extraction conditions, the experimental *pf* values were also detected. The relative errors between predicted and experimental *pf* for Phe, Hphe, Nphe, and Cpheg were 0.79%, 1.85%, 1.23%, and 1.78%, which indicated that the models are efficient in the prediction of optimal extraction conditions and *pf* values.

## 3.7 | Recognition mechanism between Taniaphos-Cu and amino acid enantiomers

Analysis of the recognition mechanism between Taniaphos-Cu and amino acid enantiomers is important for design and synthesizing new chiral extractants in future work. The results in Table 2 showed that

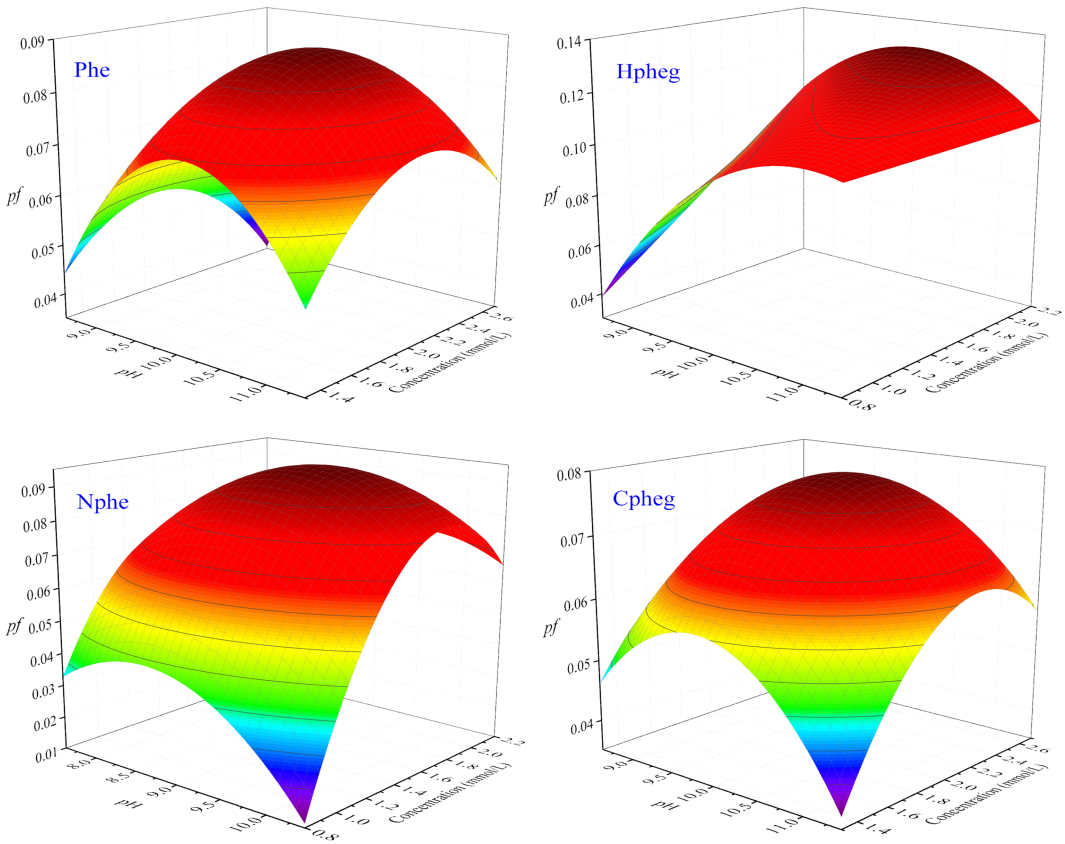


FIGURE 5 The three-dimensional response surface graphs of pf at different pH and Taniaphos-Cu concentration

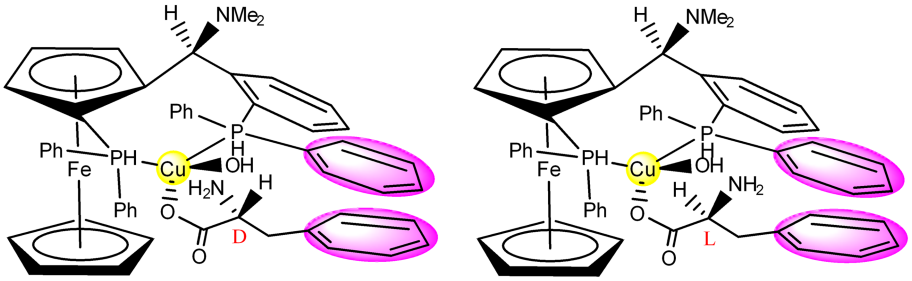


**FIGURE 6** The possible recognition mechanism between Taniaphos-Cu and amino acid enantiomers

Taniaphos-Cu exhibited low enantioselectivities to amino acid enantiomers in the solvent of Chlorobenzene. This phenomenon suggested that Chlorobenzene would disturb the π-π interaction of phenyl groups between chiral extractants and substrates.[26] Accordingly, π-π interaction between Taniaphos-Cu and amino acid enantiomers might be an important acting force in chiral extraction. The results in Figure 2 revealed that Taniaphos-Cu is conducive to combine with the anionic amino acid. Thus, the complexation between —$COO^-$ and Taniaphos-Cu is another important acting force in chiral extraction.[12,15] After chiral extraction, the organic solution was further analyzed by mass spectrometry to verify the complexes of Taniaphos-Cu enantiomers. The mass spectrometries of organic solution extracted with D-Phe and L-Phe were shown in Figures S1 and S2. The molecular ion peaks at 934.2 $[M + 1]^+$ indicated that molecular weights of Taniaphos-Cu-D-Phe and Taniaphos-Cu-L-Phe were both 933.2. Based on the above discussion, the possible chemical structures of Taniaphos-Cu-D-Phe and Taniaphos-Cu-L-Phe were proposed in Figure 6. The molecular formulas of Taniaphos-Cu-D-Phe and Taniaphos-Cu-L-Phe were $C_{52}H_{52}CuFeN_2O_3P_2$ with calculated molecular mass of 933.2. In chiral extraction, amino acid enantiomers and —OH were extracted into organic phase and combined with Taniaphos-Cu to form a tetrahedral complex. Hydroxide ion was directly involved in extraction process. It explained why the optimal pH for Taniaphos-Cu is much higher than other chiral diphosphine ligands reported in previous work (Figure 3). The steric-hindrance between —$NH_2$ and —OH would decrease the combining capacity between Taniaphos-Cu and L-amino acid. Consequently, Taniaphos-Cu-D-Phe is more stable than Taniaphos-Cu-L-Phe. And more D-amino acid enantiomers were extracted into organic phase in extraction.

## 4 | CONCLUSIONS

This work provided a chiral extractant that has good abilities to enantioseparate various amino acid enantiomers. Taniaphos-Cu is more conducive to combine with D-Phe, D-Hphe, D-Nphe, and D-Cpheg with the highest $\alpha$ of 3.13, 2.10, 2.32, and 2.14, respectively. The influences of pH, Taniaphos-Cu concentration, and extraction temperature on extraction were comprehensively evaluated. The results showed that Taniaphos-Cu is conducive to combine with the anionic amino acid. And the enantioselectivity of Taniaphos-Cu is insensitive to extraction temperature. After optimization by CCD, the highest *pf* for Phe, Hphe, Nphe, and Cpheg were 0.08892, 0.1250, 0.09621, and 0.08021, respectively. The coordination interaction between Taniaphos-Cu and —$COO^-$, π-π interaction between Taniaphos-Cu and amino acid enantiomers are important acting forces in chiral extraction. The steric-hindrance between —$NH_2$ and —OH lead to Taniaphos-Cu-D-Phe is more stable than Taniaphos-Cu-L-Phe.

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## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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