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ArPNO-Catalyzed Acylative Dynamic Kinetic Resolution of 3-Hydroxyphthalides: Access to Enantioenriched Phthalidyl Esters

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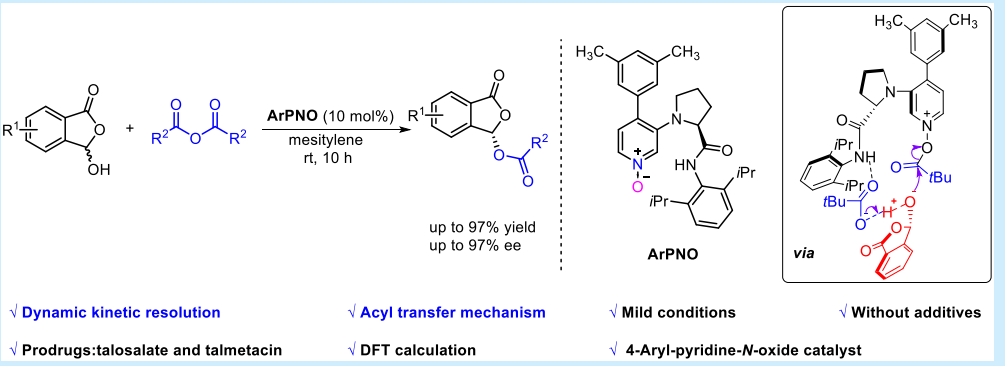

ABSTRACT: A chiral 4-aryl-pyridine-*N*-oxide nucleophilic organocatalyst was used to synthesize chiral phthalidyl ester prodrugs by the acylative dynamic kinetic resolution process. By using the 3,5-dimethylphenyl-derived ArPNO catalyst, the phthalidyl esters were obtained in up to 97% yield with 97% ee at room temperature. Two phthalidyl esters of prodrugs, talosalate and talmetacin, were generated. By control experiments and density functional theory calculations, an acyl transfer mechanism was proposed.

Phthalides are the major structures present in biologically active molecules and various natural products.[1] Phthalidyl ester drugs are widely used in clinical applications, which play specific roles in pain, anti-inflammatory, and other aspects.[2] Among these drugs, talosalate is a new phthalidyl ester with anti-inflammatory and analgesic properties.[3] All of the above phthalates contain unstable acetal structures with a chiral center, and formation of the corresponding enantiomeric structures is difficult. Therefore, constructing an enantioenriched phthalidyl ester is challenging.[4] The synthesis of chiral phenol ester prodrugs has significant implications for the future biomedical field and methodology.

Acylative dynamic kinetic resolution (DKR)[5] is an effective method for constructing chiral phthalidyl ester derivatives.[6−10] In 2008, Yamada and co-workers pioneered the synthesis of optical phthalidyl esters by an acylative DKR reaction with chiral DMAP catalysts using hemiaminal and acid anhydrides, albeit with moderate enantioselectivities.[6] In 2019, Chi and co-workers developed a carbene-catalyzed acylative DKR reaction for rapid access to optically enriched phthalidyl esters.[7] The stereoselective control of the conversion of carboxylic acid into phthalidyl ester via hemiacetal was successfully achieved (Scheme 1a). Then, Chi's group successfully conducted the asymmetric acylation of hydroxyphthalide to afford enantioenriched phthalidyl esters using carbene as the catalyst and quinone as the oxidant (Scheme 1b).[8] In 2021, Zhang and co-workers synthesized phthalidyl esters in up to 97% yield with 99% ee using a chiral bicyclic imidazole organocatalyst at −80 °C by the acylative DKR process. Significantly, this reaction follows a type of a base-catalyzed mechanism (Scheme 1c).[9] The DKR studies of phthalidyl esters were realized by the groups of Chi and Zhang using carbene and bicyclic imidazole catalysts, respectively. Although these methods exhibited excellent enantioselectivities, developing mild and effective methods to synthesize chiral phthalidyl ester drugs is imperative.

The acylative DKR reaction is widely used to synthesize chiral secondary alcohols.[11] In 2012, Fu and co-workers first reported the DMAP-catalyzed enantioselective acylative DKR of secondary alcohols.[12] Later, the Piotrowski and Kamlet group synthesized azole hemiaminal esters by the DKR reaction using chiral DMAP as the catalyst.[13] Zhang's group developed a chiral bicyclic imidazole catalyst, which was used for the acyl transfer reaction to synthesize some chiral prodrugs.[14] Recently, chiral DMAP-*N*-oxides[15,16] and 4-aryl-pyridine-*N*-oxides (ArPNO) were developed as acyl transfer

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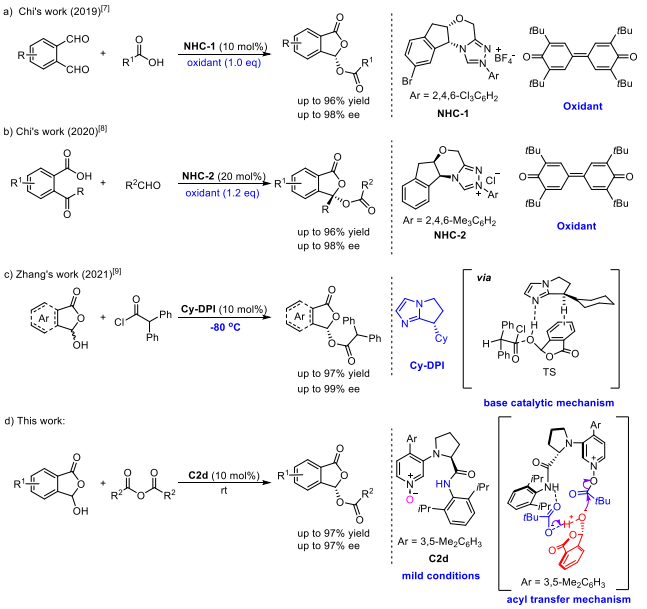
Scheme 1. Strategies for the Construction of Chiral Phthalidyl Esters

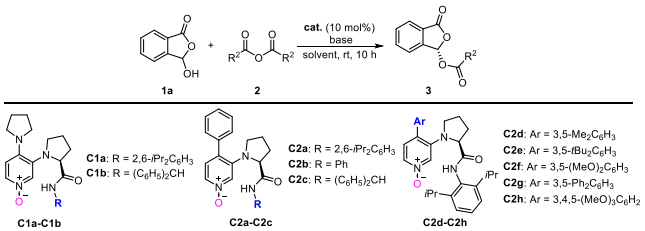


catalysts.[17] Therefore, an alternative nucleophilic catalytic mechanism was discovered by an acylative DKR reaction to obtain chiral phthalidyl ester prodrugs using chiral ArPNO catalysts at room temperature (Scheme 1d). Compared with Zhang's work[9] using acyl chlorides as electrophiles at −80 °C through a base-catalyzed mechanism, our work could use anhydrides or acyl chlorides as electrophiles at room temperature through an acyl transfer mechanism, which was a good complement to Zhang's work.

Initially, the DKR reaction of 3-hydroxyphthalide **1a** with acid anhydride **2a** was selected as the model reaction (Table 1). By using chiral DMAP-*N*-oxides **C1a** and **C1b** as the catalysts, product **3aa** was obtained in 22% and 14% ee, respectively (entries 1 and 2). Comparatively, in the presence of chiral ArPNO **C2a**, adduct **3aa** was obtained in 94% yield with 83% ee (entry 3). Subsequently, several chiral ArPNO compounds **C2b−h** were evaluated. In the case of chiral ArPNO **C2a**, containing two bulky isopropyl groups at the *ortho* positions of the aniline moiety, better results were obtained (entry 3 vs entries 4 and 5). Then, ArPNO derivatives **C2d−h** with different aryl groups at the C4 position of pyridine were investigated (entries 6−10). When 3,5-dimethyl-substituted catalyst **C2d** was used, product **3aa** was obtained with better enantioselectivity with 85% (entry 6). Next, different bases and solvents were screened. Varying the bases did not lead to improved results (entries 11−15). In the absence of a base, when mesitylene was used as the solvent, adduct **3aa** was obtained in 95% yield with 89% ee (entry 16). Furthermore, several acid anhydrides were screened, and pivalic anhydride was found to be the best one, affording **3ac** in 95% yield with 94% ee (entry 18). By increasing the amount of substrate **2c** to 4.0 equiv, the enantioselectivity was improved to 97% ee (entry 20). It is worth noting that the enantioselectivity of the product **3ac** was decreased to 95% when the amount of catalyst reduced to 5 mol % (entry 21).

With the optimal reaction conditions (Table 1, entry 20), the scope of phthalide derivatives was explored (Scheme 2). When pivaloyl chloride was used as the substrate, product **3ac**

Table 1. Screening of the Reaction Conditions[a]



entry	cat.	R^2	2	solvent	base	yield (%)[b]	ee (%)[c]
1	**C1a**	Me	**2a**	CH_2Cl_2	Et_3N	87	22
2	**C1b**	Me	**2a**	CH_2Cl_2	Et_3N	96	14
3	**C2a**	Me	**2a**	CH_2Cl_2	Et_3N	94	83
4	**C2b**	Me	**2a**	CH_2Cl_2	Et_3N	86	75
5	**C2c**	Me	**2a**	CH_2Cl_2	Et_3N	95	81
6	**C2d**	Me	**2a**	CH_2Cl_2	Et_3N	95	85
7	**C2e**	Me	**2a**	CH_2Cl_2	Et_3N	91	83
8	**C2f**	Me	**2a**	CH_2Cl_2	Et_3N	83	67
9	**C2g**	Me	**2a**	CH_2Cl_2	Et_3N	84	68
10	**C2h**	Me	**2a**	CH_2Cl_2	Et_3N	89	69
11	**C2d**	Me	**2a**	THF	Et_3N	95	4
12	**C2d**	Me	**2a**	toluene	Et_3N	97	86
13	**C2d**	Me	**2a**	mesitylene	Et_3N	97	87
14	**C2d**	Me	**2a**	mesitylene	DIPEA	95	77
15	**C2d**	Me	**2a**	mesitylene	K_2CO_3	89	57
16	**C2d**	Me	**2a**	mesitylene	no	95	89
17	**C2d**	Et	**2b**	mesitylene	no	92	88
18	**C2d**	*t*Bu	**2c**	mesitylene	no	95	94
19	**C2d**	*i*Pr	**2d**	mesitylene	no	91	92
20[d]	**C2d**	*t*Bu	**2c**	mesitylene	no	96	97
21[de]	**C2d**	*t*Bu	**2c**	mesitylene	no	95	95

[a]Unless otherwise noted, the reaction conditions are as follows: **1a** (0.05 mmol), **2** (2.0 equiv), catalyst (10 mol %), and base (1.0 equiv) in solvent (1.0 mL) at room temperature. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]**2c** (4.0 equiv). [e]**C2d** (5 mol %).

was obtained in 91% yield with 95% ee. Substrates bearing fluoro and chloro groups at the 5- or 6-position of the phenyl ring were acylated, affording corresponding products **3bc−3ec** with 92−94% ee. Additionally, the desired products **3fc−3hc** with the bromide group at different positions were obtained in high yields and enantioselectivies. 5-Iodide-substituted reactant **1i** also was used as a suitable reactant to afford product **3ic**. When a substrate bearing a methoxy group at the 6- or 4-position of the phenyl ring was employed, desired products **3jc** and **3kc** were obtained in 84% and 90% yields with 88% and 95% ee, respectively. The substrate with an ester group at position 6 of the phenyl ring was acylated to obtain product **3lc** in 93% yield with 94% ee. Furthermore, when two strong electron-withdrawing-group-substituted reactants **1m** and **1n** were used, **3mc** and **3nc** were obtained in 97% and 89% yields, respectively, with corresponding ee values of 93% and 95%. Notably, the ee of product **3oc** containing an alkenyl framework instead of an aryl group was maintained at 97%. When diphenyl acetyl chloride (DPACl) was used to replace pivalic anhydride for the reaction, the corresponding adduct **3af** was obtained in 91% yield and 92% ee. Under the optimized conditions, the gram scale of product **3ac** was conducted with 88% yield (1.02 g) and 91% ee. Single-crystal X-ray diffraction analysis revealed that the absolute configuration of the desired product **3ac** was the *S*-configuration.

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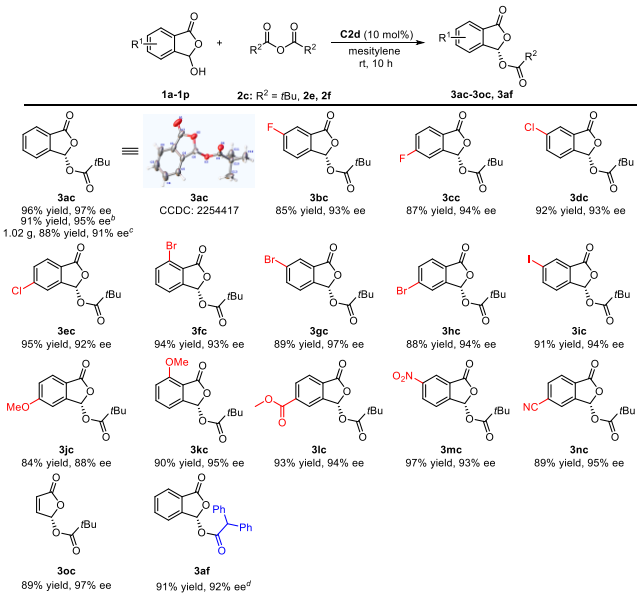
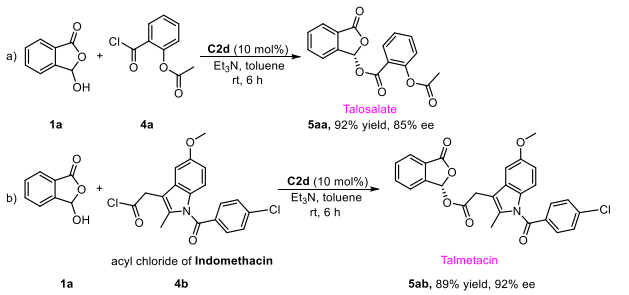
Scheme 2. Substrate Scope[a]



[a]Unless otherwise noted, the reaction conditions are as follows: **1** (0.1 mmol), **2c** (4.0 equiv), **C2d** (10 mol %) in mesitylene (2.0 mL) at rt. Isolated yields are reported. The ee values were determined by chiral HPLC analysis. [b]**2e** (pivaloyl chloride) (2.0 equiv), **C2d** (10 mol %), Et_3N (1.0 equiv) in toluene (2.0 mL) at rt for 6 h. [c]**1a** (4.4 mmol). [d]**2f** (DPACl = $Ph_2CHCOCl$) (2.0 equiv), **C2d** (10 mol %), Et_3N (1.0 equiv) in toluene (2.0 mL) at rt for 6 h.

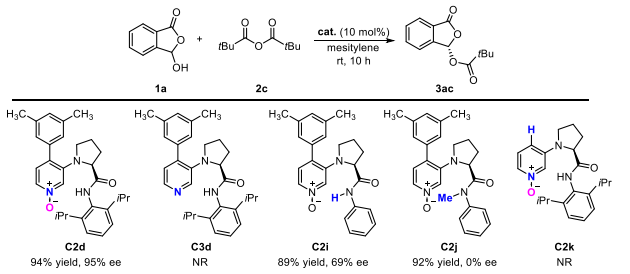
Due to the easier availability of acyl chloride compared to anhydride, we attempted to use acyl chloride for the synthesis of prodrugs. The prodrug molecules talosalate and talmetacin were obtained in 85% and 92% ee, respectively (Scheme 3). Although an excellent enantioselectivity (88% ee) for talmetacin was obtained in Zhang's work,[9] our method has higher enantioselectivity (92% ee) under mild conditions.

Scheme 3. Synthesis of Prodrugs



Several control experiments were performed (Scheme 4). When 4-aryl-pyridine **C3d**, a reduced product of ArPNO **C2d**, was used, the reaction did not occur, indicating that the *N*-oxide group was essential for the reaction. The importance of the N−H proton of the amide was investigated using chiral ArPNO **C2i** and its N−Me derivative **C2j**. When **C2j** was used, product **3ac** was obtained in 0% ee, suggesting that the N−H proton of the amide framework was critical for the enantioselectivity of the reaction. The target product was not obtained by using the 4-*H*-pyridine-*N*-oxide **C2k** catalyst, indicating that the aryl group at the C-4 position was necessary.

Scheme 4. Control Experiments



Density functional theory (DFT) calculations were performed to investigate our proposed reaction mechanism and obtain a theoretical explanation for the observed high stereoselectivity. As shown in Figure 1, a quadrant model was

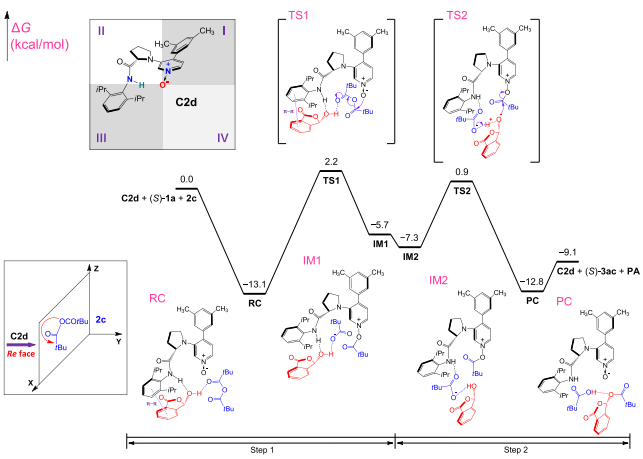


Figure 1. Relative energy profiles (in kcal/mol) of **C2d** nucleophilic attack along the *Re* face of the **2c** plane obtained.

used to explore the active center of catalyst **C2d**, where the oxygen atom was used as the coordinate origin. As the activity and stereoselectivity of the N−H proton on the amide play key roles in the reaction, the substrates were placed in the second and third quadrants. Moreover, as the 2,6-diisopropylphenyl group was present in the third quadrant, the reactant was permitted to approach only the second quadrant.

The DKR reaction mechanism was divided into two steps: Nucleophilic attack of catalyst **C2d** with pivalic anhydride **2c** generated the acyloxypridinium cation (step 1), followed by nucleophilic substitution of (*S*)-**1a** with the acyloxypridinium cation (step 2). Step 1 commences via hydrogen bonding (H-bond) between (*S*)-**1a**, catalyst **C2d**, and pivalic anhydride **2c**, and the $\pi-\pi$ interaction between the 2,6-diisopropylphenyl group on catalyst **C2d** and the phenyl ring on substrate (*S*)-**1a** afforded complex **RC**. Then, with the oxygen atom of the *N*-oxide acting as the nucleophilic center, the nucleophilic addition of catalyst **C2d** occurred along the *Re* face of pivalic anhydride **2c**. The activation free energy was calculated to be 15.3 kcal/mol via transition state **TS1**. At the same time, the C−O single bond of pivalic anhydride **2c** was cleaved to generate the pivalate anion, which was captured by the H-bond from (*S*)-**1a**. In intermediate **IM1**, the *o*-acylated pyridinium cation was formed and (*S*)-**1a** was linked together with the amide N−H bond and the pivalate anion via H-bonds. In step 2, the less hindered intermediate **IM2** was formed with the concomitant destruction of the H-bond between the amide

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N−H on **C2d** and (*S*)-**1a**, as well as the creation of an H-bond between the amide N−H on **C2d** and the pivalate anion. Subsequently, intermediate **IM2** could undergo acyl transfer via **TS2** with an energy barrier of 14.0 kcal/mol, generating pivalic acid (**PA**) as the product and eventually product (*S*)-**3ac**.

To further analyze the stereoselectivity of the reaction, the stereoselectivity of enantio-determining transition states **TS2** was further investigated. As shown in Figure 2a,b, the relative

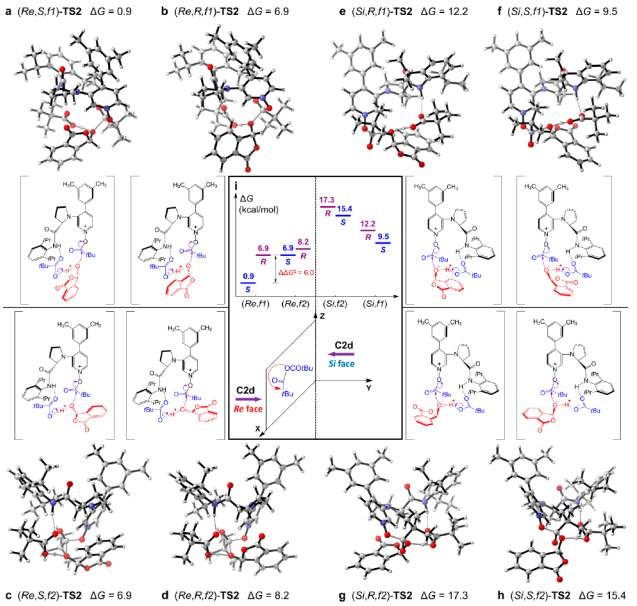

Figure 2. DFT-computed relative free energies (Δ*G*, kcal/mol) of enantio-determining transition states (direction,chirality,conformer)-TS2 at the M06-2X-D3/6-31G(d,p)/SMD(mesitylene) level of theory.

free energy of (*Re,S,f1*)-**TS2** was 6.0 kcal/mol ($\Delta\Delta G^{\ddagger}$) less than that of (*Re,R,f1*)-**TS2**. The conformers with (*S*)-**3ac** are more stable than the conformers with (*R*)-**3ac**. The experimental results also confirmed that (*S*)-**3ac** was a major product. Other conformers of **TS2** were also determined by theoretical calculations, as shown in Figure 2c,d. (*Re,S,f1*)-**TS2** was 6.0 kcal/mol less favorable than (*Re,S,f2*)-**TS2**, and similarly, (*Re,R,f1*)-**TS2** was 1.3 kcal/mol less favorable than (*Re,R,f2*)-**TS2**.

When catalyst **C2d** attacked pivalic anhydride **2c** from the *Si* face (Figure 2e,f), the relative free energy value of (*Si,S,f1*)-**TS2** was 2.7 kcal/mol less than that of (*Si,R,f1*)-**TS2**, indicating that (*S*)-**3ac** was the main compound. Also, the relative free energy values of (*Si,R,f2*)-**TS2** and (*Si,S,f2*)-**TS2** were higher than those of (*Si,R,f1*)-**TS2** and (*Si,S,f1*)-**TS2**, respectively (Figure 2g,h). Moreover, the relative free energy values of (*Si,R,f1*)-**TS2** and (*Si,S,f1*)-**TS2** were significantly higher than those of (*Re,R,f1*)-**TS2** and (*Re,S,f1*)-**TS2**, respectively. The above theoretical chemical study showed that comparing the attack of the *Re* and *Si* faces was crucial for understanding the accurate reaction pathway. The results showed that (*Re,S,f1*)-**TS2** exhibited the lowest relative free energy, which was consistent with the experimental results, in that (*S*)-**3ac** was the dominant enantiomer.

Based on previous studies,[6−10] a possible mechanism of acylated DKR was proposed in Figure 3. First, the ring opening of phthalide occurred, affording *o*-carboxybenzaldehyde.

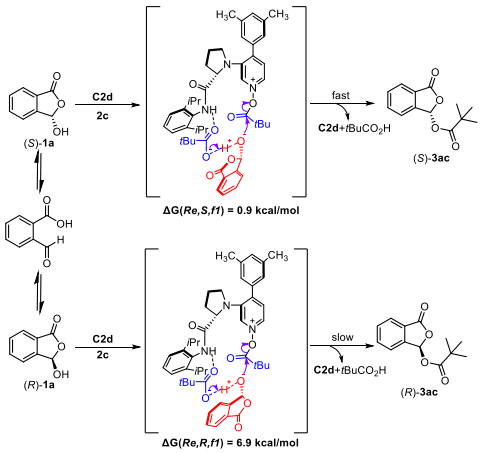

Figure 3. Proposed reaction mechanism.

Second, *o*-carboxybenzaldehyde underwent intramolecular acylation to obtain two substrates with different configurations. At the same time, ArPNO **C2d** and pivalic anhydride **2c** underwent nucleophilic attack to form an acyloxypyridinium cation. (*S*)-**1a** underwent a nucleophilic substitution reaction via a lower relative free-energy transition state, generating the main product (*S*)-**3ac** while simultaneously releasing catalyst **C2d**. For (*R*)-**1a**, owing to the inability to effectively generate van der Waals forces with the pivalic acid anion, the corresponding transition state exhibited a higher relative free energy, thereby slowly producing (*R*)-**3ac**. Therefore, unreacted (*R*)-**3ac** in turn was converted to *o*-carboxybenzaldehyde, leading to in situ racemization.

In conclusion, an acylative DKR for racemic 3-hydroxyphthalates using a chiral ArPNO nucleophilic organocatalyst was reported for the synthesis of chiral phthalates under mild conditions without additives. By using ArPNO **C2d** as the catalyst, various chiral phthalates were synthesized in 84−97% yields and 85−97% ee. The developed method was used to prepare the phthalate prodrugs talosalate and talmetacin. Our developed reaction applied anhydrides or acyl chlorides at room temperature through an acyl transfer mechanism. This was a good complement to Zhang's work,[9] which utilized acyl chlorides as electrophiles at −80 °C through a base-catalyzed mechanism.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c01915.

Experimental details, characterization data, mechanistic studies, DFT calculations, and NMR spectra (PDF)

Accession Codes

CCDC 2254417 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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