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# Enzyme- and Ruthenium-Catalyzed Dynamic Kinetic Resolution of Functionalized Cyclic Allylic Alcohols

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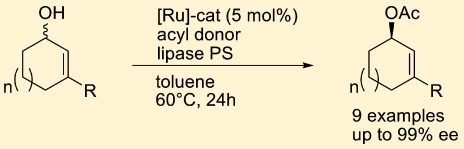
Supporting Information

**ABSTRACT:** Enantioselective synthesis of functionalized cyclic allylic alcohols via dynamic kinetic resolution has been developed. Cyclopentadienylruthenium catalysts were used for the racemization, and lipase PS-IM or CALB was employed for the resolution. By optimization of the reaction conditions the formation of the enone byproduct was minimized, making it possible to prepare a range of optically active functionalized allylic alcohols in good yields and high ee's.

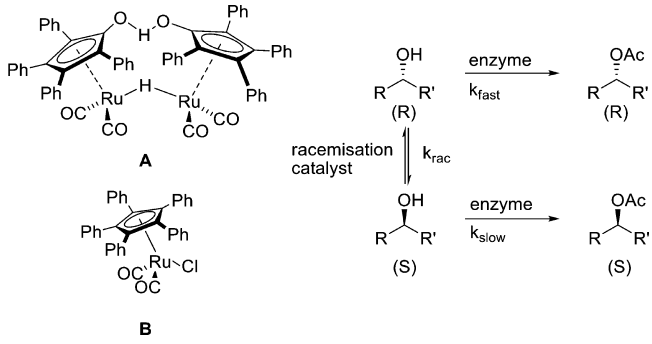



## INTRODUCTION

Enantiomerically pure allylic alcohols are versatile intermediates and building blocks in the synthesis of pharmaceuticals, agrochemicals, and natural products; hence, the enantioselective synthesis of allylic alcohols has been the subject of many studies.[1] Cyclic allylic alcohols have attracted considerable interest and are important in connection with Claisen technology,[2] epoxidations,[3] and various $S_N2'$ substitution reactions.[4] Cyclic allylic alcohols are also found as common starting materials and intermediates in various synthetic applications.[5] Traditional protocols for the production of enantiopure allylic alcohols often include asymmetric reduction of vinyl ketones by the use of chiral catalysts[6] or enzymes,[7] enantioselective addition of alkenyl metal reagents to aldehydes,[8] and kinetic resolution or dynamic kinetic resolution of racemic allylic alcohols.[9] One problem associated with several of the enantioselective reactions of cyclic allylic alcohols is the need of a large group at the 2-position in order to achieve a high enantiomeric excess (ee). If a large group is not present it has to be introduced before the enantioselective reaction and then removed, thus creating two additional steps.[6b]

Enzymatic kinetic resolution (KR) is a highly chemo- and stereoselective method in organic synthesis. For the KR of secondary alcohols and amines a hydrolase can be employed as a transesterification or hydrolysis catalyst reacting with the substrate enantiomers with two different rates. This makes it possible to selectively convert one of the enantiomers into product while leaving enantiomerically enriched starting material behind. A drawback with a KR is that the yield of the enantiomerically pure compounds (retained starting material or converted product) can never exceed 50%. To overcome this limitation a racemization catalyst can be introduced to the system, thus turning it into a dynamic kinetic resolution (DKR). In the latter process the substrate is continuously racemized, making it possible to obtain the product in a theoretical yield of 100% and with an ee of up to 100% (Scheme 1). To this date, a wide range of enantiomerically pure alcohols and amines have been prepared according to this method.[10−12] Two racemization catalysts that have been used extensively for secondary alcohols are dimeric catalyst **A**, also known as Shvo's catalyst, which is activated by heat,[13] and monomeric catalyst **B**, activated by base.[14] The aim of the present study was to utilize these transition metal complexes to extend the protocol of enzymatic DKR to also include functionalized cyclic allylic alcohols.

**Scheme 1. Two Examples of Ruthenium-Based Racemization Catalysts (A and B) and a Schematic Picture of an (*R*)-Selective Dynamic Kinetic Resolution**




In the course of the *in situ* racemization of allylic alcohols with catalysts **A** and **B** a conjugated enone-intermediate (noncoordinated or coordinated) is formed together with a ruthenium hydride. In order to achieve racemization the *α,β*-unsaturated carbonyl intermediate must be reduced by the metal hydride at the carbonyl position. However, competing hydride addition may occur at the olefin bond resulting in an isomerization of the starting material to the saturated ketone.[15] Also, the *α,β*-unsaturated carbonyl intermediate may escape reduction leading to an oxidized side product.

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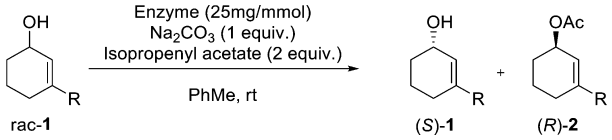
**Table 1. KR of Cyclic Allylic Alcohols Bearing a C3-Substituent**[a]




| Entry | Substrate | Enzyme | time (h) | conversion[b] (%) | $ee_{OH}$ (%)[c] | $ee_{OAc}$ (%)[c] | $E$ value[d] |
|---|---|---|---|---|---|---|---|
| 1 | | CALB | 4 | 46 | 83 | 97 | 160 |
| 2 |  | PS-IM | 4 | 23 | 34 | 98 | 170 |
| 3 | | AK Amano 20 | 4 | 4 | nd | nd | nd |
| 4 | **1a** | PS-C1 | 4 | 8 | nd | nd | nd |
| 5 | | IL1-PS | 4 | 1 | nd | nd | nd |
| 6 |  | CALB | 1 | 22 | 27 | 96 | 63 |
| 7 | **1b** | PS-IM | 1 | 7 | 5 | 82 | 11 |
| 8 |  | CALB | 1 | 40 | 20 | 30 | 2.2 |
| 9 | **1c** | PS-IM | 1 | 65 | 31 | 17 | 1.8 |

[a]Reaction conditions: **1** (0.2 mmol), isopropenyl acetate (2 equiv), $Na_2CO_3$ (1 equiv), and enzyme (25 mg/mmol) stirred in dry toluene (0.8 mL) at room temperature. [b]Determined by $^1$H NMR [c]Determined by chiral GC or HPLC (see the Supporting Information for further details). nd: not determined. [d]calculated by $ee_{OH}$ and $ee_{OAc}$ according to formula.[16]

## RESULTS AND DISCUSSION

Our study started with a screening of lipases to find the most suitable enzyme for the KR. Five immobilized enzymes were tested for the transesterification of 3-phenylcyclohex-2-enol (**1a**) employing isopropenyl acetate as acyl donor and toluene as solvent. Both *Candida antarctica* lipase B (CALB) and lipase PS from *Burkholderia cepacia* (previously named *Pseudomonas cepacia*) immobilized on Celite (PS-IM) were found to catalyze the reaction with high enantioselectivity giving $E$ values of 160 and 170, respectively.[16] CALB was the faster of the two lipases with a conversion of 46% after 4 h compared to 23% for PS-IM (Table 1, entries 1 and 2). Lipase AK Amano 20 and PS immobilized on ceramics (PS-C1) or coated with ionic liquid (IL1-PS) delivered the acetate with a poor rate, and therefore, these enzymes were not considered suitable for further studies (Table 1, entries 3−5). Encouraged by the high selectivity displayed by CALB and PS-IM for substrate **1a**, kinetic resolutions of cyclohexenyl alcohols with smaller groups in the C-3 position were performed. For substrate **1b** having a methyl substituent at the vinylic position, the selectivity displayed by CALB was still rather high with an $E$ value of 63 (Table 1, entry 6). For PS-IM on the other hand, the methyl was too small for the enzyme to catalyze the formation of (*R*)-**2b** in high enantioselectivity and a moderate $E$ value of 11 was obtained (Table 1, entry 7). Surprisingly, even for an unsubstituted olefin like **1c** the enzymes were capable of showing enantioselectivity, however the $E$ values were too low for the substrate to be practical for a DKR.

Having identified two suitable lipases for the DKR protocol, we investigated the suitability of racemization catalysts **A** and **B** by subjecting **1a** to a DKR with 5 mol % of either catalyst together with CALB (25 mg/mmol) as the enzyme. The reaction with catalyst **A** was performed at 60 °C with *p*-chlorophenyl acetate (2 equiv) as acyl donor and afforded **2a** in 90% yield and 80% ee after 24 h (Table 2, entry 1).[17] DKR with catalyst **B**, activated by 5 mol % of *t*-BuOK and using isopropenyl acetate as acyl donor, gave 47% yield of the desired acetate **2a** in 86% ee with the remaining components being 14% of unreacted **1a**, 10% of oxidation product 3-phenylcyclohex-2-enone (**3a**), and 29% of ether **4a** (Table 2, entry 2). The origin of ether **4a** is not clear, but previous studies on 3-arylcyclohex-2-enols have shown that compounds with electron-rich substituents at C3 give spontaneous ether formation even at room temperature.[18] However, compound **1a** could be stored for several weeks without any signs of **4a**. Clearly, one or several of the components in the DKR with catalyst **B** induced this undesired reaction. To establish the origin of **4a** a racemization test was conducted mixing only (*S*)-3-phenylcyclohex-2-enol ((*S*)-**1a**) and the activated ruthenium catalyst **B** in toluene. Within 1 h all of the alcohol had been converted to ether **4a**. This undesired side reaction makes **B** a less suitable catalyst for DKR of these substrates. Catalyst **A** was therefore chosen for the further studies of the DKR protocol, and the rate of the racemization was increased by increasing the temperature. This did not deliver (*R*)-**2a** in significant higher ee; however, the ketone formation increased (Table 2, entries 3 and 4). Lowering the enzyme loading with the aim of obtaining a better match between the transesterification rate and racemization rate did raise the ee to 90%, but again the ketone formation increased due to the slower reaction (Table 2, entry 5).

By changing to the slower biocatalyst PS-IM, which had shown a slightly higher selectivity in the KR, it was possible to


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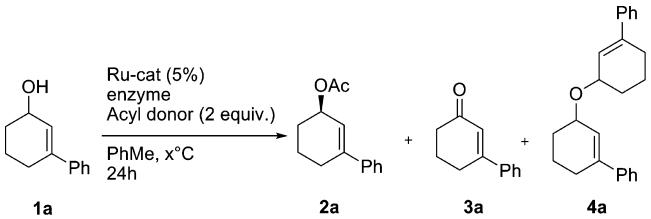
**Table 2. Optimization of Dynamic Kinetic Resolution of 3-Phenylcyclohex-2-enol (1a) with Lipase and Ruthenium Catalyst A or B[a]**




| entry | catalyst | enzyme | temp (°C) | $ee_{OAc}$[b] (%) | 1a (%) | 2a[c] (%) | 3a[c] (%) | 4a[c] (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | **A** | CALB (25 mg/mmol) | 60 | 80 | | 90 | 10 | |
| 2 | **B** | CALB (25 mg/mmol) | rt | 86 | 14 | 47 | 10 | 29 |
| 3 | **A** | CALB (25 mg/mmol) | 70 | 80 | | 88 | 12 | |
| 4 | **A** | CALB (25 mg/mmol) | 80 | 84 | | 86 | 14 | |
| 5 | **A** | CALB (2 mg/mmol) | 60 | 90 | | 74 | 26 | |
| 6 | **A** | PS-IM (50 mg/mmol) | 60 | 97 | | 91 | 9 | |
| 7[d] | **A** | PS-IM (50 mg/mmol) | 60 | 96 | | 92 | 8 | |
| 8[e] | **A** | PS-IM (50 mg/mmol) | 60 | 95 | 17 | 70 | 13 | |
| 9[f] | **A** | PS-IM (50 mg/mmol) | 60 | 94 | 12 | 62 | 26 | |
| 10[g] | **A** | PS-IM (50 mg/mmol) | 60 | 91 | | 86 | 14 | |

[a]Conditions using catalyst **A**: **1a** (0.25 mmol), **A** (13.6 mg), lipase, PCPA (2 equiv) stirred in dry toluene (1 mL) for 24 h. Conditions using catalyst **B**: **1a** (0.25 mmol), **B** (8 mg), *t*-BuOK (1.7 mg), $Na_2CO_3$ (26.5 mg), lipase, isopropenyl acetate (2 equiv) stirred in dry toluene (1 mL) for 24 h [b]Determined by GC analysis with chiral stationary phase. [c]Determined after 24 h by NMR analysis. [d]20 mol % of degassed 2,6-dimethylheptan-4-ol added. [e]Reaction performed in cyclohexane. [f]Reaction performed in acetonitrile. [g]Reaction performed in diisopropyl ether.

obtain (*R*)-3-phenylcyclohex-2-enyl acetate ((*R*)-**2a**) in 97% ee and 91% yield (Table 2, entry 6). Addition of 2,6-dimethylheptan-4-ol as a hydride donor gave similar results (entry 7), and therefore, this additive was later omitted to keep the protocol as simple as possible.[19] Other hydrophobic solvents were investigated, but none managed to compete with the results from the reaction made in toluene. In cyclohexane, the reaction reached 83% conversion after 24 h, where 70% was (*R*)-**2a** with an ee of 95% (Table 2, entry 8). In acetonitrile, the reaction rate was higher converting 88% of **1a**; however, the product ee was lower (94%) and ketone formation higher than in both toluene and cyclohexane (entry 9). In diisopropyl ether the reaction reached full conversion within 24 h and furnished acetate (*R*)-**2a** in 86% yield with an ee of 91% (entry 10).

3-(4-Chlorophenyl)cyclohex-2-enol (**1d**) was converted into (*R*)-3-(4-chlorophenyl)cyclohex-2-enyl acetate ((*R*)-**2d**) in 90% yield and 96% ee (Figure 1). However, with a *p*-methoxy substituent on the phenyl group (**1e**) a considerable amount of ketone was formed along with ether dimer **4e**. The acetate that was formed was racemic, even though the enzyme was supposed to be selective for **1e** showing an *E* value of 146. A plausible explanation for the formation of racemic acetate is racemization of the product via the stabilized carbocation.[20]

Next, we turned our attention to various allylic alcohols with scaffolds of interest for further transformation to more functionalized molecules. (*R*)-3-(Phenylsulfonyl)cyclohex-2-enyl acetate ((*R*)-**2f**) was obtained in full conversion with an ee of 94%. Compound (*R*)-**2f** is highly interesting due to the electrophilic site that the sulfonyl creates in the 2-position of the cyclic allylic alcohol derivative. This structural feature has been used extensively and has made it possible to reach a wide range of useful products.[21]

3-Iodocyclohex-2-enol (**1g**) gave 71% of the corresponding acetate **2g**, with an ee of 96%. However, by using racemization catalyst **B** the yield could be further increased to 99% (90% isolated) with 99% ee. No ether formation was observed for this substrate, plausibly due to the electron-withdrawing nature of the iodine. Enantiomerically pure **2g** is a useful synthetic intermediate. By performing an iodine−metal exchange this intermediate can be trapped by various electrophiles, making it possible to reach a wide range of optically active 3-subsituted allylic alcohols.[22] Also, a transition-metal-catalyzed cross coupling of **2g** allows for the introduction of a variety of substituents in the 3-position. Herein we demonstrate the possibility to acquire enantiomerically pure allylic alcohol **1c** by lithium−hydrogen exchange and diene **5** by Stille coupling. In both reactions, the stereochemistry is fully retained (Scheme 2).

(*R*)-3-Undecylcyclohex-2-enol (**1h**) was transformed into (*R*)-**2h** in 87% yield (79% isolated) and an ee of 91%. As previously shown this substrate can be used in the synthesis of the antifungal Tanikolide.[23]

When the DKR was performed on 3-(phenylsulfonyl)-cyclopent-2-enol (**1i**) a considerable amount of ketone was formed. Even after further elaboration the result could not be improved. The ee of (*R*)-**2i** was 88%, which can be considered reasonable due to the selectivity displayed by the enzyme.[24] By changing the 3-substituent to cyanide (**1j**), the ketone formation was completely suppressed, but the ee of the acetate **2j** was as low as 26%. Again, a full screening of available enzymes was performed, showing that none of the enzymes gave good enantioselectivity.

(*R*)-3-Methylcyclohex-2-enyl acetate ((*R*)-**2b**), used in the total synthesis of dysidiolide,[25] was acquired by the same protocol and was delivered in full conversion with an ee of 60%.

Due to the similarity of the acyl donor *p*-chlorophenyl acetate and some of the products a slow column chromatography with low polarity of the solvent was required in order to yield a pure product. In those cases where this was not possible, selective hydrolysis of the acyl donor was performed, prior to the chromatography.[26]

In summary, a DKR of cyclic allylic alcohols has been described. Most of the substrates are transformed to their corresponding acetates in high yields and high enantioselectivity. Electron-rich compounds are not suitable for this DKR protocol due to the formation of ether products. 3-Iodocyclohex-2-enyl acetate (**2g**), obtained by this method, is a useful synthetic intermediate, and its transformation toward chiral alcohol derivatives **1c** and **5** was demonstrated.

## ■ EXPERIMENTAL SECTION

**General Procedures.** All reactions were carried out using dry conditions in flame-dried glassware. DKR and KR were carried out under dry argon atmosphere using standard Schlenk techniques. Dry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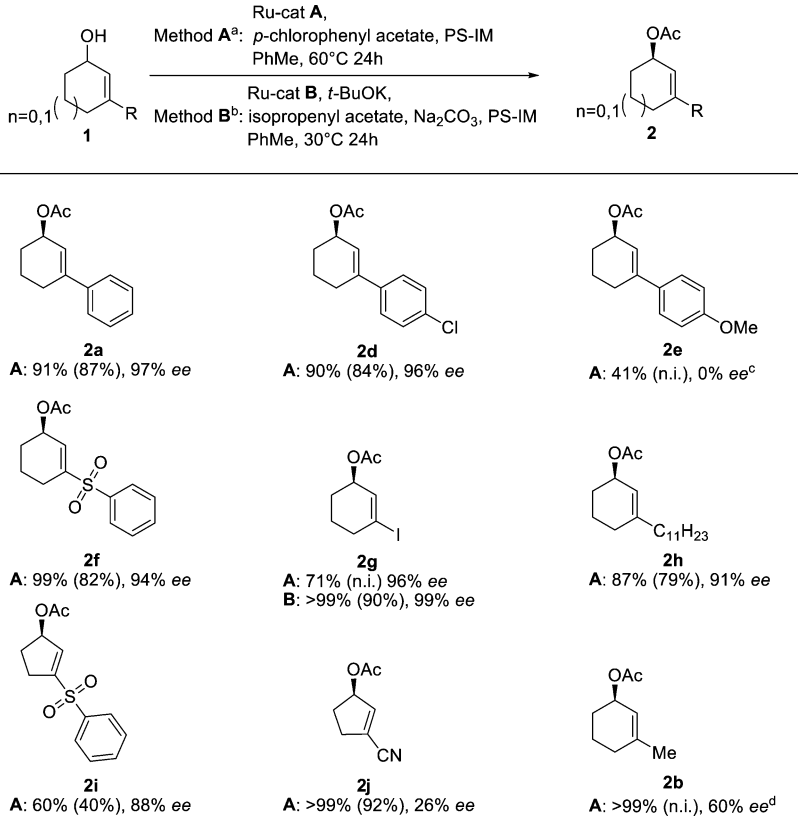
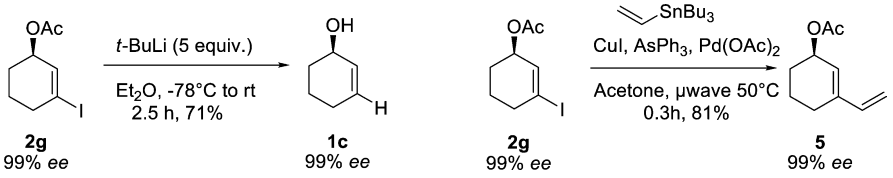



**Figure 1.** Substrate scope for the dynamic kinetic resolution of cyclic allylic alcohols. The conversion was measured by NMR with remaining material consisting of oxidation product **3** unless otherwise noted. Isolated yields in parentheses. n.i. = not isolated. Enantiomeric excess was determined by chiral GC or HPLC analysis. (a) Method A: substrate (0.25 mmol), **A** (5 mol %), PS-IM (50 mg/mmol), *p*-chlorophenyl acetate (2 equiv) stirred in dry toluene (1 mL) for 24 h. (b) Method B: substrate (0.25 mmol), **B** (5 mol %), *t*-BuOK (5 mol %), $Na_2CO_3$ (1 equiv), PS-IM (25 mg/mmol), isopropenyl acetate (2 equiv) stirred in dry toluene (1 mL) for 24 h. (c) 31% ketone, 28% ether **4e**. (d) CALB (5 mg/mmol) used instead of PS-IM and 2,6-dimethylpentan-4-ol (1 equiv) added.

**Scheme 2. Alteration of Substrate 2g by Reduction of the Iodine to Compound 1c and Stille coupling yielding 5[a]**




**2g** 99% *ee* → **1c** 99% *ee*; **2g** 99% *ee* → **5** 99% *ee*

[a]In both reactions the stereochemistry is fully retained.

solvents were obtained from VAC solvent purifier. Isopropenyl acetate was dried over $CaCl_2$ and distilled before use. $Na_2CO_3$ was dried for 1 h in vacuo at 220 °C before use. All other chemicals and solvents were used as purchased. The enantiomeric excess of the compounds was determined by chiral HPLC or chiral GC using racemic compounds as references. Racemic acetates **2** were obtained from the corresponding alcohols by standard acylation. Shvo's complex **A**[27] and catalyst **B**[11c] were synthesized according to literature procedures. CALB (Novozyme 435), PS-IM, AK Amano 20, PS-C1 are commercially available. IL1-PS can be prepared according to literature procedures.[28]

Silica column chromatography was performed with Davisil chromatographic silica media for separation and purification applications (35−70 $\mu$m). HPLC samples were analyzed by UV detection. GC samples were run on an IVADEX-1 chiral column with FID detector and $N_2$ as a carrier gas with a flow of 1.8 mL/min. $^1$H and $^{13}$C NMR were recorded at 400 and 100 MHz, respectively. $^1$H NMR data are presented as follows: chemical shift $\delta$ (in ppm) [multiplicity, coupling constant(s) *J*, relative integral]. The signal due to residual $CHCl_3$ appearing at $\delta_H$ 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at $\delta_C$ 77.16 were used to reference the $^1$H and $^{13}$C NMR spectra, respectively. HRMS spectra were recorded with either a TOF-ESI detector or using CI with methane as carrier gas. Microwave reactions were performed in a Biotage Initiator 2.5.3, with an external IR sensor for temperature monitoring.

*3-Phenylcyclohex-2-enol (**1a**).* Compound **1a** was prepared according to a literature procedure.[29] $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 7.35−7.22 (m, 5H); 3.84−3.78 (m, 1H); 3.50 (s, 1H); 2.56−2.48 (m, 4H); 2.30−2.20 (m, 1H); 1.85−1.74 (m, 1H); 1.65−1.46 (m, 3H). HPLC: Chiralpak OB column, 5% *i*-PrOH/isohexane, 1 mL·min$^{-1}$, 35 °C, 211 nm, $t_{R1}$ = 10 min (*R*), $t_{R2}$ = 18 min (*S*).

Alcohol **1b** and **1c** were both commercial available.

The remaining alcohols **1d−j** were prepared by reduction of the corresponding ketone. The ketones were prepared according to the following methods: ref 30 (ketones for **1d** and **1e**), ref 21b (ketones for **1f** and **1i**), ref 31 (ketone for **1g**), ref 32 (ketone for **1h**), ref 33 (ketone for **1j**).

**General Procedure for Ketone Reduction. Synthesis of 1d−j.** $CeCl_3{\cdot}7H_2O$ (1.2 equiv) was dissolved in MeOH (10 mL/mmol). After addition of the corresponding ketone (1 equivalent), the mixture was cooled to 0 °C. $NaBH_4$ (1.2 equiv) was added in one portion, and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the reaction mixture was allowed to stir for 3 h. After addition of a satd $NH_4Cl$ (aq), the product was extracted twice with $Et_2O$. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification through flash chromatography ($SiO_2$, pentane/EtOAc) gave the corresponding allylic alcohol in approximately quantitative yields.

*3-(4-Chlorophenyl)cyclohex-2-enol (**1d**).* Experimental data were in accordance with those reported in the previous literature.[34] $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.35−7.28 (m, 4H), 6.14−6.09 (m, 1H), 4.40 (s, 1H), 2.47−2.29 (m, 2H), 2.00−1.87 (m, 2H), 1.79−1.64 (m, 2H). No chiral separation found on GC or HPLC.

*3-(4-Methoxyphenyl)cyclohex-2-enol (**1e**).* Experimental data were in accordance with those reported in the previous literature.[29] $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.35 (d, 2H, $J$ = 8.9 Hz), 6.86 (d, 2H, J = 8.9 Hz), 6.09−6.02 (m, 1H), 4.43−4.33 (m, 1H), 3.81 (s, 3H), 2.50−2.40 (m, 1H), 2.38−2.29 (m, 1H), 1.98−1.85 (m, 2H), 1.79−1.63 (m, 2H). Chiral separation: GC: IVADEX-I, 100−1 °C/min−180 °C, $t_{R1}$ = 79.8 min ($S$), $t_{R2}$ = 80.3 min ($R$).

*3-(Phenylsulfonyl)cyclohex-2-enol (**1f**).* Experimental data were in accordance with those reported in the previous literature.[21b] $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.44−7.39 (m, 2H), 7.36−7.28 (m, 3H), 5.74−5.71 (m, 1H), 4.28−4.21 (m, 1H), 2.20−2.03 (m, 2H), 1.90−1.74 (m, 2H), 1.68−1.58 (m, 2H). Chiral separation: HPLC: Chiralpak OJ column, 95:5 isohexane/$i$-PrOH, 0.5 mL·min$^{-1}$, 30 °C, 211 nm, $t_{R1}$ = 23 min ($R$), $t_{R2}$ = 24.6 min ($S$).

*3-Iodocyclohex-2-enol (**1g**).* Experimental data were in accordance with those previous reported.[35] $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 6.46−6.42 (m, 1H), 4.19−4.13 (m, 1H), 2.60−2.41 (m, 2H), 1.95−1.87 (m, 2H), 1.86−1.76 (m, 1H), 1.69−1.57 (m, 2H). Chiral separation: GC: IVADEX-I, 70−1 °C/min−140 °C, $t_{R1}$ = 57.1 min ($R$), $t_{R2}$ = 60.2 min ($S$).

*3-Undecylcyclohex-2-enol (**1h**).* Experimental data were in accordance with those reported in the previous literature.[32] $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 5.52−5.48 (m, 1H), 4.21−4.17 (m, 1H), 2.05−1.89 (m, 4H), 1.86−1.70 (m, 2H), 1.64−1.55 (m, 2H), 1.47−1.36 (m, 2H), 1.34−1.24 (m, 16H), 0.92−0.89 (m, 3H). No chiral separation found on GC or HPLC.

*3-(Phenylsulfonyl)cyclopent-2-enol (**1i**).* Experimental data were in accordance with those reported in the previous literature.[21b] $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.96−7.91 (m, 2H), 7.72−7.65 (m, 1H), 7.61−7.55 (m, 2H), 6.69−6.65 (m, 1H), 5.05−4.97 (m, 1H), 2.73−2..63 (m, 1H), 2.56−2.44 (m, 2H), 1.97−1.82 (m, 2H). HPLC: Chiralpak IA column, 10% $i$-PrOH/isohexane, 0.5 mL·min$^{-1}$, 30 °C, 211 nm, $t_{R1}$ = 50 min ($R$), $t_{R2}$ = 57 min ($S$).

*3-Hydroxycyclopent-1-enecarbonitrile (**1j**).* Experimental data were in accordance with those reported in the previous literature.[33] $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 6.63−6.60 (m, 1H), 5.04−4.96 (m, 1H), 2.81−2.71 (m, 1H), 2.60−2.49 (m, 1H), 2.46−2.36 (m, 1H), 1.88−1.78 (m, 2H). HPLC: Chiralpak IA column, 5% $i$-PrOH/isohexane, 0.5 mL·min$^{-1}$, 30 °C, 211 nm, $t_{R1}$ = 30 min ($R$), $t_{R2}$ = 33 min ($S$).

**General Procedure for Kinetic Resolution.** Substrate (0.2 mmol), isopropenyl acetate (2 equiv), lipase (25 mg/mmol), and $Na_2CO_3$ (1 equiv) was dissolved in dry toluene (0.8 mL) and stirred at room temperature. Aliquots (50 $\mu$L) were taken by syringe at the indicated time and filtered with EtOAc through a Celite plug. After evaporation of the solvent, the enantiomeric excess and conversion were check by HPLC and NMR spectroscopy, respectively.

**General Procedure Dynamic Kinetic Resolution.** *Method A.* Shvo's complex (A) (13.6 mg, 0.0125 mmol), lipase (12.5 mg, 50 mg/mmol substrate), and the racemic alcohol **1** (0.25 mmol) were added to a dry Schlenk tube under argon atmosphere. Dry toluene (1 mL) and then $p$-chlorophenyl acetate (0.875 mmol) were added. The reaction was heated to 60 °C. After 24 h, the mixture was filtered through cotton and concentrated under vacuum.

*Method B.* Ruthenium complex B ($\eta^5C_5Ph_5$)Ru(CO)$_2$Cl (8 mg, 0.0125 mmol), lipase (6.25 mg, 25 mg/mmol substrate), and $Na_2CO_3$ (26.5 mg, 0.25 mmol) were added to a dry Schlenk tube under argon atmosphere. Dry toluene (0.5 mL) was added, and the resulting yellow solution was stirred. A THF solution of $t$-BuOK (25 $\mu$L, 0.5 M in dry THF, 0.0125 mmol) was added to the reaction mixture. The reaction turned orange. After approximately 5 min of stirring, racemic alcohol **1** (0.25 mmol) dissolved in dry toluene (0.5 mL) was added to the reaction mixture. After an additional 5 min, isopropenyl acetate (110 $\mu$L, 2 mmol) was added. The reaction was heated to indicated temperature. After 24 h, the reaction mixture was filtered and concentrated.

*(R)-3-Phenylcyclohex-2-enyl Acetate (**2a**).* The reaction was performed according to method A using the enzyme preparation Amano PS-IM. Excess $p$-chlorophenyl acetate was hydrolyzed by stirring the concentrated residue in a $NaHCO_3$-saturated 4:1 mixture of MeOH/$H_2O$ for 1 h. $SiO_2$ chromatography (pentane/EtOAc 20:1) was performed to obtain pure product in 87% yield (47 mg) and 97% ee. Experimental data were in accordance with those reported in the previous literature.[36] $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.44−7.40 (m, 2H), 7.37−7.28 (m, 3H), 6.10−6.04 (m, 1H), 5.48 (s, 1H), 2.59−2.36 (m, 2H), 2.07 (s, 3H), 1.95−1.85 (m, 2H), 1.82−1.74 (m, 2H). Chiral separation: GC: IVADEX-I, 100−1 °C/min−180 °C, $t_{R1}$ = 55.5 min ($S$), $t_{R2}$ = 56.4 min ($R$), 97% ee.

The NMR data for side product **4a** were in accordance with those reported in the previous literature.[37] Mixture of two diastereomers. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.46−4.42 (m, 4H), 7.36−7.30 (m, 4H), 6.21−6.14 (m, 2H), 4.34−4.24 (m, 2H), 2.55−2.46 (m, 2H), 2.44−2.35 (m, 2H), 2.06−1.91 (m, 4H), 1.86−1.72 (m, 4H).

*(R)-3-(4-Chlorophenyl)cyclohex-2-enyl Acetate (**2d**).* The reaction performed according to method A using the enzyme preparation Amano PS-IM. Compound isolated after column chromatography ($SiO_2$, pentane/EtOAc 19:1) in 84% yield (53 mg) and 96% ee. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.39−7.27 (m, 4H), 6.09−6.05 (m, 1H), 5.47−5.41 (m, 1H), 2.51−2.45 (m, 1H), 2.39−2.30 (m, 1H) 2.08 (s, 3H), 1.95−1.90 (m, 2H), 1.79−1.75 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 171.0, 141.2, 139.6, 133.6, 128.6, 126.7, 122.3 69.0, 28.0, 27.4, 21.5, 19.5. HR-MS (ESI): calcd for $C_{14}H_{15}ClO_2^+$ 273.0652, found 273.0653 [M + Na]$^+$. Chiral separation: GC: IVADEX-I, 100−1 °C/min−180 °C, $t_{R1}$ = 75.7 min ($S$), $t_{R2}$ = 76.2 min ($R$), $[\alpha]^{22}_D$ = +85.4 ($c$ 0.80, $CHCl_3$), 96% ee.

*(R)-3-(4-Methoxyphenyl)cyclohex-2-enyl Acetate (**2e**).* The reaction was performed according to method A using the enzyme preparation Amano PS-IM. After 24 h, the reaction mixture consisted of 41% **2e**, 31% of the ketone adduct, and 28% of ether dimer. No enantiomeric excess was obtained. The compound was not isolated. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.38−7.33 (m, 2H), 6.88−6.83 (m, 2H), 6.03−6.00 (m. 1H), 5.47−5.42 (m, 1H), 3.81 (s, 3H), 2.54−2.46 (m, 1H), 2.39−2.30 (m, 1H), 2.07 (s, 3H), 1.94−1.87 (m, 2H), 1.82−1.75 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 171.0, 159.4, 141.6, 133.6, 126.6, 120.7, 113.8, 69.2, 55.4, 28.1, 27.5, 21.6, 19.5. HR-MS (CI): calcd for $C_{15}H_{18}O_3$ 246.1256, found 246.1255 [M]$^+$. Chiral separation: GC: IVADEX-I, 100−1 °C/min−200 °C, $t_{R1}$ = 81.1 min ($S$), $t_{R2}$ = 82.5 min ($R$), 0% ee.

*(R)-3-(Phenylsulfonyl)cyclohex-2-enyl Acetate (**2f**).* The reaction was performed according to method A using the enzyme preparation Amano PS-IM. The compound was isolated after column chromatography ($SiO_2$, pentane/EtOAc 4:1) in 82% yield (27 mg), 94% ee. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.90−7.84 (m, 2H), 7.67−7.61 (m, 1H), 7.58−7.51 (m, 2H) 6.93−6.88 (m, 1H), 5.46−5.40 (m, 1H), 2.32−2.22 (m, 1H), 2.19−2.11 (m, 1H), 2.08 (s, 3H), 1.93−1.59 (m, 4H). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 170.4, 144.5, 138.7, 134.7, 133.7, 129.4, 128.4, 67.4, 27.2, 23.0, 21.2, 19.2. HR-MS (ESI): calcd for $C_{14}H_{16}NaO_4S^+$ 303.0671, found 303.0662 [M + Na]$^+$. Chiral separation: HPLC: Chiralpak OJ column, 97:3 isohexane/$i$-PrOH, 0.5 mL·min$^{-1}$, 30 °C, 211 nm, $t_{R1}$ = 22 min ($R$), $t_{R2}$ = 23 min ($S$). $[\alpha]^{20}_D$ = +95.0 ($c$ 0.92, $CHCl_3$), 94% ee.

*(R)-3-Iodocyclohex-2-enyl Acetate (**2g**).* The reaction was performed at 30 °C according to method B using the enzyme preparation Amano PS-IM. Compound isolated after column chromatography ($SiO_2$, pentane/EtOAc 20:1) in 90% yield (58 mg). >99% ee. Experimental data were in accordance with those previous reported.[35] $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 6.46−6.42 (m, 1H), 4.19−4.13 (m, 1H), 2.60−2.41 (m, 2H), 1.95−1.87 (m, 2H), 1.86−1.76 (m, 1H), 1.69−1.57 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ =


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170.4, 135.7, 103.8, 69.4, 39.4, 26.9, 21.5, 21.4. Chiral separation: GC: IVADEX-I, 70−1 °C/min−140 °C, $t_{R1}$ = 52 min (*S*), $t_{R2}$ = 54 min (*R*). $[\alpha]^{20}_{D}$ = +127.9 (*c* 1.90, THF), >99% ee.

*(R)-3-Undecylcyclohex-2-enyl Acetate (**2h**).* The reaction was performed according to method A using the enzyme preparation Amano PS-IM. The compound was isolated after column chromatography ($SiO_2$, pentane/EtOAc 19:1) in 79% yield (59 mg). 91% ee. Experimental data were in accordance with those previous reported.[36] $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 5.46−5.43 (m, 1H), 5.28−5.24 (m, 1H), 2.04 (s, 3H), 2.01−1.88 (m, 4H), 1.83−1.59 (m, 4H), 1.44−1.36 (m, 2H), 1.29−1.23 (m, 16H), 0.91 (t, 3H *J* = 6.5). Chiral separation: HPLC: Chiralpak ID column, 100% isohexane, 0.5 mL·min$^{-1}$, 22 °C, 211 nm, $t_{R1}$ = 54 min (*R*), $t_{R2}$ = 61 min (*S*). $[\alpha]^{20}_{D}$ = +90.2 (*c* 0.58, $CHCl_3$), 91% ee.

*(R)-3-(Phenylsulfonyl)cyclopent-2-enyl Acetate (**2i**).* The reaction was performed according to method A using the enzyme preparation Amano PS-IM. The compound was isolated after column chromatography ($SiO_2$, pentane/EtOAc 4:1) in 40% yield (27 mg). 88% ee. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.94−7.89 (m, 2H), 7.69−7.63 (m, 1H), 7.60−7.53 (m, 2H), 6.62−6.57 (m, 1H), 5.75−5.68 (m, 1H), 2.76−2.64 (m, 1H), 2.56−2.42 (m, 2H), 2.03 (s, 3H), 1.98−1.83 (m, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 170.5, 150.0, 138.8, 138.2, 134.0, 129.5, 128.4, 78.3, 30.7, 29.5, 21.1. HR-MS (ESI): calcd for $C_{13}H_{14}O_4S^+$ 289.0498, found 289.0505 $[M + Na]^+$. Chiral separation: HPLC: Chiralpak IA column, 10% *i*-PrOH/isohexane, 0.5 mL·min$^{-1}$, 30 °C, 211 nm, $t_{R1}$ = 24 min (*R*), $t_{R2}$ = 26 min (*S*), 88% ee.

*(R)-3-Cyanocyclopent-2-enyl Acetate (**2j**).* The reaction was performed according to method A using the enzyme preparation Amano PS-IM. The compound was isolated after column chromatography ($SiO_2$, pentane/EtOAc 4:1) in 92% yield (35 mg). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 6.63−6.59 (m, 1H), 5.77−5.71 (m, 1H), 2.82−2.72 (m, 1H), 2.64−2.54 (m, 1H), 2.49−2.38 (m, 1H), 2.05 (s, 3H), 1.88−1.78 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 170.5, 144.8, 120.3, 115.7, 78.7, 33.2, 29.7, 21.0. HR-MS (CI): calcd for $C_8H_{10}NO_2$ 152.0712, found 152.0718 $[M + H]^+$. Chiral separation: HPLC: Chiralpak IA column, 1% *i*-PrOH/isohexane, 0.5 mL·min$^{-1}$, 30 °C, 211 nm, $t_{R1}$ = 20.6 min (*R*), $t_{R2}$ = 21.9 min (*S*), 26% ee.

*(R)-3-Methylcyclohex-2-enyl Acetate-3 (**2b**).* Reaction performed according to method A with 2,6-dimethylheptan-4-ol (1 equiv) and *Candida antarctica* lipase B, enzyme preparation Novozyme-435 (5 mg/mmol). The product was obtained in 60% ee but not isolated. Experimental data in accordance with those previous reported.[38] $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 5.49−5.45 (m, 1H), 5.27−5.21 (m, 1H), 2.04 (s, 3H), 2.00−1.89 (m, 2H), 1.82−1.59 (m, 4H), 1.71 (s, 3H). Chiral separation: GC: IVADEX-I, 70−1 °C/min−140 °C, $t_{R1}$ = 20.6 min (*S*), $t_{R2}$ = 22.42 min (*R*), 60% ee.

*(R)-3-Vinylcyclohex-2-enyl Acetate (**5**).* Perpared according to the procedure of Pinkerton et al.[22a] To a flame-dried microvial were added (*R*)-**2e** (45 mg, 0.27 mmol, 99% ee), $Pd(OAc)_2$ (5 mg, 0.02 mmol), CuI (4 mg, 0.02 mmol), and $Ph_3As$ (19 mg, 0.06 mmol). The vial was capped with a Teflon septum and evacuated for 1 h under reduced pressure before argon was introduced to the flask. Tributylvinyltin (204 μL, 0.6 mmol) and acetone (1.2 mL) were added, and the mixture was stirred at 50 °C under microwave heating for 20 min and then cooled to room temperature. The black mixture was filtered through $SiO_2$ by EtOAc, concentrated under reduced pressure, and purified by column chromatography ($SiO_2$, pentane/EtOAc 50:1) yielding **5** in 81% yield and retained ee. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 6.35 (dd, *J* = 17.6 Hz 10.7 Hz, 1H), 5.73−5.70 (m, 1H), 5.39−5.33 (m, 1H), 5.24 (d, 17.6 Hz, 1H), 5.07 (d, 10.7 Hz, 1H), 2.28−2.06 (m, 2H), 2.05 (s, 3H), 1.90−1.77 (m, 1H), 1.76−1.65 (m, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 171.0, 140.8, 139.1, 126.5, 113.6, 69.0, 28.5, 23.8, 21.5, 18.9. HR-MS (CI): calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0998 $[M + H]^+$. Chiral separation: HPLC: Chiralpak OJ column, 1% *i*-PrOH/isohexane, 0.5 mL·min$^{-1}$, 22 °C, 211 nm, $t_{R1}$ = 10.1 min (*S*), $t_{R2}$ = 11.1 min (*S*). $[\alpha]^{20}_{D}$ = +90.172 (c 0.58, $CHCl_3$), $[\alpha]^{25}_{D}$ = +92.5 (*c* 0.4, $CHCl_3$), 99 ee.

*(R)-Cyclohex-2-enol (**1c**).* *t*-BuLi (1.7 M hexane solution, 1.1 mL, 1.88 mmol) was added to a dry $Et_2O$ (2 mL) solution of **2e** (100 mg, 0.38 mmol, 99% ee) at −78 °C. The resulting solution was stirred at −78 °C for 20 min and then allowed to reach rt for 2 h. The reaction was quenched by addition of 3 mL of $NH_4Cl$ (aq) followed by wash of the organic phase by 3 mL of $H_2O$. The organic phase was separated and dried with $MgSO_4$. The solvent was reduced by evaporation at 50 mbar pressure. The product was isolated with 15 mol % of the remaining diethyl ether that could not be evaporated without losing large amounts of product. Yield: **1c** + 15% $Et_2O$: 28 mg (71%) 99% ee. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 5.87−5.81 (m, 1H), 5.78−5.72 (m, 1H), 4.20 (br s, 1H), 2.10−1.95 (m, 2H), 1.94−1.83 (m, 1H), 1.79−1.68 (m, 1H), 1.66−1.50 (m, 3H). Chiral separation: GC: IVADEX-I, 70 °C-1 °C/min-140 °C, $t_{R1}$ = 12.4 min (*S*), $t_{R2}$ = 13.0 min (*R*), 99% ee.

## ■ ASSOCIATED CONTENT

### Supporting Information

Mechanism for formation of racemic **2e** and **4e**, additional kinetic resolution data, and copies of $^1$H and $^{13}$C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org/.

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### Notes

The authors declare no competing financial interest.

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