A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: Chiral Bicyclic Imidazole-Catalyzed Acylative Dynamic Kinetic Resolution for the Synthesis of Chiral Phthalidyl Esters

Authors: Muxing Zhou, Tatiana Gridneva, Zhenfeng Zhang, Ende He, Yangang Liu, and Wanbin Zhang

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202012445

Link to VoR: https://doi.org/10.1002/anie.202012445

WILEY-VCH

10.1002/anie.202012445

WILEY-VCH

COMMUNICATION

Chiral Bicyclic Imidazole-Catalyzed Acylative Dynamic Kinetic Resolution for the Synthesis of Chiral Phthalidyl Esters

Muxing Zhou,[a] Tatiana Gridneva,[b] Zhenfeng Zhang,[a] Ende He,[a] Yangang Liu,[a] and Wanbin Zhang*[ab]

[a] M. Zhou, Z. Zhang, E. He, Y. Liu, W. Zhang
Shanghai Key Laboratory for Molecular Engineering of Chiral Drugs, School of Pharmacy
Shanghai Jiao Tong University
800 Dongchuan Road, Shanghai 200240, China
E-mail: wanbin@sjtu.edu.cn
[b] T. Gridneva, W. Zhang
School of Chemistry and Chemical Engineering, Frontiers Science Center for Transformative Molecules
Shanghai Jiao Tong University
800 Dongchuan Road, Shanghai 200240, China

Supporting information for this article is given via a link at the end of the document.

Abstract: Utilizing a chiral bicyclic imidazole organocatalyst and adopting a continuous injection process, an alternative route has been developed for the efficient synthesis of chiral phthalidyl ester prodrugs via dynamic kinetic resolution of 3-hydroxyphthalides by enantioselective acylation (up to 99% ee). The computational studies suggest a general base catalytic mechanism differing from the widely accepted nucleophilic catalytic mechanism. The structure analysis of the key transition states shows that the CH-π interactions and not the previously considered cation/π-π interactions between the catalyst and substrate is the dominant factor giving rise to the observed stereocontrol.

Prodrugs, especially the carrier-linked type, provide possibilities to overcome various barriers in pharmaceutical, pharmacokinetic, and pharmacodynamic phases by changing the physicochemical properties of the parent drugs. Among them, ester-based prodrugs, which are generally formed by acylation of the initial carboxylic acids or alcohols drugs and which can be easily cleaved by enzymatic hydrolysis, have attracted extensive attention (Figure 1).[1] However, due to deficiencies in concept identification and technological developments, a strategy to introduce chirality into the carriers has not gained the attention it should, as it would greatly expand the chemical space and biological activities of prodrugs. As a representative example, the racemic phthalidyl carrier has already been applied in several marketed prodrugs including Talosalate, Talniflumate, Talmetacin, and Talampicilin (Figure 1).[2] It was only recently that Chi and co-workers developed a reaction to access chiral phthalidyl ester prodrugs via an intermolecular acetalization and NHC-catalyzed intramolecular asymmetric acylation sequence (Scheme 1).[3] However, poor regioselectivity using unsymmetrical dialdehydes greatly limits structural diversity and thus further drug development. In addition, the utilization of hard-to-get catalysts and stoichiometric amounts of oxidants further diminishes the practical applicability of this methodology. An alternative route via an intramolecular acetalization and intermolecular asymmetric acylation sequence (that is the acylative dynamic kinetic resolution of 3-hydroxyphthalides as shown in Scheme 1) is envisaged to overcome the above limitations and is therefore worthy of further investigations.

Acylative dynamic kinetic resolution (DKR), combining alcohol racemization and acylative kinetic resolution steps,[4] is one of the most promising but less studied methods for the high-yielding synthesis of chiral esters. In 2010, Qu and co-workers developed an efficient DKR of *meso*-1,2-diol monodichloroacetates based on a DABCO-mediated racemization and modified histidine-catalyzed enantioselective acylation.[5] Later in 2012, inspired by enzyme-catalyzed transformation, Fu and coworkers introduced a Ru-catalyzed racemization of secondary alcohols into the DMAP-catalyzed enantioselective acylation and realized the non-enzymatic DKR of secondary alcohols.[6] In addition to these two developments, other examples utilize the spontaneous equilibrium between aldehyde and hemiacetal/hemiaminal states in the Lewis base-catalyzed acylative DKR for the synthesis of tetrazole-, 5-fluorouracil-, and purine-derived prodrugs.[7] However, in contrast to these successful acylative DKRs of acyclic hemiaminals, the acylative DKR of cyclic hemiacetals such as 3-hydroxyphthalides remains challenging.[8] To overcome these deficiencies, a new and efficient catalytic system with appropriate catalyst-substrate interactions is required.

In the last ten years, our group has developed a new type of easily synthesized Lewis base organocatalysts derived from the bicyclic imidazole skeleton.[9] Recently, carbamyloxy-substituted catalysts were selected as the superior ones in enantioselective phosphorylations for the synthesis of some important ProTide drugs including Remdesivir.[9j] Futhermore, alkyloxy- and acyloxy-substituted catalysts have been successfully applied in several enantioselective *C*-acylation reactions, while the alkyl-substituted catalysts show high catalytic activity and excellent enantioselectivity in the *O*-acylative KR of secondary alcohols.[9c] Considering that the corresponding acylation may proceed via a similar catalytic mechanism and stereocontrol mode involving the π-interactions, we applied the chiral bicyclic imidazole organocatalysts to the acylative DKR of 3-hydroxyphthalides, envisaging that excellent results would be obtained (Scheme 1).

10.1002/anie.202012445

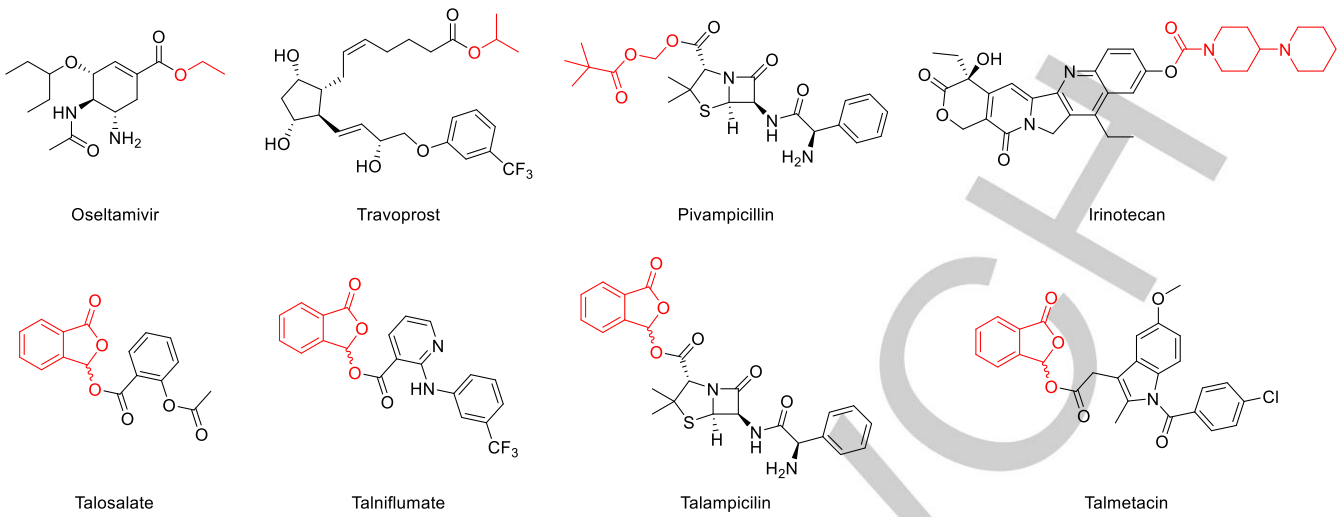
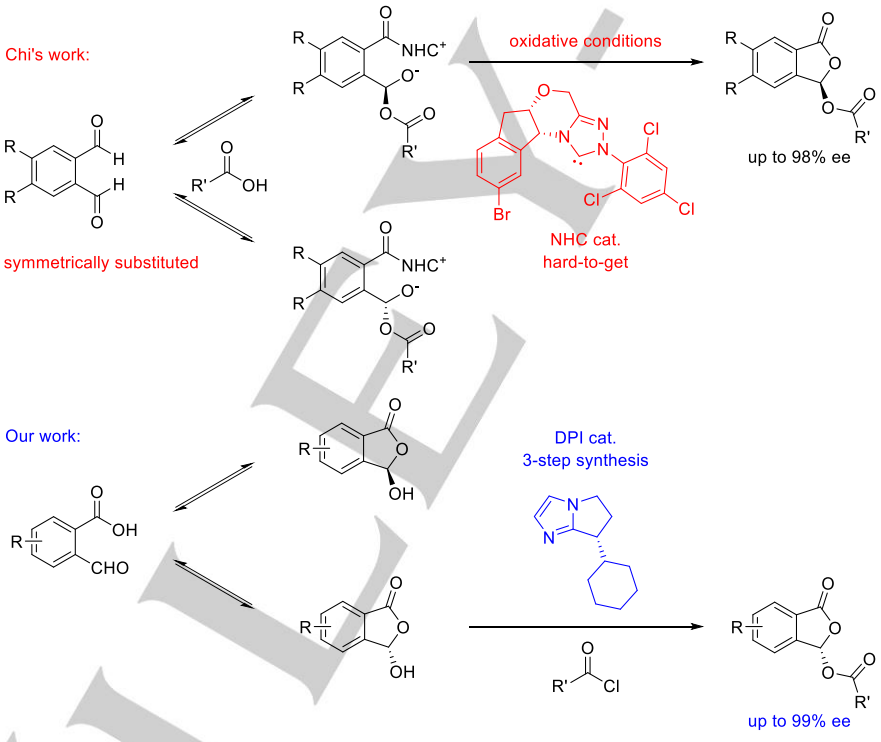


Figure 1. Representative Ester-Based Prodrugs.



Scheme 1. Asymmetric Synthesis of Chiral Phthalidyl Esters.

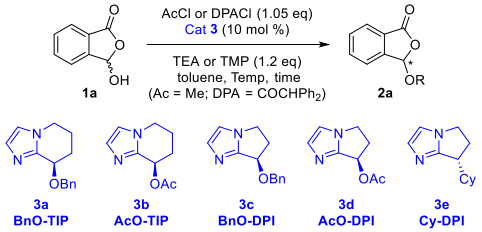
Initially, the alkyloxy- and acyloxy-substituted bicyclic imidazole catalysts **3a-d** were applied in the acylative DKR of 3-hydroxyphthalide (**1a**) under general reaction conditions (Table 1, entries 1-4). Catalysts with five-membered pyrrolidine (**3c**,**d**) provided only slightly better results than that of catalysts bearing a six-membered piperidine (**3a**,**b**), and catalysts with an OAc substituent (**3b**,**d**) gave the desired product with better enantioselectivities than that of catalysts with an OBn substituent (**3a**,**c**). To our delight, the alkyl-substituted catalyst Cy-DPI (**3e**) provided the best results to give the desired product **2a (R = Ac)** in 99% yield and with 69% ee (entry 5). Next, various bases and solvents were screened using **3e** as the catalyst. The sterically bulky secondary amine tetramethylpiperidine (TMP) improved the enantioselectivity to 76% and no better results could be obtained compared with using toluene as the solvent (entry 6 and Table S1 in SI). The influence of different acylating reagents showed that diphenyl acetyl chloride (DPACl) enabled the ee value of the desired product **2a (R = DPA)** to reach 84% (entry 7 and Table S1 in SI). Further studies on the concentration and temperature were conducted (entries 8-9 and Table S2 in SI). Reducing the

10.1002/anie.202012445

WILEY-VCH

reaction concentration from 0.1 M to 0.05 M increased the enantioselectivity from 84% to 87%, while reducing the reaction temperature from room temperature to -80 °C increased the enantioselectivity from 87% to 92% (entries 8-9). Next, a batch feeding mode was employed and the enantioselectivity was surprisingly improved by 2% (entry 10). These results show that the enantioselectivity of the reaction is not only controlled by the asymmetric acylation process, but also by the rate of the substrate racemization. Therefore, in order to improve the **1a**/DPACl ratio and ensure full racemization, a continuous feeding mode was employed and the enantioselectivity was further improved by 2% (entry 11). Increasing the injection rate from 0.2 to 0.3 mL/min did not alter the results but the reaction time to reach completion could be reduced from 15 h to 9 h (entry 12).

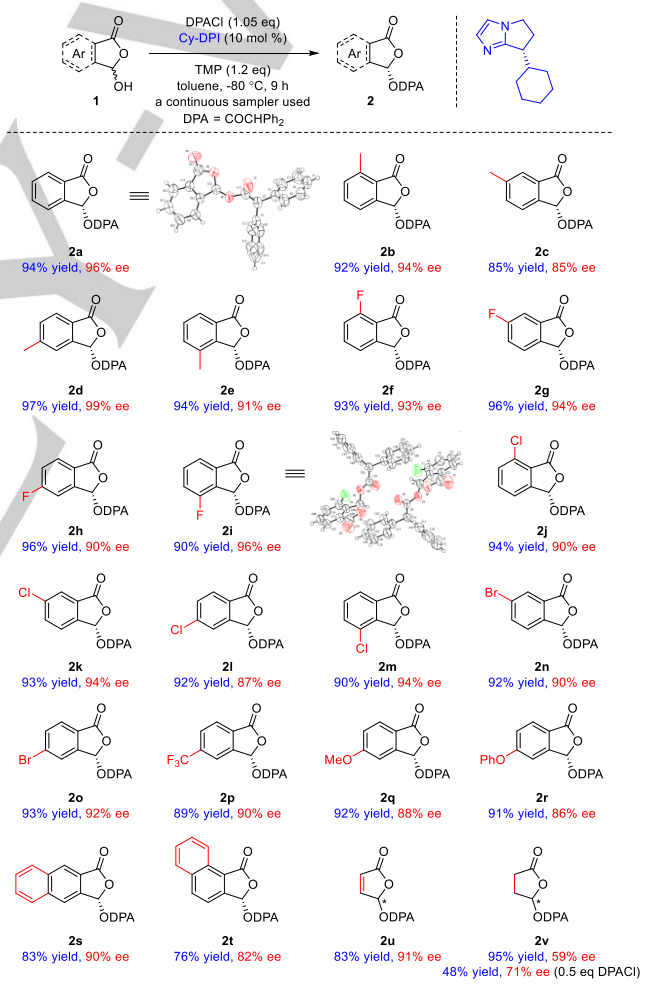
Table 1. Condition Optimization.



Entry[a]	Cat	Base	Tol/mL	R	T/°C	Yield/%[b]	ee/%[c]
1	**3a**	TEA	2	Ac	25	86	30
2	**3b**	TEA	2	Ac	25	88	41
3	**3c**	TEA	2	Ac	25	93	33
4	**3d**	TEA	2	Ac	25	93	42
5	**3e**	TEA	2	Ac	25	99	69
6	**3e**	TMP	2	Ac	25	99	76
7	**3e**	TMP	2	DPA	25	90	84
8	**3e**	TMP	4	DPA	25	87	87
9	**3e**	TMP	4	DPA	-80	84	92
10[d]	**3e**	TMP	4	DPA	-80	86	94
11[e]	**3e**	TMP	4	DPA	-80	99	96
12[f]	**3e**	TMP	4	DPA	-80	99	96

[a] Conditions: **1a** (0.2 mmol), AcCl or DPACl (1.05 eq), **3** (10 mol %), TEA or TMP (1.2 eq), toluene, 6 h, unless otherwise noted. [b] Yields were calculated from ^{1}H-NMR spectra. [c] ee values were determined by HPLC using chiral columns. [d] 12 h, DPACl was added in two batches at 0 and 6 h. [e] 15 h, DPACl in toluene (2 mL) was added via a continuous sampler at 0.2 mL/h. [f] 9 h, DPACl in toluene (2 mL) was added via a continuous sampler at 0.3 mL/h.

The substrate scope was then investigated using the optimized reaction conditions as described in entry 12 of Table 1 (Scheme 2). Substrates bearing a methyl group at the 7-, 6-, 5- or 4-position of the phenyl ring were acylated to the corresponding products **2b-e** with 94%, 85%, 99% and 91% ee respectively. Substrates bearing fluoro and chloro groups at different positions of the phenyl ring were also tested and afforded the desired products **2f-m** with high yields and enantioselectivities. The highest ee was obtained with substrates bearing a substituent at the 4-position but not 6-position. 6-Br- and 5-Br-substituted substrates were converted to the corresponding products **2n** and **2o** with 90% and 92% ee, respectively. Acylation of the substrates with CF_3, OMe, and OPh groups at the 5-position of the phenyl ring gave the desired products **2p-r** in about 90% yield and with 86-90% ee. The performance on the 5-position-substituted substrates shows that the electronic properties have little effect on the reaction results. Substrates possessing naphthyl groups also provided their corresponding products **2s-t** with lower reactivity compared with the above substrates (83% and 76% yield) and with distinctly different enantioselectivities from each other (90% and 82% ee). To our delight, the ee of product **2u** bearing an alkenyl skeleton instead of an arene was only slightly reduced to 91% from 96%. Further changing the carbon-carbon double bond to a single bond reduced the ee of product **2v** to 59%. When 0.5 equivalents of diphenyl acetyl chloride were applied, the enantioselectivity increased to 71%, indicating that the dynamic equilibrium between the two isomers of this substrate is not fast enough.

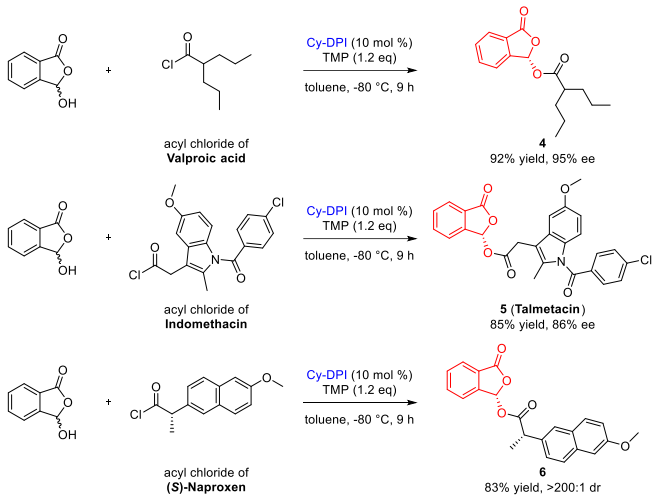


Scheme 2. Substrate Scope (the absolute configurations of **2a** and **2i** were assigned to (*S*) by X-ray single crystal diffraction and others except **2u** and **2v** are thought to be the same as **2a** and **2i**).

To investigate the generality of the reaction, the prodrugs of some important carboxylic acid drugs were synthesized (Scheme 3). Using our catalytic system and under the optimized reaction conditions, Valproic acid, Indomethacin and (*S*)-Naproxen were

10.1002/anie.202012445

converted to the corresponding chiral phthalidyl ester prodrugs with excellent stereoselectivity. In particular, the target compound **6** was synthesized with >200:1 dr.



Scheme 3. Practical Applications in the Synthesis of Prodrugs.

In order to elucidate the mechanism of stereoselection, computational studies of two mechanisms wherein (*S*)-Cy-DPI acts as a nucleophilic catalyst or a general base catalyst were performed (Figures 2-3, and Figure S1 in SI). The nucleophilic catalytic mechanism is considered to be favoured according to previous research on similar asymmetric acylations.[4d,g,10] We have computed numerous conformational modifications for both possibilities, and selected the lowest energy pathway in each case. In our hands both mechanisms were computed to be very similar energetically. However, only the general base catalytic mechanism coincides with the experimentally observed handedness of the product, whereas nucleophilic catalytic mechanism, forecasts formation of the product with an opposite configuration (Figure S1 in SI).

The general base catalytic mechanism starts from the formation of substrate-catalyst complexes **7*R*** and **7*S*** stabilized by H-bond and CH-π interactions. The acylating reagent is introduced to form the substrate-catalyst-reagent complexes **8*R*** and **8*S***. Through the corresponding transition states **TS*R*** and **TS*S*** with energies of 7.8 and 9.3 kcal/mol, the catalytically assisted acylation affords product-catalyst complexes **9*R*** and **9*S*** as the HCl salt form. Elimination of HCl with TMP recovers the catalyst and yields the product **2a** (Figure 2).

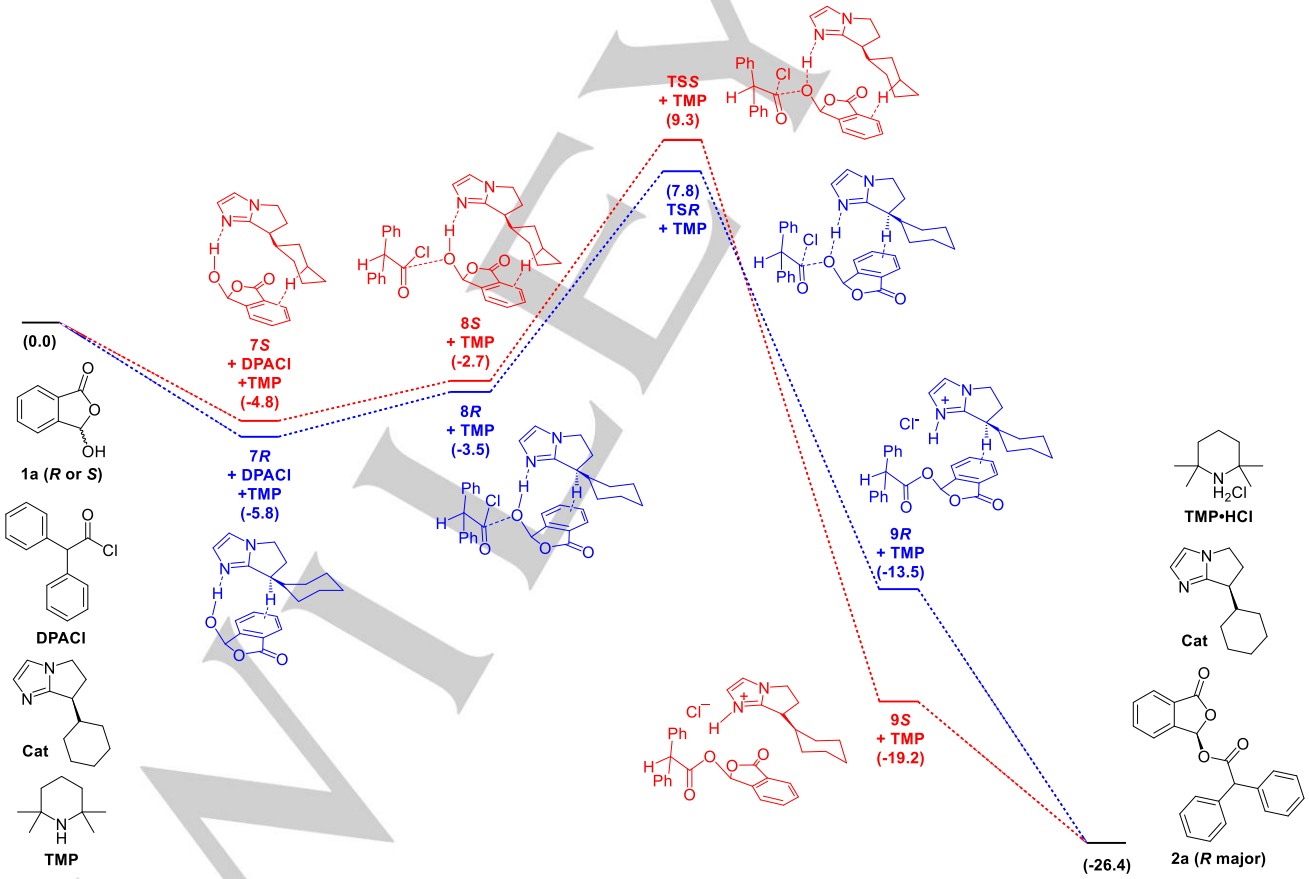


Figure 2. Free Energy Profile (ΔG_{298}) of General Base Catalytic Mechanism Calculated at ωB97XD/6-31G(d,p) Level of Theory.

Optimized structures of **TS*R*** and **TS*S*** are shown in Figure 3. **TS*R*** is 1.5 kcal/mol more stable than **TS*S***, which is in good agreement with the experimentally observed high enantioselectivity. Figure 3a shows that both are 4-membered transition states with

10.1002/anie.202012445

simultaneous movement of four atoms (O-C-Cl-H). Figure 3b shows the most significant structural differences accounting for the relative stability of **TS*R***. In this transition state two different protons of the catalyst form two CH-π interactions with the phenyl rings of **1a** and DPACl, thus maintaining the three-molecule framework essential for the reaction to proceed. Two CH-π interactions of the phenyl rings of **1a** and DPACl are also possible in the structure of **TS*S*.** However, to form the 4-membered transition state, a significantly different conformation must be stabilized. In this case**,** the CH-π interactions in **TS*S*** are notably longer (especially that with the phenyl ring of **1a**), resulting in the greater stability of **TS*R***.

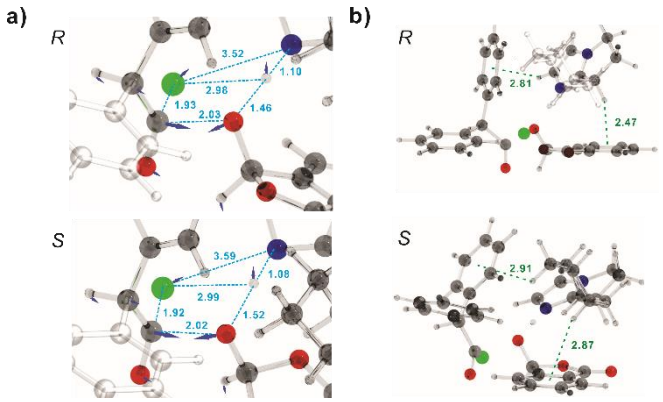


Figure 3. Optimized Structures of **TS*R*** (up; 7.8 kcal/mol) and **TS*S*** (bottom; 9.3 kcal/mol). a) Interatomic distances (Å), light blue dashed lines and displacement vectors (blue arrows) in the corresponding transition states. b) Complete optimized structures of the transition states with the CH-π interactions shown as green dashed lines and the distances (Å) between a proton and the center of the corresponding phenyl ring as green numbers. Carbon: grey, hydrogen: white, oxygen: red, nitrogen: blue, chlorine: green.

In conclusion, the acylative dynamic kinetic resolution of 3-hydroxyphthalides has been efficiently implemented and successfully applied in the synthesis of several chiral phthalidyl ester prodrugs. Utilizing a chiral bicyclic imidazole organocatalyst Cy-DPI and adopting a continuous injection process, a wide range of phthalidyl esters were synthesized with high yields and excellent enantioselectivities (up to 99% ee). Computational studies suggest a general base catalytic mechanism and a CH-π interaction-dominated stereocontrol mode.

Acknowledgements

This work was partially supported by National Natural Science Foundation of China (Nos. 91856106, 21620102003 and 21991112) and National Key R&D Program of China (No. 2018YFE0126800). We thank the Instrumental Analysis Center of Shanghai Jiao Tong University.

Keywords: organocatalyst • bicyclic imidazole • dynamic kinetic resolution • enantioselective acylation • phthalidyl ester prodrugs

[1] V. Abet, F. Filace, J. Recio, J. Alvarez-Builla, C. Burgos, *Eur. J. Med. Chem.* **2017**, *127*, 810.

[2] a) Q. Dang, B. S. Brown, P. D. van Poelje, T. J. Colby, M. D. Erion, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1505; b) R. G. Matheny, *US20130122108*, **2013**; c) D. Camp, A. Garavelas, M. Campitelli, *J. Nat. Prod.* **2015**, *78*, 1370.

[3] Y. Liu, Q. Chen, C. Mou, L. Pan, X. Duan, X. Chen, H. Chen, Y. Zhao, Y. Lu, Z. Jin, Y. R. Chi, *Nat. Commun.* **2019**, *10*, 1675.

[4] Examples for kinetic resolution of alcohols: a) J. C. Ruble, H. A. Latham, G. C. Fu, *J. Am. Chem. Soc.* **1997**, *119*, 1492; b) G. T. Copeland, S. J. Miller, *J. Am. Chem. Soc.* **2001**, *123*, 6496; c) E. Vedejs, M. Jure, *Angew. Chem. Int. Ed.* **2005**, *44*, 3974; *Angew. Chem.* **2005**, *117*, 4040; d) X. Li, P. Liu, K. N. Houk, V. B. Birman, *J. Am. Chem. Soc.* **2008**, *130*, 13836; e) B. Hu, M. Meng, Z. Wang, W. Du, J. S. Fossey, X. Hu, W.-P. Deng, *J. Am. Chem. Soc.* **2010**, *132*, 17041; f) B. Hu, M. Meng, J. S. Fossey, W. Mo, X. Hu, W.-P. Deng, *Chem. Commun.* **2011**, *47*, 10632; g) E. Larionov, M. Mahesh, A. C. Spivey, Y. Wei, H. Zipse, *J. Am. Chem. Soc.* **2012**, *134*, 9390; h) G. Ma, J. Deng, M. P. Sibi, *Angew. Chem. Int. Ed.* **2014**, *53*, 11818; *Angew. Chem.* **2014**, *126*, 12012; i) T. Yamanaka, A. Kondoh, M. Terada, *J. Am. Chem. Soc.* **2015**, *137*, 1048; j) N. Mittal, K. M. Lippert, C. K. De, E. G. Klauber, T. J. Emge, P. R. Schreiner, D. Seidel, *J. Am. Chem. Soc.* **2015**, *137*, 5748; k) M. D. Greenhalgh, S. M. Smith, D. M. Walden, J. E. Taylor, Z. Brice, E. R. T. Robinson, C. Fallan, D. B. Cordes, A. M. Z. Slawin, H. C. Richardson, M. A. Grove, P. H.-Y. Cheong, A. D. Smith, *Angew. Chem. Int. Ed.* **2018**, *57*, 3200; *Angew. Chem.* **2018**, *130*, 3254; l) X. Dong, Y. Kita, M. Oestreich, *Angew. Chem. Int. Ed.* **2018**, *57*, 10728; *Angew. Chem.* **2018**, *130*, 10888.

[5] J.-L. Cao, J. Qu, *J. Org. Chem.* **2010**, *75*, 3663.

[6] a) S. Y. Lee, J. M. Murphy, A. Ukai, G. C. Fu, *J. Am. Chem. Soc.* **2012**, *134*, 15149; b) A. E. Díaz-Álvarez, L. Mesas-Sánchez, P. Dinér, *Angew. Chem. Int. Ed.* **2013**, *52*, 502-504; *Angew. Chem.* **2013**, *125*, 522; c) S. Agrawal, E. Martínez-Castro, R. Marcos, B. Martín-Matute, *Org. Lett.* **2014**, *16*, 2256.

[7] a) A. Ortiz, T. Benkovics, G. L. Beutner, Z. Shi, M. Bultman, J. Nye, C. Sfouggatakis, D. R. Kronenthal, *Angew. Chem. Int. Ed.* **2015**, *54*, 7185; *Angew. Chem.* **2015**, *127*, 7291; b) D. W. Piotrowski, A. S. Kamlet, A.-M. R. Dechert-Schmitt, J. Yan, T. A. Brandt, J. Xiao, L. Wei, M. T. Barrila, *J. Am. Chem. Soc.* **2016**, *138*, 4818; c) A. Kinens, M. Sejejs, A. S. Kamlet, D. W. Piotrowski, E. Vedejs, E. Suna, *J. Org. Chem.* **2017**, *82*, 869; d) M.-S. Xie, Y.-G. Chen, X.-X. Wu, G.-R. Qu, H.-M. Guo, *Org. Lett.* **2018**, *20*, 1212.

[8] Low enantioselectivities were obtained by using chiral DMAP and cinchonine organocatalysts: a) S. Yamada, K. Yamashita, *Tetrahedron Lett.* **2008**, *49*, 32; b) D. Niedek, S. M. M. Schuler, C. Eschman, R. C. Wende, A. Seitz, F. Keul, P. R. Schreiner, *Synthesis* **2017**, *49*, 371.

[9] a) Z. Zhang, F. Xie, J. Jia, W. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 15939; b) S. Liu, Z. Zhang, F. Xie, N. A. Butt, L. Sun, W. Zhang, *Tetrahedron: Asymmetry* **2012**, *23*, 329; c) Z. Zhang, M. Wang, F. Xie, H. Sun, W. Zhang, *Adv. Synth. Catal.* **2014**, *356*, 3164; d) M. Wang, Z. Zhang, S. Liu, F. Xie, W. Zhang, *Chem. Commun.* **2014**, *50*, 1227; e) M. Wang, Z. Zhang, F. Xie, W. Zhang, *Chem. Commun.* **2014**, *50*, 3163; f) M. Wang, X. Zhang, Z. Ling, Z. Zhang, W. Zhang, *Chem. Commun.* **2017**, *53*, 1381; g) L. Zhang, M. Wang, M. Zhou, Z. Zhang, M. Muraoka, W. Zhang, *Asian J. Org. Chem.* **2019**, *8*, 1024; h) M. Zhou, E. He, L. Zhang, J. Chen, Z. Zhang, Y. Liu, W. Zhang, *Org. Chem. Front.* **2019**, *6*, 3969; i) M. Wang, M. Zhou, L. Zhang, Z. Zhang, W. Zhang, *Chem. Sci.* **2020**, *11*, 4801; j) M. Wang, L. Zhang, X. Huo, Z. Zhang, Q. Yuan, P. Li, J. Chen, Y. Zou, Z. Wu, W. Zhang, *Angew. Chem. Int. Ed.* **2020**, doi: 10.1002/anie.202011527; *Angew. Chem.* **2020**, doi: 10.1002/ange.202011527. Also utilized by other groups for the synthesis of phosphonate prodrugs: k) D. A. DiRocco, Y. Ji, E. C. Sherer, A. Klapars, M. Reibarkh, J. Dropinski, R. Mathew, P. Maligres, A. M. Hyde, J. Limanto, A. Brunskill, R. T. Ruck, L.-C. Campeau, I. W. Davies, *Science* **2017**, *356*, 426; l) D. A. Glazier, J. M. Schroeder, S. A. Blaszczyk, W. Tang, *Adv. Synth. Catal.* **2019**, *361*, 3729.

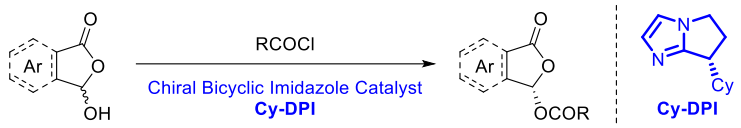
[10] Q. Deng, F. Mu, Y. Qiao, D. Wei, *Org. Biomol. Chem.* **2020**, *18*, 6781.

10.1002/anie.202012445

WILEY-VCH

COMMUNICATION

Entry for the Table of Contents



- Dynamic kinetic resolution
- Continuous injection process adopted
- General base catalytic mechanism
- Excellent enantioselectivities obtained (up to 99% ee)
- CH-π interaction-dominated stereocontrol
- Chiral phthalidyl ester prodrugs synthesized

Utilizing a chiral bicyclic imidazole organocatalyst and adopting a continuous injection process, the acylative dynamic kinetic resolution of 3-hydroxyphthalides has been implemented for the synthesis of a wide range of phthalidyl esters in high yields and with excellent enantioselectivities (up to 99% ee). Computational studies suggest a general base catalytic mechanism and a CH-π interaction-dominated stereocontrol mode.