DOI 10.1002/chir.22658

WILEY

REGULAR ARTICLE

Effects of solvent on inclusion complexation of a chiral dipeptide toward racemic BINOL

Xiaoyun Hu[1] | Yuyuan Yang[1] | Shuai Shi[1] | Zixing Shan[2]

[1] College of Chemistry and Materials, South-Central University for Nationalities, Wuhan, Republic of China

[2] College of Chemistry and Molecular Sciences, Wuhan University, Wuhan, Republic of China

Correspondence
Xiaoyun Hu, PhD, College of Chemistry and Materials, South-Central University for Nationalities, 182, Minzu Road, Hongshan District, Wuhan, Peoples Republic of China.
Email: xyhu@mail.scuec.edu.cn

Abstract

The effects of reaction solvent on inclusion complexation of a chiral dipeptide (3*S*,6*S*)-**1** derived from (*S*)-proline toward racemic BINOL was investigated, discovering that the reaction solvent played a crucial role in determining the inclusion complexation behavior of dipeptide (3*S*,6*S*)-**1** toward *rac*-BINOL. (3*S*,6*S*)-**1** did not show any chiroselective or achiroselective complexation toward *rac*-BINOL in polar protic solvents such as methanol and ethanol, polar aprotic solvents including trichloromethane and THF, while in polar aprotic solvent ethyl acetate and apolar aprotic solvents benzene, (3*S*,6*S*)-**1** displayed achiroselective complexation toward *rac*-BINOL. However, the resulting heterocomplex HC-**2** from benzene and HC-**3** from ethyl acetate have a different composition. Single crystal X-ray diffraction analysis demonstrates that the two heterocomplexes are formed via different H-bond interaction patterns, in which the reaction solvent has a dramatic effect. Furthermore, this work provides a relatively green method for quantitative enantiomeric enrichment of nonracemic BINOL, in which unacceptable and toxic benzene was replaced by ethyl acetate.

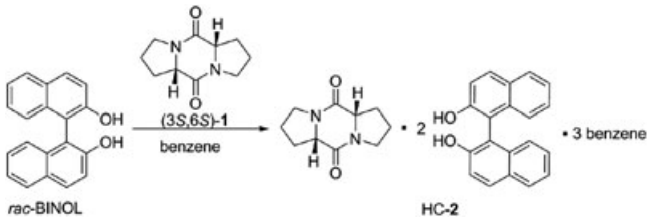
KEYWORDS

achiroselectivity, chiral dipeptide, heterocomplexation, inclusion complexation, racemic BINOL

1 | INTRODUCTION

Chiral discrimination of a chiral host to a racemic guest, which plays an important role for the separation of enantiomers and the resolution of chiral drugs, is an important part of molecular recognition.[1–3] The inclusion resolution method, which is established based on the chiral host stereoselectively interacting with one enantiomer of the racemic guests via intermolecular forces such as π–π interactions, hydrogen bonding, and Van der Waals' force, has been developed as an important chiral resolution method in the past two decades.[4–7] However, simultaneous complexation of a chiral host to two enantiomers of a racemic guest is seldom observed, although heterorecognition of an achiral host to a racemic guest has been reported.[8,9] In 2008, our group reported that a chiral dipeptide (3*S*,6*S*)-**1** generated from (*S*)-proline[10] was refluxed with *rac*-1,1′-bi-naphthol (BINOL) in benzene to afford a 1:2:3 complex **2** consisting of the dipeptide (3*S*,6*S*)-**1**, *rac*-BINOL, and benzene (Scheme 1), while (3*S*,6*S*)-**1** did not interact with (*R*)- or (*S*)-BINOL under the same conditions.[11] This achiroselective complexation between a chiral host to a racemic guest is called heterocomplexation.

In 2010, we examined the chiral discrimination of (3*S*,6*S*)-**1** with different chiral diols derived from *L*-tartaric acid, and observed that chiral dipeptide (3*S*,6*S*)-**1** showed different chiral discrimination patterns toward chiral diols. For example, (3*S*,6*S*)-**1** displayed chiroselective complexation with (4*R*,5*R*)-2,3-O-iso- propylidene-1,1,4,4-tetraphenylthreitol, while it exhibited heterocomplexation with racemic 2,3-O-cyclohexylidene-1,1,4,4-tetraphenylthreitol.[12] However, in our recent study it was discovered that reaction solvents played a crucial role in determining inclusion complexation behavior of (3*S*,6*S*)-**1** toward *rac*-BINOL and the composition of the resulting heterocomplex. Furthermore, this work furnished a relatively green method for almost



SCHEME 1 Heterocomplexation of chiral dipeptide (3*S*,6*S*)-**1** with *rac*-BINOL in benzene

quantitative enantiomeric enrichment of nonracemic BINOL, in which unacceptable and toxic benzene was replaced by ethyl acetate. Herein we report these results.

2 | MATERIALS AND METHODS

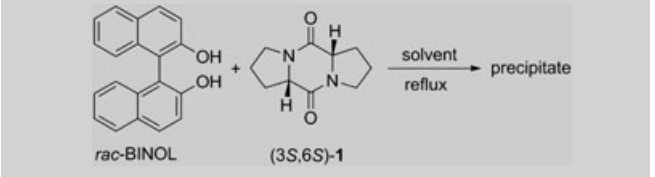
Racemic BINOL was purchased from Guangxi Xinjing Science and Technology (China), and recrystallized from Et_2O, mp 218–220°C; (3*S*,6*S*)-**1** was prepared according to the literature,[10] mp 144–146°C, $[a]_D^{25}$ = +44.5 (*c* = 1.0 in CH_3OH). Toluene, ethyl acetate, methanol, and ethanol were used in AR grade. Other reagents were purchased and directly used without special treatment.

^1H and ^{13}C NMR spectra were performed on a Varian (Palo Alto, CA) Mercury VS 300 and 400. Optical rotations were measured on a PE-341 Mc polarimeter. Melting points were determined on a RY-1 apparatus and are uncorrected.

2.1 | Heterocomplexation of (3*S*,6*S*)-1 toward *rac*-BINOL

A mixture of *rac*-BINOL (0.286 g, 1 mmol) and (3*S*,6*S*)-**1** (0.194 g, 1 mmol) was dissolved in toluene (5 mL) with heating and refluxed for 2 h, and then cooled to ambient temperature to isolate a 1:1 colorless crystalline complex HC-**3** (0.472 g) consisting of (3*S*,6*S*)-**1** and *rac*-BINOL, yield: 98%. mp 192–194°C, $[a]_D^{25}$ = −27.6 (*c* = 1.0 in THF). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.98 (d, *J* = 9.0 Hz, 2H; Ar H), 7.90 (d, *J* = 8.1 Hz, 2H; Ar H), 7.28–7.41 (m, 6H; Ar H), 7.16 (d, *J* = 8.1 Hz, 2H; Ar H), 5.27 (s, 2H; OH), 4.12–4.17 (t, *J* = 8.1 Hz, 2H; NCH), 3.50–3.54 (dd, *J* = 8.1 Hz, *J* = 6.0 Hz, 4H; NCH_2),1.89–2.32 (m, 8H; CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 166.4 (C = O), 152.8 (Ar-C), 133.5 (Ar-C), 131.2 (Ar-C), 129.4 (Ar-C), 128.4 (Ar-C), 127.4 (Ar-C), 124.3 (Ar-C), 124.0 (Ar-C), 117.9 (Ar-C), 111.2 (Ar-C), 60.5 (N-CH), 45.2 (N-CH_2), 27.7 (CH_2), 23.3(CH_2) .

TABLE 1 Examination of inclusion complexation behavior of (3S,6S)-1 toward *rac*-BINOL in different reaction solvents



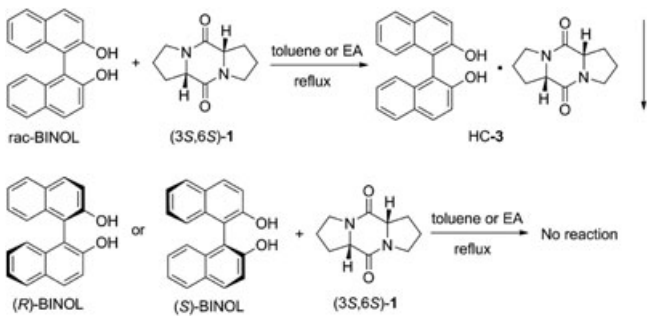
Entry	Solvent	Reaction time (h)	Precipate
1	CH_3OH	4	*Rac*-BINOL
2	C_2H_5OH	5	*Rac*-BINOL
3	$CHCl_3$	3	*Rac*-BINOL
4	THF	2	*Rac*-BINOL
5	$CH_3COOC_2H_5$	2	Complex
6	$C_6H_5CH_3$	2	Complex

2.2 | X-ray crystal structure analysis of the heterocomplex HC-3

A single crystal suitable for X-ray structural analysis was obtained by slowly cooling a hot ethanol solution of the complex to room temperature. A colorless crystal of dimensions 0.32 × 0.28 × 0.25 mm was mounted on a glass fiber. X-ray diffraction intensity data collection and cell refinement were performed on Bruker (Billerica, MA) APEX-II CCD. A total of 9003 unique reflections were collected using MoKa (k = 0.71073 Å) radiation by fine-focus sealed tube at 273(2)K. The corrections for *Lp* factors and empirical absorption were applied to the intensity data. All calculations were performed on Enraf-Nonius Molen/VAX Software using the program SHELXL-97. The structure was solved by direct methods and refined on F^2 using a full-matrix least-squares technique. The nonhydrogen atoms were also refined by a full-matrix least-squares technique, anisotropically, and hydrogen atoms were included but not refined. Cell dimensions were obtained by the least-squares refinement of well-centered reflections in the range of $2.0^o < \theta < 25.5^o$. Convergence with unweighted and weighted agreement factors was achieved at *R* = 0.0587 and Rw =0.1412 (w = 1/ [\s^2(F_o^2) + (0.0740P)^2 + 4.2576P] where P = (F_o^2 + 2Fc^2)/3, S = 0.0006(8), and Fc^* = kFc [1 + 0.001 × Fc^2\l^3/sin(2/q)]$^{-1/4}$). The maximum and minimum peaks on the final difference Fourier map correspond to 0.574 and −0.667 eÅ^{-3}.

2.2.1 | Crystal data for heterocomplex HC-3

Empirical formula, C_{30} $H_{28}N_2O_4$; formula weight, 480.54; calculated density, 1.313 g/cm^3; volume (V), 4862.1(10)



SCHEME 2 Interaction of (3*S*,6*S*)-**1** with *rac*-BINOL, (*R*)-BINOL, or (*S*)-BINOL in toluene or ethyl acetate

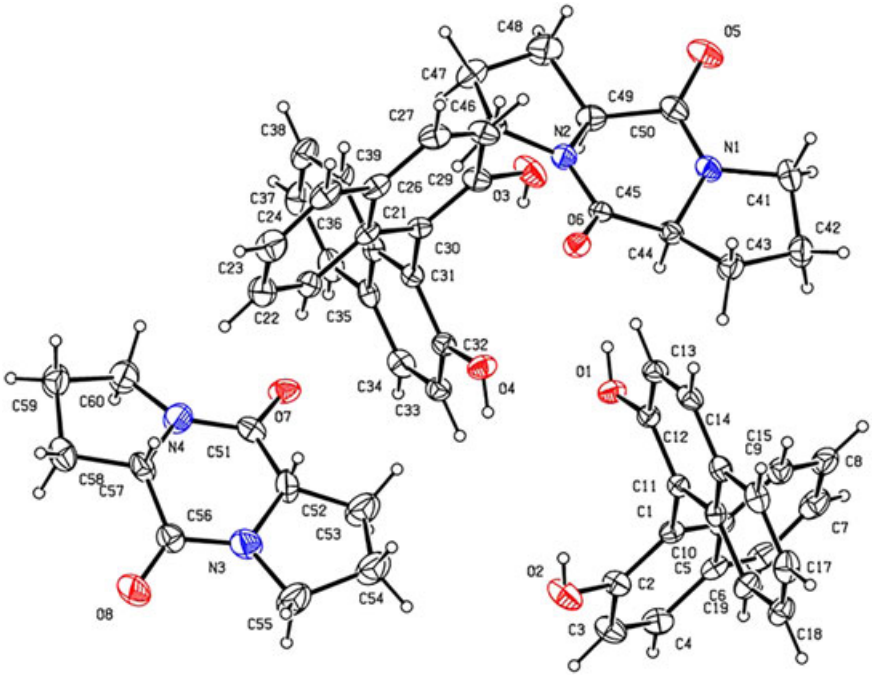


FIGURE 1 Perspective view of the complex HC-**3**

Å^3; crystal system, Orthorhombic; space group, P2(1)2(1)2(1); Z = 8; unit cell dimensions, a = 8.9875(11), b = 22.559(3), c = 23.980(3), α = 90°, β = 90°, γ = 90°; absorption coefficient (μ), 0.087 mm^{-1}; index ranges −10 < =h < =10, −26 < =k < =27, −29 < =l < =24; F (000), 2032; GOF, 1.034.

2.3 | Representative procedure for enantiomeric enrichment for non-*rac*-BINOL

10% enantiomeric excess (ee) (*R*)-BINOL (2.86 g, 10 mmol) and (3*S*,6*S*)-**1** (1.75 g, 9 mmol) were dissolved in hot ethyl acetate (20 mL) and refluxed for 2 h, then cooled to room temperature and isolated as a 1:1 colorless crystalline heterocomplex HC-**3.** The mother liquid was concentrated to give a white solid of (*R*)-BINOL (0.27 g, 96% yield based on the amount of (*R*)-BINOL in non-*rac*-BINOL(10% ee)), mp 208–210°C, $[a]_D^{25}$ = +35.2 (*c* = 1.0 in THF). The white crystal was recrystallized in toluene to afford massy colorless transparent crystal of (*R*)-BINOL, mp 208–210°C, $[a]_D^{25}$ = +35.5 (*c* = 1.0 in THF).

3 | RESULTS AND DISCUSSION

Even though quantitative separation of the nonracemic BINOL via hexterocomplexation of (3*S*,6*S*)-**1** toward *rac*-BINO in benzene has been reported previously,[11] this method still has some limitations in practical application, especially in large-scale application. On the one hand, benzene is a highly toxic and unacceptable solvent.[13] On the other hand, just as pointed out in our previous report,[11] this enrichment method is more suitable for non-*rac*-BINOL with medium or higher enantiomeric purity because of low solubility of *rac*-BINOL in benzene even under reflux condition.* Besides, the existence of benzene molecules in the molecular chains of heterocomplex HC-**2** proves to be crucial for the stability of HC-**2** based on our observation.* From the perspective of green chemistry, seeking an alternative enrichment method becomes a top priority.

Initially, inclusion complexation of dipeptide (3*S*,6*S*)-**1** with *rac*-BINOL in different solvents was examined. A 1:1 mixture of *rac*-BINOL and (3*S*,6*S*)-**1** was allowed to completely dissolved in a hot solvent and refluxed for several hours, then cooled to room temperature to give a precipitate. Comparable results are listed in Table 1 using different solvents, involving polar protic solvents methanol and ethanol, polar aprotic solvents trichloromethane, THF, and ethyl acetate, and apolar aprotic solvent toluene. It may be seen that only using apolar aprotic solvent toluene and polar aprotic solvent ethyl acetate as a reaction solvent can afford the corresponding complex of (3*S*,6*S*)-**1** with BINOL, while in other solvents, *rac*-BINOL precipitated. That is to say, in toluene or ethyl acetate, (3*S*,6*S*)-**1** exerts inclusion complexation toward *rac*-BINOL, while in other examined solvents, (3*S*,6*S*)-**1** showed no inclusion complexation toward *rac*-BINOL.

NMR spectra analysis indicates that the complex formed in toluene or ethyl acetate has the same composition including equal mole of (3*S*,6*S*)-**1** and BINOL without solvent molecules. To further determine the inclusion complexation behavior of (3*S*,6*S*)-**1** toward *rac*-BINOL in toluene or ethyl acetate, the complex was dissociated by H_2O–CH_3COOEt

*We have observed that heterocomplex HC-2 would be gradually degenerated once the benzene molecules in HC-2 were lost. So the heterocomplex HC-2 was conserved in benzene solvent if it was kept for a long time.

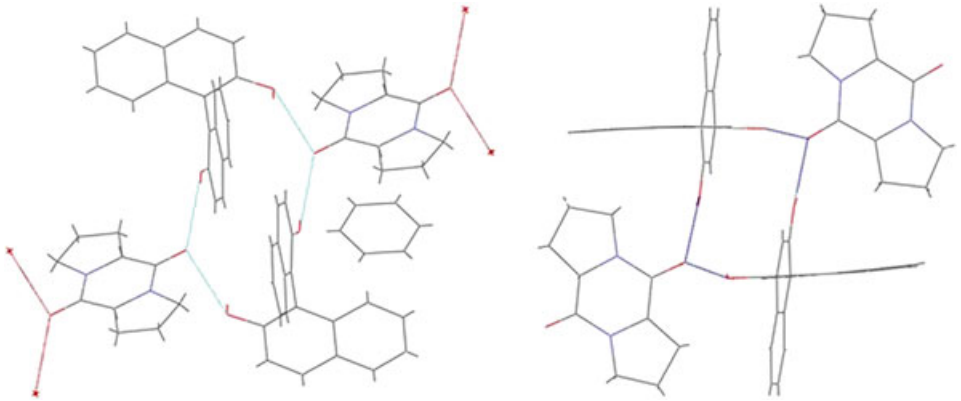
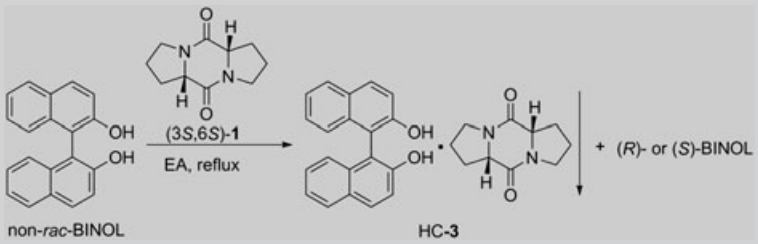


FIGURE 2 Hydrogen bonding in the heterocomplex HC-**2** (left) and HC-**3** (right). Hydrogen bonds are shown as dotted lines

TABLE 2 Enantiomeric enrichment of non-*rac*-BINOLs by heterocomplexation of (3S,6S)-**1** in ethyl acetate



Entry	Non-*rac*-BINOL[a]	Yield of enantiomeric pure BINOL (%)[b]	$[\alpha]_D^{25}$ of optically active BINO[c]	ee of enantiomeric pure BINOL (%)[d]
1	80% ee (R)-BINOL	96	+35.6	>*99*
2	50% ee (R)-BINOL	95	+35.4	>*99*
3	20% ee (R)-BINOL	95	+*35.6*	>*99*
4	10% ee (*R*)-BINOL	90	+35.5	>99
5	10% ee (S)-BINOL	90	-35.4	>99

[a]Non-*rac*-BINOLs were made up by mixing of rac-BINOL with an appropriate amount of enantiopure (*R*)- or (*S*)-BINOL.

[b]Yield of enantiomeric pure BINOL is calculated based on the sum of two or three crops by crystallization.

[c]$[\alpha]_D^{25}$ (c = 1.0 in THF).

[d]Ee of optically active BINOL is analyzed by HPLC a Chiralcel AD column (4.6 × 250 mm) with *n*-hexane/*i*-propanol (4:1) as eluent chiral and the specific rotation.

mixture, from which *rac*-BINOL and (3*S*,6*S*)-**1** were recovered separately. Furthermore, the following experiments were carried out. As shown in Scheme 2, enantiopure (*R*)-BINOL and (*S*)-BINOL were separately allowed to reflux with (3*S*,6*S*)-**1** in toluene or ethyl acetate for several hours, then cooled to room temperature; no corresponding complex precipitated. These results clearly show that heterocomplexation of (3*S*,6*S*)-**1** toward *rac*-BINOL also took place in toluene or ethyl acetate.

It should be noted that the optimum molar ratio of *rac*-BINOL and (3*S*,6*S*)-**1** is 1:1 in ethyl acetate or toluene. Under this optimized condition, pure heterocomplex HC-**3** could be directly isolated from the mother liquid. While the molar ratio is higher than 1:1, a coprecipitation of HC-**3** with *rac*-BINOL occurs, and recrystallization is required to obtain pure HC-**3**.

Achiroselective complexation of (3*S*,6*S*)-**1** toward *rac*-BINOL can be achieved in different solvents including benzene, toluene, and ethyl acetate, but different heterocomplexes are afforded. How can reaction solvents have such a dramatic effect on the heterocomplexation behavior of (3*S*,6*S*)-**1** with *rac*-BINOL? Single-crystal X-ray analysis of HC-**3** is used to discover more information. As shown in Figure 1, single-crystal X-ray diffraction analysis[†] of HC-**3** further confirms that it is a 1:1 complex consisting of (3*S*,6*S*)-**1** and *rac*-BINOL. In the crystal, there are eight inclusion complex molecules in a unit cell, where the configuration of (3*S*,6*S*)-**1** is retentive; while the configuration of the two molecules of BINOL are the opposite, namely, they are two different enantiomers.

Figure 2 is the comparison of the H-bonding interaction of chiral dipeptide (3*S*,6*S*)-**1** toward *rac*-BINOL in heterocomplex HC-**2** and HC-**3**. It can be seen that both OH groups of each BINOL molecule are involved in H-bonds with neighboring carbonyl groups of the dipeptides in

[†]Final atomic coordinates of the crystal, along with lists of anisotropic thermal parameters, hydrogen coordinates, bond lengths, and bond angles have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-738033. Data can be obtained free of charge, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk; web: http//www.ccdc.cam.ac.uk).

heterocomplex HC-**2** and HC-**3**. However, in HC-**2**, each peptide carbonyl group is hydrogen-bonded with two BINOL molecules, and benzene molecules are locked between the chains to form a more stable three-dimensional network; while in HC-**3**, only one carbonyl group of each dipeptide molecule is hydrogen-bonded with two BINOL molecules, and the other one is keeping unbound state. Obviously, in different reaction solvents, (3*S*,6*S*)-**1** exerts different H-bond interaction pattern toward *rac*-BINOL. In HC-3, the solvent molecules are not participated in the forming of heterocomplex, that is to say, the H-bond interaction pattern of chiral dipeptide (3*S*,6*S*)-**1** toward *rac*-BINOL in HC-**3** is favorable to its stability. In contrast, the H-bond interaction pattern in HC-**2** is unfavorable to its stability. We have observed that HC-**2** would be gradually degenerated if the benzene molecules locked in the chains are lost. It is likely that different H-bond interaction pattern results in different composition of the corresponding heterocomplex.

Considering that ethyl acetate is a less toxic and acceptable solvent, and it has a relatively good solubility in *rac*-BINOL compared with benzene, quantitative enantiomeric enrichment of non-*rac*-BINOL via a heterocomplexation strategy in ethyl acetate was examined. As shown in Table 2, under the above optimum conditions different enantiomeric purity of non-*rac*-BINOLs and an appropriate loading of (3*S*,6*S*)-**1**, which can be calculated based on the formation of 1:1 complex with *rac*-BINOL, were allowed to reflux in ethyl acetate, and then cooled to room temperature. The *Rac*-BINOL portion precipitated directly from the solution as the heterocomplex HC-**3**, and enantiopure (*R*)- or (*S*)-BINOL was obtained from the ethyl acetate filtrate. It should be pointed out that this heterocomplexation strategy was successfully applied to enantiomeric enrichment of a wide range of nonracemic BINOL, even that with low enantiomeric purity (entries 4 and 5).

4 | CONCLUSION

In summary, the effects of reaction solvent on inclusion complexation behavior of chiral dipeptide (3*S*,6*S*)-**1** toward *rac*-BINOL was studied. It was discovered that the reaction solvent played a crucial role in determining the inclusion complexation behavior of dipeptide (3*S*,6*S*)-**1** toward *rac*-BINOL. In polar protic solvents methanol and ethanol, polar aprotic solvents trichloromethane and THF, (3*S*,6*S*)-**1** could not form any complex with *rac*-BINOL, while in benzene or ethyl acetate it displayed achiroselective complexation toward *rac*-BINOL to furnish heterocomplex HC-**2** and HC-**3**, respectively. Single-crystal X-ray diffraction analysis indicated that a different H-bond interaction pattern existed in HC-**3** and HC-**2**, which likely determined their different composition. And the heterocomplexation strategy in ethyl acetate was successfully used to achieve almost quantitative enantiomeric enrichment of non-*rac*-BINOL, especially that with low enantiomeric purity. This work provides a relatively green method for quantitative separation of the non-*rac*-BINOL, in which unacceptable and toxic benzene was replaced by ethyl acetate.

ACKNOWLEDGMENTS

The work was supported by the National Nature Science Foundation of China (No. 21302233) and the Nature Science Foundation of Hubei Province of China (No. 2012FFB07410).

REFERENCES

1. Izake EL. Chiral discrimination and enantioselective analysis of drugs: An overview. *Pharm J Sci*. 2007;96:1659.
2. Ohrui H. Development of highly potent chiral discrimination methods that solve the problems of the diastereomer method. *Proc Jpn Acad, Ser B*. 2007;83:127.
3. Okamoto Y, Yashima E, Yamamoto C. Optically active polymers with chiral recognition ability. *Top Stereochem*. 2003;24:157.
4. Toda F. *Enantiomer Separation: Fundamentals and Practical Methods*. Berlin: Springer Science & Business Media; 2007.
5. Toda F, Yoshizawa K, Hyoda S, Toyota S, Chatziefthimiou S, Mavridis IM. Efficient resolution of 2,2'-dihydroxy-1,1'-binaphthyl by inclusion complexation with chiral N-(3-chloro-2-hydroxypropyl)-N,N,N-trimethylammonium chloride. *Org Biomol Chem*. 2004;2:449.
6. Kano K, Nishiyabu R. Chiral recognition by cyclodextrins: a general mechanism. *Adv Supramol Chem*. 2003;9:39.
7. Feng XM, Zeng DC, Jiang YZ. A novel method of resolution-chiral inclusion complexation. *Chin J Org Chem*. 2000;20:131.
8. Nakamura D, Kakiuchi K, Koga K, Shirai R. Design and synthesis of novel C2-symmetric chiral piperazines and an application to asymmetric acylation of σ-symmetric 1,2-diols. *Org Lett*. 2006;8:6139.
9. Tang HY, Zhao GF, Zhou ZH, Zhou QL, Tang CC. Synthesis of some new tertiary amines and their application as co-catalysts in combination with *L*-proline in enantioselective Baylis–Hillman reaction between o-nitrobenzaldehyde and methyl vinyl ketone. *Tetrahedron Lett*. 2006;47:5717.
10. Harri BD, Bhat KL. Synthetic studies of detoxin complex II: syntheses of detoxin B1 and B3. *Hetereocycles*. 1986;24:1045.
11. Shan ZX, Xiong Y, Yi J, Hu XY. Heterocomplexation of a chiral dipeptide and quantitative enantiomeric enrichment of nonracemic 1,1′-Bi-2-naphthol. *J Org Chem*. 2008;73:9158.
12. Hu XY, Shan ZX, Li W. Second example for the heterocomplexation of chiral diols and complete disproportionation of enantiomers for non-racemic 2,3-O-cyclohexylidene-1,1,4,4-tetraphenylthreitols. *J Fluor Chem*. 2010;131:505.
13. Sheldon RA, Arends I, Hanefeld U. *Green Chemistry and Catalysis*. New York: John Wiley & Sons; 2007: 295.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Hu X., Yang Y., Shi S., and Shan Z. Effects of solvent on inclusion complexation of a chiral dipeptide toward racemic BINOL, *Chirality*, 2016; 00, DOI: 10.1002/chir.22658 00-00