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Enantioselective hydrolysis of 1-arylallyl acetates catalyzed by *Candida antarctica* lipase

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Abstract—(*R*)-1-Arylallyl alcohols were obtained with excellent enantioselectivities via kinetic resolution of the corresponding acetates using immobilized *Candida antarctica* lipase. The scope and limitations of this reaction were investigated. The best results are obtained using the water/acetonitrile solvent system, and the reaction tolerates a variety of aryl and heteroaryl substituents.

1. Introduction

Lipases, obtained from various microorganisms, are the most widely used enzymes in organic synthesis, mainly due to their great enantioselectivity.[1] They catalyze hydrolysis, esterification, trans-esterification, including alcoholysis, and amidation of many substrates. Since enzyme reactivity, selectivity, and stability in organic solvents is often worse than that in aqueous solutions, efforts have been devoted to finding appropriate enzyme formulations for use in organic media. For example, immobilization of lipases in or on a solid support enhances their stability, catalytic activity, and their recyclability.[2–4]

Enantiomerically enriched allylic alcohols and allylic acetates are very useful intermediates in the asymmetric synthesis of more complex molecules.[5,6] One of the most straightforward ways to make these intermediates is enantioselective acylation[4,6–8] of secondary allylic alcohols and enantioselective hydrolysis[9] of the corresponding esters catalyzed by enzymes or various non-enzymatic chiral catalysts.

While racemic secondary cinnamyl alcohols (1-alkyl-3-arylallyl alcohols) or their acetates have been successfully resolved using both enzymatic and non-enzymatic chiral catalysts and reagents,[6,7,9–11] kinetic resolution of more sterically-hindered α-vinylbenzylic alcohols (1-arylallyl alcohols) proved significantly more challenging.[12] Only one resolution of the parent 1-phenylallyl alcohol to the corresponding acetate was reported, with a moderate enantioselectivity (81% ee, in a dynamic kinetic resolution).[13] Two other reported examples of kinetic resolution of 1-phenylallyl alcohol employed oxidation (45% ee)[10] or epoxidation (95% ee) reactions.[14]

Herein, we report the first example of preparation of various enantiomerically-pure (*R*)-1-arylallyl alcohols via the lipase-catalyzed kinetic resolution of racemic 1-arylallyl acetates with very high enantioselectivities (greater than 99%).[15]

2. Results and discussion

2.1. Rationale

While the chemoenzymatic approach to many allylic substrates has historically relied on the enantioselective conversion of racemic alcohols to chiral acetates via lipase-catalyzed esterification with acyl donors such as vinyl acetate,[4,16] we envisioned using the reverse process for our substrates, namely, the enantioselective conversion of racemic acetates to chiral alcohols via hydrolysis or alcoholysis in organic solvents or co-solvents. The milder and more easily tunable conditions of the latter approach are advantageous for development of other kinetic resolution regimes, such as chemoenzymatic dynamic kinetic resolution,[9,17] which is the ultimate goal of this project.

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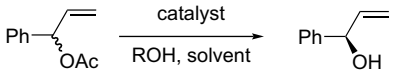
2.2. Optimization of reaction conditions

For the initial screening experiments we chose two lipases known to catalyze the esterification process, reverse to our hydrolysis, with structurally similar substrates. *Candida antarctica* lipase B catalyzes the acylation of 1-phenylallyl alcohol,[13] while *Candida cylindracea* lipase (*Cc*L) catalyzes the acylation of 1-phenyl-2,3-allenol.[18] *Cc*L was immobilized by encapsulation in hydrophobic sol–gel glass, which was recently shown to improve the reactivity, selectivity, and stability of *Cc*L.[3] For the other lipase, a commercially-available immobilized version of the enzyme (Novozym® 435), where the lipase is covalently attached to acrylamide beads, was employed.

Hydrolysis of 1-phenylallyl acetate **1a** in water/acetonitrile solvent system in the presence of *C. cylindracea* lipase encapsulated in a hydrophobic sol–gel glass (*Cc*L@glass) afforded 1-phenylallyl alcohol **1b** in low yields and with low enantioselectivities, even at high catalyst-to-substrate ratios and longer reaction times (Table 1, entries 1 and 2).

Table 1. Optimization of reaction conditions for the kinetic resolution of 1-phenylallyl acetate[a]



1a (±) **2a** (*R*)

Entry	Catalyst	ROH and solvent	Time	Yield[b] (%)	ee[c] (%)
1	*Cc*L@glass[d]	H_2O in CH_3CN[e]	8 d	16	24.1
2			18 d	33	7.7
3	*Ca*L[f]	H_2O in CH_3CN[e]	3 h	33	>99
4			1 d	51	>99
5			7 d	53	>99
6	*Ca*L[f]	*i*-PrOH in THF[g]	3 h	2	>99
7			1 d	19	>99
8			7 d	47	>99
9	*Ca*L[f]	*i*-PrOH in toluene[g]	3 h	20	>99
10			1 d	47	>99
11			4 d	50	>99
12	*Ca*L[f]	*i*-PrOH in acetone[g]	4 h	13	>99
13			1 d	23	nd[h]
14			7 d	49	>99
15	*Ca*L[f]	H_2O in toluene[g]	3 h	32	>99
16			1 d	35	>99
17			14 d	50	>99

[a] (*R*)-1-phenylallyl alcohol was the predominant enantiomer of the product, as concluded from the comparison with an authentic sample.
[b] Integration error 5–10% for NMR yields.
[c] An *ee* value listed as '>99' means that the peak for the opposite enantiomer of the product was not observed; since the relative GC peak area integration error, as determined from the resolution of racemates, was 0.5–1.0%, then >99% is a conservative estimate.
[d] *Candida cylindracea* lipase, immobilized (encapsulated) into hydrophobic sol–gel silica glass, 1.8 g/ mmol substrate.
[e] 1:1 (v/v), 0.05 M (0.2 mmol) substrate.
[f] *C. antarctica* lipase B, covalently immobilized onto acrylamide beads (Novozym 435), 0.4 g/ mmol substrate.
[g] 2.5 M (10 equiv) *i*-PrOH, 0.25 M (0.2 mmol) substrate.
[h] Not determined.

In contrast, when *C. antarctica* lipase B covalently bound to acrylamide beads (*Ca*L) was used as a catalyst, the same reaction resulted in excellent yields and enantioselectivities after 1 day even at a much lower loading of the enzyme (entries 3 and 4). When this reaction was allowed to run for six more days, no significant increase in product yield or decrease in enantioselectivity was observed, indicating that after the (*R*)-enantiomer of the starting material is consumed, the enzymatic hydrolysis is virtually halted. Thus, *Ca*L catalyzes kinetic resolution (KR) of 1-phenylallyl acetate.

The *Ca*L-catalyzed hydrolysis of this acetate was then screened in several other acyl acceptor/solvent systems, such as water or isopropanol (0.25 M or 1:1 (v/v)) in THF, toluene, or acetone. All systems provided (*R*)-1-phenylallyl alcohol in excellent enantioselectivities (>99% ee, see footnote b in Table 1), but at different rates. Kinetic resolution (ca. 50% yield of 1-phenylallyl alcohol with ee >99%) was achieved after one day in water/acetonitrile (entries 3–5) and isopropanol/toluene (entries 9–11) solvent systems, while in isopropanol/THF (entries 6–8), isopropanol/acetone (entries 12–14), and water/toluene (entries 15–17) solvent systems it took several days.

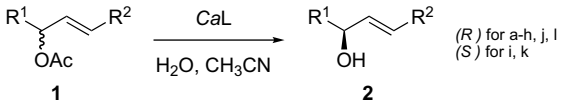
After initial screening, *Ca*L proved to be superior to *Cc*L for the resolution of 1-phenylallyl alcohol, and the inexpensive and safe water/acetonitrile (1:1) solvent system was used for further experiments reported here.

2.3. Kinetic resolution of various allylic acetates by *Ca*L

After establishing the optimal reaction conditions, we studied the lipase-catalyzed hydrolysis of various 1-arylallyl acetates **1** by varying the *para*-substituent on the phenyl ring (Table 2, entries 1–6).

Substrates with electron-withdrawing substituents **1b–d** (entries 2–4) exhibited a considerably faster rate of hydrolysis than the parent unsubstituted substrate (entry 1), while still maintaining the excellent ee values. Conversely, a strong electron-donating substituent **1e** slowed down the reaction so much that even after several days only a minute yield of alcohol was obtained (entry 5). This result is consistent with the accepted 'bi bi ping-pong' mechanism for *C. antarctica* lipase B (see Scheme 1),[19,20] if the formation of enzyme-acyl intermediate (so-called acylation step) is the rate-determining step. In the acylation step, the serine from the catalytic triad attacks the ester substrate $R'CO_2R''$, resulting in the subsequent departure of the alcohol ($R''OH$) and a formation of enzyme-acyl intermediate (lipase—O_2CR'). Indeed, if acylation is the rate-determining step, an electron-poor alcohol would be a better leaving group than an electron-rich alcohol, thus resulting in faster reaction rates. On the other hand, the rate of the deacylation step (hydrolysis of enzyme-acyl intermediate) would be the same for all the substrates in our system. For *Ca*L, either the acylation or deacylation step could be rate-determining, depending on the substrates and the reaction conditions.[19,21,22] The acylation becomes the rate-determining step in our system, because the steric bulk of the alkoxy part of our esters results in a significant

Table 2. Kinetic resolution of various allylic acetates **1** into the corresponding chiral allylic alcohols **2**[a]



1 2

Entry	R^1	R^2	1	Time (h)	Yield of 2[b,c] (%)	ee[b,d,e] (%)
1	Ph	H	**a**	24	51.2 ± 0.7	>99
2	*p*-CN–C_6H_4	H	**b**	3.0	52.6 ± 0.0[f]	>99
3	*p*-Cl–C_6H_4	H	**c**	3.0	52.7 ± 0.6[g]	>99
4	*p*-O_2N–C_6H_4	H	**d**	3.0	51.3 ± 0.6	>99
5	*p*-CH_3O–C_6H_4	H	**e**	48	6.1 ± 0.4	nd
6	*p*-CH_3–C_6H_4	H	**f**	24	53.0 ± 0.2	96.5 ± 0.1
7	3-Pyridyl	H	**g**	24	48.1 ± 0.4	>99
8	2-Naphthyl	H	**h**	6.0	51.2 ± 1.2	>99
9	CH_3	CH_3	**i**	3.0	51.8 ± 0.6	>99
10	Ph	Ph	**j**	24	92.6 ± 0.3	nd
11[h]	CH_3	H	**k**	12	90.0 ± 1.7	nd
12	–$(CH_2)_3$–		**l**	24	66.9 ± 0.2	10.5 ± 0.1

[a] General conditions: 0.05 M (0.2 mmol) substrate, CH_3CN/H_2O (1:1 v/v), *Ca*L (0.4 g catalyst/mmol substrate), room temperature (23 °C). See Section 4 for details on absolute configurations.

[b] Average of two independent experiments ± standard deviation.

[c] Integration error 5–10% for NMR yields. Isolated yields are also reported for **2b** (footnote f) and **2c** (footnote g).

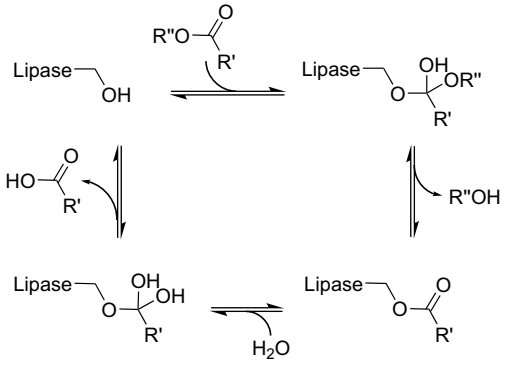
[d] An ee value listed as '>99' means that the peak for the opposite enantiomer of the product was not observed; since the relative GC peak area integration error, as determined from the resolution of racemates, was 0.5–1.0%, then >99% is a conservative estimate.

[e] 'nd' means not determined.

[f] In the preparative-scale kinetic resolution of **1b** (1.0 mmol scale) the isolated yield of the product **2b** was 49% and the ee was >99%. See Section 4.8.

[g] In the preparative-scale kinetic resolution of **1c** (1.025 mmol scale) the isolated yield of the product **2c** was 48% and the ee was >99%. See Section 4.8.

[h] This alcoholysis reaction was performed in a THF/*i*-PrOH solvent system (2.5 M (10 equiv) *i*-PrOH, 0.25 M (0.2 mmol) substrate).



Scheme 1. Mechanism of ester hydrolysis catalyzed by *Candida antarctica* lipase B.

decrease in the rate of the attack of the serine on the carbonyl group of the ester. A similar observation was recently made by Kobayashi, who showed that in his *Ca*L-based lactone polymerization system acylation was the rate-determining step, since the increase in the sterical bulk of the alkoxy part of the ester led to lower reaction rates.[21]

1-*p*-Tolylallyl acetate **1f** (entry 6) reacted as fast as 1-phenylallyl acetate **1a** (entry 1) but it yielded the only 1-arylallyl alcohol product, for which a minor enantiomer was observed; however, the ee value was still very high. Other aromatic acetates (R^1 = 3-pyridyl or 2-naphthyl) were also efficiently resolved under our optimal conditions, affording the corresponding alcohols with excellent enantioselectivities (entries 7 and 8). Overall, with the exception of 1-(4-methoxyphenyl)allyl acetate **1e**, a kinetic resolution of all 1-arylallyl acetates was achieved with excellent enantioselectivities.

To further examine the scope and limitations of our system, the same reaction conditions were also applied to 'symmetrical' allylic acetates **1i–j**, in which both ends of the allylic system bear the same substituents, as well as the simplest secondary allylic acetate **1k** and a cyclic substrate **1l** (entries 9–12). *Ca*L was very efficient and highly enantioselective in achieving the kinetic resolution of pent-3-en-2-yl acetate **1i** (entry 9). However, the kinetic resolution of **1j–l** was not as successful. High yields obtained in enzymatic hydrolysis of **1j** (entry 10) and enzymatic alcoholysis of acetate **1k** (entry 11) indicated that discrimination between enantiomers may not have occurred in this case. Enzymatic hydrolysis of **1l** (entry 12) proceeds at lower rate, but still only low ee was observed.

3. Conclusion

In conclusion, *C. antarctica* lipase B covalently immobilized on acrylamide beads (Novozym® 435) catalyzes hydrolytic kinetic resolution of various readily available racemic 1-arylallyl acetates, affording enantiomerically-pure (*R*)-1-arylallyl alcohols in high yields. The rate of the reaction depends on the electronic properties of the substrate, and is faster for electron-poor aryl substituents.

A detailed investigation of enantioselective hydrolysis and alcoholysis reactions of other aryl- and heteroaryl-substituted allylic acetates, as well as other related unsaturated substrates, is currently underway. Regimes other than simple kinetic resolution are also being studied.

4. Experimental

4.1. Chemicals

All reagents, catalysts, and solvents were obtained from commercial suppliers and were used without further purification, except as noted below. Anhydrous tetrahydrofuran (THF) was distilled prior to use from sodium benzophenone ketyl, or purchased in an inhibitor-free form. Triethylamine was dried over calcium hydride and then distilled. Immobilized *Cc*L was prepared by encapsulation into hydrophobic sol–gel glass as described previously.[3] *C. antarctica* lipase B covalently immobilized on acrylamide beads (Novozym® 435) was obtained from Sigma

(L4777). Column chromatography was performed on silica gel (70–230 mesh, 63–200 μm particle size).

4.2. Instrumentation

^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra were recorded at 100 MHz, in $CDCl_3$. The chemical shifts are reported as δ values (ppm) relative to TMS, the integration error was 5–10%. Baseline separation of enantiomers of allylic alcohols **2a**–**d**, **2f**–**i**, and **2l** was achieved on a gas chromatograph/mass-spectrometer (GC–MS) instrument with Chiraldex B-PM column (Astec, 30 m × 0.25 mm), using helium (99.9995%) as a carrier gas, a split ratio of 30:1, and an injection volume of 1–3 μL; the relative GC peak area integration error, as determined from the resolution of racemates, was 0.5–1%. The various GC temperature programs for baseline separation are summarized in Table 3, and the retention times for separated enantiomers of alcohols are shown in Table 4. The solvent delay for MS acquisition was 5 min.

Table 3. GC programs for separation of enantiomers

Program	Program segment	T_{start} (°C)	Rate (°C/min)	T_{end} (°C)	Hold time at T_{end} (min)
A	1	50	0	50	4
	2	50	10	90	2
	3	90	5	200	25
B	1	50	0	50	4
	2	50	10	90	2
	3	90	5	120	4
	4	120	2	160	10
	5	160	5	200	10
C	1	50	0	50	4
	2	50	5	90	2
	3	90	2	150	2
	4	150	10	200	15
D	1	35	0	35	4
	2	35	1	70	4
	3	70	10	200	5
E	1	50	0	50	2
	2	50	2	80	2
	3	80	2	90	1

Table 4. Retention times for (*R*)- and (*S*)-enantiomers of alcohols

Program	Alcohol	t_R (min)	t_S (min)
A	**1a**	18.89	19.55
	1b	27.19	27.50
	1c	23.18	23.62
	1d	30.03	30.39
	1f	19.99	20.44
B	**1h**	43.48	44.26
C	**1g**	35.65	36.29
D	**1i**	20.32	18.50
E	**1l**	7.75	8.10

4.3. Identification of chiral alcohols

The alcohol products were identified by their ^{1}H NMR and mass-spectra and by GC retention times, in comparison with racemic authentic samples (**2a**, **2i**, **2j**, **2k**, and **2l**) and previously published data (**2b**,[23] **2c**,[24] **2d**,[25] **2e**,[26] **2f**,[24] **2g**,[27] and **2h**[28]). The absolute configuration of chiral 1-phenylprop-2-en-1-ol (*R*)-**2a** was confirmed by comparison with an authentic sample using a chiral GC analysis. (*R*)-Configurations of chiral 1-arylallyl alcohols **2b**–**h** are assigned because of their structural analogy to (*R*)-**2a**. The expected configurations of alcohols **2i**–**l** were deduced using Kazlauskas rule.[29]

4.4. General procedure for the preparation of allylic alcohols[23]

Aldehyde (3.5 mmol) was dissolved in anhydrous THF (7.0 mL), and the resulting clear solution was cooled to −78 °C. Vinyl magnesium bromide (1.0 M in THF, 4.5 mmol) was then added dropwise to the reaction mixture at −78 °C, and the reaction was allowed to slowly warm to room temperature (23 °C). After 3 h, the reaction mixture was diluted with diethyl ether and quenched with a saturated NH_4Cl solution. The organic layer was separated, washed twice with water, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residual oil was purified by flash chromatography (silica gel, EtOAc/hexanes) to yield the corresponding allylic alcohol.

The following racemic allylic alcohols were previously prepared by the same or similar procedure and characterized by at least ^{1}H NMR and MS: 1-(4-cyanophenyl)prop-2-en-1-ol **2b**,[23] 1-(4-chlorophenyl)prop-2-en-1-ol **2c**,[24] 1-(4-nitrophenyl)prop-2-en-1-ol **2d**,[25] 1-(4-methoxyphenyl)-prop-2-en-1-ol **2e**,[26] 1-(*p*-tolyl)prop-2-en-1-ol **2f**,[24] 1-(pyridin-3-yl)prop-2-en-1-ol **2g**,[27] and 1-(naphthalen-2-yl)prop-2-en-1-ol **2h**.[28]

4.5. General procedure for the preparation of allylic acetates[24]

The mixture of allylic alcohol (3.5 mmol), 4-dimethylaminopyridine (4.5 mmol), acetic anhydride (4.5 mmol), triethylamine (4.2 mmol), and methylene chloride (7 mL) was stirred at room temperature (23 °C) overnight and then poured into water. The reaction mixture was washed with 2 M HCl, and the aqueous phase was extracted with methylene chloride. The combined organic extracts were washed with satd $NaHCO_3$, water, and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residual oil was purified by flash chromatography (silica gel, EtOAc/hexanes) to yield the corresponding allylic acetate.

The following allylic acetates were previously prepared by the same or similar procedure and characterized by at least ^{1}H NMR and MS: 1-(4-chlorophenyl)allyl acetate **1c**,[24,30] 1-(4-methoxyphenyl)allyl acetate **1e**,[30] 1-(*p*-tolyl)allyl acetate **1f**,[24,30] 1-(4-nitrophenyl)allyl acetate **1d**,[30] (*E*)-1,3-diphenylallyl acetate **1j**,[31] and cyclohex-2-enyl acetate **1l**.[32]

Two allylic acetates, 1-(4-cyanophenyl)allyl acetate **1b**[33] and 1-(naphthalen-2-yl)allyl acetate **1h**,[34] were previously reported, but not characterized. 1-(Pyridin-3-yl)allyl acetate **1g** has not been reported before. The identity and purity of these three compounds were confirmed by at least ^{1}H

NMR, ^{13}C NMR, and GC–MS (GC programs used to check for purity of acetates were the same as the programs used for enantiomer separation of the corresponding alcohols, see Table 3).

1-(4-Cyanophenyl)allyl acetate **1b**: ^1H NMR: δ 7.66 (d, $J = 8.4$ Hz, 2H), 7.46 (d, $J = 8.0$ Hz, 2H), 6.26 (d, $J = 6.0$ Hz, 1H), 5.90–6.00 (m, 1H), 5.29–5.35 (m, 2H), 2.14 (s, 3H). ^{13}C NMR: δ 169.7, 144.0, 135.1, 132.4, 127.6, 118.5, 118.2, 111.9, 75.3, 21.0.

1-(Naphthalen-2-yl)allyl acetate **1h**: ^1H NMR: δ 7.82–7.88 (m, 4H), 7.45–7.52 (m, 3H), 6.45 (d, $J = 5.6$ Hz, 1H), 6.06–6.16 (m, 1H), 5.29–5.40 (m, 2H), 2.16 (s, 3H). ^{13}C NMR: δ 169.98, 136.16, 133.10, 133.07, 128.36, 128.03, 127.64, 126.25, 126.23, 124.85, 117.10, 76.26, 21.27 (two aromatic peaks are missing because of overlaps).

4.6. Synthesis of 1-(pyridine-3-yl)allyl acetate 1g

A mixture of racemic 1-(pyridine-3-yl)prop-2-en-1-ol (**2g**, 300 mg, 2.22 mmol), acetic anhydride (0.72 mL), and DMAP (67.0 mg) was stirred in triethylamine (2.59 mL, distilled over KOH) for 18 h at room temperature (23 °C). The clear yellow reaction mixture turned dark red at the end of the reaction. Methanol (5.0 mL) was added, and after 20 min the mixture was concentrated in vacuo. Ether was then added, and the organic phase was washed with saturated aqueous $NaHCO_3$ and dried over anhydrous $MgSO_4$. Evaporation of the solvent and purification by flash chromatography (80% ethyl acetate in hexanes) resulted in the title compound as a yellow oil (340 mg, 87.2%).

^1H NMR: δ 8.62 (d, $J = 2.0$ Hz, 1H), 8.57 (dd, $J = 4.8$ Hz, 1.6 Hz, 1H), 7.65 (m, 1H), 7.28 (m, 1H), 6.29 (d, $J = 6.0$ Hz, 1H), 5.96–6.05 (m, 1H), 5.29–5.36 (m, 2H), 2.13 (s, 3H). ^{13}C NMR: δ 169.8, 149.5, 148.9, 135.3, 134.8, 134.4, 123.4, 117.9, 74.0, 21.1. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90; Found: C, 67.5 ± 0.09; H, 6.21 ± 0.05; N, 8.39 ± 0.09 (average of two analyses, all elements within 0.4%).

4.7. General procedures for the kinetic resolution experiments in various solvent systems

4.7.1. Water/acetonitrile. Allylic acetate (0.2 mmol), *C. antarctica* lipase B immobilized on acrylic resin (Novozym® 435) (80 mg), acetonitrile (2 mL), and water (2 mL) were mixed in a 15-mL vial and vigorously stirred at room temperature (23 °C). The progress of the kinetic resolution was monitored by ^1H NMR spectroscopy. A typical procedure for NMR sample preparation involved withdrawing a small aliquot (40.0 μL) of the reaction mixture, separating lipase from the liquid phase by centrifugation, extracting the liquid phase with methylene chloride, drying the combined organic layers with anhydrous $MgSO_4$, filtering, concentrating in vacuo, and dissolving in $CDCl_3$ or CD_2Cl_2. The yield was measured by ^1H NMR spectroscopy (the relative peak area error up to 5–10%), and the enantiomeric excess was determined by chiral GC–MS (the relative peak area error up to 0.5–1%), as described above. Kinetic resolution experiments in this solvent system were performed in duplicates.

4.7.2. Water/toluene. The reaction procedure was the same as in Section 4.7.1 except that toluene (0.8 mL per 0.2 mmol of substrate) was used as the solvent instead of acetonitrile and only 10 equiv (2.0 mmol, 0.036 mL) of water was used.

4.7.3. Propan-2-ol/THF. The reaction procedure was the same as in Section 4.7.1 except that THF (0.8 mL per 0.2 mmol of substrate) was used as the solvent instead of acetonitrile and 2-propanol (10 equiv, 2.0 mmol, 0.160 mL) was used as the acyl acceptor instead of water.

4.7.4. Propan-2-ol/acetone and propan-2-ol/toluene. The reaction procedure was the same as in Section 4.7.3 except that acetone or toluene (0.8 mL per 0.2 mmol of substrate) was used instead of THF.

4.7.5. Immobilized *C. cylindracea* lipase as a catalyst. The reaction procedure was the same as in Section 4.7.1. except that *C. antarctica* lipase B immobilized on acrylic resin was replaced by *C. cylindracea* lipase immobilized in hydrophobic sol–gel glass (180 or 360 mg per 0.2 mmol of substrate).

4.8. Preparatory-scale kinetic resolutions

For a preparatory-scale kinetic resolution the procedure for the water/acetonitrile system described above (Section 4.7.1.) was scaled up 5.17 times (1.034 mmol (208 mg) of substrate **1b**, 414 mg of immobilized lipase, 10.3 mL of acetonitrile, and 10.3 mL of water). After the reaction was allowed to run for 24 h, immobilized lipase was filtered off, and the filtrate was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography on silica gel (2:1 hexanes/ethyl acetate) yielded 80 mg (0.503 mmol, 49%) of the desired chiral (*R*)-1-(4-cyanophenyl)prop-2-en-1-ol **2b** as a very pale yellow oil. In the same experiment, unreacted enantiomer of **1b** ((*S*)-1-(4-cyanophenyl)allyl acetate) was also isolated as a colorless oil (91 mg, 0.454 mmol, 44%).

Similarly, for the kinetic resolution of **1c** the procedure described in Section 4.7.1 was scaled up 5.125 times (1.025 mmol (216 mg) of substrate **1c**, 410 mg of immobilized lipase, 10.25 mL of acetonitrile, and 10.25 mL of water), chiral (*R*)-1-(4-chlorophenyl)prop-2-en-1-ol **2c** was isolated as a colorless oil (83 mg, 0.492 mmol, 48%). In the same experiment, unreacted enantiomer of **1c** ((*S*)-1-(4-chlorophenyl)allyl acetate) was also isolated as a slightly yellow oil (105 mg, 0.486 mmol, 49%).

Isolated chiral compounds were >99.7% pure (by GC, program A) and were identified as described above (Section 4.3). The ee values were all >99% for isolated (*R*)-**2b**, (*S*)-**1b**, (*R*)-**2c**, and (*S*)-**1c**, as determined by the chiral GC–MS (see footnote d in Table 2).

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