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Enantioselective liquid-liquid extraction of 3-chloro-phenylglycine enantiomers using (*S*,*S*)-DIOP as extractant

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Abstract

(*S*,*S*)-DIOP, a common catalyst used in asymmetric reaction, was adopted as chiral extractant to separate 3-chloro-phenylglycine enantiomers in liquid-liquid extraction. The factors affecting extraction efficiency were studied, including metal precursors, organic solvents, extraction temperature, chiral extractant concentration, and pH of aqueous phase. (*S*,*S*)-DIOP-Pd exhibited good ability to recognize 3-chloro-phenylglycine enantiomers, and the operational enantioselectivity (α) is 1.836. The highest performance factor (*pf*) was obtained under the condition of extraction temperature of 9.1°C, (*S*,*S*)-DIOP-Pd concentration of 1.7 mmol/L, and pH of aqueous phase of 7.0. In addition, the possible recognition mechanism of (*S*,*S*)-DIOP-Pd towards 3-chloro-phenylglycine enantiomers was discussed.

KEYWORDS

(*S*,*S*)-DIOP, 3-chloro-phenylglycine, enantioselective liquid-liquid extraction, response surface methodology

1 | INTRODUCTION

In the past decades, considerable efforts have been undertaken for the preparation of enantiomerically pure drugs.[1-5] Asymmetric synthesis and raceme separation are the common methods that are widely used in pharmaceutical industry to obtain compounds with high enantiomeric excess (*ee*).[6-9] Recently, some diphosphine ligands used as chiral catalysts in asymmetric reactions have been proved to be effective chiral selectors in enantioselective liquid-liquid extraction (ELLE).[10-15] For instance, (*S*)-BINAP-metal, (*S*)-MeO-BIPHEP-metal, and (*S*)-SEGPHOS-metal complexes have considerable abilities to separate amino acid and mandelic acid enantiomers.[16-18] Since the chiral ligands in asymmetric reactions may be the good chiral selectors, it seemed interesting to further study this field with the goal of finding more ligands with favorable enantiomeric recognition and separation potency in ELLE.

(*S*,*S*)-DIOP((4*S*,5*S*)-4,5-Bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane) is a well-known ligand that is widely used as catalyst in asymmetric reactions. The chemical structure of (*S*,*S*)-DIOP is shown in Figure 1. (*S*,*S*)-DIOP and (*S*)-BINAP are both excellent phosphorus-containing chiral ligands. For instance, (*S*,*S*)-DIOP-metal complexes are effective catalysts in asymmetric hydrogenation,[19] hydroformylation,[20] isomerization,[21] and macrolactonization.[22] (*S*,*S*)-DIOP may also be a good chiral extractant in ELLE.

In this work, (*S*,*S*)-DIOP was employed as chiral extractant to recognize 3-chloro-phenylglycine enantiomers. 3-Chloro-phenylglycine is an important material that could be used to synthesize fungicides and pest control drugs. The influences of temperature, chiral extractant concentration, and pH of water phase on extraction behaviors were studied. The optimal extraction condition was obtained by response surface methodology (RSM). In addition, the possible recognition mechanism of (*S*,*S*)-

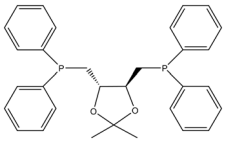

FIGURE 1 The chemical structure of (*S*,*S*)-DIOP

DIOP towards 3-chloro-phenylglycine enantiomers was discussed.

2 | MATERIALS AND METHODS

2.1 | Materials and reagents

(*S*,*S*)-DIOP (99%) is purchased from Sinocompound Catalysts Co, Ltd (China). Metal precursors, including Tetrakis(acetonitrile)copper ($[(CH_3CN)_4Cu]PF_6$, 98%) and bis(acetonitrile)dichloropalladium ($(CH_3CN)_2PdCl_2$, 99%), were purchased from J&K Scientific Ltd. 3-Chloro-phenylglycine enantiomers (99%) were purchased from Adamas Reagent Co, Ltd. Organic solvents and other chemicals were analytically pure and used without further treatment.

2.2 | Preparation of the solutions of chiral extractant and 3-chloro-phenylglycine

(*S*,*S*)-DIOP-metal complexes were prepared as follows: 0.1 mmol of (*S*,*S*)-DIOP and 0.1 mmol of metal precursors were dissolved in 50 mL of 1,2-dichloroethane. After stirring for 6 hours, the mixture was diluted to 100 mL to obtain chiral extractants with concentration of 1.0 mmol/L. 3-Chloro-phenylglycine enantiomers in aqueous phase were prepared as follows: 0.1 mmol of 3-chloro-phenylglycine was dissolved in 0.1 mmol/L of PBS solution to obtain aqueous phase with concentration of 2.0 mmol/L.

2.3 | ELLE of 3-chloro-phenylglycine

The ELLE was performed as follows: 2.0 mL of aqueous phase and 2.0 mL of organic phase were added into a 10-mL tube; the mixture in tube was constantly shaken (150 rpm) for 12 hours at temperature of 5°C to 25°C, then let stand for 12 hours. After equilibrium is attained, the aqueous phase was filtered by 0.45-μm filter membrane, and the concentrations of D/L-3-chloro-phenylglycine were determined by HPLC. The HPLC analysis was carried out using the method described in our precious work.[17] The concentrations of D/L 3-chloro-phenylglycine in organic phase were calculated through the subtraction method.

2.4 | Calculations

The distribution ratios of L-3-chloro-phenylglycine (k_L) and D-3-chloro-phenylglycine (k_D) between organic phase and aqueous phase were defined in Equations (1) and (2), respectively. The operational enantioselectivity (α), enantiomeric excess (*ee*), fraction of substrate in organic phase (f), and performance factor (*pf*) were defined in Equations (3), (4), (5), and (6), respectively.[17]

$$k_L = {}^{C_{L,org}}\!/_{C_{L,w}}, \tag{1}$$

$$k_D = {}^{C_{D,org}}\!/_{C_{D,w}}, \tag{2}$$

$$\alpha = {}^{k_D}\!/_{k_L} or \alpha = {}^{k_L}\!/_{k_D}, \tag{3}$$

$$ee_{org} = \frac{C_{D,org} - C_{L,org}}{C_{D,org} + C_{L,org}}, \tag{4}$$

$$f = \frac{C_{L,org}}{\left(C_{L,org} + C_{L,w}\right),} \tag{5}$$

$$pf = f \times ee_{org}, \tag{6}$$

where $C_{L,w}$ and $C_{D,w}$ are the concentrations of L- and D-3-chloro-phenylglycine in water phase at equilibrium, respectively. $C_{L,org}$ and $C_{D,org}$ are the concentrations of L- and D-3-chloro-phenylglycine in the aqueous phase at equilibrium, respectively.

2.5 | Optimization of ELLE

Response surface methodology (RSM) is a famous method that is widely used to search the optimal technological condition.[23-27] In this work, a three-level and three-variable of Box-Behnken design (BBD) was applied to optimize the processing parameters. According to the results of single factor tests, temperature (X_1), (*S*,*S*)-DIOP-Pd concentration (X_2), and pH (X_3) were selected as variables, and each variable was tested at three different levels. The model for response (*pf*) can be given as

$$pf = \beta_0 + \sum_{i=1}^{3}\beta_i X_i + \sum_{i=1}^{3}\beta_{ii} X_i^2 + \sum_{i=1}^{2}\sum_{j=i+1}^{3}\beta_{ij} X_i X_j, \tag{7}$$

where *pf* is response, X_i and X_j are the independent variables, and β_0, β_i, β_{ii}, and β_{ij} are constant, linear

coefficient, quadratic coefficient, and cross-product coefficient of the model, respectively.[26]

3 | RESULTS AND DISCUSSION

3.1 | Influence of metal precursors on ELLE

In this work, $(CH_3CN)_2PdCl_2$ and $[(CH_3CN)_4Cu]PF_6$ were the metal precursors used in extraction. As shown in Table 1, (*S*,*S*)-DIOP-Pd exhibited good ability to recognize 3-chloro-phenylglycine enantiomers with α of 1.836. While (*S*,*S*)-DIOP-Cu exhibited poor enantiomeric recognition with α of 1.065. In addition, k_L is bigger than k_D, indicating that the combining capacity between (*S*,*S*)-DIOP-metal and L-3-chloro-phenylglycine is much bigger and more L-3-chloro-phenylglycine were extracted into organic phase. The results in Table 1 revealed that (*S*,*S*)-DIOP-Pd showed good enantiomeric recognition to 3-chloro-phenylglycine enantiomers. (*S*,*S*)-DIOP-Pd was selected as chiral extractant in the following experiments.

3.2 | Influence of solvents on ELLE

Solvents can significantly influence the enantiomeric recognition of the chiral extractants through solution effects. The enantiomeric recognition of (*S*,*S*)-DIOP-Pd with four chlorinated solvents was investigated, and the results were tabulated in Table 2. The results showed that (*S*,*S*)-DIOP-Pd exhibited good abilities to recognize 3-chloro-phenylglycine enantiomers with dichloromethane, chloroform, and 1,2-dichloroethane used as organic solvents. However, chlorobenzene showed a negative effect on enantiomeric recognition with α of 1.049. This result suggested that π-π interaction is an important acting force in chiral recognition.[13] After evaluation, 1,2-dichloroethane was chosen as the organic solvent for further studies.

TABLE 1 Influence of metal precursors on ELLE

Chiral Extractants[a]	k_L	k_D	α
(*S*,*S*)-DIOP-Pd	0.6623	0.3607	1.836
(*S*,*S*)-DIOP-Cu	1.876	1.761	1.065

[a]Extraction temperature is 5°C, (*S*,*S*)-DIOP-metal concentration is 1.0 mmol/L, pH of aqueous phase is 7.0, and organic solvent is 1,2-dichloroethane.

TABLE 2 Influence of solvents on ELLE

Solvents[a]	k_L	k_D	α
Dichloromethane	0.5644	0.3322	1.699
Chloroform	0.6731	0.4523	1.488
1,2-Dichloroethane	0.6623	0.3607	1.836
Chlorobenzene	0.0749	0.0714	1.049

[a]Extraction temperature is 5°C, (*S*,*S*)-DIOP-Pd concentration is 1.0 mmol/L, and pH of aqueous phase is 7.0.

3.3 | Influence of extraction temperature on ELLE

The combining capacities between (*S*,*S*)-DIOP-Pd and DL-3-chloro-phenylglycine could be affected by extraction temperature. In this work, the extraction temperature was investigated at temperature of 5°C, 10°C, 15°C, 20°C, and 25°C. The results in Figure 2A showed that distribution ratios were both increased with increasing of temperature. This phenomenon indicated that more 3-chloro-phenylglycine enantiomers were extracted into organic phase at higher temperature. This is probably because that the physical solubility of 3-chloro-phenylglycine in 1,2-dichloroethane increased at high temperature. High extraction temperature leads to more racemic 3-chloro-phenylglycine extracted into organic phase. Thus, values of α and *ee* in Figure 2B,C were both decreased with increasing temperature. The curves in Figure 2A,C revealed that high temperature lead to high distribution ratios but low *ee*. It is difficult to determine the optimal extraction temperature that L-3-chloro-phenylglycine in organic phase was obtained with high yield and high *ee* simultaneously. Performance factor (*pf*) is defined as the product of *ee* in the organic phase and the fraction of enantiomer extracted into the organic phase (*f*). High *pf* means that L-3-chloro-phenylglycine was purified with good yield and good *ee* simultaneously.[28] Figure 2D showed the curve of *pf* with increasing temperature. It is obvious that high *pf* were obtained with temperature in range of 5°C to 15°C.

3.4 | Influence of pH on ELLE

The existing forms of carboxyl and amino groups in structure of 3-chloro-phenylglycine could be significantly affected by pH of aqueous phase. Thus, pH of aqueous phase may affect the enantiomeric recognition in ELLE. As shown in Figure 3, the influence of pH on ELLE was investigated in range of 5.0 to 9.0. It is obviously that k_D and k_L are both increased with increasing pH and the higher α were obtained with pH around 7. This results indicated that (*S*,*S*)-DIOP-Pd complex is conducive to combine with anionic 3-chloro-phenylglycine. Figure 3C revealed that *ee* firstly increased and then decreased with increase of pH. The highest *ee* was obtained with pH around 7.0. The influence of pH on *pf* was shown in

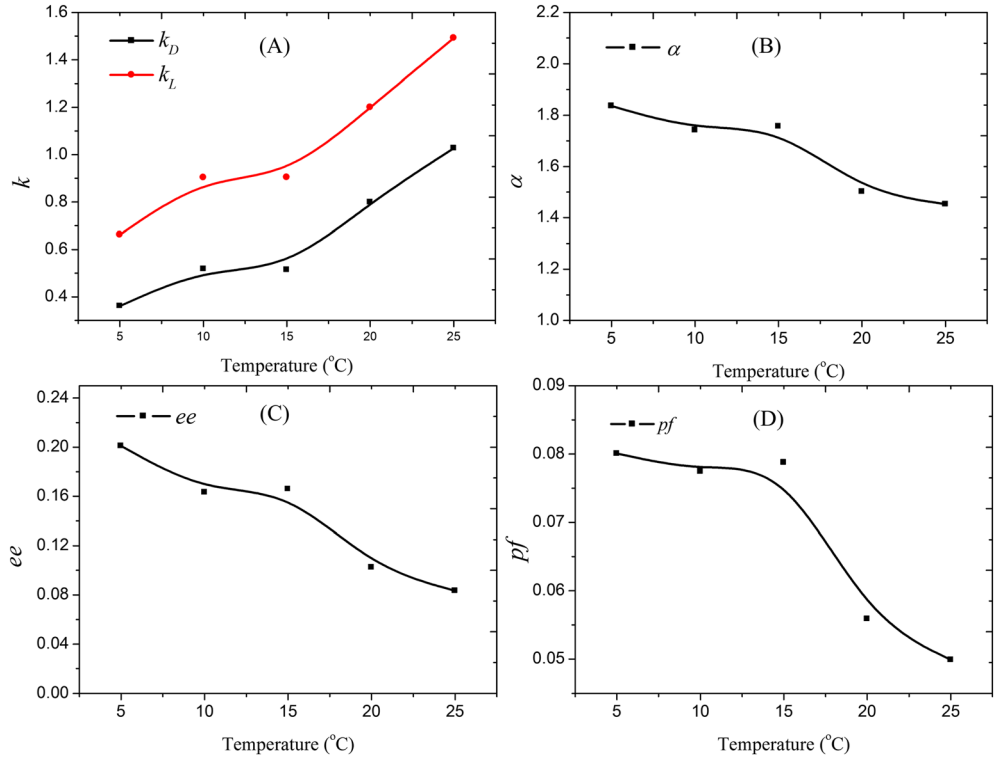

FIGURE 2 The influence of extraction temperature on ELLE. Other conditions: (*S*,*S*)-DIOP-Pd concentration is 1.0 mmol/L, and pH of aqueous phase is 7.0

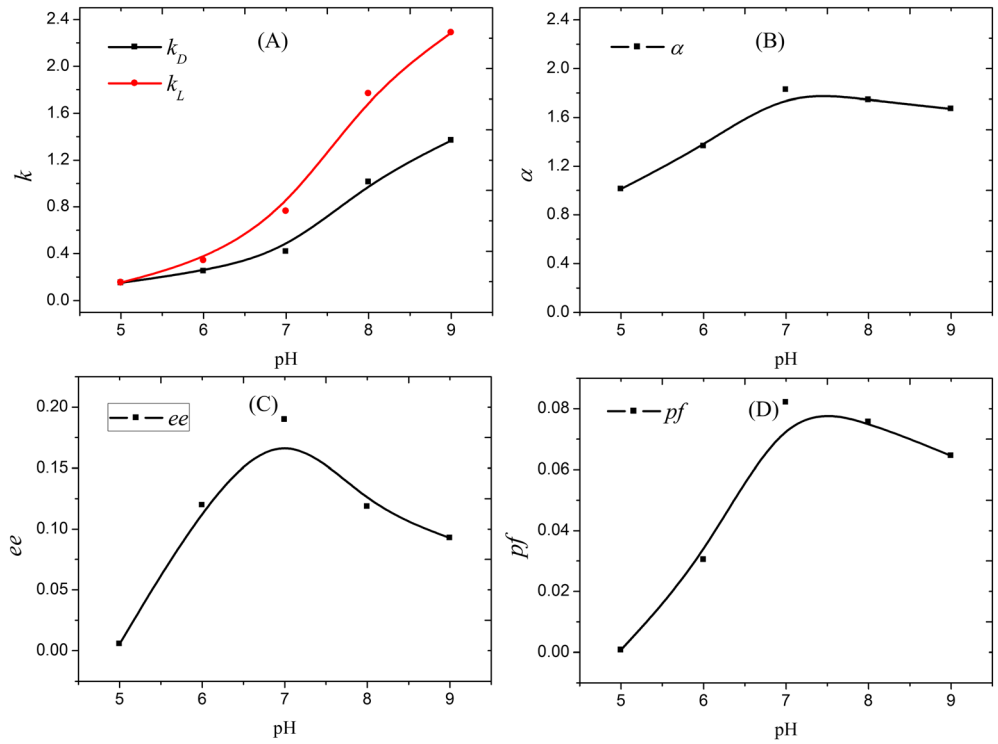

FIGURE 3 The influence of pH on ELLE. Other conditions: Temperature is 5°C, and (*S*,*S*)-DIOP-Pd concentration is 1.0 mmol/L

Figure 3D. Similarly, the highest *pf* was obtained with pH around 7.0.

3.5 | Influence of (*S,S*)-DIOP-Pd concentration on ELLE

The concentration of (*S,S*)-DIOP-Pd was investigated in range of 0.25 to 3.0 mmol/L, and the results were shown in Figure 4. With the increasing of (*S,S*)-DIOP-Pd concentration, there were more ligands that could combine with substrates; thus, the values of k_D and k_L are both increased with increasing concentration. The curve of α in Figure 4B increased sharply at first and then reached equilibrium with values around 1.8. When (*S,S*)-DIOP-Pd concentration was below 0.5 mmol/L, the ligands in organic phase were insufficient to recognize substrates. The competition in DL-3-chloro-phenylglycine was high. Thus, curve of *ee* in Figure 4C increased with increasing of concentration. When (*S,S*)-DIOP-Pd concentration was higher than 0.5 mmol/L, there were enough ligands to combine with substrates. The competition between D-3-chloro-phenylglycine and L-3-chloro-phenylglycine was low, and values of *ee* decreased with further increasing of concentration. According to the curve in Figure 4D, the highest *pf* was obtained at concentration around 1.5 mmol/L.

3.6 | Optimization of the extraction process

Based on the results discussed above, extraction temperature, pH of aqueous phase, and (*S,S*)-DIOP-Pd concentration in RSM were investigated in ranges of 5.0 to 15.0°C, 6.0 to 8.0, and 1.0 to 2.0 mmol/L, respectively. The low, middle, and high levels of each variable were coded as −1, 0, and 1, respectively, as tabulated in Table 3. Seventeen randomized runs for *pf* were carried out, and the results were shown in Table 4. The data were fitted by quadratic polynomial model. The polynomial equation describing *pf* as a simultaneous function of temperature (X_1), (*S,S*)-DIOP-Pd concentration (X_2), and pH (X_3), as shown in Equation (8).

$$pf = 0.087 + 0.00167X_1 + 0.006036X_2 + 0.0007396X_3 - 0.002517X_1X_2 - 0.006018X_1X_3 - 0.008657X_2X_3 - 0.006402{X_1}^2 - 0.001308{X_2}^2 - 0.033{X_3}^2. \quad (8)$$

TABLE 3 Experimental range and level of independent variables

Factors	−1	0	1
X_1: Temperature, °C	5	10	15
X_2: Concentration, mmol/L	1.0	1.5	2.0
X_3: pH	6.0	7.0	8.0

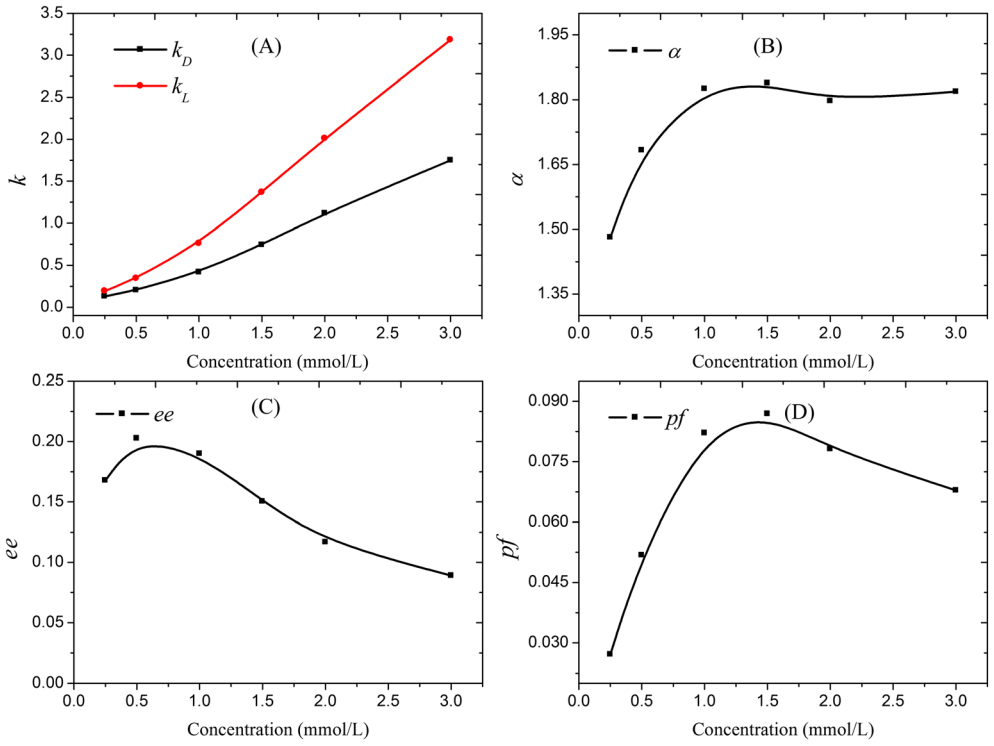

FIGURE 4 The influence of chiral extractant concentration on ELLE. Other conditions: Temperature is 5.0°C, and pH of aqueous phase is 7.0

TABLE 4 Experimental data with different combinations of temperature (X_1), concentration (X_2) and pH (X_3)

Run	X_1	X_2	X_3	*pf*
1	−1	1	0	0.08404
2	−1	0	−1	0.04104
3	0	1	−1	0.06554
4	1	−1	0	0.07894
5	0	−1	−1	0.03477
6	0	0	0	0.08497
7	1	1	0	0.08459
8	0	−1	1	0.05611
9	-1	0	1	0.05201
10	0	0	0	0.08555
11	0	1	1	0.05225
12	-1	-1	0	0.06832
13	1	0	-1	0.05417
14	0	0	0	0.08721
15	0	0	0	0.08829
16	0	0	0	0.08739
17	1	0	1	0.04107

TABLE 5 ANOVA for the second-order polynomial response model

Sources	Sum of Squares	Degree of Freedom	Mean Square	*F* Value	*P* Value
Model	5.764×10^{-3}	9	6.404×10^{-4}	130.14	<.0001
X_1	2.231×10^{-5}	1	2.231×10^{-5}	4.53	.0707
X_2	2.914×10^{-4}	1	2.914×10^{-4}	59.22	.0001
X_3	4.376×10^{-6}	1	4.376×10^{-6}	0.89	.3771
X_1X_2	2.535×10^{-5}	1	2.535×10^{-5}	5.15	.0575
X_1X_3	1.448×10^{-4}	1	1.448×10^{-4}	29.43	.0010
X_2X_3	2.998×10^{-4}	1	2.998×10^{-4}	60.92	.0001
X_1^2	1.726×10^{-4}	1	1.726×10^{-4}	35.07	.0006
X_2^2	7.198×10^{-6}	1	7.198×10^{-6}	1.46	.2657
X_3^2	4.643×10^{-3}	1	4.643×10^{-3}	943.57	<.0001
Residual	3.445×10^{-5}	7	4.921×10^{-6}		
Lack of fit	2.687×10^{-5}	3	8.956×10^{-6}	4.73	0.0838
Pure error	7.678×10^{-6}	4	1.895×10^{-6}		
Cor total	5.798×10^{-3}	16			

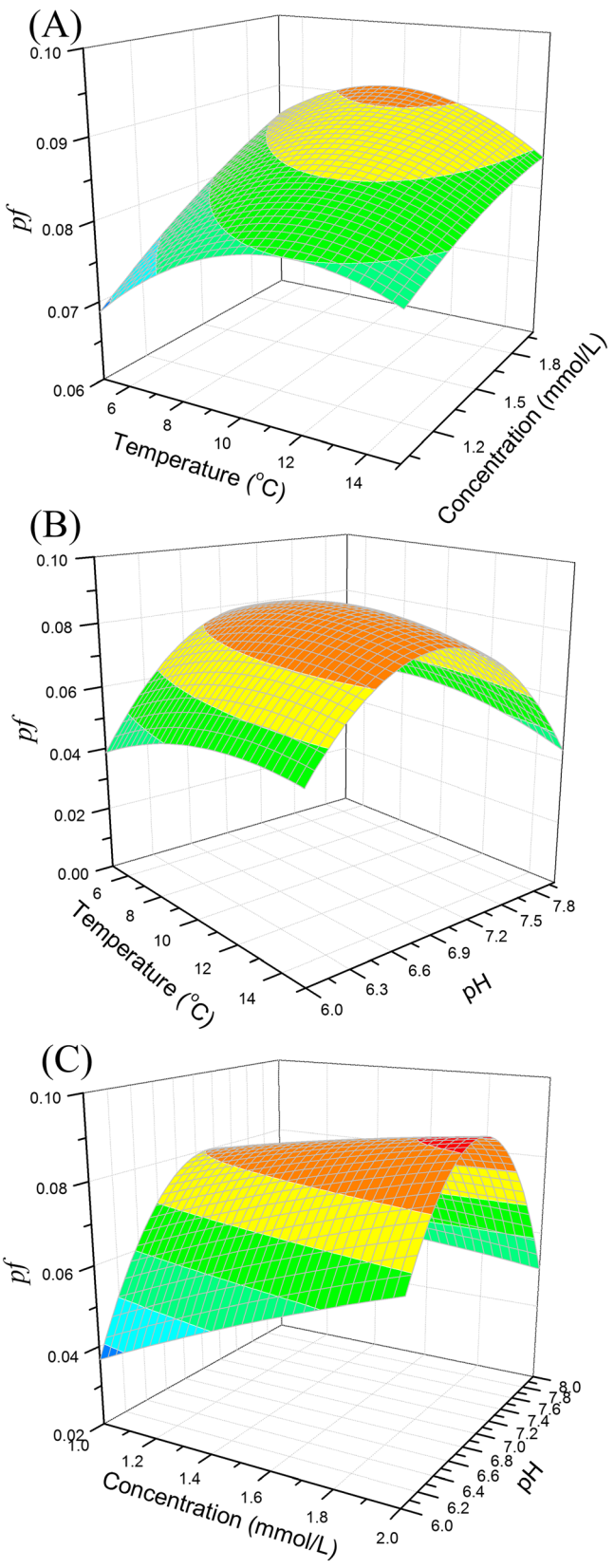

FIGURE 5 The 3D response surface plots of *pf* influenced by interactions between (A) temperature and concentration, (B) temperature and pH, and (C) concentration and pH

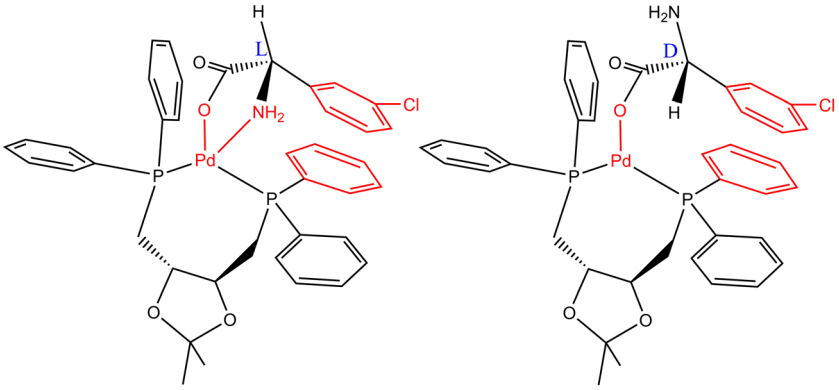

FIGURE 6 The possible recognition mechanism of (*S*,*S*)-DIOP-Pd towards 3-chloro-phenylglycine enantiomers

The validity of the predicted model was evaluated by analysis of variance (ANOVA), and the results were shown in Table 5. The *P* value of model is <.0001, indicating that Equation (8) showed good fitness to the experimental data. The *P* value of lack of fit is 0.0838, indicating that Equation (8) is suitable to predict the *pf* values. The *P* values for X_2, X_1X_3, X_2X_3, X_1^2, and X_3^2 are all below .05, indicating that (*S,S*)-DIOP-Pd concentration, interaction between temperature and pH, interaction between concentration and pH, quadratic level of temperature, and quadratic level of pH have statistically significant effects on *pf*. Other parameters ($P > .05$), including X_1, X_3, X_1X_2, and X_2^2, showed insignificant effect on *pf*. After removal of these insignificant parameters, the model could be changed to Equation (9).

$$pf = 0.087 + 0.006036X_2 - 0.006018X_1X_3 - 0.008657X_2X_3 - 0.006402X_1^2 - 0.033X_3^2. \quad (9)$$

The 3D response surface plots of *pf* influenced by interactions between temperature and concentration, temperature and pH, and concentration and pH were depicted in Figure 5A-C, respectively. Generally, *pf* firstly increased and then declined with increasing temperature. The higher *pf* were obtained at temperature around 10°C. (*S,S*)-DIOP-Pd concentration showed a positive effect on *pf*. Figure 5A,C revealed that increasing chiral extractants concentration could increase *pf*. Figure 5B,C revealed that *pf* firstly increased with the increase in pH and then declined with further increase in pH. The highest value for response located on pH around 7.0.

3.7 | The optimal extraction condition and the highest value of *pf*

The optimal condition for extraction of 3-chloro-phenylglycine enantiomers was calculated by Equation (9). Theoretically, the highest *pf* (0.08867) was obtained at the condition of temperature of 9.1°C, (*S,S*)-DIOP-Pd concentration of 1.7 mmol/L, and pH of 7.0. In addition, experiments were conducted using the optimized parameters for detecting *pf*. The experimental *pf* is 0.08996, which is in close agreement with the predicted data with relative error of 1.45%. Thus, Equation (9) could be effectively used to optimize the *pf* in ELLE.

3.8 | The possible recognition mechanism

In this paper, the possible recognition mechanism of (*S*, *S*)-DIOP-Pd towards 3-chloro-phenylglycine enantiomers was also analyzed. The result in "Influence of solvents on ELLE" revealed that π-π interaction plays an important role in chiral recognition. Thus, the interaction between phenyl groups in 3-chloro-phenylglycine and (*S*,*S*)-DIOP is an important acting force in chiral recognition. The results in Figure 3A indicated that (*S*,*S*)-DIOP-Pd is conducive to combine with anionic 3-chloro-phenylglycine. Thus, the interaction between $-COO^-$ and (*S*,*S*)-DIOP-Pd is another important acting force in recognition progress. Based on the results discussed above and the stereochemical structures of (*S*,*S*)-DIOP-Pd and 3-chloro-phenylglycine, the possible recognition mechanism was proposed. As shown in Figure 6, the π-π interaction between phenyl groups and the complexation between $-COO^-$ and palladium are two important acting forces in chiral recognition. When L-3-chloro-phenylglycine used as substrate, the amino could also interact with chiral selector by coordination with palladium. However, the amino in D-3-chloro-phenylglycine cannot interact with palladium for long space distance. Thus, (*S*,*S*)-DIOP-Pd showed higher combining capacity towards L-3-chloro-phenylglycine, and k_L is higher than k_D in extraction.

4 | CONCLUSION

(*S*,*S*)-DIOP-Pd was successfully employed to separate 3-chloro-phenylglycine enantiomers in ELLE. After optimization by RSM, the optimal extraction condition is

extraction temperature of 9.1°C, (*S*,*S*)-DIOP-Pd concentration of 1.7 mmol/L, and pH of aqueous phase of 7.0. At this optimal condition, the highest *pf* was obtained with value of 0.08996. In addition, the possible recognition mechanism of (*S*,*S*)-DIOP-Pd toward 3-chloro-phenylglycine enantiomers was discussed. The interactions between carboxyl and palladium, phenyl groups in 3-chloro-phenylglycine and (*S*,*S*)-DIOP, amino and palladium are three important acting forces in chiral recognition.

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REFERENCES

1. Liu X, Ma Y, Liu Q, Wei X, Yang J, Yu L. Chiral extraction of amino acid and mandelic acid enantiomers using chiral diphosphine ligands with tunable dihedral angles. *Sep. and Purif. Technol*. 2019;221:159-165. https://doi.org/10.1016/j.seppur.2019.03.085
2. Tan Z, Li F, Zhao C, Teng Y, Liu Y. Chiral separation of mandelic acid enantiomers using an aqueous two-phase system based on a thermo-sensitive polymer and dextran. *Sep Purif Technol*. 2017;172:382-387.
3. Wang R, Sun D, Wang C, Liu L, Li F, Tan Z. Biphasic recognition chiral extraction of threonine enantiomers in a two-phase system formed by hydrophobic and hydrophilic deep-eutectic solvents. *Sep Purif Technol*. 2019;215:102-107.
4. Zou J, Huang L, Jiang X, Jiao F, Yu J. Enhanced chiral electrochemical recognition of tryptophan enantiomers using a novel triple-layered GO/BSA/CS modified glassy carbon electrode. *Nanosci Nanotechnol Lett*. 2017;9(11):1700-1707.
5. Zou J, Chen XQ, Zhao GQ, Jiang XY, Jiao FP, Yu JG. A novel electrochemical chiral interface based on the synergistic effect of polysaccharides for the recognition of tyrosine enantiomers. *Talanta*. 2019;195:628-637.
6. van der Boon LJP, Fuku-en S-i, Slootweg JC, Lammertsma K, Ehlers AW. Toward asymmetric synthesis of pentaorganosilicates. *Top Catal*. 2018;61(7–8):674-684. https://doi.org/10.1007/s11244-018-0967-5
7. Lu R, He Q, Feng C, Peng Y. Enantioselective resolution of 4-chloromandelic acid by liquid-liquid extraction using 2-chloro-*N*-carbobenzyloxy-L-amino acid. *Chirality*. 2017;29(11):708-715. https://doi.org/10.1002/chir.22738
8. Romero-Fernandez MP, Babiano R, Cintas P. On the asymmetric autocatalysis of aldol reactions: the case of 4-nitrobenzaldehyde and acetone. A critical appraisal with a focus on theory. *Chirality*. 2018;30(4):445-456.
9. Straniero V, Casiraghi A, Fumagalli L, Valoti E. How do reaction conditions affect the enantiopure synthesis of 2-substituted-1,4-benzodioxane derivatives? *Chirality*. 2018;30(7):943-950.
10. Liu J-J, Wu G-H, Tang K-W, Liu X, Zhang P-L. Equilibrium of chiral extraction of 4-nitro-D,L-phenylalanine with BINAP metal complexes. *Chem. Pap.* 2014;68(1):80-89. https://doi.org/10.2478/s11696-013-0419-4
11. Tang K, Fu T, Zhang P. Equilibrium studies on enantioselective liquid-liquid extraction of homophenylalanine enantiomers with metal-BINAP complexes. *Process Biochem*. 2012;47(12):2275-2283.
12. Tang K, Fu T, Zhang P, Yang C, Zhou C, Liang E. Modeling and experimental evaluation of enantioselective liquid-liquid extraction of (D, L)-4-chlorophenylglycine in a biphasic system. *Chem Eng Res des*. 2015;94:290-300.
13. Verkuijl BJV, Minnaard AJ, de Vries JG, Feringa BL. Chiral separation of underivatized amino acids by reactive extraction with palladium-BINAP complexes. *J Org Chem*. 2009;74(17):6526-6533. https://doi.org/10.1021/jo901002d
14. Verkuijl BJV, Schuur B, Minnaard AJ, de Vries JG, Feringa BL. Chiral separation of substituted phenylalanine analogues using chiral palladium phosphine complexes with enantioselective liquid-liquid extraction. *Org Biomol Chem*. 2010;8(13):3045-3054.
15. Zhang P, Liu C, Tang K, Liu J, Hua J, Zhong M. Modeling and optimizing the biphasic enantioselective partitioning of 2-fluoro-phenylalanine enantiomers with BINAP-metal complexes as chiral selector. *J Solution Chem*. 2015;44(1):112-130.
16. Liu X, Zhou W, Xu L. Synthesis of $CuPF_6$-(*S*)-BINAP loaded resin and its enantioselectivity toward phenylalanine enantiomers. *Chirality*. 2017;29(9):541-549.
17. Liu X, Ma Y, Cao T, et al. Enantioselective liquid-liquid extraction of amino acid enantiomers using (*S*)-MeO-BIPHEP-metal complexes as chiral extractants. *Sep Purif Technol*. 2019;211:189-197.
18. Ma Y, Liu X, Zhou W, Cao T. Enantioselective liquid-liquid extraction of DL-mandelic acid using chiral diphosphine ligands as extractants. *Chirality*. 2019;31(3):248-255.
19. Sento T, Shimazu S, Ichikuni N, Uematsu T. Asymmetric hydrogenation of itaconates by hectorite-intercalated Rh-DIOP complex. *J Mol Catal A-Chem*. 1999;137(1–3):263-267.
20. Haelg P, Consiglio G, Pino P. Asymmetric hydroformylation of the linear butenes by [(*R*,*R*)-Diop]Pt($SnCl_3$)Cl. *J Organomet Chem*. 1985;296(1–2):281-290.
21. Frauenrath H, Reim S, Wiesner A. Asymmetric double-bond isomerization of cyclic allyl acetals by using diop and chiraphos modified nickel complexes. *Tetrahedron:Asymmetry*. 1998;9(7):1103-1106.
22. Ganss S, Breit B. Enantioselective rhodium-catalyzed atom-economical macrolactonization. *Angew Chem Int Ed*. 2016;55(33):9738-9742.
23. Chew S-C, Tan C-P, Nyam K-L. Application of response surface methodology for optimizing the deodorization parameters in chemical refining of kenaf seed oil. *Sep Purif Technol*. 2017;184:144-151.

24. Choudhury S, Ray SK. Filled copolymer membranes for pervaporative dehydration of ethanol-water mixture. *Sep Purif Technol*. 2017;179:335-348.
25. Liu X, Yang D-L, Liu J-J, Xu K, Wu G-H. Modeling of supercritical fluid extraction of flavonoids from *Calycopteris floribunda* leaves. *Chem Pap*. 2014;68(3):316-323. https://doi.org/10.2478/s11696-013-0451-4
26. Long A, Zhang H, Lei Y. Surfactant flushing remediation of toluene contaminated soil: optimization with response surface methodology and surfactant recovery by selective oxidation with sulfate radicals. *Sep Purif Technol*. 2013;118:612-619.
27. Sun Y, Liu Z, Fatehi P. Treating thermomechanical pulping wastewater with biomass-based fly ash: modeling and experimental studies. *Sep Purif Technol*. 2017;183:106-116.
28. Koska J, Haynes CA. Modelling multiple chemical equilibria in chiral partition systems. *Chem Eng Sci*. 2001;56(20):5853-5864.

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