Letter

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Dynamic Kinetic Resolution of N-Protected Amino Acid Esters via Phase-Transfer Catalytic Base Hydrolysis

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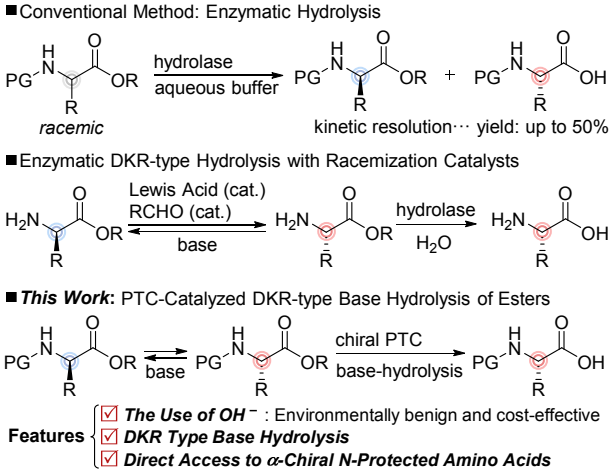
Supporting Information Placeholder

ABSTRACT: Asymmetric base hydrolysis of α-chiral esters with synthetic small-molecule catalysts is described. Quaternary ammonium salts derived from quinine were used as chiral phase-transfer catalysts to promote the base hydrolysis of N-protected amino acid hexafluoroisopropyl esters in a $CHCl_3$/NaOH (aq) via dynamic kinetic resolution, providing the corresponding products in moderate to good yields (up to 99%) with up to 96:4 er. Experimental and computational mechanistic studies using DFT calculation and pseudo-transition state (TS) conformational search afforded a TS model accounting for the origin of the stereoselectivity. The model suggested π-stacking and H-bonding interactions play essential roles in stabilizing the TS structures.

KEYWORDS: *base hydrolysis, conformational search, ester, dynamic kinetic resolution, phase-transfer catalysis*

Asymmetric ester hydrolysis, one of the most fundamental transformations in biological systems, has been widely employed for the preparation of optically active building blocks in both laboratory- and industrial-scale chemistry.[1] However, notwithstanding the recent advances in asymmetric catalysis, including reactions with water,[2] stereocontrol in ester hydrolysis with synthetic catalysts has remained a formidable challenge, probably due to the small size of water, formation of complex hydrogen bonding networks, and low reactivity of ester substrates toward hydrolysis under neutral to acidic conditions. In fact, precedent studies on asymmetric ester hydrolysis with synthetic catalysts, such as metal complexes,[3] micellar catalysts,[4] and biomimetic catalysts,[5] had limited scopes, and the systems usually required highly diluted conditions and a large excess of the catalyst.

Chiral phase-transfer catalysis is one of the major catalytic principles involving ionic reagents in asymmetric synthesis.[6] Previously, we reported the enantioselective protonation of alkenyl esters via phase-transfer catalytic base hydrolysis using environmentally benign and inexpensive alkali-metal hydroxide bases.[7,8] Encouraged by the success of phase-transfer catalytic base hydrolysis, we envisioned that chiral quaternary ammonium hydroxide species could also discriminate the two enantiomers of the α-chiral esters in the nucleophilic attack of hydroxide on carbonyls. Herein, we describe phase-transfer catalytic asymmetric base hydrolysis of N-protected amino acid esters, affording the corresponding α-chiral unnatural amino acids[9] with up to 96:4 er. This reaction is suitable for the synthesis of enantioenriched amino acid derivatives bearing a bulky or aryl substituent at the α-tertiary chiral center, which are difficult to prepare by phase-transfer catalyst (PTC)-catalyzed asymmetric alkylation and S_NAr reactions.[10–12] In addition, the reaction proceeded through dynamic kinetic resolution by racemization of the α-proton. In contrast, conventional enzymatic hydrolysis of amino acid esters[13] has been reported to involve kinetic resolution, which inherently has a theoretical maximum yield of 50%, and dynamic kinetic resolution-type enzymatic hydrolysis developed by Aron group requires additional racemization catalysts and limited to unprotected amino acid esters (Scheme 1).[14] Detailed experimental and computational studies with DFT calculation and rapid conformational search were also performed to elucidate the origin of the stereoselectivity.

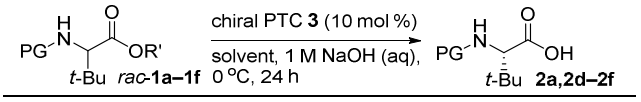


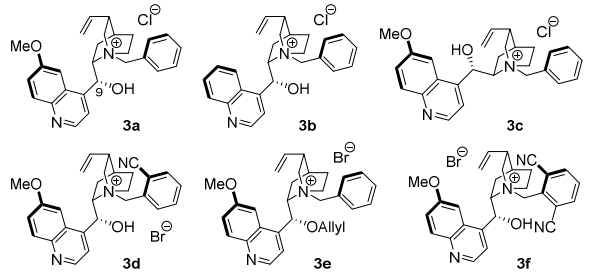
Scheme 1. Asymmetric hydrolysis of N-protected amino acid esters.

We initially explored the reaction with *N*-benzoyl *tert*-leucine methyl ester (**1a**) and PTC **3a** derived from quinine (Table 1). Base hydrolysis of **1a** at 0 °C in $CHCl_3$ as solvent

proceeded to afford the corresponding hydrolyzed product **2a** but resulted in poor yield (entry 1, 6%). To improve the reactivity, esters prepared from fluoroalcohols were examined, and reactions with 2,2,2-trifluoroethyl or hexafluoroisopropyl esters (**1b** and **1c**, respectively) resulted in a significant increase in both the stereoselectivity and the reactivity (entries 2 and 3). The reaction with PTC **3b** derived from cinchonidine or pseudo-enantiomeric PTC **3c** showed lower selectivity and a significant decrease in the yield (entries 4 and 5). Fortunately, PTC **3d** bearing a 2-cyanobenzyl group afforded the product in quantitative yield with high stereoselectivity (entry 6, 95:5 er, >99%). The use of O-allylated PTC **3e** resulted in a considerable decrease in yield and er (entry 7), and incorporation of a 2,6-dicyanobenzyl group into PTC **3f** led to a loss of most of the catalytic activity, providing almost racemic product (entry 8). These results indicated that the 9-OH group of the catalyst is essential for this transformation and that the reaction occurred close to the 9-OH group. For the other solvents screened, CH_2Cl_2 showed slightly lower yield and stereoselectivity, and other non-halogenated solvents resulted in significantly lower ers. (entries 9–12). Next, we investigated the effect of the N-protecting group. Introduction of electron-rich or electron-deficient substituents onto the benzoyl group led to lower yields and ers (entries 13 and 14, ester **1d**, 23%, 88:12 er; ester **1e**, 45%, 82.5:17.5 er, respectively). The reaction with *N*-Boc substrate **1f** resulted in a significant loss of stereoselectivity (entry 15, 52%, 64:36 er).

Table 1. Optimization of the reaction conditions.[a]



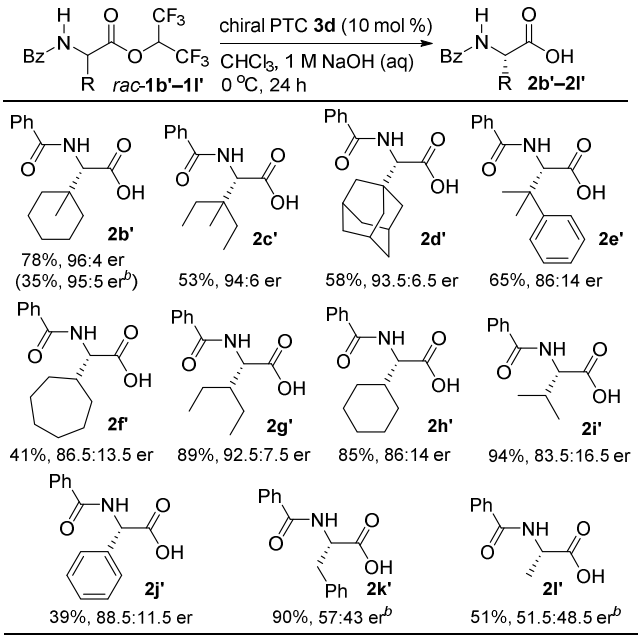


Entry	PTC	PG	R	Solvent	Yield[b]	er
1	**3a**	Bz	Me	$CHCl_3$	6	–
2	**3a**	Bz	CF_3CH_2	$CHCl_3$	26	67:33
3	**3a**	Bz	$(CF_3)_2CH$	$CHCl_3$	79	86.5:13.5
4	**3b**	Bz	$(CF_3)_2CH$	$CHCl_3$	14	80:20
5	**3c**	Bz	$(CF_3)_2CH$	$CHCl_3$	17	27:73
6	**3d**	Bz	$(CF_3)_2CH$	$CHCl_3$	>99	95:5
7	**3e**	Bz	$(CF_3)_2CH$	$CHCl_3$	trace	–
8	**3f**	Bz	$(CF_3)_2CH$	$CHCl_3$	5	47:53
9	**3d**	Bz	$(CF_3)_2CH$	toluene	31	61:39
10	**3d**	Bz	$(CF_3)_2CH$	Mes	16	55.5:44.5
11	**3d**	Bz	$(CF_3)_2CH$	CH_2Cl_2	91	93:7
12	**3d**	Bz	$(CF_3)_2CH$	Et_2O	56	56:44
13	**3d**	4-OMe-Bz	$(CF_3)_2CH$	$CHCl_3$	23	88:12
14	**3d**	4-CF_3-Bz	$(CF_3)_2CH$	$CHCl_3$	45	82.5:17.5
15	**3d**	Boc	$(CF_3)_2CH$	$CHCl_3$	52	64:36

[a]Reaction conditions: N-Protected amino acid ester (0.10 mmol), 1 M NaOH (aq) (250 μL), chiral PTC **3** (10 mol %) in $CHCl_3$ (400 μL) at 0 °C for 24 h. Stirring speed: 200 rpm. [b]Isolated yield of **2**.

With the optimized conditions in hand, we then explored the substrate scope for this reaction (Table 2). Initially, sterically hindered substrate **1b'** was examined, and it provided product **2b'** in low yield (35% with 95:5 er). After further exploration of the reaction conditions, we found that the use of 8 equiv of 1 M NaOH (aq) improved the yield significantly (**2b'**, 78%, 96:4 er). Thus, these reaction conditions were also applied to other substrates. Esters with bulky substituents provided the corresponding *N*-benzoyl amino acids with good to high ers in moderate to good yields (**2c'**, 53%, 94:6 er; **2d'**, 58%, 93.5:6.5 er; **2e'**, 65%, 86:14 er). Reactions with esters having secondary alkyl groups also showed good ers and moderate yields (**2f'**, 41%, 86.5:13.5 er; **2g'**, 89%, 92.5:7.5 er; **2h'**, 85%, 86:14 er; **2i'**, 94%, 83.5:16.5 er). *N*-Benzoyl phenyl glycine ester **1j'** also afforded the corresponding product **2j'** with good er in moderate yield (39%, 88.5:11.5 er). The stereoselectivity of the reactions with substrates containing a primary alkyl group at the α-position decreased significantly (**2k'**, 90%, 57:43 er; **2l'**, 51%, 51.5:48.5 er).

Table 2. Scope of *rac*-*N*-benzoyl amino acid esters 1'.[a]

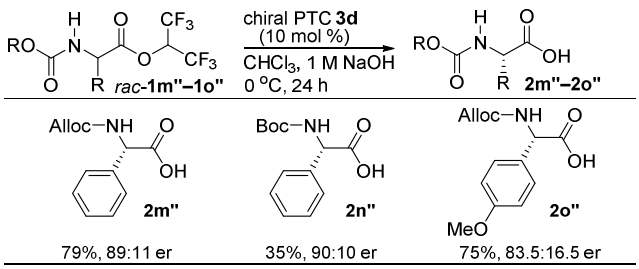


[a]Reaction conditions: *N*-Benzoyl amino acid ester (0.20 mmol), 1 M NaOH (aq) (1.6 mL), PTC **3d** (10 mol %) in $CHCl_3$ (800 μL) at 0 °C for 24 h. Stirring speed: 200 rpm. Isolated yields are presented. [b]1 M NaOH (aq) (2.5 eq, 500 μL) was used.

N-Alloc and *N*-Boc aryl glycine esters were also examined (Table 3). Substrate **1m"** provided the corresponding *N*-Alloc phenyl glycine (**2m"**) in good yield and er (79% with 89:11 er), while Boc substrate **1n"** provided the product in low yield (35%, 90:10 er). An *N*-Alloc substrate bearing a 4-methoxyphenyl group provided the corresponding *N*-Alloc

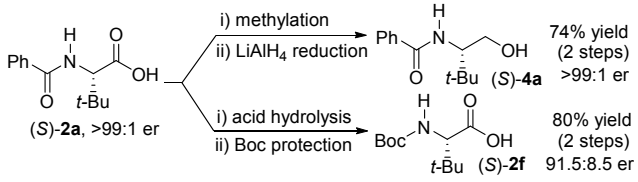
aryl glycine **2o**" in good yield with moderate er (75%, 83.5:16.5 er).

Table 3. Scope of racemic N-carbamate protected aryl glycine esters 1".[a]



[a]Reaction conditions are the same as described in Table 2, footnote a. Isolated yields are presented.

To highlight the utility of this reaction, we conducted transformations of hydrolyzed product **2a** (Scheme 2). Compound **2a** was subjected to methylation/$LiAlH_4$ reduction reactions, providing the corresponding alcohol **4a** in good yield without any loss of optical purity. In addition, we also carried out acid hydrolysis and subsequent Boc protection of the hydrolyzed product. The corresponding *N*-Boc *tert*-leucine **2f** was obtained in 80% yield with 91.5:8.5 er.

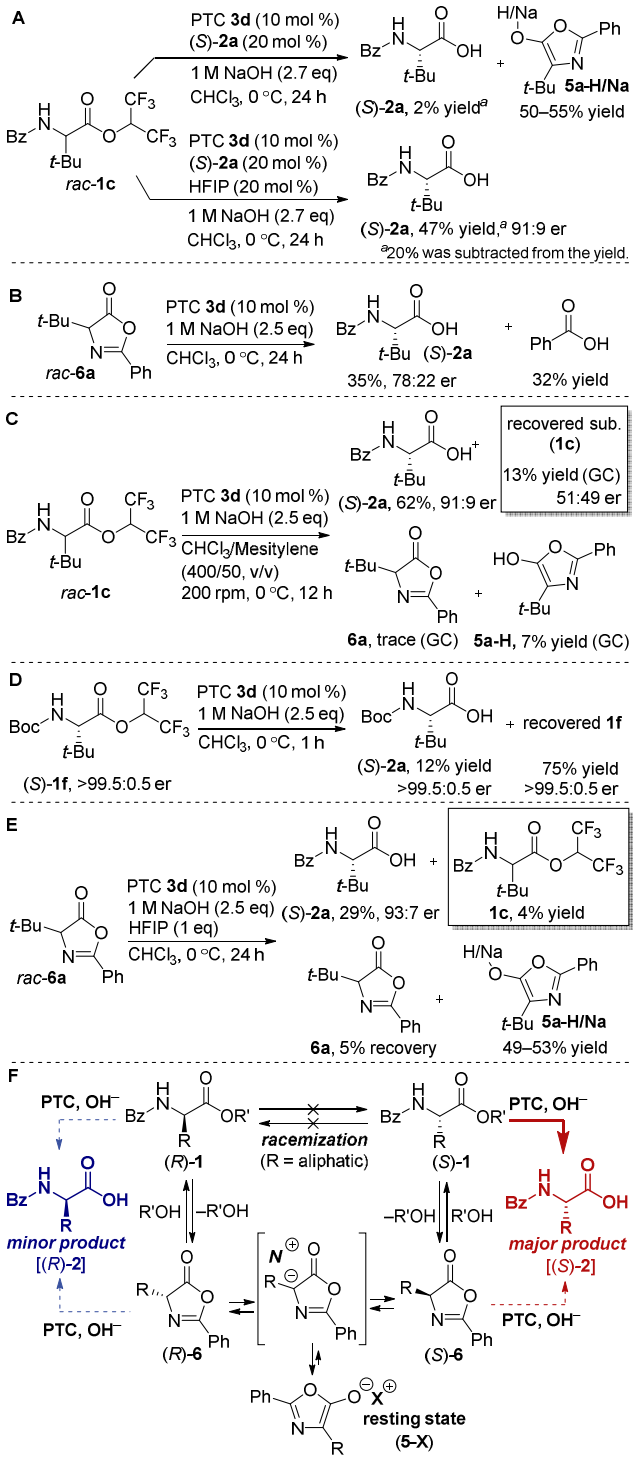


Scheme 2. Transformations of hydrolyzed product 2a.

To obtain mechanistic insights, we investigated the stability of the nitrile group in the PTC **3d** under the reaction conditions. After the asymmetric hydrolysis reaction of ester **1c** with 8 equivalent of 1 M NaOH (aq) for 24 h, the PTC **3d** was recovered in 77%, and nitrile-hydrated PTC was not observed based on ^{1}H NMR analysis (See, Supporting Information).

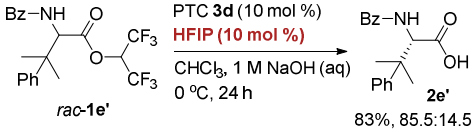
Next, we explored the byproducts formed in the reaction. As mentioned in Table 2, increasing the amount of 1 M NaOH (aq) from 2.5 eq to 8.0 eq improved the yield (ester **1b**', 35% vs 78%). We hypothesized that product inhibition by forming the ammonium carboxylate ion pair would occur. Consistent with this hypothesis, addition of (*S*)-**2a** (>99.5:0.5 er) resulted in obtaining the product in low yield and the formation of hydroxyoxazole **5a-H** or the corresponding salt **5a-Na** in 50–55% yield (Scheme 3A). In addition, ammonium benzoate salt derived from PTC **3d** also showed low catalytic activity, which also supports the hypothesis (See, Supporting Information). Furthermore, the reaction of **1c** in the presence of a catalytic amount of (*S*)-**2a** and hexafluoroisopropyl alcohol (HFIP) proceeded to provide the product **2a** in 47% yield in 91:9 er (Scheme 3A). These results indicate that the alkoxide derived from HFIP mitigates the inhibition effect.

The observation of cyclic byproduct **5a-H/Na** suggests that azlactone **6a** was formed in the system and dynamic kinetic resolution of **6a** via base hydrolysis would subsequently occur. To assess the hypothesis, we performed the reaction with **6a**, which provided the hydrolyzed product **2a** in significantly lower er than that obtained with substrate **1c** (78:22 er, Scheme 3B). In addition, hydrolytic kinetic resolution of ester **1c** and following dynamic kinetic resolution of **6a** is a possible reaction pathway. Thus, we confirmed the er of recovered substrate **1c** under standard conditions (Scheme 3C). The recovered substrate **1c** was almost racemic (13% yield, 51:49 er), excluding the scenario. Furthermore, two possible racemization/hydrolysis pathways still remains; direct deprotonation/protonation of ester **1c** followed by base hydrolysis of ester **1c** (pathway **A**) or racemization via azlactone **6a** formation/ring opening with HFIP followed by base hydrolysis of ester **1c** (pathway **B**). To assess the direct racemization of **1c**, enantiopure *N*-Boc substrate (S)-**1f** (>99.5:0.5 er) was subjected to the standard reaction conditions (Scheme 3D). The er of the recovered **1f** was >99.5:0.5 as well as the hydrolyzed product **2a**, suggesting that direct racemization of **1c** is unlikely in this system. Furthermore, to investigate the possibility of azlactone ring opening with HFIP, the reaction of azlactone **6a** in the presence of 1 equivalent of HFIP was performed, and ester formation was observed (Scheme 3E). These results support racemization/hydrolysis pathway **B**. Taking these results into consideration, the pathway affording the major enantiomer is likely to be the direct base hydrolysis of ester **1c** while both base hydrolysis of **1c** and azlactone **6a** are possible for the pathways providing the minor enantiomer (Scheme 3F).



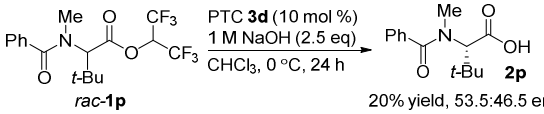
Scheme 3. Mechanistic Investigations and Proposed mechanism.

Based on the above mechanistic considerations, we expected that addition of a catalytic amount of HFIP would suppress the product inhibition by forming the ammonium carboxylate ion pair and lead to improve the reaction efficiency with substrates that provided the products in low to moderate yield. Thus, the reaction of substrate **1e'** in the presence of a catalytic amount of HFIP (10 mol %) was conducted to provide the corresponding hydrolyzed product **2e'** in high yield without significant loss of the stereoselectivity (83% yield, 85.5:14.5 er, Scheme 4).



Scheme 4. Improvement of Product Yield by the Addition of Catalytic Amount of HFIP.

To investigate the necessity of the N–H group in the substrate, the reaction of N-methylated substrate **1p** was carried out, affording the corresponding product in significantly lower er (Scheme 5). This result suggests that either the H-bonding interaction of the N–H group or the steric effect of the N–Me group in the substrate is significantly involved in the stereodetermining step.



Scheme 5. Reaction with racemic N–Me substrate 1p.

We further performed a theoretical investigation to elucidate the origin of the stereoselectivity (Figure 1). Importantly, identification of intermolecular transition state (TS) structures determining the stereoselectivity of a reaction has been a difficult issue in the field of asymmetric organocatalysis due to the complex non-covalent interactions and the generation of numerous complex TS candidates.[15,16] Thus, a conformational search for the active species-substrate complex in which the distances of the atoms directly involved in the bond formation or dissociation are fixed to an appropriate length for the presumed TS structure (pseudo-TS conformational search) was performed with the ConFinder program, which adopts a low-mode conformational search method with semiempirical quantum mechanical calculations.[15b] We considered four initial structures of the substrate **1c**-PTC **3d** complex classified by the stereochemistry of the enantiofaces attacked by the hydroxide and the substrate's α-carbon center: *Re-R*, *Si-R*, *Re-S*, *Si-S*. The C···O distance between the carbonyl carbon of the substrate ester and oxygen atom of the hydroxide was fixed to 2.0 Å in the conformational search to keep the geometry close to the corresponding TS structures. The conformation search generated 2103 to 3275 conformations for each of the complexes, and the energies for the obtained conformers were further assessed by single-point energy (SPE) calculations at the RI-B97D/SV(P) level of theory. After the refinement of the conformers, further partial optimization was carried out at the RI-B97D/SV(P) level of theory (see the Supporting Information for details). The geometries of the TS structures were then optimized at the M06-2X/TZVP level of theory. The most stable TS structures leading to the *S*- or *R*-product were successfully located, as shown in Figure 1 (TS-*Re-S* and TS-*Si-R*, respectively). The difference in Gibbs free energy at 273.15 K between TS-*Re-S* and TS-*Si-R* is in good agreement with the $\Delta\Delta G$ values based on the experimental results [2.1 (calcd.) vs 1.6 (exptl.) kcal/mol]. In addition, both TS structures indicate the π-stacking between the quinoline ring or 2-cyanophenyl ring in **3d** and Ph group in **1c** and H-bonding interactions between the hydrogen atoms in the MeO group or one of the benzylic protons in the 2-cyanobenzyl group and the oxygen atom in the Bz group (O–CH_2H···O=C and N^+CHH···O=C).[17] These non-bonding interactions play important roles in sta-

bilizing the TS structures. Furthermore, the H-bonding interaction between the hydrogen atom in the MeO group and the nitrogen atom in the cyano group was observed in the TS-*Re-S* structure, whereas the two groups were distant in the TS-*Si-R* structure (2.72 and 3.49 Å, respectively). Other TS structures without the H-bonding interaction (O–CH_2H···O=C) also resulted in a significant increase in energy (>3.8 kcal/mol; see the Supporting Information), indicating the importance of the interactions. Furthermore, the favored TS-*Re-S* structure demonstrates the existence of a H-bonding interaction between the oxygen atom in the ester group and the *ortho*-hydrogen atom in the 2-cyanobenzyl group in PTC **3d** (2.45 Å), which was not observed in the TS-*Si-R* structure. Thus, the lack of this H-bonding interaction would explain the energy differences between the TS structures. The N–H group in the substrate does not display H-bonding interactions in the TS structures, suggesting that the significant loss of selectivity with N–Me substrate **1p** is attributable to the conformational change caused by the steric effect.

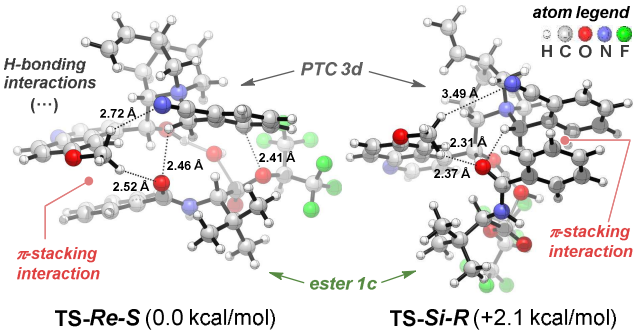


Figure 1. Calculated TS structures leading to each enantiomer at the M06-2X/TZVP level of calculation.

In conclusion, we reported the first asymmetric base hydrolysis of α-chiral esters based on phase-transfer catalysis. This reaction proceeded via dynamic kinetic resolution, affording the hydrolyzed products in moderate to good yields with up to 96:4 er. Detailed experimental studies suggest that the stereodetermining step is the nucleophilic attack of the hydroxide on the carbonyl carbon in the ester substrate. In addition, computational studies using pseudo-TS conformational search with ConFinder and DFT calculation indicated the essential non-covalent interactions between the substrate and the catalyst. Further studies on developing new PTCs that provide high stereocontrol in reactions with α-chiral esters and applying the pseudo-TS conformational search method with the ConFinder program are now underway in our group.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interests.

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REFERENCES

1) a) Straathof, A. J. J.; Panke, S.; Schmid, A. The production of fine chemicals by biotransformations. *Curr. Opin. Biotechnol.* **2002**, *13*, 548–556. b) Wohlgemuth, R. *In Asymmtric Catalysis on Industrial Scale: Challenges, Approaches and Solutions*, 2nd Ed.; Blaser, H.-U.; Federsel, H.-J. Ed.; Wiley-VCH: Weinheim, Germany, 2010, pp 249.

2) For asymmetric catalysis with water as a nucleophile, see: a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. Asymmetric Catalysis with Water: Efficient Kinetic Resolution of Terminal Epoxides by Means of Catalytic Hydrolysis *Science* **1997**, *277*, 936–938. b) Lüssem, B. J.; Gais, H.-J. Palladium-Catalyzed Deracemization of Allylic Carbonates in Water with Formation of Allylic Alcohols: Hydrogen Carbonate Ion as Nucleophile in the Palladium-Catalyzed Allylic Substitution and Kinetic Resolution. *J. Am. Chem. Soc.* **2003**, *125*, 6066–6067. c) Aoyama, H.; Tokunaga, M.; Hiraiwa, S.; Shirogane, Y.; Obora, Y.; Tsuji, Y. Hydrolysis of Alkenyl Esters and Ethers Catalyzed by Metal Complexes. *Org. Lett.* **2004**, *6*, 509–512. d) Zhu, S.-F.; Chen, C.; Cai, Y.; Zhou, Q.-L. Catalytic Asymmetric Reaction with Water: Enantioselective Synthesis of α-Hydroxyesters by a Copper–Carbenoid O–H Insertion Reaction. *Angew. Chem. Int. Ed.* **2008**, *47*, 932–934. e) Zhu, S.-F.; Cai, Y.; Mao, H.-X.; Xie, J.-H.; Zhou, Q.-L. Enantioselective Iron-Catalysed O–H Bond Insertions. *Nat. Chem.* **2010**, *2*, 546–551. f) Guan, X.-Y.; Yang, L.-P.; Hu, W. Cooperative Catalysis in Multicomponent Reactions: Highly Enantioselective Synthesis of γ-Hydroxyketones with a Quaternary Carbon Stereocenter. *Angew. Chem. Int. Ed.* **2010**, *49*, 2190–2192. g) Kamezaki, S.; Akiyama, S.; Kayaki, Y.; Kuwata, S.; Ikariya, T. Asymmetric Nitrile-Hydration with Bifunctional Ruthenium Catalysts Bearing Chiral N-Sulfonyldiamine Ligands. *Tetrahedron: Asymmetry* **2010**, *21*, 1169–1172. h) Kanbayashi, N.; Onitsuka, K. Ruthenium-Catalyzed Regio- and Enantioselective Allylic Substitution with Water: Direct Synthesis of Chiral Allylic Alcohols. *Angew. Chem. Int. Ed.* **2011**, *50*, 5197–5199. i) Boersma, A. J.; Coquière, D.; Geerdink, D.; Rosati, F.; Feringa, B. L.; Roelfes, G. Catalytic Enantioselective *syn* Hydration of Enones in Water Using a DNA-Based Catalyst. *Nat. Chem.* **2010**, *2*, 991–995. j) Gärtner, M.; Mader, S.; Seehafer, K.; Helmchen, G. Enantio- and Regioselective Iridium-Catalyzed Allylic Hydroxylation. *J. Am. Chem. Soc.* **2011**, *133*, 2072–2075. k) Hashimoto, T.; Nakatsu, H.; Yamamoto, K.; Maruoka, K. Chiral Brønsted Acid-Catalyzed Asymmetric Trisubstituted Aziridine Synthesis Using α-Diazoacyl Oxazolidinones. *J. Am. Chem. Soc.* **2011**, *133*, 9730–9733. l) Gulyás, H.; Rivilla, I.; Curreli, S.; Freixa, Z.; van Leeuwen, P. W. N. M. Highly Active, Chemo- and Enantioselective Pt-SPO Catalytic Systems for the Synthesis of Aromatic Carboxamides. *Catal. Sci. Technol.* **2015**, 5, 3822–3828.

3) a) Murakami, M.; Itatani, H.; Takahashi, K.; Kang, J.; Suzuki, K. Stereospecific Reactions of Amino Acids with Co Complexes. *Mem. Inst. Sci. Ind. Res. Osaka Univ.* **1963**, *20*, 95. b) Hix Jr., J. E.; Jones, M. M. Stereoselectivity in the Metal-Complex-Catalyzed Hydrolysis of Amino Acid Esters. *J. Am. Chem. Soc.*

1968, *90*, 1723–1728. c) Weijnen, J. G. J.; Koudijs, A.; Engbersen, J. F. J. Synthesis of Chiral 1,10-Phenanthroline Ligands and the Activity of Metal-Ion Complexes in the Enantioselective Hydrolysis of N-protected Amino Acid Esters. *J. Org. Chem.* **1992**, *57*, 7258–7265.

4) For selected examples, see: a) Bunton, C. A.; Robinson, L.; Stam, M. F. Stereospecific Micellar Catalyzed Ester Hydrolysis. *Tetrahedron Lett.* **1971**, 121–124. b) Yamada, K.; Shosenji, H.; Ihara, H. The Hydrolysis of *p*-Nitrophenyl Esters of α-Amino Acids by *N*-Lauroyl *L* or *D*-Histidine in Cationic Micelles. *Chem. Lett.* **1979**, *8*, 491–494. c) Ueoka, R.; Matsumoto, Y.; Moss, R. A.; Swarup, S.; Sugii, A.; Harada, K.; Kikuchi, J.; Murakami, Y. Membrane Matrix for the Hydrolysis of Amino Acid Esters with Marked Enantioselectivity. *J. Am. Chem. Soc.* **1988**, *110*, 1588–1595. d) Ihara, Y.; Igata, Y.; Okubo, Y.; Nango, M. Chiral Reaction Field for Highly Stereoselective Hydrolysis of Enantiomeric Esters. *J. Chem. Soc., Chem. Commun.* **1989**, 1900–1902. e) Cleij, M. C.; Drenth, W.; Nolte, R. J. M. Mechanism of Enantioselective Ester Cleavage by HistidineContaining Dipeptides at a Micellar Interface. *J. Org. Chem.* **1991**, *56*, 3883–3891. f) Kida, T.; Kajihara, K.; Isogawa, K.; Zhang, W.; Nakatsuji, Y.; Ikeda, I.; Akashi, M. Sugar-Amide Surfactant Micelles as Effective Reaction Fields for Enantioselective Hydrolysis of α-Amino Acid Esters. *Langmuir* **2004**, *20*, 8504–8509.

5) a) Trainor, G. L.; Breslow, R. High Acylation Rates and Enantioselectivity with Cyclodextrin Complexes of Rigid Substrates. *J. Am. Chem. Soc.* **1981**, *103*, 154–158. b) Breslow, R.; Trainor, G. L.; Ueno, A. Optimization of Metallocene Substrates for Beta-cyclodextrin Reactions. *J. Am. Chem. Soc.* **1983**, *105*, 2739–2744. c) Davies, R. R.; Distefano, M. D. A Semisynthetic Metalloenzyme Based on a Protein Cavity That Catalyzes the Enantioselective Hydrolysis of Ester and Amide Substrates. *J. Am. Chem. Soc.* **1997**, *119*, 11643–11652.

6) For reviews, see; a) Ooi, T.; Maruoka, K. Recent Advances in Asymmetric Phase-Transfer Catalysis. *Angew. Chem. Int. Ed.* **2007**, *46*, 4222–. b) Shirakawa, S.; Maruoka, K. Recent Developments in Asymmetric Phase-Transfer Reactions. *Angew. Chem. Int. Ed.* **2013**, 52, 4312–4348.

7) a) Yamamoto, E.; Nagai, A.; Hamasaki, A.; Tokunaga, M. Catalytic Asymmetric Hydrolysis: Asymmetric Hydrolytic Protonation of Enol Esters Catalyzed by Phase-Transfer Catalysts. *Chem. Eur. J.* **2011**, *17*, 7178–7182. b) Yamamoto, E.; Gokuden, D.; Nagai, A.; Kamachi, T.; Yoshizawa, K.; Hamasaki, A.; Ishida, T.; Tokunaga, M. Hydrolytic Enantioselective Protonation of Cyclic Dienyl Esters and a β-Diketone with Chiral Phase-Transfer Catalysts. *Org. Lett.* **2012**, *14*, 6178–6181.

8) For a related example of PTC-catalyzed base hydrolysis of carbonyl compounds, see: Frisch, K.; Jørgensen, K. A. Organocatalytic Asymmetric Destruction of 1-Benzylated Reissert Compounds Catalysed by Quaternary Cinchona Alkaloids. *Org. Biomol. Chem.* **2007**, 5, 2966–2974.

9) (a) Wang, L.; Shultz, P. G. Expanding the Genetic Code. *Angew. Chem. Int. Ed.* **2005**, *44*, 34–66. (b) Tsantrizos, Y. S. Peptidomimetic Therapeutic Agents Targeting the Protease Enzyme of the Human Immunodeficiency Virus and Hepatitis C Virus. *Acc. Chem. Res.* **2008**, *41*, 1252–1263.

10) For selected examples of PTC-catalyzed enantioselective alkylation, see: a) O'Donnell, M. J.; Bennett, W. D.; Wu, S. The Stereoselective Synthesis of α-Amino Acids by Phase-Transfer Catalysis. *J. Am. Chem. Soc*. **1989**, *111*, 2353–2355. b) Lygo, B.; Wainwright, P. G. A New Class of Asymmetric Phase-Transfer Catalysts Derived from Cinchona Alkaloids — Application in the Enantioselective Synthesis of α-Amino Acids. *Tetrahedron Lett*. **1997**, *38*, 8595–8598. c) Corey, E. J.; Xu, F.; Noe, M. C. A Rational Approach to Catalytic Enantioselective Enolate Alkylation Using a Structurally Rigidified and Defined Chiral Quaternary Ammonium Salt under Phase Transfer Conditions. *J. Am. Chem. Soc*. **1997**, *119*, 12414–12415. d) Ooi, T.; Kameda, M.; Maruoka, K. Molecular Design of a C_2-Symmetric Chiral Phase-Transfer Catalyst for Practical Asymmetric Synthesis of α-Amino Acids. *J. Am. Chem. Soc*. **1999**, *121*, 6519–6520. For a review, see: e) Maruoka, K.; Ooi, T. Enantioselective Amino Acid Synthesis by Chiral Phase-Transfer Catalysis. *Chem. Rev.* **2003**, *103*, 3013–3028.

11) No examples of constructing α-tertiary chiral center in PTC-catalyzed asymmetric S_NAr reactions of amino acid Schiff bases, probably due to the lability of the C-H bond at the α-position; see: a) Shirakawa, S.; Yamamoto, K.; Tokuda, T.; Maruoka, K. Phase-Transfer-Catalyzed Asymmetric α-Arylation of α-Amino Acid Derivatives. *Asian J. Org. Chem.* **2014**, *3*, 433–436. b) Shirakawa, S.; Yamamoto, K.; Maruoka, K. Phase-Transfer-Catalyzed Asymmetric S_NAr Reaction of α-Amino Acid Derivatives with Arene Chromium Complexes. *Angew. Chem. Int. Ed.* **2015**, *54*, 838–840.

12) A selected example of potent access methods to asymmetric synthesis of amino acids having bulky or aryl substituent, see: Zuend, S. J.; Coughlin, M. P.; Lalonde, M. P.; Jacobsen, E. N. Scaleable Catalytic Asymmetric Strecker Syntheses of Unnatural α-Amino Acids. *Nature* **2009**, *461*, 968–971.

13) Agosta, E.; Caligiuri, A.; D'Arrigo, P.; Servi, S.; Tessaro, D.; Canevotti, R. Enzymatic Approach to Both Enantiomers of N-Boc Hydrophobic Amino Acids. *Tetrahedron: Asymmetry* **2006**, *17*, 1995–1999.

14) Felten, A. E.; Zhu, G.; Aron, Z. D. Simplifying Pyridoxal: Practical Methods for Amino Acid Dynamic Kinetic Resolution. *Org. Lett.* **2010**, *12*, 1916–1919.

15) (a) Kamachi, T.; Yoshizawa, K. Enantioselective Alkylation by Binaphthyl Chiral Phase-Transfer Catalysts: A DFT-Based Conformational Analysis. *Org. Lett.* **2014**, *16*, 472–475. (b) Kamachi, T.; Yoshizawa, K. Low-Mode Conformational Search Method with Semiempirical Quantum Mechanical Calculations: Application to Enantioselective Organocatalysis. *J. Chem. Inf. Model.* **2016**, *56*, 347–353.

16) (a) Odagi, M.; Furukori, K.; Yamamoto, Y.; Sato, M.; Iida, K.; Yamanaka, M.; Nagasawa, K. Origin of Stereocontrol in Guanidine-Bisurea Bifunctional Organocatalyst that Promotes α-Hydroxylation of Tetralone-Derived β-Ketoesters: Asymmetric Synthesis of β- and γ-Substituted Tetralone Derivatives via Organocatalytic Oxidative Kinetic Resolution. *J. Am. Chem. Soc.* **2015**, *137*, 1909–1915. (b) Trujillo, C.; Rozas, I.; Botte, A.; Connon, S. J. A DFT Mechanistic Study of the Organocatalytic Asymmetric Reaction of Aldehydes and Homophthalic Anhydride. *Chem. Commun.* **2017**, *53*, 8874–8877. (c) He, C. Q.; Simon, A.; Lam, Y.-H.; Brunskill, A. P. J.; Yasuda, N.; Tan, J.; Hyde, A. M.; Sherer, E. C.; Houk, K. N. Model for the Enantioselectivity of Asymmetric Intramolecular Alkylations by Bis-Quaternized Cinchona Alkaloid-Derived Catalysts. *J. Org. Chem.* **2017**, *82*, 8645–8650.

17) Yang, H.; Wong, M. W. Oxyanion Hole Stabilization by C–H···O Interaction in a Transition State—A Three-Point Interaction Model for *Cinchona* Alkaloid-Catalyzed Asymmetric Methanolysis of *meso*-Cyclic Anhydrides**.** *J. Am. Chem. Soc.* **2013**, *135*, 5808–5818.

Table of Contents