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Solanaceous plant species, such as *Atropa belladonna* L., *Datura stramonium* L., and *Hyoscyamus niger* L. can produce hyoscyamine ((S)-1), a potent parasympathetic blocker belonging to the tropane alkaloid family. The achiral tropine (2) and chiral (S)-tropic acid ((S)-3) are the two major subcomponents of (S)-1. Although (S)-1 exhibits a potent activity, its enantiomer, (R)-1 is significantly less active. Consequently, the chirality of the tropic acid moiety plays a critical role in the parasympathetic blocking activity (Scheme 1).^{1,2}

The saponification of (S)-1 is the most straightforward method to synthesize the enantioenriched (S)-3. However, the chiral center of (S)-1 is easily racemized under alkaline conditions to yield atropine ((RS)-1) with equimolar amounts of (S)-1 and (R)-1. Thereafter, hydrolysis proceeds slowly to yield the racemic tropic acid ((RS)-3) (Scheme 1).³ This process was proposed by Kitagawa *et al.* after carefully monitoring the reaction by ¹H-NMR.⁴

Hanefeld *et al.* reported the excellent enzymatic kinetic resolution (KR) of racemic tropic acid esters.⁵ Initially, they attempted the enzymatic hydrolysis of the racemic 3-phenyl-2-oxetanone ((RS)-4), a tropic acid β -lactone. However, (RS)-4 was too labile in a phosphate buffer (pH 7), and their preliminary investigation resulted in a complete hydrolysis to racemic 3, even in the absence of an enzyme. Therefore, (RS)-4 was converted to more stable esters, such as butyl troponoate ((RS)-5). Some studies reported an enzymatic KR with good selectivity using *Candida antarctica* lipase B on (RS)-5 (Scheme 2).^{6,7} The hydrolytic enzymatic KR of the tropic acid esters were successfully done, however, the chemical yields of the respective enantiomers do not exceed the barrier of theoretical yield of 50%. We planned to develop a new method to produce chiral

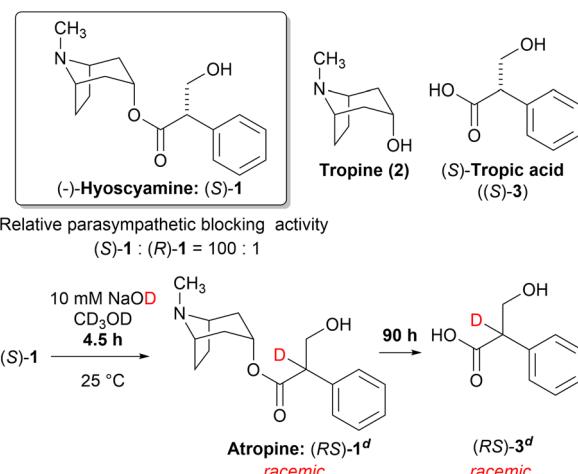
Hydrolytic dynamic kinetic resolution of racemic 3-phenyl-2-oxetanone to chiral tropic acid†

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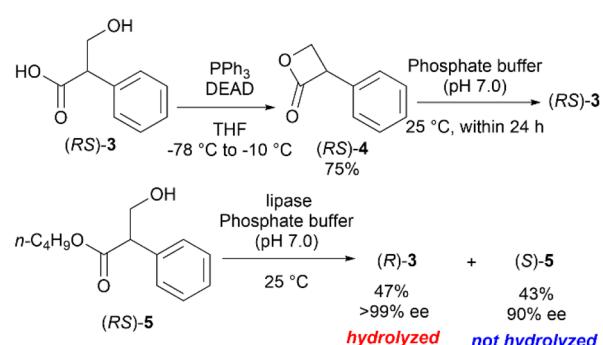
Tropic acid was synthesized in a good yield and with high enantioselectivity (81% ee) under non-biphasic conditions via the novel hydrolytic dynamic kinetic resolution of racemic 3-phenyl-2-oxetanone (tropic acid β -lactone) in the presence of a chiral quaternary ammonium phase-transfer catalyst and strongly basic anion exchange resin as the hydroxide ion donor.

tropic acid by hydrolytic dynamic kinetic resolution of racemic tropic acid esters by organocatalysis.

Several studies investigated the application of quaternary ammonium salts as positively charged species in enantioselective ion-pair catalysis.^{8,9}



Scheme 1 Fast racemization of (S)-1 followed by slow hydrolysis to give (RS)-3 under basic methanolysis.



Scheme 2 Enzymatic hydrolytic kinetic resolution of the esters of (RS)-3.

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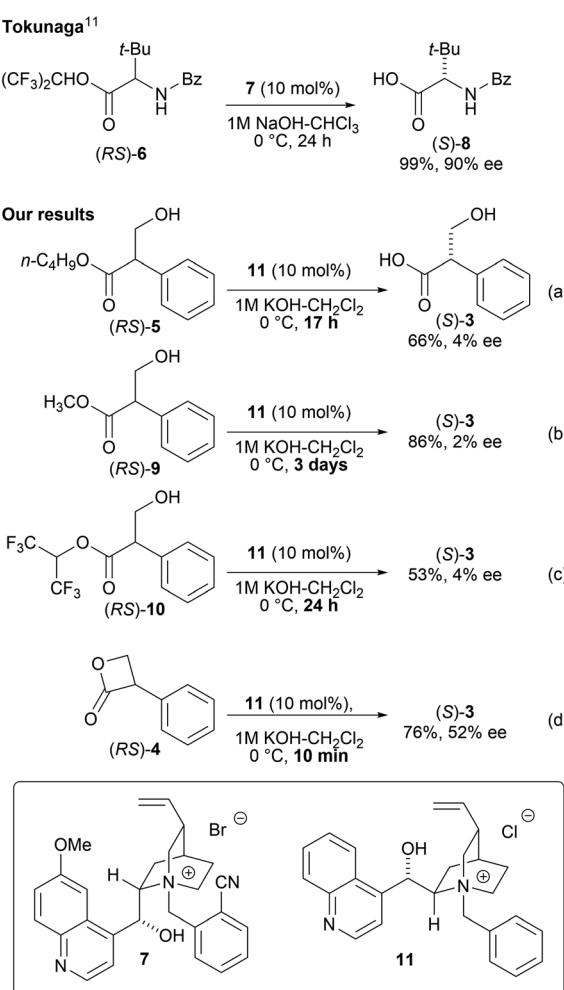
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In 2018, Tokunaga *et al.* reported the asymmetric hydrolysis of a racemic amino acid ester (**6**) with a high enantioselectivity using a chiral phase-transfer catalyst (PTC) **7** (Scheme 3).^{10,11} The reaction relied on an equilibrium-based racemization process between the two ester enantiomers prior to hydrolysis which enabled the hydrolytic dynamic kinetic resolution (DKR) of amino acid esters using a chiral phase-transfer catalyst under basic conditions. Inspired by this method, we attempted to obtain (*S*)-**3** *via* a PTC-mediated DKR hydrolysis.

As a proof-of-concept study, the asymmetric hydrolysis of each of butyl tropanoate (*RS*)-**5**, methyl tropanoate (*RS*)-**9**, and 1,1,1,3,3,3-hexafluoro-2-propyl tropanoate (*RS*)-**10** was attempted under alkaline biphasic conditions similar to those reported by Tokunaga *et al.* using a chiral PTC (**11**) derived from cinchona alkaloids (Scheme 3a–c); however, the optical purity of the obtained tropic acid was not as expected which can be attributed to the conformational fluidity of these esters. It was thus hypothesized that using the sterically and conformationally rigid (*RS*)-**4** might improve the DKR reaction.



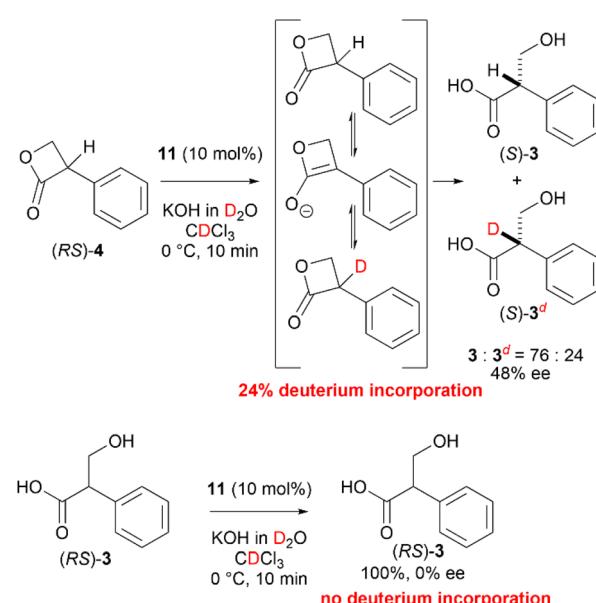
Scheme 3 Enantioselective hydrolysis of racemic esters by chiral phase-transfer catalysts (PTC).

In 1985, Vederas *et al.* reported the nucleophilic ring-opening reaction of serine-derived chiral β -lactones with various nucleophiles.¹² They investigated the basic methanolysis of chiral β -lactone to produce the corresponding methyl ester. Although the original chirality on the β -lactone was completely lost, this result demonstrated that fast racemization took place prior to methanolysis. This study led us to attempt the hydrolytic DKR of racemic β -lactones.

To achieve an enantioselective DKR hydrolysis, an equilibrium must exist between the enantiomers of **4**. To confirm the racemization equilibrium prior to lactone hydrolysis, the hydrolysis of (*RS*)-**4** in a KOD solution was performed and the $^1\text{H-NMR}$ analysis results revealed that 24% of the hydrolyzed product was deuterated at the α -carbon of the carboxyl group. In contrast, upon exposure of (*RS*)-**3** to the KOD solution, **3** was recovered without any deuteration and with an optical purity of 0% ee. These results demonstrated that the DKR of **4** can be achieved *via* a chiral PTC-catalyzed hydrolysis (Scheme 4).

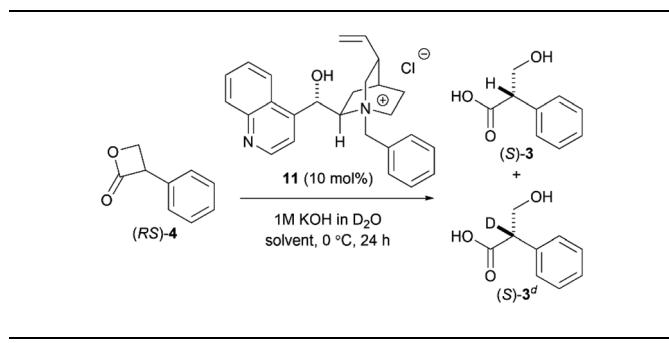
As predicted, the asymmetric hydrolysis of (*RS*)-**4** using **11** afforded (*S*)-**3** in a good yield and with improved enantioselectivity (52% ee, Scheme 3d). Although the reaction of acyclic esters was quite sluggish, the hydrolysis of lactone (*RS*)-**4** was completed within 10 min. Based on these results, we decided to further investigate the hydrolysis of DKR using (*RS*)-**4** as a promising substrate.

Initially, the effect of the solvent was investigated, and the results revealed that the optical purity of **3** was low in hexane, toluene, diethyl ether, THF, and CCl_4 (Table 1, entries 1–5). Notably, a relatively high enantioselectivity was obtained in each of CHCl_3 and CH_2Cl_2 (entries 6, 7). In these two halogenated solvents, the physicochemical properties, such as the dipole moment (μ), dielectric constant (ϵ_r), and acceptor number (AN), were significantly greater than those in the other solvents, thus



Scheme 4 Confirmation of the racemic equilibrium between both enantiomers of (*RS*)-**3** and (*RS*)-**4**.

Table 1 Solvent effects and physical properties of the solvents



Entry	Solvent	μ^a	ϵ_r^b	DN ^c	AN ^d	(S)-3 : (S)-3 ^d	Yield (%)	% ee ^e
1	Hexane	0.0	1.9	0.00	0.0	36 : 64	99	0
2	Toluene	1.0	2.4	<0.01	8.2 ^f	60 : 40	96	8
3	(C ₂ H ₅) ₂ O	3.8	4.2	0.49	3.9	52 : 48	96	2
4	THF	5.8	7.6	0.52	8.0	14 : 86	98	18
5	CCl ₄	0.0	2.2	0.00	8.6	59 : 41	97	0
6	CHCl ₃	3.8	4.8	0.10	23.1	74 : 26	93	48
7	CH ₂ Cl ₂	5.2	8.9	0.03	20.4	56 : 44	98	52

^a Dipole moments (μ , 10^{-30} Cm). ^b Dielectric constants (ϵ_r). ^c Donor numbers (DN). ^d Acceptor numbers (AN). ^e Optical purity was determined by Chiral HPLC (Daicel IC, *t*-butyl methyl ether:TFA = 100 : 0.1). ^f The value of benzene is shown.

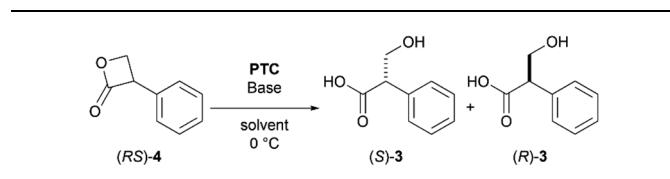
indicating that solvents with a larger AN solvate the hydroxide ion to form a favored derivative of the lactone carbonyl.¹³ On the other hand, the low deuteration rate indicated that hydrolysis occurred before attaining a sufficient enolate equilibrium, which is necessary to improve enantioselective DKR.

The contribution of the hydroxyl group on the catalyst was then investigated. Since enantioselectivity was completely lost in the presence of the *O*-methyl and Maruoka catalysts (12 (ref. 14) and 13 (ref. 15) respectively) (Table 2, entries 4–6), it was thus concluded that the free hydroxyl group on the catalyst was essential for enantioselectivity.¹¹

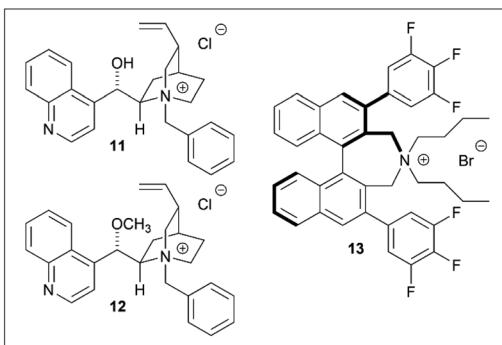
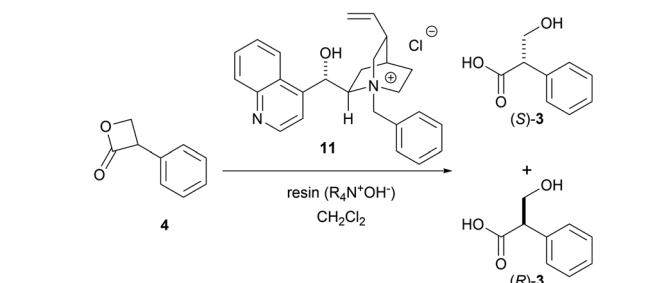
However, we were concerned that the exposure of 4 to excess hydroxide ions dispersed in the organic phase can result in a non-specific hydrolysis and poor enantioselectivity due to the high instability of the β -lactone under aqueous alkaline conditions. Therefore, we employed a strongly basic anion-exchange resin ($R_4N \cdot OH^-$, 8% cross-linked) as the hydroxide ion (OH^-) donor under water-free conditions instead of the basic biphasic conditions relying an aqueous hydroxide solution. The hydrolysis was thus performed using $R_4N \cdot OH^-$ in CH_2Cl_2 with catalyst 11. The asymmetric yield dramatically improved to 72% ee while the yield was acceptable (Table 3, entry 5). Notably, the asymmetric hydrolysis of both (S)- and (R)-4 yielded (S)-3 predominantly (entries 6, 7).

As our next task, we thought we should consider two possibilities for the reaction mechanism whether the enantioselective DKR was the result of chiral PTC catalyzed enantio-enrichment of (S)-4 through deprotonation-protonation process followed by non-enantioselective hydrolysis, or enantioselective hydrolysis of (S)-4 catalyzed by chiral PTC.

Table 2 Effect of the free hydroxyl group on the catalyst



Entry	PTC (10 mol%)	Base	Solvent	Time	Yield (%)	% ee
1	11	1 M KOH	CHCl ₃	10 min	77	48 (S)
2	11	1 M KOH	CH ₂ Cl ₂	10 min	76	52 (S)
3	11	1 M NaOH	CH ₂ Cl ₂	10 min	88	54 (S)
4	12	1 M NaOH	CH ₂ Cl ₂	24 h	74	0
5	13	1 M KOH	CHCl ₃	24 h	66	0
6	13	1 M KOH	Toluene	10 min	45	0

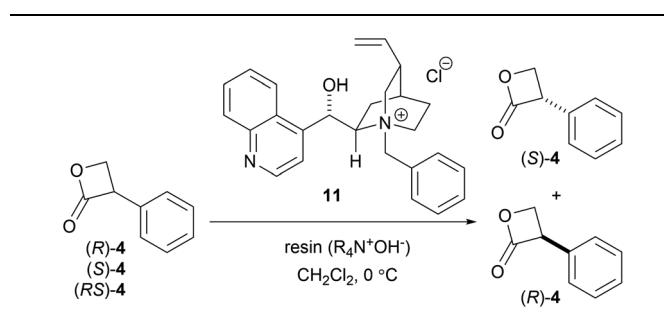
Table 3 Hydrolysis of racemic and chiral β -lactones

Entry	β -lactone	11 (mol%)	Temp. (°C)	Yield (%)	% ee
1	(RS)-4	10	-10	28	80 (S)
2	(RS)-4	10	-20	18	78 (S)
3	(RS)-4	20	0	90	74 (S)
4	(RS)-4	5	0	84	68 (S)
5	(RS)-4	10	0	71	72 (S)
6	(S)-4	10	0	71	76 (S)
7	(R)-4	10	0	67	66 (S)

In the former case, we assumed that the major enantiomer presented in the reaction solution would be (S)-4. In order to confirm this working hypothesis, the time course HPLC analysis of the reaction solution was performed to see the time dependent change of the ratio of (S)-4 and (R)-4 (Table 4).



Table 4 Time course analyses of the ratio of β -lactone enantiomers under PTC catalyzed hydrolysis condition



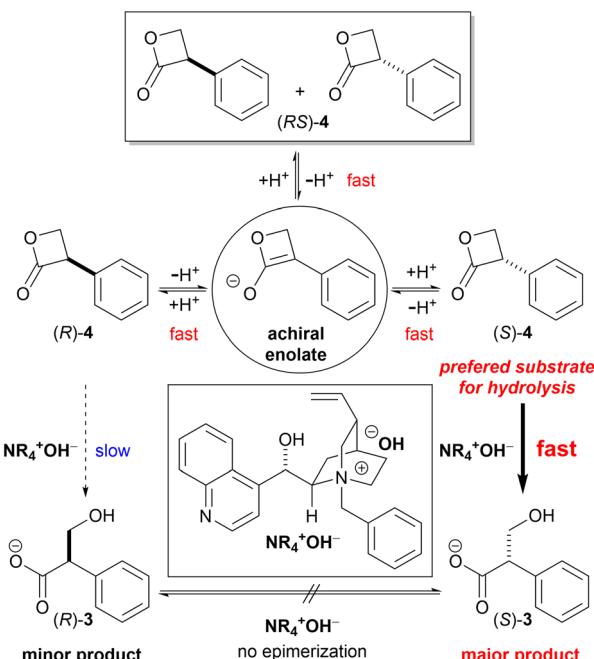
Time Substrate (S)-4 : (R)-4 Substrate (S)-4 : (R)-4 Substrate (S)-4 : (R)-4

0 h	(R)-4 ^a	0 : 100	(S)-4 ^a	98 : 2	(RS)-4	50 : 50
1 h		45 : 55		56 : 44		44 : 56
2 h		45 : 55		49 : 51		47 : 53
4 h		45 : 55		46 : 54		46 : 54

^a The optical purities of (R)-4 and (S)-4 were 100% ee and 96% ee, respectively.

As the results, it turned out that the major enantiomer presented in the reaction solution was (R)-4. These results indicated that enantiodifferentiation took place during the hydrolysis process of (S)-4, rather than the enantioenrichment of (S)-4 by deprotonation–protonation prior to hydrolysis (Scheme 5).

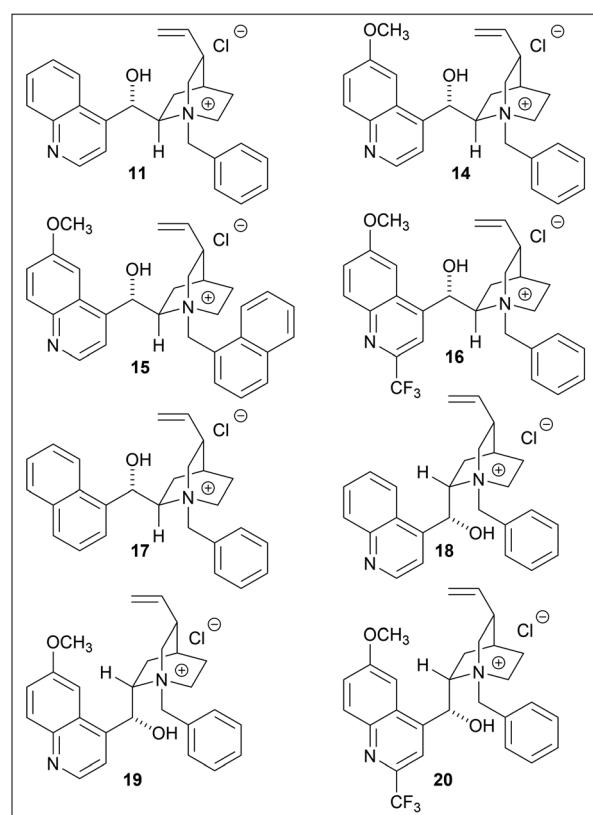
Several phase-transfer catalysts were then screened under the optimal reaction conditions (Table 5). The best result was



Scheme 5 Proposed mechanism of the hydrolytic dynamic kinetic resolution of 4.

Table 5 Screening of the hydrolysis catalysts

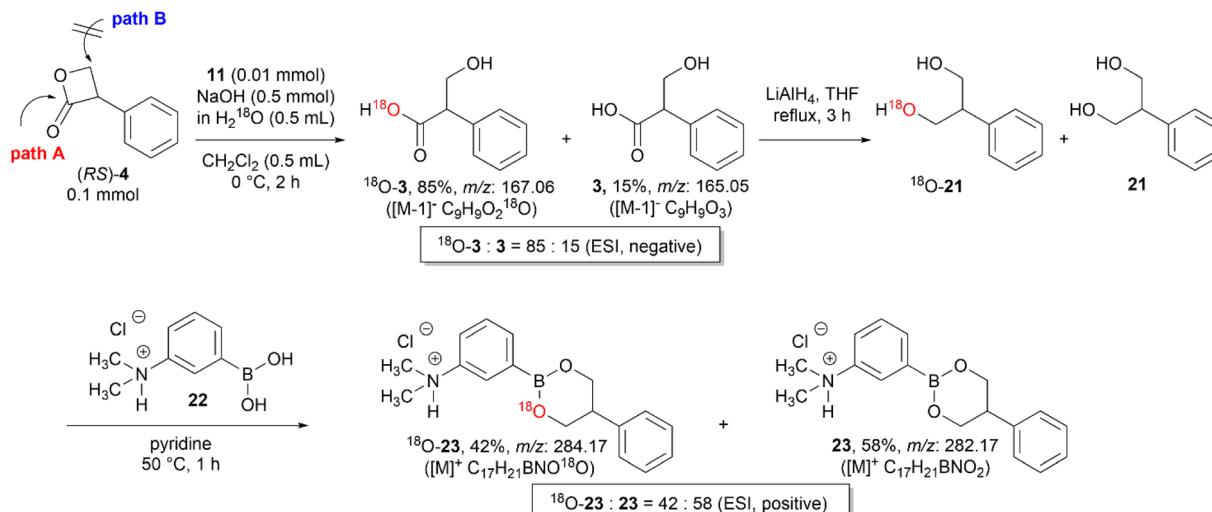
Entry	PTC	Time (h)	Yield (%)	% ee
1	11	22	71	72 (S)
2	14	30	85	81 (S)
3	15	27	74	78 (S)
4	16	20	52	74 (S)
5	17	21	64	56 (S)
6	18	22	85	66 (R)
7	19	30	86	64 (R)
8	20	40	77	62 (R)



obtained using catalyst **14**, which afforded (S)-3 in an 85% yield and 81% ee. Replacing the quinoline moiety with naphthalene (entry 5) resulted in a significant decrease in the asymmetric yield. The electron deficiency of the quinoline ring may contribute to a favorable approach for hydroxyl ions, while the introduction of a trifluoromethyl group at the quinoline 2-position did not have any significant effect (entries 4, 8).¹⁶ In this hydrolysis, the contribution of the methoxy group on the quinoline moiety was minor, while the stereogenic center adjacent to the vinyl group affected the enantioselectivity.

The spatial proximity of the vinyl group and the quinoline moiety in the structures of **11/14** and **18/19**, provided a more





Scheme 6 Determination of the reaction pathway by nucleophilic attack of hydroxide ion.

favorable reaction field, thus resulting in a higher enantioselectivity. Although the enantioselectivities of **11/14** and **18/19** were not identical with respect to the stereochemistries of the products, they were treated as pseudoenantiomers.

Vederas *et al.* investigated various nucleophiles in the ring-opening reaction of serine-derived β -lactones. The results revealed that depending on the class of the nucleophiles, the hydrolysis reaction can occur through a substitution reaction either in an addition–elimination fashion at the carbonyl carbon or in an S_N2 -fashion at the β -carbon.^{12,17} Therefore, to identify whether the hydroxide ions attack the carbonyl carbon (path A) or the β -carbon center (path B) of **4** (Scheme 6), an isotope labeling experiment with $H_2^{18}O$ was performed.

A mixture of ^{18}O -incorporated tropic acid ($^{18}O\text{-}3$) and **3** was obtained by the hydrolysis of *(RS)*-**4** with KOH (1 M) in $H_2^{18}O$ under general biphasic conditions using **11**. The negative ESI mass spectrum revealed that the ^{18}O content of the hydrolyzed mixture was 85%. Then, the mixture of $^{18}O\text{-}3$ and **3** was reduced to 2-phenyl-1,3-propanediol ($^{18}O\text{-}21$ and **21**) by LiAlH₄ and then converted to the corresponding cyclic boronates ($^{18}O\text{-}23$ and **23**) of 3-dimethylaminophenylboronic acid (**22**) because the detection sensitivity of $^{18}O\text{-}21$ and **21** in mass spectrometry was extremely poor.¹⁸ The positive ESI mass spectra of the mixture of $^{18}O\text{-}23$ and **23** revealed that after the LiAlH₄ reduction of the carboxyl group the ^{18}O content decreased from 85% to 42%, thus demonstrating the nucleophilic attack of the hydroxide ion at the carbonyl carbon (Scheme 6).

The reaction mechanism of this asymmetric hydrolysis is considered as follows. Since the free OH group on the catalyst was not essential for the hydrolysis reaction itself but was needed to achieve high enantioselectivity, it was indicated that the free OH group acts as a general acid catalyst to activate the carbonyl group and control the lactone orientation. The hydroxide ion solvated by dichloromethane approached the less hindered face of the β -lactone carbonyl and interacted with the electron-deficient quinoline ring to produce tropic acid

carboxylate *via* a tetrahedral intermediate. The geometry optimized structures of **TS-1** (**11**·(*S*)-**4**·OH[−]) and **TS-2** (**11**·(*R*)-**4**·OH[−]) obtained by density functional theory (DFT) calculations are shown in Fig. 1. The preferred orientation **TS-1**, which produced (*S*)-**3** as the major enantiomer, showed better aromatic π – π interaction than **TS-2**. The value of energy difference (1.83 kcal mol^{−1}) between **TS-1** and **TS-2** was reasonably in good accordance with the enantioselectivity.

This study reported a successful DKR with high enantioselectivity under non-aqueous bi-phasic conditions where the asymmetric hydrolysis of racemic 3-phenyl-2-oxetanone (tropic acid β -lactone) was achieved using a chiral PTC and water-free basic anion exchange resin as the hydroxide ion donor. These

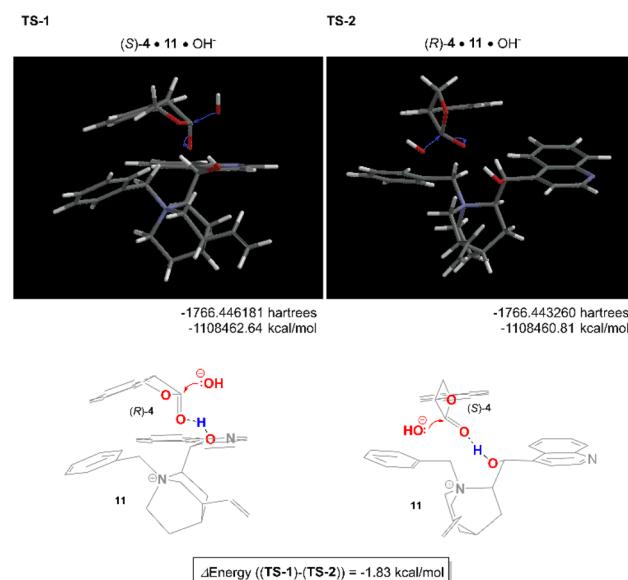


Fig. 1 The geometry optimized structures of **TS-1** (**11**·(*S*)-**4**·OH[−]) and **TS-2** (**11**·(*R*)-**4**·OH[−]) by density functional theory (DFT) calculations (ω B97X-D/6-31G*) in CH_2Cl_2 .



findings open the potential for the PTC-catalyzed asymmetric transformations of water-labile substrates.

Conflicts of interest

There are no conflicts to declare.

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