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Note

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Base-free Dynamic Kinetic Resolution of Secondary Alcohols with a Ruthenium–Lipase Couple

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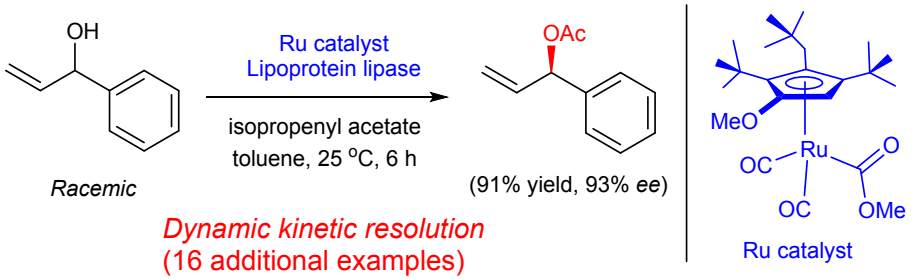
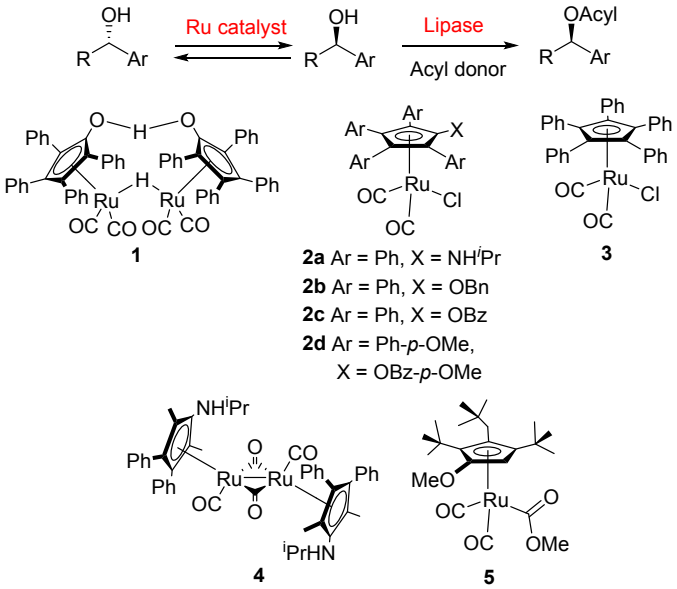


ABSTRACT

We report the dynamic kinetic resolution (DKR) of various secondary alcohols by the combination of a ruthenium catalyst and an anionic surfactant-activated lipoprotein lipase. The DKR reactions performed under totally base-free conditions at room temperature provided the products of excellent enantiopurities (91–99% *ee* or greater) in high yields (92−99%). More importantly, the DKR of α-arylallyl alcohols was achieved for the first time with high yields (87−91%).

Dynamic kinetic resolution (DKR) provides a powerful methodology for the transformations of racemic substrates to enantiomerically-enriched products.[1] Since the first report by the Williams group on the coupling of a metal-catalyzed racemization and an enzymatic kinetic resolution for DKR,[2] various metal complexes have been reported to be useful as racemization catalysts for the chemoenzymatic DKR of secondary alcohols.[3] Among them, cyclopentadienylruthenium complexes **1**–**3** were most widely utilized in DKR[4] (Scheme 1). The Shvo's dimeric ruthenium complex **1** needs thermal activation into two active monomeric forms, thus requiring a thermally stable enzyme such as *Candida antarctica* lipase B (CALB) as the partner for the efficient DKR.[5] Ruthenium catalysts **2a-d** reported by our group[6] display good activities at ambient temperature, which are thus compatible with a wider range of enzymes in DKR. The ruthenium catalyst **3** also displays a good activity at ambient temperature. [7] Ru catalysts **2** and **3**, however, require a base (KO*t*Bu or K_2CO_3) for the activation, which makes the DKR process less practical. Thus, we have tried to develop a ruthenium catalyst undergoing base-free activation at ambient temperature. The first example was a dimeric Ru complex **4** displaying good racemization activity under the base-free conditions if photoactivated.[8] However, the DKR with **4** needed still a weak base to remove acid formed as byproduct. We now report that ruthenium catalyst **5**[9] is a good alternative for the base-free racemization and DKR of secondary alcohols at ambient temperature.[10] In particular, this ruthenium catalyst is useful for the DKR of α-substituted allyl alcohols that was previously difficult to achieve with other Ru catalysts.[6b, 11]

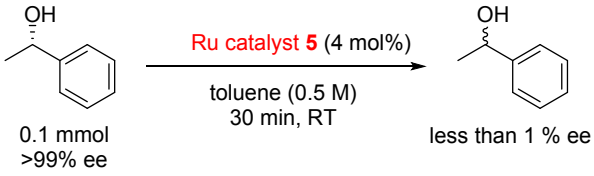
Scheme 1. Dynamic kinetic resolution of secondary alcohols and ruthenium catalysts



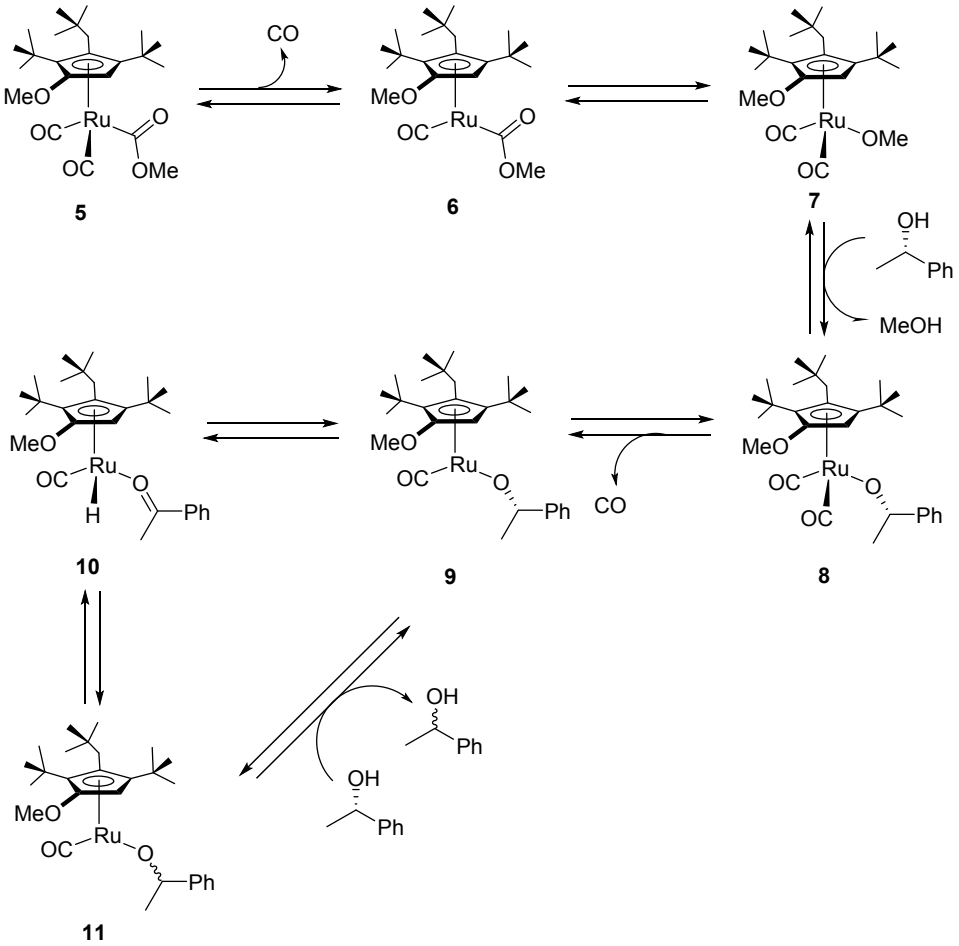
At first, we examined the racemization of (*S*)-1-phenylethanol with **5** in the absence of base. The racemization in the presence of 4 mol% **5** proceeded to completion within 30 min at room temperature (Scheme 2). At the early stage of racemization, the color of solution was changed from yellow to red.

This color change implies the formation of new ruthenium complex **7** as the active catalyst form leading to racemization (Scheme 3). The active catalyst **7** then reacts with nonracemic alcohol to give ruthenium-alkoxide complex **8**, which undergoes decarbonylation and reductive elimination to yield ruthenium-ketone complex **10** via **9**. The subsequent reduction of ketone coordinated to ruthenium leads to racemic alkoxide complex **11**. The alkoxide exchange then gives ruthenium-alkoxide complex **9** with release of racemic alcohol.[12] It is noted that the racemization activity of **5** is rather surprising because the Bäckvall group reported that the pentaphenylcyclopentadienylruthenium analogue of **5** was thermally stable and displayed no racemization activity.[12] As a rationale of the racemization activity of **5**, we suggest that the conversion of **5** into its active catalyst form **7** via 16-electron complex **6** could take place owing to the presence of electron-rich cyclopentadienyl ring.

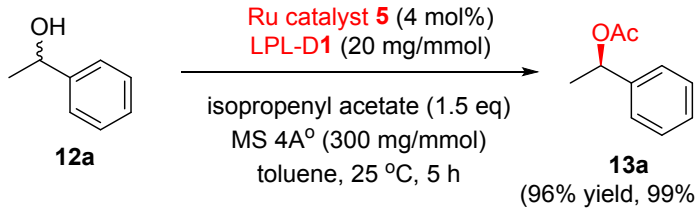
Scheme 2. Racemization of (*S*)-1-phenylethanol with Ru catalyst



Scheme 3. Proposed pathway for the racemization of (*S*)-1-phenylethanol



Scheme 4. DKR of 1-phenylethanol



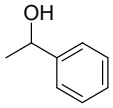
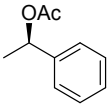
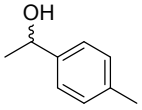
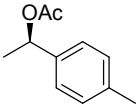
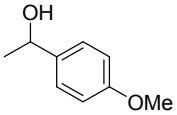
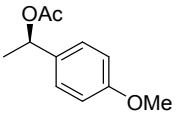
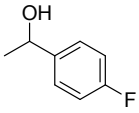
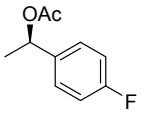
The successful racemization of (*S*)-1-phenylethanol with **5** encouraged us to explore the base-free DKR of racemic 1-phenylethanol **12a** by the combination of **5** and an (*R*)-selective lipoprotein lipase (LPL) from *Burkholderia* species. LPL was treated with anionic surfactant before use to ensure its high activity in organic solvent. In our earlier study,[13] it was found that the anionic surfactant-treated LPL (LPL-D**1**) was three orders of magnitude more active than its native counterpart in toluene. The DKR reaction of racemic 1-phenylethanol was then performed with a solution containing substrate (0.2 mmol), LPL-D**1** (20 mg/mmol), **5** (4 mol%), isopropenyl acetate (0.3 mmol), and MS 4Å (60 mg) in toluene (0.5 M) at room temperature. The DKR was complete in 5 h and gave the product of excellent enantiopurity (99 % *ee*) with high yield (96 %) (Scheme 4). The results thus proved that the base-free DKR was successful.

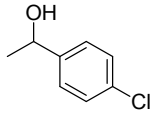
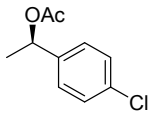
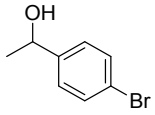
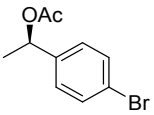
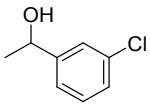
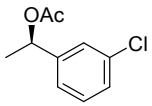
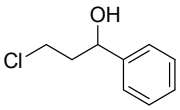
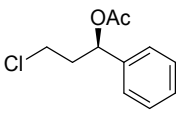
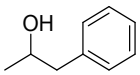
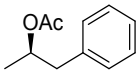
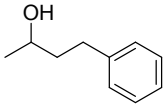
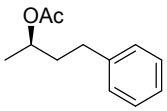
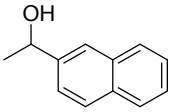
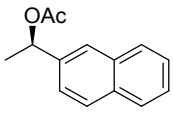
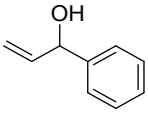
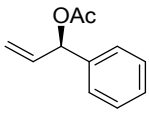
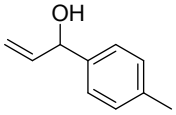
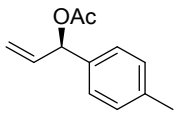
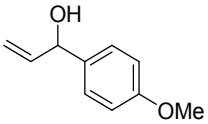
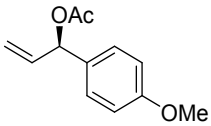
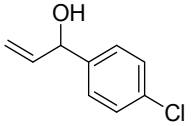
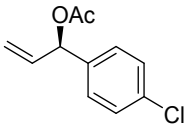
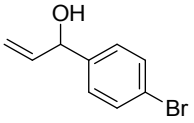
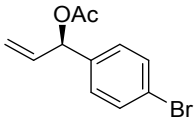
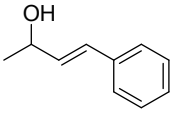
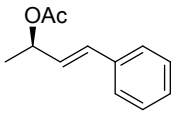
Other secondary benzylic alcohols, **12b-f** with a *para*-substituent on the benzene ring, were also subject to DKR under base-free conditions. All of them were transformed into the products of excellent enantiopurities (99 % *ee* or greater) with high yields (95−97 %), although two of them, **12e** and **12f**, required a longer reaction time (entries 2−6, Table 1). The need for a longer reaction time implies that electron-poor substrates are less reactive in both Ru-catalyzed racemization and lipase-catalyzed acylation. The results from the DKR of **12g** with an electron-withdrawing *meta*-substituent were similar to those from the DKR of **12e** (compare entries 5 and 7, Table 1). It is expected that other secondary benzylic alcohols with a *meta*-substituent also should react similarly to their *para*-substituted counterparts in DKR. Secondary benzylic alcohols with an *ortho*-substituent were not tested for DKR because they are poor substrates of LPL. The chloroethyl carbinol **12h** reacted even more slowly owing to the presence of an electron-withdrawing, relatively larger alkyl substituent at the hydroxymethine center, thus requiring the use of a larger amount of enzyme and much longer reaction time (entry 8, Table 1). Although the yield of **13h** was high, the enantioselectivity was slightly lower. On the other hand, non-benzylic alcohols, **12i** and **12j**, were as good as benzylic alcohols in DKR (entries 9 and 10, Table 1). Excellent yields and enantioselectivities were obtained. The DKR of naphthyl carbinol **12k** was also successful with excellent yield and enantioselectivity (entry 11, Table 1).

In the previous study,[6b] we found that α-phenylallyl alcohol **12l** was poor substrate in the DKR employing **2a** as the racemization catalyst. This DKR performed in the presence of one equivalent of Na_2CO_3 provided 62% yield with a relatively large amount of saturated ketone (38% yield) as the side

product. In the present work, we also found that a significant amount of saturated ketone (23% yield) was produced in the DKR of **12l** employing **2d** as the racemization catalyst in the presence of one equivalent of K_2CO_3. It is noted that **2d** requires one equivalent of K_2CO_3 for pre-activation and DKR. It was previously reported that the rates in the Ru-catalyzed isomerization of allylic alcohols to saturated ketone were dramatically enhanced by K_2CO_3.[14] We also observed such a dramatic rate enhancement by K_2CO_3 in the Ru-catalyzed isomerization of **12l**. In the presence of ruthenium catalyst **2d** (4 mol%) and K_2CO_3 (1 equiv) in toluene at room temperature, **12l** was isomerized almost quantitatively to saturated ketone within 6 h. Under the same conditions without base, however, no significant isomerization took place. These results thus suggest that the use of base-free racemization catalyst system should lead to the successful DKR of **12l**. As expected, the base-free DKR of **12l** with **5** provided high yield (91%) with a small amount of ethyl phenyl ketone (7%) (entry 12, Table 1). To the best of our knowledge, this is the first successful DKR of **12l** that has been reported up to date. This success encouraged us to further test the *p*-substituted derivatives of **12l** in DKR. Allylic alcohols with an electron-donating substituent, **12m** and **12n**, displayed also satisfactory performance. Products, **13m** and **13n**, were obtained in high yields (90–91% yield) with good enantiopurities (95–96% *ee*) (entries 13 and 14, Table 1). In contrast to these results, allylic alcohols with an electron-withdrawing substituent, **12o** and **12p**, were problematic and required a lower amount of enzyme for giving a good enantioselectivity. The DKR reactions of these alcohols thus proceeded rather slowly and provided relatively lower yields and enantiomeric excesses (entries 15 and 16, Table 1). Finally, the DKR of γ-substituted allyl alcohol **12q** proceeded successfully and provided enantiomerically pure **13q** in 94% yield (entry 17, Table 1).

Table 1. DKR of secondary alcohols[a]

Entry	Substrate		LPL-D**1** (mg/mmol)	*t* (h)	Product[b]		Yield[c] (%)	*ee*[d] (%)
1		**12a**	20	5		**13a**	96	99
2		**12b**	20	6		**13b**	96	>99
3		**12c**	20	6		**13c**	95	99
4		**12d**	20	6		**13d**	97	99

5		**12e**	20	12		**13e**	95	>99
6		**12f**	20	12		**13f**	97	>99
7		**12g**	20	12		**13g**	93	>99
8		**12h**	40	24		**13h**	95	95
9		**12i**	20	6		**13i**	92	>99
10		**12j**	20	12		**13j**	94	97
11		**12k**	20	9		**13k**	99	>99
12		**12l**	20	6		**13l**	91	93
13		**12m**	20	9		**13m**	90	96
14		**12n**	20	9		**13n**	91	95
15		**12o**	10	48		**13o**	89	91
16		**12p**	10	48		**13p**	87	91
17		**12q**	20	12		**13q**	94	>99

[a] Alcohol (0.2 mmol), LPL-D**1** (10–40 mg/mmol), Ru catalyst **5** (4 mol%), isopropenyl acetate (0.3 mmol), and MS 4Å (60 mg) were stirred in toluene (0.5 M) at room temperature under an argon atmosphere. [b] The signs of optical rotations and the chromatogram patterns from chiral HPLC analyses indicate that all the products have (*R*)-stereochemistry. [c] Isolated yield. [d] Determined by chiral HPLC.

In summary, we explored the DKR of various secondary alcohols employing ruthenium complex **5** as the racemization catalyst and LPL-D**1** as the resolution catalyst under totally base-free conditions. The DKR reactions of simple secondary alcohols proceeded smoothly and provided high yields and excellent enantiomeric excesses. Furthermore, we have demonstrated for the first time that the DKR of α-arylallyl alcohols provided good to high yields. Our DKR process is simpler and easier to perform compared to those requiring base for the pre-activation of racemization catalyst. Thus, we have established a useful protocol for the base-free DKR of a wider range of secondary alcohols, leading to the synthesis of enantiomerically-enriched esters.[15]

EXPERIMENTAL SECTION

General procedure for dynamic kinetic resolution. In a flame-dried Schlenk flask, substrate (0.2 mmol), LPL-D**1**[16] (10−20 mg/mmol), ruthenium catalyst **5**[17] (4 mol%), and molecular sieves (4Å, powder, 60 mg) were added under an argon atmosphere, followed by addition of distilled toluene (400 μL) and isopropenyl acetate (0.3 mmol, 34 μL). The reaction mixture was stirred at room temperature for 5–48 h. After the reaction was completed, the mixture was filtered through a celite pad and concentrated under reduced pressure, and purified by column chromatography (*n*-hexane/EtOAc = 10:1).

Analytical data of DKR products. ***(R)-1-Phenylethyl acetate (13a)***: 31.6 mg (96% yield, 99% *ee*); $[\alpha]^{25}_{D}$ = + 96.3 (c = 1.0, $CHCl_3$) [lit.[18] $[\alpha]^{25}_{D}$ = + 102 (*c* = 1, $CHCl_3$, >99% ee)]; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.41-7.27 (m, 5H), 5.92-5.85 (q, *J* = 6.6 Hz, 1H), 2.07 (s, 3H), 1.55-1.53 (d, *J* = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): 170.3, 141.7, 128.5, 127.0, 125.3, 72.3, 22.2, 21.4; HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm; retention times: 4.91 min (*S*), 8.59 min (*R*). The NMR data are in good agreement with those reported in the literature.[18]

(R)-1-(p-Tolyl)ethyl acetate (13b): 34.4 mg (96% yield, >99% *ee*); $[\alpha]^{25}_{D}$ = + 111.5 (c = 1.0, $CHCl_3$) [lit.[17] $[\alpha]^{25}_{D}$ = + 113 (*c* = 0.87, $CHCl_3$, 98% *ee*)]; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.23-7.16 (m, 2H), 7.09-7.02 (m, 2H), 5.81-5.75 (q, *J* = 6.6 Hz, 1H), 2.28 (s, 3H), 2.05 (s, 3H), 1.46-1.43 (d, *J* = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): 170.4, 138.7, 137.6, 129.5, 125.7, 72.4, 22.2, 21.4, 21.1; HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm; retention times: 4.91 min (*S*), 10.04 min (*R*). The NMR data are in good agreement with those reported in the literature.[18]

(R)-1-(4-Methoxyphenyl)ethyl acetate (13c): 36.9 mg (95% yield, 99% *ee*); $[\alpha]^{25}_{D}$ = + 107.1 (c = 1.0, $CHCl_3$) [lit.[18] $[\alpha]^{25}_{D}$ = + 121.7 (*c* = 1, $CHCl_3$, 99% *ee*)]; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.30-7.20 (m, 2H), 6.83-6.78 (m, 2H), 5.80-5.74 (q, *J* = 6.6 Hz, 1H), 3.79 (s, 3H), 2.04 (s, 3H), 1.46-1.44 (d, *J* = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): 170.4, 159.3, 133.8, 127.6, 113.8, 72.0, 55.3, 22.0, 21.4;

HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm; retention times: 6.81 min (*S*), 19.10 min (*R*). The NMR data are in good agreement with those reported in the literature.[18]

(R)-1-(4-Fluorophenyl)ethyl acetate (13d): 37.3 mg (97% yield, 99% *ee*); [$[\alpha]^{25}_{D}$ = + 103.6 (c = 1.0, $CHCl_3$) [lit.[18] $[\alpha]^{25}_{D}$ = + 113 (*c* = 0.9, $CHCl_3$, 99% *ee*)]; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.34-7.29 (m, 2H), 7.06-6.99 (m, 2H), 5.89-5.82 (q, *J* = 6.6 Hz, 1H), 2.06 (s, 3H), 1.46-1.44 (d, *J* = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): 169.2, 162.9, 159.7, 136.5, 127.2, 114.5, 114.2, 70.6, 21.2, 20.4; HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm; retention times: 4.85 min (*S*), 8.30 min (*R*). The NMR data are in good agreement with those reported in the literature.[18]

(R)-1-(4-Chlorophenyl)ethyl acetate (13e): 37.7 mg (95% yield, >99% *ee*); $[\alpha]^{25}_{D}$ = + 71.2 (c = 1.0, $CHCl_3$) [lit.[18] $[\alpha]^{25}_{D}$ = + 80 (*c* = 1.25, $CHCl_3$, 99% *ee*)]; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37-7.24 (m, 4H), 5.87-5.80 (q, *J* = 6.6 Hz, 1H), 2.05 (s, 3H), 1.48-1.46 (d, *J* = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): 170.2, 140.2, 133.6, 128.7, 127.5, 71.6, 22.2, 21.3; HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm; retention times: 4.95 min (*S*), 10.62 min (*R*). The NMR data are in good agreement with those reported in the literature.[18]

(R)-1-(4-Bromophenyl)ethyl acetate (13f): 47.3 mg (97% yield, >99% *ee*); $[\alpha]^{25}_{D}$ = + 94.3 (c = 1.0, $CHCl_3$) [lit.[18] $[\alpha]^{25}_{D}$ = + 91 (*c* = 1, $CHCl_3$, 99% ee)]; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48-7.45 (m, 2H), 7.24-7.21 (m, 2H), 5.85-5.79 (q, *J* = 6.6 Hz, 1H), 2.06 (s, 3H), 1.52-1.49 (d, *J* = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): 170.2, 140.8, 131.6, 127.9, 121.7, 71.6, 22.1, 21.3; HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm; retention times: 5.00 min (*S*), 11.81 min (*R*). The NMR data are in good agreement with those reported in the literature.[18]

(R)-1-(3-Chlorophenyl)ethyl acetate (13g): 37.2 mg (93% yield, >99% ee); $[\alpha]^{25}_{D}$ = + 95.3 (c = 1.0, $CHCl_3$) [lit.[19] $[\alpha]^{25}_{D}$ = + 103.0 (*c* = 1.05, $CHCl_3$, 95% *ee*)]; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36-7.22 (m, 4H), 5.88-5.82 (q, *J* = 6.6 Hz, 1H), 2.06 (s, 3H), 1.55-1.52 (d, *J* = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): 172.0, 145.6, 136.3, 131.7, 129.9, 128.1, 126.1, 73.4, 24.1, 23.1; HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 90/10, flow rate = 0.5 mL/min, UV = 217 nm; retention times: 8.01 min (*S*), 12.13 min (*R*). The NMR data are in good agreement with those reported in the literature.[19]

(R)-3-Chloro-1-phenylpropyl acetate (13h): 40.6 mg (95% yield, 95% *ee*); $[\alpha]^{25}_{D}$ = + 53.8 (c = 1.0, $CHCl_3$) [lit.[6g] $[\alpha]^{25}_{D}$ = - 58.2, (*S*)-form (*c* = 1.34, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.31-7.18 (m, 5H), 5.88-5.83 (m, 1H), 3.50-3.35 (m, 2H), 2.36-2.28 (m, 1H), 2.15-2.01 (m, 1H), 1.97 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): 170.0, 129.7, 127.5, 125.3, 72.8, 42.6, 40.6, 38.7, 21.2; HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm;

retention times: 5.64 min (*S*), 9.43 min (*R*). The NMR data are in good agreement with those reported in the literature.[6g]

(R)-1-Phenylpropan-2-yl acetate (13i): 32.9 mg (92% yield, >99% *ee*); $[\alpha]^{25}_{D} = -14.1$ (c = 1.0, $CHCl_3$) [lit.[18] $[\alpha]_D^{25} = -5.6$ (*c* = 1, $CHCl_3$, 99% *ee*)]; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.35-7.18 (m, 5H), 5.16-5.10 (m, 1H), 2.96-2.89 (m, 1H), 2.78-2.71(m, 1H), 2.06 (s, 3H), 1.22-1.20 (d, *J* = 6.3 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): 170.4, 137.6, 129.4, 128.3, 126.4, 71.4, 42.3, 21.2, 19.4; HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 98/2, flow rate = 1.0 mL/min, UV = 217 nm; retention times: 5.14 min (*S*), 5.70 min (*R*). The data are in good agreement with those reported in the literature.[18]

(R)-4-Phenylbutan-2-yl acetate (13j): 36.0 mg (94% yield, 97% *ee*); $[\alpha]^{25}_{D} = +12.2$ (c = 1.0, $CHCl_3$) [lit.[18] $[\alpha]^{25}_{D} = +7.82$ (*c* = 1, $CHCl_3$, 99% *ee*)]; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.28-7.08 (m, 5H), 4.91-4.81 (m, 1H), 2.61-2.53 (m, 2H), 1.96 (s, 3H), 1.86-1.53 (m, 2H), 1.19-1.17 (d, *J* = 6.3 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): 170.8, 141.6, 129.3, 128.5, 125.0, 71.2, 37.6, 31.9, 21.4, 20.1; HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 99/1, flow rate = 0.5 mL/min, UV = 217 nm; retention times: 12.11 min (*S*), 13.56 min (*R*). The NMR data are in good agreement with those reported in the literature.[18]

(R)-1-(Naphthalen-2-yl)ethyl acetate (13k): 42.3 mg (99% yield, >99% *ee*); $[\alpha]^{25}_{D} = +121.6$ (c = 1.0, $CHCl_3$) [lit.[18] $[\alpha]^{22}_{D} = +122$ (*c* = 1, $CHCl_3$, >99% *ee*)]; $CHCl_3$)]; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.90-7.80 (m, 4H), 7.50-7.43 (m, 3H), 6.08-6.02 (q , *J* = 6.6 Hz, 1H), 2.04 (s, 3H), 1.41-1.39 (d, *J* = 6.6 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): 170.4, 139.0, 133.0, 128.6, 126.9, 126.3, 125.4, 124.1, 123.3, 71.4, 22.2, 21.4; HPLC conditions: Chiracel-OD, *n*-hexane/2-propanol = 99/1, flow rate = 0.5 mL/min, UV = 217 nm; retention times: 20.27 min (*S*), 16.64 min (*R*). The NMR data are in good agreement with those reported in the literature.[18]

(R)-1-Phenylallyl acetate (13l): 31.9 mg (91% yield, 93% *ee*); $[\alpha]^{25}_{D} = +37.0$ (c = 1.0, $CHCl_3$) [lit.[20] $[\alpha]^{25}_{D} = +30.42$(c = 0.48, $CHCl_3$), 96% *ee*]; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.27-7.25 (m, 5H), 6.19 (d, *J* = 5.9 Hz, 1H), 6.00-5.88 (m, 1H), 5.25-5.16 (m, 2H), 2.03 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): 168.9, 138.0, 135.4, 127.5, 127.1, 126.1, 115.9, 75.2, 20.2; HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 98/2, flow rate = 0.5 mL/min, UV = 217 nm; retention times: 9.79 min (*S*), 13.45 min (*R*). The NMR data are in good agreement with those reported in the literature.[20]

(R)-1-(p-Tolyl)allyl acetate (13m): 34.2 mg (90% yield, 96% *ee*); $[\alpha]^{25}_{D} = +56.4$ (c = 1.0, $CHCl_3$) [lit.[21] $[\alpha]^{25}_{D} = -224$ (c = 0.17, $CHCl_3$), 97% *ee* for (*S*)-enantiomer]; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.35-7.15 (m, 4H), 6.23 (d, *J* = 5.8 Hz, 1H), 6.06-5.95 (m, 1H), 5.31-5.21 (m, 2H), 2.34 (s, 3H), 2.08 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): 169.9, 138.0, 136.5, 136.0, 129.2, 127.1, 116.6, 76.1, 21.2, 21.1; HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 98/2, flow rate = 0.5 mL/min, UV = 217 nm; retention times: 9.85 min (*S*), 14.65 min (*R*); HRMS (EI, magnetic sector) m/z: M+ Calcd for $[C_{12}H_{14}O_2]^+$ 190.0994; Found 190.0994.

(R)-1-(4-Methoxyphenyl)allyl acetate (13n): 37.5 mg (91% yield, 95% *ee*); $[\alpha]^{25}_{D}$ = + 67.6 (c = 1.0, $CHCl_3$) [lit.[22] $[\alpha]^{25}_{D}$ = + 55.42(c = 1.43, $CHCl_3$), 99% *ee*]; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.30-7.26 (m, 2H), 6.91-6.86 (m, 2H), 6.22 (d, *J* = 5.6 Hz, 1H), 6.06-5.95 (m, 1H), 5.30-5.21 (m, 2H), 3.80 (s, 3H), 2.09 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): 169.9, 159.6, 136.5, 131.1, 128.7, 116.4, 114.0, 75.8, 55.3, 21.2; HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 98/2, flow rate = 0.5 mL/min, UV = 217 nm; retention times: 13.83 min (*S*), 25.95 min (*R*). The NMR data are in good agreement with those reported in the literature.[22]

***(R)-1-(4-Chlorophenyl)allyl acetate (13o)*:** 37.2 mg (89% yield, 91% *ee*); $[\alpha]^{25}_{D}$ = + 33.5 (c = 1.0, $CHCl_3$) [lit.[22] $[\alpha]^{25}_{D}$ = + 28.0 (c = 1.25, $CHCl_3$), 99% *ee*]; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.34-7.27 (m, 4H), 6.22 (d, *J* = 5.8 Hz, 1H), 6.02-5.91 (m, 1H), 5.31-5.24 (m, 2H), 2,11 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): 169.7, 137.5, 135.9, 134.0, 129.4, 128.8, 117.3, 75.4, 21.1; HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 98/2, flow rate = 0.5 mL/min, UV = 217 nm; retention times: 10.36 min (*S*), 17.73 min (*R*). The NMR data are in good agreement with those reported in the literature.[22]

(R)-1-(4-Bromophenyl)allyl acetate (13p): 44.6 mg (87% yield, 91% *ee*); $[\alpha]^{25}_{D}$ = + 36.2 (c = 1.0, $CHCl_3$) [lit.[21] $[\alpha]_{D}^{25}$ = + 5 (c = 1.43, $CHCl_3$), 53% *ee*]; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.84-7.81 (m, 2H), 7.25-7.21 (m, 2H), 6.20 (d, *J* = 5.9 Hz, 1H), 5.98-5.93 (m, 1H), 5.31-5.24 (m, 2H), 2.11 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): 169.7, 138.0, 135.8, 131.7, 128.8, 122.1, 117.3, 75.4, 21.1; HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 98/2, flow rate = 0.5 mL/min, UV = 217 nm; retention times: 10.82 min (*S*), 17.94 min (*R*). The NMR data are in good agreement with those reported in the literature.[20]

(R,E)-4-Phenylbut-3-en-2-yl acetate (13q): 35.8 mg (94% yield, >99% *ee*); $[\alpha]^{25}_{D}$ = +139.2 (c = 1.0, $CHCl_3$) [lit.[6b] $[\alpha]^{25}_{D}$ = + 144.5 (*c* = 1, $CHCl_3$, 98% ee)]; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.39-7.24 (m, 5H), 6.63-6.57 (m, 1H), 6.22-6.15 (m, 1H), 5.55-5.50 (m, 1H), 2.06 (s, 3H), 1.42-1.40 (d, *J* = 6.5 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): 170.3, 136.4, 131.7, 128.8, 128.6, 127.9, 126.7, 71.0, 21.4, 20.4; HPLC conditions: (*R*,*R*)-Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 217 nm; retention times: 5.48 min (*S*), 13.66 min (*R*). The NMR data are in good agreement with those reported in the literature.[6b]

ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge on the ACS Publication website at DOI:

NMR spectra and HPLC chromatograms of products (PDF)

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Notes

The authors declare no competing financial interest.

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