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Kinetic resolution of primary alcohols having remote stereogenic centers: lipase mediated kinetic resolution of (±)-3-chloro-3-arylpropanols

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Abstract—Kinetic resolutions of (±)-3-chloro-3-arylpropanols by lipase mediated acetylation are described for the first time. Acetylation with CCL provided the best enantioselectivity amongst the enzymes used. Enantiomerically enriched products were obtained with up to 78% ee after two successive lipase-catalyzed acetylations. Different substituents on the aromatic ring and bromide, instead of chloride, on the substrates were found to have no drastic influence on the enantioselectivity of the reaction.

1. Introduction

Benzanilide derivatives are dual-acting agents, which have both α-1-adrenoceptor antagonistic action and steroid 5α reductase inhibitory activity.[1] These properties make them potent therapeutic agents for urethral obstruction caused by benign prostatic hyperplasia, which is a common disease in aging men.[2] 3-Chloro-3-arylpropanols are key intermediates in the synthesis of biologically active benzanilide derivatives.[1] Recently, a new methodology was developed in our group for the one-pot synthesis of racemic 3-chloro-3-arylpropanols.[3] The synthesis of enantiopure 3-chloro-3-arylpropanols is a challenge for the synthesis of the corresponding enantiopure benzanilide derivatives, which might possibly display better biological activities.

The chemo-enzymatic approach for asymmetric synthesis is becoming increasingly accepted in synthetic strategies, while the use of biocatalysts as routine chiral catalysts has already found widespread application in preparative organic chemistry over the last decade.[4] Lipases are able to catalyze asymmetric hydrolysis[5] and esterification[6] in a wide range of substrates. However, in most cases, the substrates undergoing the enzymatic reaction have the chiral/prochiral center only one or two bonds away from the reacting carbonyl or alcohol group. Very limited examples have been reported in which the chiral/prochiral center is three or more bonds away from the reacting carbonyl/alcohol center.[7] In one of these examples, Cambou and Klibanov[7b] used pig liver esterase to esterify alcohols having three bonds between the alcohol and the stereogenic center with ees generally above 90%. However, the method suffers from poor reproducibility and a low operational stability of the enzyme.[8] In order to overcome these problems, Ruppert and Gais colyophilized pig liver esterase with methoxypolyethylene glycol to obtain a catalyst (PLE/MPEG), which showed an enhanced activity in organic solvents but ees did not exceed 38% for the resolution of 3-methoxy butanol.[9] Goj et al. studied the kinetic resolutions of (±)-1-acetoxy-2-fluoro-2-phenylalkanes by enzymatic hydrolysis and of (±)-1-hydroxy-2-fluoro-2-phenylalkanes by lipase-catalyzed acetylation.[10] Although the reactive center was two bonds away from the tertiary chiral center, hydrolysis of 1-acetoxy-2-fluoro-2-stereogenic using CCL gave 2-fluoro-2-phenylpropanol in 37% ee and 1-acetoxy-2-fluoro-2-phenylpropane in 27% ee with 46% conversion. When Amano PS was used in the hydrolysis of the same substrate, an improved selectivity (79% ee for the alcohol and 88% ee for the acetate with 42% conversion) was obtained with an opposite specific rotation relative to the CCL catalyzed hydrolysis. It was also reported that enzymatic esterification of 2-fluoro-2-phenylpropanol yielded 1-acetoxy-2-fluoro-2-phenylpropane in 95% ee with 46% conversion.

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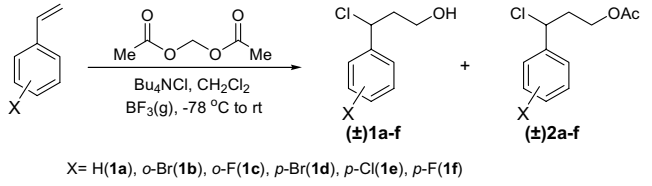
From these limited examples, it is difficult to make a generalization that the enzymes studied are suitable for the transformations of substrates with remote stereogenic centers. The promising results obtained in the literature[7b,10] triggered us to study the enzymatic resolution of (±)-1-hydroxy-3-chloro-3-arylpropanes and (±)-1-acetoxy-3-chloro-3-arylpropanes. Herein, we report the details of our study.

2. Results and discussion

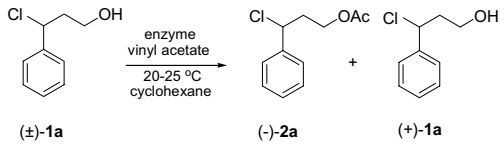
For the synthesis of starting materials **1a**–**f**, we have already reported a one-pot procedure.[3] When the styrenes were reacted with methylene diacetate in the presence of BF_3 and *tetra*-*n*-butylammonium chloride, (±)-3-chloro-3-arylpropanols **1a**–**f** were obtained in 45–84% yield along with minor amounts (<5%) of (±)-1-acetoxy-3-chloro-3-arylpropanes **2a**–**f** (Scheme 1).



X= H(**1a**), *o*-Br(**1b**), *o*-F(**1c**), *p*-Br(**1d**), *p*-Cl(**1e**), *p*-F(**1f**)

Scheme 1.

Over the course of our studies on the biotransformations of (±)-3-chloro-3-phenylpropanol **1a**, screening reactions were first examined with CCL, PPL, PLE, HLE, Amano PS, and Amano PSC-II (Scheme 2). Among the enzymes studied, CCL mediated esterification of substrate (±)-**1a** gave the highest enantioselectivity by giving (+)-alcohol **1a** in 45% yield with 25% ee and (−)-ester **2a** in 35% yield with 28% ee (Table 1, entry 1). HLE mediated esterification of the same substrate, on the other hand, gave the products in slightly lower yields and ees with an opposite configuration (Table 1, entry 4). We also planned to study the enzymatic hydrolysis of (±)-1-acetoxy-3-chloro-3-phenylpropane **2a**, but (±)-**2a** was found to decompose almost completely in both phosphate and tris buffer conditions in the absence of enzymes. This was presumably due to the side reactions of the benzylic chloride group, which might undergo elimination and displacement reactions under aqueous conditions. Due to these uncontrolled side reactions, we continued our studies with enantioselective esterification in the organic medium.



Scheme 2.

After finding out that CCL is the best enzyme for the acetylation of racemic **1a**, we studied the effect of amount of the enzyme and acetylating reagent as well as the solvent. The results of these studies are summarized in Table 2. As can be seen in Table 2, stoichiometric amounts of CCL and 0.6 equiv of vinyl acetate with respect to substrate **1a** gave the best results. Among the solvents tested, cyclohexane and toluene gave good results. Although the yields are very similar, the reaction in toluene requires a longer time and the ee of alcohol **1a** is lower compared to cyclohexane (Table 2, entries 4 and 5). When *tert*-butyl vinyl ether was used as solvent, comparable ees relative to cyclohexane were obtained, although the chemical yields were too low (Table 2, entry 6). In the case of tetrahydrofuran the reaction was sluggish. Six days were required for 49% conversion even with the addition of fivefold excess of vinyl acetate. Although the reaction in THF proceeded slowly, there was no improvement in the enantioselectivity (Table 2, entry 7). We also tried the reaction at 14 °C in cyclohexane, which slowed down the reaction, 30% conversion obtained after 22 h, but had no effect on the enantioselectivity.

Due to the relatively lower enantioselectivities of the enzymatic acetylation of (±)-**1**, we tried a multiple resolution strategy. When substrate (±)-**1a** was subjected to CCL mediated double enzymatic resolution, alcohol (+)-**1a** was obtained in 78% ee (Scheme 3). However, the same strategy with HLE gave (−)-**1a** in 42% ee. In the second kinetic resolution step, for both CCL and HLE, a reversal of enantioselectivity for the acetylated product **2a** relative to the first kinetic resolution step was observed. This result can be attributed to the increased rate of the acyl transfer to a less reactive enantiomeric form of alcohol due to the increase in its concentration relative to the first kinetic resolution step. We also tried a third acetylation run with CCL (not shown in Scheme 3), which diminished the ee of alcohol (+)-**1a** from 78% to 68% after a 30% conversion. Ester (+)-2**a** was isolated in 42% ee in the third run.

In the study of Goj et al., they observed that the isobutyl group on the aromatic ring of (±)-1-acetoxy-2-fluoro-2-(*p*-isobutylphenyl)propane decreased the ee value dramatically in enzymatic hydrolysis.[10] This result clearly demonstrates the importance of the substituents on the aromatic ring in chiral recognition of such compounds. In the light of this observation, we thought that it would be interesting to find out the substituent effect on the enzymatic acetylation of our substrates. For this reason, various racemic 3-chloro-3-arylpropanols **1a**–**f** and 3-bromo-3-phenylpropanol **3** were subjected to single enzymatic acetylation by CCL (Scheme 4). The results of these studies are summarized in Table 3. Enantiomeric excesses for the unreacted alcohols ranged between 21% and 43%, while those of acetylated products were between 24% and 38%. Based on these results, it can be concluded that different substituents at different position of the aromatic ring have no real effect on the lipase CCL selectivity. A slight increase in ees was observed in case of bromide at the *ortho* position (Table 3, entry 6). This result can be explained with the better fit into the enzyme's pocket due to fixed conformation of substrate **1f** caused by restricted rotation of the aromatic ring because of proximal halides in the molecule. In order to determine whether a different halide at the benzylic position of substrate **1** had any effect on the selectivity,

Table 1. Enzymatic acetylation studies of (±)-**1a** with various enzymes

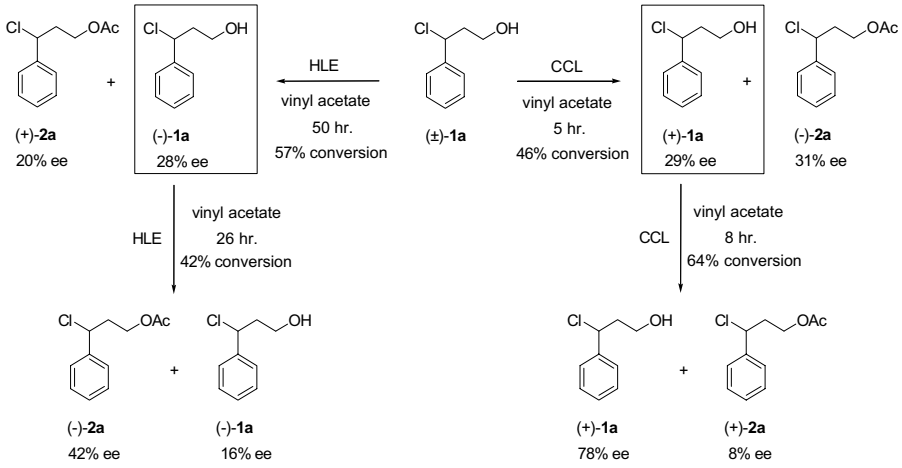
Entry	Enzyme[a]	Time	Conv. (%)[b]	Alcohol **1a**		Ester **2a**	
				Yield (%)[c]	ee (%)[d]	Yield (%)[c]	ee (%)[d]
1	CCL	3 h	44	47	25	33	28
2	PPL	1 d	43	35	4	20	6
3	PLE	1 d	30	34	2	16	5
4	HLE	1 d	52	31	−21	29	−20
5	Amano PS	2 h	37	57	5	33	8
6	Amano PSC-II	1 d	64	20	4	30	1

[a] 175.0 mg of enzyme/mmol (±)-**1a** and same equivalent of vinyl acetate as that of (±)-**1a** was used in reactions.
[b] Determined by ^{1}H NMR analysis.
[c] Yields are isolated yields.
[d] Determined by HPLC using Chiralcel ODH column.

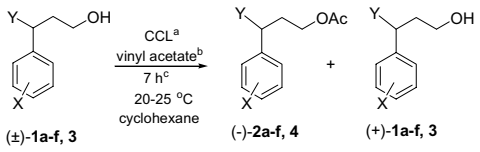
Table 2. Effect of the amount of CCL and vinyl acetate on enzymatic acetylation of (±)-**1a**

Entry	Amount of CCL[a]	Equiv of vinyl acetate	Solvent	Time	Conversion (%)[b]	Alcohol **1a**		Ester **2a**	
						Yield (%)[c]	ee (%)[d]	Yield (%)[c]	ee (%)[d]
1	17.5	38	—	3 d	49	29	21	31	22
2	175.0	38	—	35 min	53	44	24	46	21
3	175.0	1.2	Cyclohexane	165 min	61	27	35	54	23
4	175.0	0.6	Cyclohexane	225 min	44	45	29	33	33
5	175.0	0.6	Toluene	455 min	50	41	24	39	24
6	175.0	0.6	TBVE	22 h	46	5	27	6	30
7[e]	175.0	0.6	THF	6 d	49	28	14	22	26

[a] In mg CCL/mmol (±)-**1a**.
[b] Determined by ^{1}H NMR analysis.
[c] Yields (%) are given as isolated yields.
[d] Enantiomeric excess values were determined by HPLC using Chiralcel ODH column.
[e] Total of fivefold excess of vinyl acetate was added in portions during 6 days.



Scheme 3.



Scheme 4. Reagents and conditions: (a) 175.0 mg CCL/mmol (±)-**1** or (±)-**3** was used in reactions; (b) 0.6 equiv vinyl acetate was used relative to substrate (±)-**1** or (±)-**3**; (c) except substrate **1a**, for which reaction time was 225 min.

we synthesized compound **3**. When this substrate was subjected to CCL mediated acetylation under the same reaction conditions as previous substrates, similar results were obtained in terms of yield and enantioselectivity (Table 3, entry 7). This experiment showed that the bromide has a larger size than chloride and had no effect on the enzyme selectivity. Interestingly, enantiomerically enriched compound **3** racemized completely within a few days upon standing in solution (*n*-hexane/2-propanol, 10:1, v/v) at +4 °C. This can be attributed to the better

Table 3. Enzymatic acetylation of (±)-3-halo-3-aryl-propanols **1a–f** and **3** with CCL

Entry	Substrate	X, Y	Conversion (%)[a]	Alcohol **1**, **3**				Ester **2**, **4**			
				Yield (%)[b]	ee (%)[c]	E_s[d]	$[\alpha]_D^{25}$	Yield (%)[b]	ee (%)[c]	E_P[d]	$[\alpha]_D^{25}$
1	**1a**	H, Cl	44	45	29	2.8	+12.1	33	33	2.5	−13.8
2	**1b**	*p*-F, Cl	40	60	21	2.3	+15.4	36	32	2.4	−16.3
3	**1c**	*p*-Cl, Cl	39	51	21	2.4	+10.0	29	37	2.7	−19.7
4	**1d**	*p*-Br, Cl	38	33	23	2.7	+8.4	17	30	2.2	−11.2
5	**1e**	*o*-F, Cl	52	45	25	2.0	+6.7	44	24	2.1	−18.0
6	**1f**	*o*-Br, Cl	52	24	43	3.4	+6.0	28	36	3.0	−11.8
7	**3**	H, Br	38	27	21	2.5	+14.2	19	38	2.8	−28.7

[a] Determined by ^{1}H NMR analysis.
[b] Yields (%) are given as isolated yields.
[c] Enantiomeric excess values were determined by HPLC using Chiralcel ODH column.
[d] Calculated using Sih et al.'s method.[11]

leaving ability of bromide than chloride. Under the same conditions, racemization of compound **4** (acetylated form of **3**) was not observed. This may indicate that hydroxyl group plays a role in the racemization process.

3. Conclusion

We have studied enzymatic resolutions of (±)-3-halo-3-arylpropanols for the first time. Among the enzymes used under the esterification conditions, CCL showed the best enantioselectivity. Even though these substrates have a stereogenic center three bonds away from the reaction site, they showed enantioselectivities up to 43% for the alcohols and 38% for the esters. We have also showed that the enantiopurity of alcohol **1a** can be raised to 78% by double enzymatic acetylation. It was also found that CCL and HLE show opposite stereoselectivity in the products. Substituents on the aromatic ring or benzylic bromide instead of chloride were found to have no drastic influence on the enantioselectivity of the reaction.

4. Experimental

The ^{1}H and ^{13}C NMR spectra were recorded in CCl_4/$CDCl_3$ (2:3, v/v) solvent system on a Bruker Spectrospin Avance DPX 400 spectrometer. ^{1}H NMR spectra were reported in parts per million using TMS as an internal standard (TMS at 0.00 ppm). ^{13}C NMR spectra were reported in parts per million using solvent as an internal standard ($CDCl_3$ at 76.9 ppm). Infrared spectra were recorded on a Bruker IFS 66V/S series FT-IR spectrometer using $CHCl_3$ as the solvent. GC–MS spectra were obtained with a Thermo-Quest (TSP) TraceGC-2000 Series instrument equipped with a Phenomenex Zebron ZB-5 capillary column (5% phenylmethylsiloxane, 30 m, 250 μm), MS: Thermo Quest Finnigan multi Mass (EI, 70 eV). High resolution mass spectra (HRMS) were recorded on a Kratos MS25RFA mass spectrometer using electron impact (EI) method. Optical rotations were measured in $CHCl_3$ solutions in a 1 dm cell using a Rudolph Autopol III polarimeter at 25 °C. HPLC measurements were performed with Dionex System instrument. Separations were carried out on Chiralcel OD-H analytical column (250 × 4.60 mm) with hexane/2-propyl alcohol as eluent. Flash column chromatography was performed on silica gel (60 mesh, Merck). Analytical thin layer chromatography (TLC) was performed on precoated silica gel (60 F_{254}, Merck). Commercially available reagents and solvents were used, unless otherwise stated, without further purification. CCL (lipase, Type VII, from *Candida rugosa*), PPL (Lipase Type II, from *Porcine pancreas*), Amano PS, Amano PSC-II and HLE (Horse Liver Esterase-acetone powder) were purchased from Aldrich. PLE (Pig Liver Esterase) was purchased from Sigma as powder.

4.1. Preparation of methylene diacetate stock solution

Bu_4NOAc (11.4 g, 37.8 mmol) and dry benzene (60 mL) were placed in a round-bottomed flask equipped with a Dean–Stark apparatus. This solution was refluxed under an argon atmosphere with continuous removal of the azeotrope over a period of 1 h. Then the flask was connected to a vacuum line to remove the rest of the benzene. Finally, dry CH_2Cl_2 (37 mL) was added to the flask containing NBu_4OAc (11.2 g, 37.1 mmol) under an argon atmosphere. This stock solution was allowed to stand at rt for 3 days before use and then was kept at 4 °C.

4.2. General procedure for the synthesis of 3-chloro-3-arylpropanols

Methylene diacetate stock solution (5.0 mL) and alkene **1a–f** (0.78 mmol) were added to a 10 mL flask under an argon atmosphere. The flask was then cooled to −78 °C and BF_3 gas slowly bubbled through the solution for 20 min to give a cloudy solution. At this point, the BF_3 flow was stopped and the reaction flask allowed to warm up to rt and left stirring overnight at this temperature. In the morning, water was added (10 mL) to the reaction flask, followed by extraction with CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried over $MgSO_4$ and concentrated. Final purification was carried out by flash column chromatography on silica gel using 5:1 hexanes/ethyl acetate as the eluent.

Compounds (±)-**1a–f** were synthesized and all were in accordance with our previous report.[3]

4.2.1. Synthesis of (±)-3-bromo-3-phenylpropan-1-ol (3). Methylene diacetate (MDA) was isolated from MDA stock

solution as follows: MDA stock solution was concentrated under reduced pressure and then *n*-hexane was added to the residue. Solid particles (NBu_4Cl) were separated by filtration and the liquid part was concentrated under reduced pressure to give MDA.

MDA (155 mg, 1.17 mmol), NBu_4Br (754 mg, 2.34 mmol), and styrene **1a** (81 mg, 0.78 mmol) were added to a 10 mL flask under an argon atmosphere. The flask was then cooled to −78 °C and BF_3 gas was slowly bubbled through the solution for 20 min to give a cloudy solution. At this point, the BF_3 flow was stopped and the reaction flask was allowed to warm up to rt and left stirring overnight at this temperature. In the morning, water was added (10 mL) to the reaction flask, followed by extraction with CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried over $MgSO_4$ and concentrated. Final purification was done by flash column chromatography on silica gel using 5:1 hexanes/ethyl acetate as the eluent to give product **3** (138 mg, 82% yield) as a colorless oil. R_f (EtOAc/hexane 2:1): 0.61; IR ($CHCl_3$): $\nu = 3444$, 2926, 1456, 1253, 1093, 1005, 889, 806, 721, 626, 537 cm^{-1}; ^1H NMR ($CDCl_3$–CCl_4): δ 1.60 (br s, 1H, OH), 2.30 (m, 1H, CH_2, H-2), 2.46 (m, 1H, CH_2, H-2), 3.72 (m, 1H, CH_2, H-1), 3.81 (m, 1H, CH_2, H-1), 5.17 (dd, $J = 5.7$, 9.1 Hz, 1H, CH, H-3), 7.26 (d, $J = 7.3$ Hz, 1H, CH, Ph), 7.31 (t, $J = 7.3$ Hz, 2H, CH, Ph), 7.38 (d, $J = 7.3$ Hz, 2H, CH, Ph). ^{13}C NMR ($CDCl_3$–CCl_4): δ 42.31, 51.65, 60.49, 127.33, 128.33, 128.66, 141.88.

4.3. General procedure for enzymatic acetylation of 1a–f and 3

To a solution of racemic alcohol **1a–f/3** (0.171 mmol) and vinyl acetate (9.5 μL, 0.103 mmol) in cyclohexane (1 mL), 30 mg CCL (or lipase) was added and the reaction mixture shaken at 20–25 °C (TLC monitoring). The reaction mixture was filtered and the filtrate concentrated under reduced pressure. The products, ester **2a–f/4** and alcohol **1a–f/3**, were separated and purified by flash column chromatography (EtOAc/hexanes, 1:5).

4.3.1. (−)-3-Chloro-3-phenylpropyl acetate (2a). Light yellow oil (12.0 mg, 33% yield), $[\alpha]_D^{25} = -19.9$ (*c* 1.2, $CHCl_3$) for 33% ee; HPLC: Chiralcel OD-H column, UV detection at 230 nm, eluent: hexane/2-propanol = 98:2 flow 1.0 mL min^{-1}, 20 °C, R_f for (−)-**2a**: 9.1 min; (+)-**2a**: 12.3 min. IR ($CHCl_3$): $\nu = 2921$, 1738, 1490, 1457, 1363, 1248, 1199, 1033, 785, 543 cm^{-1}; ^1H NMR ($CDCl_3$–CCl_4): δ 2.02 (s, 3H, $COCH_3$), 2.29–2.43 (m, 2H, CH_2, H-2), 4.12 (m, 1H, CH_2, H-1), 4.21 (m, 1H, CH_2, H-1), 4.95 (dd, $J = 5.9$, 8.6 Hz, 1H, CH, H-3), 7.29–7.37 (m, 5H, CH, Ph); ^{13}C NMR ($CDCl_3$–CCl_4): δ 20.61, 38.78, 59.58, 61.31, 126.78, 128.34, 128.59, 140.89, 170.10 (C=O); MS (EI) *m*/*z* (%): 153 (55) [M^+−OAc], 151 (100), 124 (90), 118 (100), 117 (100), 103 (100), 91 (90), 77 (90), 63 (30), 51 (55), 43 (100).

4.3.2. (+)-3-Chloro-3-phenylpropan-1-ol (1a). Colorless oil (13.1 mg, 45% yield), $[\alpha]_D^{25} = +12.1$ (*c* 1.3, $CHCl_3$) for 29% ee; $[\alpha]_D^{25} = +32.3$ (*c* 1.0, $CHCl_3$) for 78% ee after double resolution; HPLC: Chiralcel OD-H column, UV detection at 230 nm, eluent: hexane/2-propanol = 98:2 flow 1.0 mL min^{-1}, 20 °C, R_f for (+)-**1a**: 36.3 min; (−)-**1a**: 53.2 min. All spectroscopic data are in agreement with those published for racemic **1a**.[3]

4.3.3. (−)-3-Chloro-3-(4-fluorophenyl)propyl acetate (2b). Colorless oil (14.2 mg, 36% yield), $[\alpha]_D^{25} = -16.3$ (*c* 1.4, $CHCl_3$) for 32% ee; HPLC: Chiralcel OD-H column, UV detection at 230 nm, eluent: hexane/2-propanol = 98:2 flow 1.0 mL min^{-1}, 20 °C, R_f for (−)-**2b**: 8.3 min; (+)-**2b**: 9.3 min. IR ($CHCl_3$): $\nu = 2925$, 1742, 1607, 1505, 1464, 1369, 1250, 1195, 1157, 1029, 724, 548 cm^{-1}; ^1H NMR ($CDCl_3$–CCl_4): δ 2.03 (s, 3H, $COCH_3$), 2.26–2.43 (m, 2H, CH_2, H-2), 4.12 (m, 1H, CH_2, H-1), 4.21 (m, 1H, CH_2, H-1), 4.94 (dd, $J = 5.9$, 8.7 Hz, 1H, CH, H-3), 7.03 (m, 2H, CH, Ar), 7.35 (m, 2H, CH, Ar); ^{13}C NMR ($CDCl_3$–CCl_4): δ 20.71, 38.99, 58.84, 61.30, 115.68 (d, $J = 21.6$ Hz), 128.64 (d, $J = 7.7$ Hz), 136.90, 162.55 (d, $J = 247.1$ Hz) 170.18 (C=O); MS (EI) *m*/*z* (%): 171 (40) [M^+−OAc], 169 (100), 142 (90), 135 (90), 134 (100), 121 (90), 108 (40), 101 (40), 95 (35), 75 (30), 43 (100).

4.3.4. (+)-3-Chloro-3-(4-fluorophenyl)propan-1-ol (1b). Colorless oil (19.4 mg, 60% yield), $[\alpha]_D^{25} = +15.4$ (*c* 1.9, $CHCl_3$) for 21% ee; HPLC: Chiralcel OD-H column, UV detection at 230 nm, eluent: hexane/2-propanol = 98:2 flow 1.0 mL min^{-1}, 20 °C, R_f for (−)-**1b**: 23.9 min; **(+)-1b**: 26.7 min. All spectroscopic data are in agreement with those published for racemic **1b**.[3]

4.3.5. (−)-3-Chloro-3-(4-chlorophenyl)propyl acetate (2c). Colorless oil (12.3 mg, 29% yield), $[\alpha]_D^{25} = -19.7$ (*c* 1.2, $CHCl_3$) for 37% ee; HPLC: Chiralcel OD-H column, UV detection at 230 nm, eluent: hexane/2-propanol = 98:2 flow 1.0 mL min^{-1}, 20 °C, R_f for (−)-**2c**: 9.6 min; (+)-**2c**: 10.8 min. IR ($CHCl_3$): $\nu = 2925$, 1741, 1492, 1458, 1363, 1257, 1201, 1095, 1008, 806, 721, 620, 530 cm^{-1}; ^1H NMR ($CDCl_3$–CCl_4): δ 2.03 (s, 3H, $COCH_3$), 2.24–2.41 (m, 2H, CH_2, H-2), 4.11 (m, 1H, CH_2, H-1), 4.21 (m, 1H, CH_2, H-1), 4.92 (dd, $J = 5.9$, 8.7 Hz, 1H, CH, H-3), 7.31 (br s, 4H, CH, Ar); ^{13}C NMR ($CDCl_3$–CCl_4): δ 20.71, 38.86, 58.75, 61.22, 128.24, 128.94, 134.43, 139.49, 170.16 (C=O); MS (EI) *m*/*z* (%): 171 (40) [M^+−OAc], 186 (15), 185 (20), 158 (10), 150 (45), 137 (10), 115 (30), 103 (20), 89 (10), 77 (15), 75 (10), 43 (100).

4.3.6. (+)-3-Chloro-3-(4-chlorophenyl)propan-1-ol (1c). Colorless oil (17.9 mg, 51% yield), $[\alpha]_D^{25} = +10.0$ (*c* 1.8) for 21% ee; HPLC: Chiralcel OD-H column, UV detection at 230 nm, eluent: hexane/2-propanol = 98:2 flow 1.0 mL min^{-1}, 20 °C, R_f for (+)-**1c**: 28.7 min; (−)-**1c**: 30.1 min. All spectroscopic data are in agreement with those published for racemic **1c**.[3]

4.3.7. (−)-3-Chloro-3-(4-bromorophenyl)propyl acetate (2d). Light yellow wax (8.5 mg, 17% yield), $[\alpha]_D^{25} = -11.2$ (*c* 0.85, $CHCl_3$) for 30% ee; HPLC: Chiralcel OD-H column, UV detection at 230 nm, eluent: hexane/2-propanol = 98:2 flow 1.0 mL min^{-1}, 20 °C, R_f for (−)-**2d**: 10.0 min; (+)-**2d**: 11.8 min. IR ($CHCl_3$): $\nu = 2932$, 1738, 1589, 1490, 1363, 1242, 1028, 816, 716, 632, 532 cm^{-1}; ^1H NMR

($CDCl_3$–CCl_4): δ 2.02 (s, 3H, $COCH_3$), 2.24–2.40 (m, 2H, CH_2, H-2), 4.11 (m, 1H, CH_2, H-1), 4.20 (m, 1H, CH_2, H-1), 4.90 (dd, $J = 6.0$, 8.5 Hz, 1H, CH, H-3), 7.24 (d, $J = 8.3$ Hz, 2H, CH, Ar), 7.47 (d, $J = 8.3$ Hz, 2H, CH, Ar); ^{13}C NMR ($CDCl_3$–CCl_4): δ 20.71, 38.81, 58.78, 61.21, 122.51, 128.56, 134.43, 131.91, 140.01, 170.18 (C=O); MS (EI) *m*/*z* (%): 231 (30) [M^+−OAc], 230 (40), 228 (30), 203 (10), 194 (10), 181 (10), 150 (40), 116 (80), 115 (100), 103 (35), 89 (30), 77 (40), 63 (20), 51 (20), 43 (100).

4.3.8. (+)-3-Chloro-3-(4-bromorophenyl)propan-1-ol (1d). Colorless oil (14.1 mg, 33% yield), $[\alpha]_D^{25} = +7.6$ (*c* 1.4, $CHCl_3$) for 23% ee; HPLC: Chiralcel OD-H column, UV detection at 230 nm, eluent: hexane/2-propanol = 98:2 flow 1.0 mL min^{-1}, 20 °C, R_f for (−)-**1d**: 33.1 min; (+)-**1d**: 34.5 min. All spectroscopic data are in agreement with those published for racemic **1d**.[3]

4.3.9. (−)-3-Chloro-3-(2-fluorophenyl)propyl acetate (2e). Colorless oil (17.4 mg, 44% yield), $[\alpha]_D^{25} = -18.0$ (*c* 1.7, $CHCl_3$) for 24% ee; HPLC: Chiralcel OD-H column, UV detection at 230 nm, eluent: hexane/2-propanol = 98:2 flow 1.0 mL min^{-1}, 20 °C, R_f for (−)-**2e**: 7.7 min; (+)-**2e**: 9.2 min. IR ($CHCl_3$): $\nu = 2937$, 1726, 1620, 1587, 1495, 1368, 1253, 1185, 1157, 1032, 818, 721, 626, 536 cm^{-1}; ^{1}H NMR ($CDCl_3$–CCl_4): δ 2.02 (s, 3H, $COCH_3$), 2.29–2.45 (m, 2H, CH_2, H-2), 4.19 (m, 2H, CH_2, H-1), 5.31 (dd, $J = 5.9$, 8.6 Hz, 1H, CH, H-3), 7.03 (t, $J = 7.6$ Hz, 1H, CH, Ar), 7.15 (t, $J = 7.6$ Hz, 1H, CH, Ar), 7.25–7.30 (m, 1H, CH, Ar), 7.47 (td, $J = 7.6$, 1.4 Hz, 1H, CH, Ar); ^{13}C NMR ($CDCl_3$–CCl_4): δ 20.68, 37.89, 52.22 (d, $J =$ 3.7 Hz), 61.20, 115.67 (d, $J = 22.0$), 124.51 (d, $J =$ 2.9 Hz), 128.07 (d, $J = 12.7$ Hz), 128.45 (d, $J = 3.0$ Hz), 129.96 (d, $J = 8.9$ Hz), 159.75 (d, $J = 250.0$), 170.25 (C=O); MS (EI) *m*/*z* (%): 171 (60) [M^+−OAc], 169 (100), 142 (80), 135 (75), 134 (100), 121 (90), 108 (40), 101 (50), 96 (40), 95 (35), 75 (30), 43 (100).

4.3.10. (+)-3-Chloro-3-(2-fluorophenyl)propan-1-ol (1e). Colorless oil (14.5 mg, 45% yield), $[\alpha]_D^{25} = +6.7$ (*c* 1.4, $CHCl_3$) for 25% ee; HPLC: Chiralcel OD-H column, UV detection at 230 nm, eluent: hexane/2-propanol = 98:2 flow 1.0 mL min^{-1}, 20 °C, R_f for (+)-**1e**: 24.5 min; (−)-**1e**: 29.8 min. All spectroscopic data are in agreement with those published for racemic **1e**.[3]

4.3.11. (−)-3-Chloro-3-(2-bromorophenyl)propyl acetate (2f). Colorless oil (14.0 mg, 28% yield), $[\alpha]_D^{25} = -11.8$ (*c* 1.4, $CHCl_3$) for 36% ee; HPLC: Chiralcel OD-H column, UV detection at 230 nm, eluent: hexane/2-propanol = 98:2 flow 1.0 mL min^{-1}, 20 °C, R_f for (−)-**2f**: 9.0 min; (+)-**2f**: 9.6 min. IR ($CHCl_3$): $\nu = 2925$, 1732, 1471, 1364, 1251, 1036, 809, 702, 623, 543 cm^{-1}; ^{1}H NMR ($CDCl_3$–CCl_4): δ 2.03 (s, 3H, $COCH_3$), 2.23–2.32 (m, 2H, CH_2, H-2), 4.22 (m, 2H, CH_2, H-1), 5.48 (dd, $J = 5.2$, 8.9 Hz, 1H, CH, H-3), 7.12 (td, $J = 7.9$, 1.4 Hz, 1H, CH, Ar), 7.34 (t, $J = 7.9$ Hz, 1H, CH, Ar), 7.53 (d, $J = 7.9$ Hz, 1H, CH, Ar), 7.59 (dd, $J = 7.9$, 1.4 Hz, 1H, CH, Ar) ; ^{13}C NMR ($CDCl_3$–CCl_4): δ 20.75, 38.27, 57.99, 61.13, 122.72, 128.01, 128.66, 129.64, 132.92, 140.13, 170.23 (C=O); MS (EI) *m*/*z* (%): 231 (40) [M^+−OAc], 230 (80), 228 (60), 203 (20), 196 (30), 194 (30), 181 (10), 150 (20), 116 (90), 115 (100), 103 (80), 102 (80), 89 (40), 77 (70), 63 (20), 51 (30), 43 (100).

4.3.12. (+)-3-Chloro-3-(2-bromorophenyl)propan-1-ol (1f). Colorless oil (10.2 mg, 24% yield), $[\alpha]_D^{25} = +4.4$ (*c* 1.00, $CHCl_3$) for 43% ee; HPLC: Chiralcel OD-H column, UV detection at 230 nm, eluent: hexane/2-propanol = 98:2 flow 1.0 mL min^{-1}, 20 °C, R_f for (+)-**1f**: 41.3 min; (−)-**1f**: 48.3 min. All spectroscopic data are in agreement with those published for racemic **1f**.[3]

4.3.13. (−)-3-Bromo-3-phenylpropyl acetate (4). Colorless oil (8.4 mg, 19% yield), $[\alpha]_D^{25} = -28.7$ (*c* 0.84) for 38% ee; HPLC: Chiralcel OD-H column, UV detection at 230 nm, eluent: hexane/2-propanol = 98:2 flow 1.0 mL min^{-1}, 20 °C, R_f for (−)-**4**: 10.1 min; (+)-**4**: 16.5 min. IR ($CHCl_3$): $\nu = 2926$, 1743, 1451, 1363, 1258, 1196, 1088, 1027, 801, 727, 626, 531 cm^{-1}; ^{1}H NMR ($CDCl_3$–CCl_4): δ 2.07 (s, 3H, $COCH_3$), 2.46 (m, 1H, CH_2, H-2), 2.59 (m, 1H, CH_2, H-2), 4.19 (m, 2H, CH_2, H-1), 5.06 (t, $J = 7.5$ Hz, 1H, CH, H-3), 7.28–7.42 (m, 5H, CH, Ph); ^{13}C NMR ($CDCl_3$–CCl_4): δ 20.70, 38.89, 50.62, 62.23, 127.23, 128.50, 128.74, 141.37, 170.08 (C=O); HRMS (EI): M^+−Br, found 177.0916, $C_{11}H_{13}O_2$ requires 177.0916.

4.3.14. (+)-3-Bromo-3-phenylpropan-1-ol (3). Yellow wax (9.9 mg, 27% yield), $[\alpha]_D^{25} = +8.8$ (*c* 0.99) for 21% ee; HPLC: Chiralcel OD-H column, UV detection at 230 nm, eluent: hexane/2-propanol = 98:2 flow 1.0 mL min^{-1}, 20 °C, R_f for (+)-**3**: 36.3 min; (−)-**3**: 53.2 min. All spectroscopic data agree with racemic **3**. Complete racemization of compound **3** within a few days upon standing in *n*-hexane/2-propanol solution (10:1, v/v) at +4 °C was observed.

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