HETEROCYCLES, Vol. 95, No. 1, 2017, pp. 277-289. © 2017 The Japan Institute of Heterocyclic Chemistry
Received, 14th July, 2016, Accepted, 6th September, 2016, Published online, 3rd October, 2016
DOI: 10.3987/COM-16-S(S)17

KINETIC RESOLUTION OF RACEMIC 2-HYDROXYACETALS BY ASYMMETRIC ESTERIFICATION USING A MIXED ANHYDRIDE PROTOCOL

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Abstract – The non-enzymatic kinetic resolution of racemic 2-hydroxyacetals via asymmetric esterification with diphenylacetic acid and pivalic anhydride catalyzed by the chiral acyl transfer catalyst (*R*)-BTM is reported. The reaction transition states were elucidated using theoretical calculations; it was found that 1,3-dioxolane is a suitable reagent for attaining high selectivity.

INTRODUCTION

Optically active 2-hydroxyacetal derivatives are versatile chiral building blocks for producing useful biologically active compounds. To obtain their related chiral compounds, such as 2-hydroxyacetals,[1] 2-hydroxythioacetals,[2] and 2-hydroxyaldehydes,[3] several efficient enzymatic kinetic resolution (KR) methods have been developed. However, to the best of our knowledge, a general chemical KR of these compounds has not yet been reported. Previously, we reported the first KR of racemic secondary benzylic alcohols by asymmetric esterification via the *in situ* formation of mixed anhydrides using free carboxylic acids, carboxylic anhydrides, and chiral acyl transfer catalysts.[4] In addition, we achieved KR of racemic 1-heteroarylalkanols using a mixed anhydride protocol (**Scheme 1**, Eq. 1).[5,6] The reaction transition states were determined using density functional theory (DFT) calculations, and it was revealed that heteroatoms on the substrates played an important role in attaining high selectivity.[5a] Thus, it was hypothesized that

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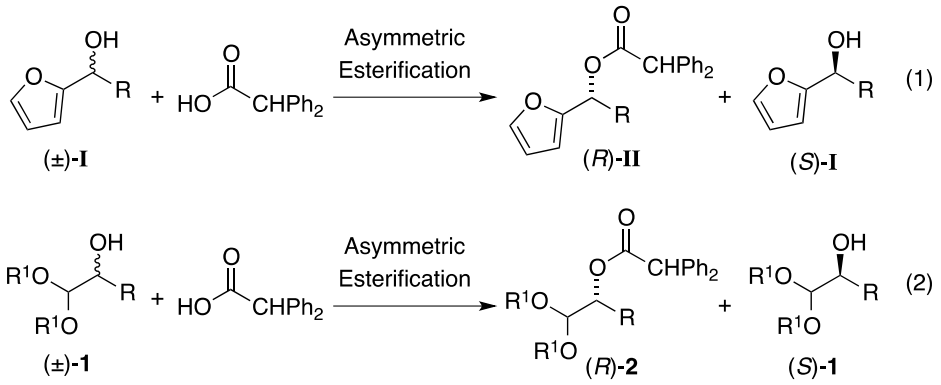
The authors dedicate this paper to Professor Dr. Masakatsu Shibasaki on the celebration of his 70th birthday.

the same KR method may be applicable to racemic 2-hydroxyacetals containing two heteroatoms at the C-1 position (**Scheme 1**, Eq. 2). Herein, we report for the first time the non-enzymatic KR of racemic 2-hydroxyacetals by asymmetric esterification.



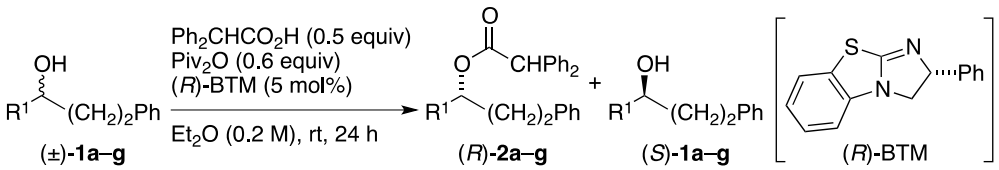
Scheme 1. A working hypothesis of this study

RESULTS AND DISCUSSION

To identify and optimize a suitable acetal moiety, we first examined KR of the racemic 2-hydroxyacetals **1a**–**e** and thioacetals **1f**–**g** with diphenylacetic acid as an acyl source and 2,2-dimethylpropanoic anhydride (Piv_2O) as a condensation reagent in the presence of (*R*)-BTM in diethyl ether at room temperature for 24 h, which are similar reaction conditions to those established in previous studies (**Table 1**). In KR of the acyclic diethylacetal **1a**, the reactivity is moderate and the chirality is unresolved (entry 1). Conversely, the reactions of the 5-membered cyclic acetals **1b** and **1c** smoothly proceed to afford high *s*-values (entries 2 and 3).[7] Interestingly, moderate *s*-values are achieved using **1d**, which contains a phenyl ring fused with 1,3-dioxolane, and the 6-membered cyclic acetal **1e** (entries 4 and 5). Furthermore, the reactions of thioacetals **1f**–**g** do not result in good *s*-values, regardless of the number of members in the cyclic ring (entries 6 and 7).

After a suitable acetal moiety was identified, we further examined the effects of co-base and solvents on KR of (±)-**1b** to optimize the reaction conditions (**Table 2**). As shown in entries 1–3, the reaction was conducted in different amounts of *i*-Pr_2NEt (0, 1.2, and 2.4 equiv) and no effect is observed. Thus, the same reaction was employed in various organic solvents without *i*-Pr_2NEt (entries 4–9). Though good *s*-values are obtained in other etheric solvents, such as cyclopentyl methyl ether (CPME), THF, and 1,2-dimethoxyethane (DME), these solvents are not superior to diethyl ether in terms of reactivity (entries 6–8).[6c] Other solvents, including toluene, CH_2Cl_2, and *N*,*N*-dimethylformamide (DMF), are ineffective for the reaction (entries 4, 5, and 9).

Table 1. Screening of the acetal moiety



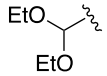
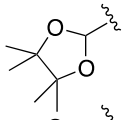
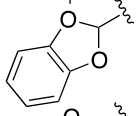
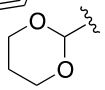
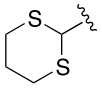
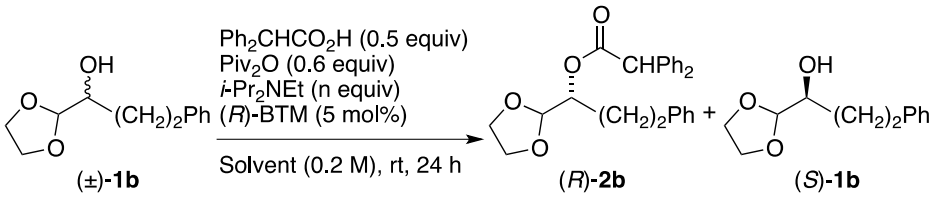
Entry	R^1		Yield (**2** ; **1**) [%]	ee (**2** ; **1**) [%]	*s*
1		(**1a**)	22 ; 72	3 ; 0	1
2		(**1b**)	43 ; 55	93 ; 72	60
3		(**1c**)	40 ; 59	93 ; 61	53
4		(**1d**)	41 ; 55	78 ; 56	14
5		(**1e**)	43 ; 48	76 ; 63	14
6		(**1f**)	32 ; 62	75 ; 42	11
7		(**1g**)	39 ; 56	42 ; 34	3

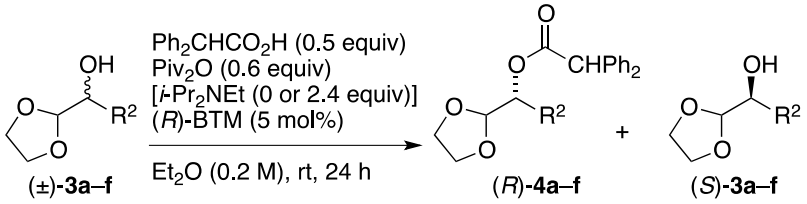
Table 2. Optimization of the reaction conditions



Entry	Solvent	n [equiv]	Yield (**2** ; **1**) [%]	ee (**2** ; **1**) [%]	*s*
1	Et_2O	0	43 ; 55	93 ; 72	60
2	Et_2O	1.2	40 ; 55	93 ; 70	56
3	Et_2O	2.4	43 ; 57	93 ; 73	63
4	toluene	0	27 ; 69	87 ; 34	21
5	CH_2Cl_2	0	16 ; 68	86 ; 18	16
6	CPME	0	25 ; 74	93 ; 32	42
7	THF	0	23 ; 73	95 ; 34	55
8	DME	0	31 ; 67	95 ; 44	57
9	DMF	0	21 ; 58	92 ; 25	31

Finally, to explore the scope of the present method, the racemic 2-hydroxyacetals **3a**–**f** were employed under the above optimized reaction conditions with and without *i*-Pr_2NEt (**Table 3**). The reactions of **3a** and **3c**, with normal aliphatic alkyl chains as the R^2 substituent, smoothly proceed to afford good *s*-values (entries 1 and 3). Although the reactivity is not satisfactory, the highest *s*-value is obtained in the reaction of **3b**, which has a branched aliphatic alkyl chain as the R^2 group (entry 2). In the reactions of **3d** and **3f**, which have phenyl-substituted aliphatic alkyl chains as the R^2 group, the selectivity is influenced by the methylene chain length; the reaction of **3d** affords poor results (entry 4), while the others give good results (entries 5 and 6). The reactions afford similar results regardless of the usage of *i*-Pr_2NEt, as shown by the values in parentheses.

Table 3. Kinetic resolution of (±)-2-hydroxyacetals



Entry	R^2	Yield[a] (**4** ; **3**) [%]	ee[a] (**4** ; **3**) [%]	*s*[a]
1	*n*-Pr (**3a**)	36 ; 34 (42 ; 32)	94 ; 71 (94 ; 76)	72 (71)
2	*i*-Pr (**3b**)	18 ; 50 (27 ; 47)	98 ; 27 (97 ; 44)	117 (119)
3	*n*-Bu (**3c**)	31 ; 38 (31 ; 46)	93 ; 61 (94 ; 57)	49 (53)
4	$PhCH_2$ (**3d**)	35 ; 64 (25 ; 73)	34 ; 19 (27 ; 9)	2 (2)
5	$Ph(CH_2)_2$ (**3e** = **1b**)	43 ; 55 (43 ; 57)	93 ; 72 (93 ; 73)	60 (63)
6	$Ph(CH_2)_3$ (**3f**)	36 ; 63 (31 ; 65)	88 ; 54 (88 ; 35)	26 (23)

[a]The values in parentheses are data obtained in the presence of *i*-Pr_2NEt.

Furthermore, the mechanism of the stereoselectivity was investigated using DFT calculations (**Figure 1**). Based on the perspectives detailed in our previous reports,[5] the determination of the transition state forming the enantiomerically active (*R*)-**2h** from the model substrate (*R*)-**1h** with diphenylacetic acid, Piv_2O, and (*R*)-BTM was performed using DFT calculations at the B3LYP/6-31G*//B3LYP/6-31G* level of theory, according to the previously reported method. The most stable transition state in the production of the desired ester (*R*)-**2h** is (*R*)-**ts-rot1**, as depicted in **Figure 1**. The high selectivity attained in the KR system can be explained by the rapid transformation of (*R*)-**1h** into (*R*)-**2h** via the stabilized transition structure containing (*R*)-**1h** and the dihydroimidazolium salt (**int-*R***), derived from the mixed anhydride (**MA**) and (*R*)-BTM. The length of the carbon–oxygen bond formed between the carbonyl carbon of the

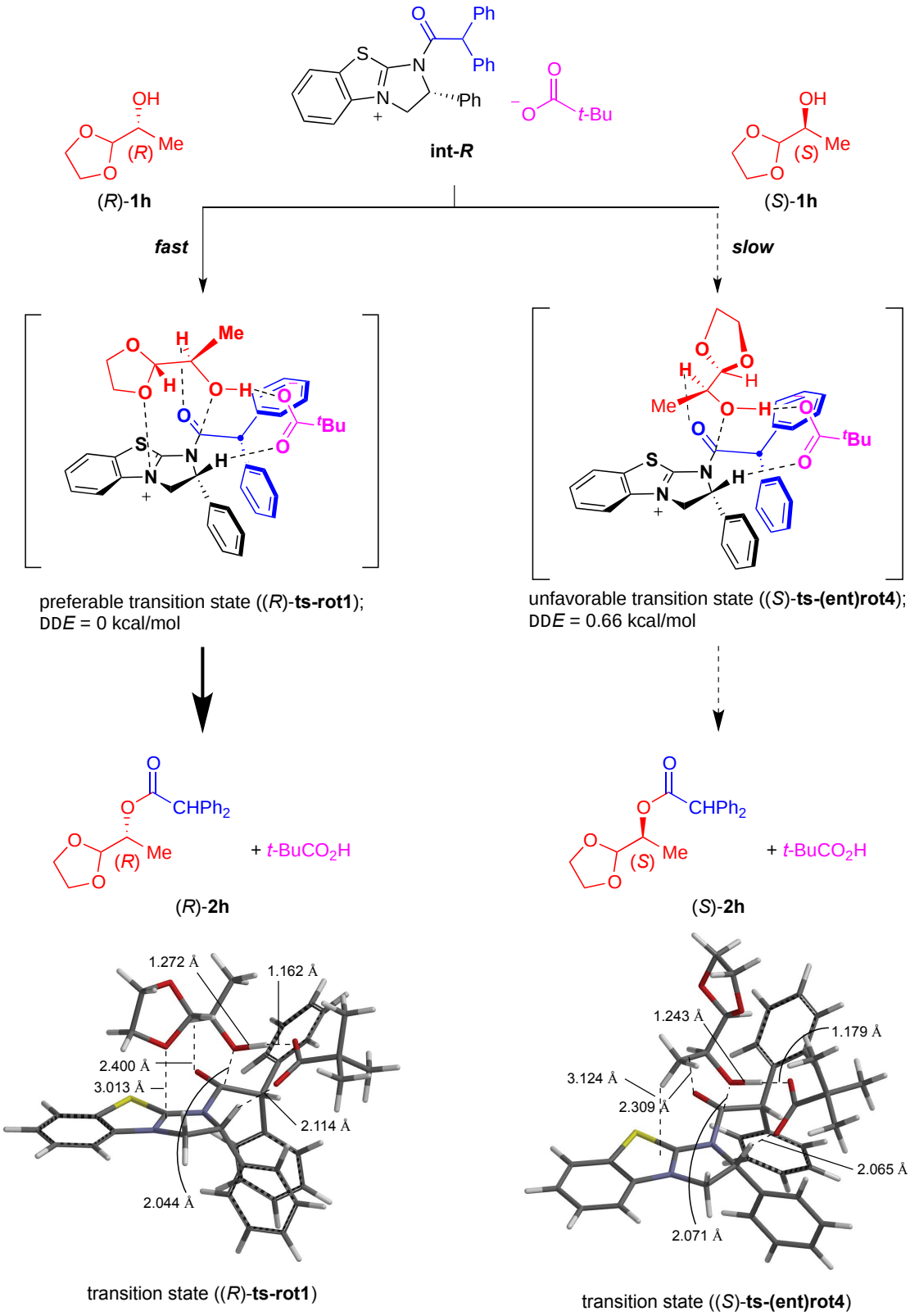


Figure 1. Calculated transition states for the kinetic resolution of **1h**

acid component and the oxygen of the hydroxyl group is 2.044 Å, which is accompanied by the coordination of the oxygen in the carbonyl moiety to the hydrogen at C-1 of the alcohol at a distance of 2.400 Å. The length of the cleaving oxygen–hydrogen bond between the oxygen and hydrogen in the

hydroxyl group is 1.272 Å. A frequency analysis of (*R*)-**ts-rot1** indicates that the nucleophilic attack of the alcohol on the carbonyl group and the deprotonation of the hydroxyl group with the pivalate anion proceed via a concerted reaction mechanism because the carbon–oxygen bond-forming step and the oxygen–hydrogen bond-cleaving process synchronously occurs. The α,α-diphenyl moiety of (*R*)-**ts-rot1** derived from diphenylacetic acid has a rigid structure wherein the conformation is restricted by the interaction between the oxygen in the conformationally stable acetal ring and the positive electronic charge on the face of **int-*R*** (3.013 Å) as well as the coordination of the oxygens in the pivalate anion onto the hydrogen of the hydroxyl group (1.162 Å) and the hydrogen at C-2 of **int-*R*** (2.114 Å). Conversely, the complex of (*S*)-**1h**, an enantiomer of (*R*)-**1h**, with **int-*R*** including (*R*)-BTM and **MA**, produces an unstable structure (*S*)-**ts-(ent)rot4**, which has a much higher energy ($\Delta\Delta E$ = +0.66 kcal/mol) owing to the weaker attractive interaction between the methyl substituent of (*S*)-**1h** and the 1-benzothiophene face of **int-*R*** (3.124 Å cf. 3.013 Å in (*R*)-**ts-rot1**) and affords the corresponding (*S*)-**2h** ($\Delta E_{(S)\text{-}\mathbf{ts\text{-}(ent)rot4}}$ = 12.98 kcal/mol). Therefore, the desired chiral (*R*)-**2h** is selectively obtained from (*R*)-**1h** with **MA** by a rapid transformation via the transition state (*R*)-**ts-rot1** ($\Delta E_{(R)\text{-}\mathbf{ts\text{-}rot1}}$ = 12.32 kcal/mol).

In summary, we have achieved the first non-enzymatic KR of 2-hydroxyacetals by an asymmetric mixed-anhydride protocol. The transition states were determined using DFT calculations to elucidate the role of the acetal moiety. Further studies on the application of the present method are now in progress in our laboratory.

EXPERIMENTAL

General Information. All melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with $CHCl_3$ (in $CDCl_3$) as internal standard. Thin layer chromatography was performed on Wakogel B5F. All reactions were carried out under argon atmosphere in dried glassware. All reagents were purchased from commercial suppliers and used without further purification unless otherwise noted. 2,2-Dimethylpropanoic anhydride (Piv_2O), diphenylacetic acid, and (*R*)-BTM were purchased from Tokyo Kasei Kogyo Co., Ltd. (TCI). Et_2O (super dehydrated) was purchased from Wako Chemicals Co., Ltd.

Typical Procedure: Asymmetric esterification of racemic 2-hydroxyacetal (($\pm$)−**1b**) with diphenylacetic acid by using Piv_2O in the presence of (*R*)-BTM was described (**Table 1**, entry 2): To a solution of racemic 2-hyroxyacetal (($\pm$)−**1b**) (41.6 mg, 0.20 mmol) in Et_2O (1.0 mL) at room temperature were successively added diphenylacetic acid (21.2 mg, 0.10 mmol), Piv_2O (24.3 μL, 0.12 mmol), and (*R*)-BTM (2.5 mg, 10.0 μmol). The reaction mixture was stirred for 24 h at the same temperature and then it was quenched with saturated aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer was

extracted with EtOAc. The combined organic layer was dried over Na_2SO_4. After filtration of the mixture and evaporation of the solvent, the crude product was purified by preparative thin layer chromatography on silica to afford the corresponding optically active ester (*R*)-**2b** (34.8 mg, 43% yield, 93% ee) and the recovered optically active alcohol (*S*)-**1b** (23.0 mg, 55% yield, 72% ee) [*s* = 60].

(Optically Active Alcohols)

(*S*)-1,1-Diethoxy-4-phenylbutan-2-ol ((*S*)-1a) [Table 1, Entry 1, 0% ee, *s* = 1]: HPLC (CHIRALPAK ID, *i*-PrOH/hexane = 1/99, flow rate = 1.0 mL/min): t_R = 12.8 min (50.0%), t_R = 17.7 min (50.0%); IR (neat): 3471, 2978, 2924, 2893, 1450, 1381, 1126, 1065, 748, 702 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.33–7.12 (m, 5H), 4.27 (d, *J* = 6.0 Hz, 1H), 3.78 (dq, *J* = 9.2, 7.0 Hz, 1H), 3.68 (dq, *J* = 9.2, 7.0 Hz, 1H), 3.63–3.48 (m, 3H), 2.89 (ddd, *J* = 13.8, 10.0, 5.0 Hz, 1H), 2.70 (ddd, *J* = 13.8, 10.0, 7.0 Hz, 1H), 2.24 (br s, 1H), 1.93 (dddd, *J* = 13.8, 10.0, 7.0, 3.2 Hz, 1H), 1.74 (ddt, *J* = 14.0, 5.0, 10.0 Hz, 1H), 1.23 (t, *J* = 7.0 Hz, 3H), 1.20 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 142.5, 128.8, 128.6, 126.0, 105.4, 71.4, 63.8, 63.7, 33.9, 32.1, 15.7, 15.7; HR MS: calcd for $C_{14}H_{22}O_3Na$ ($M+Na^+$) 261.1461, found 261.1453.

(*S*)-1-(1',3'-Dioxolan-2'-yl)-3-phenylpropan-1-ol ((*S*)-1b (= 3e)) [Table 1, Entry 2, 72% ee, *s* = 60]: HPLC (CHIRALCEL OD-H, *i*-PrOH/hexane = 1/9, flow rate = 0.5 mL/min): t_R = 24.0 min (85.9%), t_R = 29.3 min (14.1%); IR (neat): 3464, 2947, 2885, 1450, 1381, 1142, 1088, 748, 702 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.32–7.13 (m, 5H), 4.78 (d, *J* = 4.0 Hz, 1H), 4.05–3.84 (m, 4H), 3.66–3.55 (m, 1H), 2.89 (ddd, *J* = 13.8, 9.2, 5.4 Hz, 1H), 2.72 (ddd, *J* = 13.8, 9.2, 7.4 Hz, 1H), 2.06 (br s, 1H, OH), 1.95–1.75 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 142.1, 128.8, 128.7, 126.1, 105.5, 71.3, 65.8, 65.5, 33.8, 31.9; HR MS: calcd for $C_{12}H_{16}O_3Na$ ($M+Na^+$) 231.0992, found 231.0993.

(*S*)-3-Phenyl-1-(4',4',5',5'-tetramethyl-1',3'-dioxolan-2'-yl)propan-1-ol ((*S*)-1c) [Table 1, Entry 3, 61% ee, *s* = 53]: HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/9, flow rate = 0.7 mL/min): t_R = 9.3 min (80.3%), t_R = 10.8 min (19.7%); IR (neat): 3471, 2978, 2924, 2877, 1381, 1157, 1088, 1018, 741, 702 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.31–7.11 (m, 5H), 4.81 (d, *J* = 5.2 Hz, 1H), 3.55–3.42 (m, 1H), 2.89 (ddd, *J* = 14.0, 9.6, 4.8 Hz, 1H), 2.71 (ddd, *J* = 14.0, 9.6, 7.0 Hz, 1H), 2.14 (br s, 1H, OH), 1.89 (dddd, *J* = 14.0, 9.6, 7.0, 3.2 Hz, 1H), 1.76 (ddt, *J* = 14.0, 9.2, 9.6 Hz, 1H), 1.21 (s, 3H), 1.20 (s, 6H), 1.18 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 142.4, 128.8, 128.6, 126.0, 102.1, 82.8, 82.4, 72.8, 33.9, 31.9, 24.5, 24.3, 22.5, 22.4; HR MS: calcd for $C_{16}H_{24}O_3Na$ ($M+Na^+$) 287.1618, found 287.1609.

(*S*)-1-(Benzo[*d*][1',3']dioxol-2'-yl)-3-phenylpropan-1-ol ((*S*)-1d) [Table 1, Entry 4, 56% ee, *s* = 14]: Mp 51.9 °C; HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/9, flow rate = 0.5 mL/min): t_R = 21.5 min (22.0%), t_R = 24.4 min (78.0%); IR (KBr): 3394, 2931, 1489, 1242, 1119, 1088, 741, 702 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.38–7.12 (m, 5H), 6.82 (s, 4H), 5.97 (d, *J* = 4.0 Hz, 1H), 3.95–3.76 (m, 1H), 3.04–2.87 (m, 1H), 2.86–2.68 (m, 1H), 2.08 (d, *J* = 4.8 Hz, 1H, OH), 2.08–1.72 (m, 2H); ^{13}C NMR ($CDCl_3$); δ 147.5, 147.3, 141.3, 128.50, 128.45, 126.0, 121.63, 121.61, 111.4, 108.6, 108.5, 71.0, 32.4, 31.3; HR MS: calcd

for $C_{16}H_{16}O_3Na$ ($M+Na^+$) 279.0992, found 279.0979.

(*S*)-1-(1',3'-Dioxan-2'-yl)-3-phenylpropan-1-ol ((*S*)-1e) [Table 1, Entry 5, 63% ee, *s* = 14]: HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/9, flow rate = 0.7 mL/min): t_R = 13.8 min (81.6%), t_R = 20.4 min (18.4%); IR (neat): 3471, 2962, 2924, 2854, 1142, 1095, 1018, 748, 702 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.32–7.12 (m, 5H), 4.40 (d, *J* = 4.8 Hz, 1H), 4.20–4.06 (m, 2H), 3.83–3.68 (m, 2H), 3.62–3.50 (m, 1H), 2.87 (ddd, *J* = 13.6, 10.0, 4.8 Hz, 1H), 2.69 (ddd, *J* = 13.6, 10.0, 6.8 Hz, 1H), 2.31 (br s, 1H), 2.08 (dtt, *J* = 13.6, 12.8, 4.8, 1H), 1.90 (ddt, *J* = 13.6, 6.8, 10.0 Hz, 1H), 1.77 (ddt, *J* = 13.6, 4.8, 10.0 Hz, 1H), 1.35 (dt, *J* = 13.6, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 142.4, 128.8, 128.6, 126.0, 102.9, 72.1, 67.10, 67.07, 33.4, 31.9, 26.1; HR MS: calcd for $C_{13}H_{18}O_3Na$ ($M+Na^+$) 245.1148, found 245.1159.

(*S*)-1-(1',3'-Dithiolan-2'-yl)-3-phenylpropan-1-ol ((*S*)-1f) [Table 1, Entry 6, 42% ee, *s* = 11]: HPLC (CHIRALPAK IA-3, *i*-PrOH/hexane = 1/9, flow rate = 0.5 mL/min): t_R = 45.1 min (70.8%), t_R = 48.2 min (29.2%); IR (neat): 3433, 2924, 1389, 1065, 748, 702 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.35–7.13 (m, 5H), 4.47 (d, *J* = 6.0 Hz, 1H), 3.58–3.44 (m, 1H), 3.30–2.98 (m, 4H), 2.89 (ddd, *J* = 13.6, 9.6, 4.8 Hz, 1H), 2.71 (ddd, *J* = 13.6, 9.6, 6.0 Hz, 1H), 2.54 (d, *J* = 4.4 Hz, 1H), 2.05–1.88 (m, 1H), 1.78 (ddt, *J* = 13.6, 4.8, 9.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 142.0, 128.8, 128.7, 126.2, 74.4, 60.1, 39.2, 38.3, 37.2, 32.5; HR MS: calcd for $C_{12}H_{16}OS_2Na$ ($M+Na^+$) 263.0535, found 263.0538.

(*S*)-1-(1',3'-Dithian-2'-yl)-3-phenylpropan-1-ol ((*S*)-1g) [Table 1, Entry 7, 34% ee, *s* = 3]: HPLC (CHIRALPAK IA-3, *i*-PrOH/hexane = 1/9, flow rate = 0.5 mL/min): t_R = 29.4 min (66.9%), t_R = 34.7 min (33.1%); IR (neat): 3309, 2924, 2893, 1496, 1080, 748, 694 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.36–7.15 (m, 5H), 3.97–3.83 (m, 2H), 3.02–2.83 (m, 3H), 2.82–2.67 (m, 3H), 2.49 (d, *J* = 2.0 Hz, 1H), 2.27–2.15 (m, 1H), 2.15–2.03 (m, 1H), 2.03–1.83 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 141.7, 128.5, 128.4, 125.9, 71.2, 52.1, 35.7, 31.9, 28.1, 27.6, 25.6; HR MS: calcd for $C_{13}H_{18}OS_2Na$ ($M+Na^+$) 277.0691, found 277.0683.

(*S*)-1-(1',3'-Dioxolan-2'-yl)butan-1-ol ((*S*)-3a) [Table 3, Entry 1, 71% ee, *s* = 72]: IR (neat): 3464, 2954, 2877, 1165, 1119, 1026, 972 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.77 (d, *J* = 4.0 Hz, 1H), 4.08–3.84 (m, 4H), 3.61 (dt, *J* = 8.0, 4.0 Hz, 1H), 2.13 (br s, 1H), 1.67–1.32 (m, 4H), 0.95 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 105.5, 71.7, 65.8, 65.5, 34.3, 18.9, 14.3; HR MS: calcd for $C_7H_{14}O_3Na$ ($M+Na^+$) 169.0835, found 169.0843.

Enantiomeric excess of (*S*)-**3a** has been determined after converting into the corresponding diphenylacetate.

(*S*)-1-(1',3'-Dioxolan-2'-yl)-2-methylpropan-1-ol ((*S*)-3b) [Table 3, Entry 2, 27% ee, *s* = 117]: IR (neat): 3471, 2962, 2885, 1157, 1126, 1057, 1018, 964 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.90 (d, *J* = 3.6 Hz, 1H), 4.11–3.82 (m, 4H), 3.35 (dd, *J* = 6.4, 3.6 Hz, 1H), 2.15 (br s, 1H), 1.88 (dqq, *J* = 6.4, 6.8, 6.8 Hz, 1H), 1.00 (t, *J* = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ 103.8, 75.9, 65.3, 65.2, 30.1, 19.0, 17.7; HR MS: calcd for $C_7H_{14}O_3Na$ ($M+Na^+$) 169.0835, found 169.0829.

Enantiomeric excess of (*S*)-**3b** has been determined after converting into the corresponding diphenylacetate.

(*S*)-1-(1',3'-Dioxolan-2'-yl)pentan-1-ol ((*S*)-3c) [Table 3, Entry 3, 61% ee, *s* = 49]: IR (neat): 3456, 2954, 2870, 1157, 1119, 1041, 980, 949 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.77 (d, *J* = 3.6 Hz, 1H), 4.08–3.84 (m, 4H), 3.59 (dt, *J* = 3.6, 8.4 Hz, 1H), 2.06 (br s, 1H), 1.66–1.22 (m, 6H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 105.5, 72.0, 65.8, 65.5, 31.9, 27.9, 23.0, 14.3; HR MS: calcd for $C_8H_{16}O_3Na$ ($M+Na^+$) 183.0992, found 183.0993.

Enantiomeric excess of (*S*)-**3c** has been determined after converting into the corresponding diphenylacetate.

(*S*)-1-(1',3'-Dioxolan-2'-yl)-2-phenylethan-1-ol ((*S*)-3d) [Table 3, Entry 4, 19% ee, *s* = 2]: HPLC (CHIRALCEL OJ-H, *i*-PrOH/hexane = 1/9, flow rate = 1.0 mL/min): t_R = 22.9 min (40.3%), t_R = 26.0 min (59.7%); IR (neat): 3464, 2885, 1149, 1080, 1041, 980, 949, 748, 702 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.34–7.16 (m, 5H), 4.80 (d, *J* = 4.0 Hz, 1H), 4.10–3.97 (m, 2H), 3.97–3.78 (m, 3H), 2.93 (dd, *J* = 14.0, 4.4 Hz, 1H), 2.81 (dd, *J* = 14.0, 8.8 Hz, 1H), 2.17 (br s, 1H); ^{13}C NMR ($CDCl_3$); δ 138.1, 129.7, 128.7, 126.7, 104.7, 72.9, 65.8, 65.6, 38.6; HR MS: calcd for $C_{11}H_{14}O_3Na$ ($M+Na^+$) 217.0835, found 217.0843.

(*S*)-1-(1',3'-Dioxolan-2'-yl)-4-phenylbutan-1-ol ((*S*)-3f) [Table 3, Entry 6, 54% ee, *s* = 26]: HPLC (CHIRALCEL OD-H, *i*-PrOH/hexane = 5/95, flow rate = 0.75 mL/min): t_R = 19.9 min (22.9%), t_R = 22.9 min (77.1%); IR (neat): 3456, 2939, 2885, 1142, 1034, 949, 748, 702 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.32–7.22 (m, 2H), 7.21–7.12 (m, 3H), 4.76 (d, *J* = 3.6 Hz, 1H), 4.08–3.82 (m, 4H), 3.67–3.55 (m, 1H), 2.65 (t, *J* = 7.6 Hz, 2H), 1.99 (br s, 1H), 1.98–1.46 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 142.2, 128.3, 128.2, 125.6, 105.1, 71.6, 65.4, 65.1, 35.8, 31.5, 27.2; HR MS: calcd for $C_{13}H_{18}O_3Na$ ($M+Na^+$) 245.1148, found 245.1149.

(Optically Active Carboxylic Esters)

(*R*)-1,1-Diethoxy-4-phenylbutan-2-yl 2,2-diphenylacetate ((*R*)-2a) [Table 1, Entry 1, 3% ee, *s* = 1]: HPLC (CHIRALPAK IA-3, *i*-PrOH/hexane = 1/9, flow rate = 0.5 mL/min): t_R = 9.9 min (51.3%), t_R = 11.9 min (48.7%); IR (neat): 2978, 1736, 1142, 1065, 741, 702 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.43–7.18 (m, 12H), 7.18–7.10 (m, 1H), 7.02 (d, *J* = 7.2 Hz, 2H), 5.06 (s, 1H), 5.03 (ddd, *J* = 9.0, 5.6, 3.4 Hz, 1H), 4.43 (d, *J* = 5.6 Hz, 1H), 3.66–3.51 (m, 2H), 3.48–3.33 (m, 2H), 2.55–2.38 (m, 2H), 2.09–1.78 (m, 2H), 1.13 (t, *J* = 6.8 Hz, 3H), 1.08 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$); δ 172.0, 141.6, 138.7, 138.5, 128.7, 128.6, 128.5, 128.33, 128.27, 127.3, 127.2, 125.8, 101.9, 73.5, 63.4, 62.5, 57.4, 31.3, 30.8, 15.2, 15.2; HR MS: calcd for $C_{28}H_{32}O_4Na$ ($M+Na^+$) 455.2193, found 455.2214.

(*R*)-1-(1,3-Dioxolan-2-yl)-3-phenylpropyl 2,2-diphenylacetate ((*R*)-2b (= 4e)) [Table 1, Entry 2, 93% ee, *s* = 60]: Mp 81.8 °C; HPLC (CHIRALPAK IA-3, *i*-PrOH/hexane = 1/9, flow rate = 0.5 mL/min): t_R = 27.4 min (96.5%), t_R = 47.0 min (3.5%); IR (KBr): 2893, 1728, 1188, 1149, 1049, 741, 702 cm^{-1}; ^1H

NMR ($CDCl_3$): δ 7.41–7.19 (m, 12H), 7.18–7.11 (m, 1H), 7.03 (d, *J* = 6.8 Hz, 2H), 5.16–5.02 (m, 2H), 4.94 (d, *J* = 3.6 Hz, 1H), 3.88–3.65 (m, 4H), 2.58–2.38 (m, 2H), 1.92 (dt, *J* = 7.6, 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 172.3, 141.6, 138.93, 138.89, 129.1, 128.89, 128.81, 128.67, 128.63, 127.6, 127.5, 126.2, 103.6, 73.4, 65.7, 65.4, 57.6, 31.7, 31.4; HR MS: calcd for $C_{26}H_{26}O_4Na$ ($M+Na^+$) 425.1723, found 425.1716.

(*R*)-3-Phenyl-1-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)propyl 2,2-diphenylacetate ((*R*)-2c) [Table 1, Entry 3, 93% ee, *s* = 53]: HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/9, flow rate = 0.7 mL/min): t_R = 19.6 min (96.6%), t_R = 26.5 min (3.4%); IR (neat): 2978, 1743, 1149, 1026, 741, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.42–7.27 (m, 12H), 7.27–7.69 (m, 1H), 7.01 (d, *J* = 7.2 Hz, 2H), 5.09 (s, 1H), 5.04 (ddd, *J* = 8.8, 4.8, 4.0 Hz, 1H), 4.95 (d, *J* = 4.8 Hz, 1H), 2.46 (t, *J* = 8.2 Hz, 2H), 2.03–1.76 (m, 2H), 1.16 (s, 6H), 1.14 (s, 3H), 1.11 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 172.0, 141.5, 138.84, 138.76, 128.9, 128.8, 128.6, 128.4, 128.3, 128.2, 127.3, 127.1, 125.8, 99.6, 82.5, 82.1, 74.3, 57.2, 31.6, 31.2, 24.0, 23.7, 22.2, 22.0; HR MS: calcd for $C_{30}H_{34}O_4Na$ ($M+Na^+$) 481.2349, found 481.2367.

(*R*)-1-(Benzo[*d*][1,3]dioxol-2-yl)-3-phenylpropyl 2,2-diphenylacetate ((*R*)-2d) [Table 1, Entry 4, 78% ee, *s* = 14]: Mp 115.5 °C; HPLC (CHIRALCEL OD-H, *i*-PrOH/hexane = 1/9, flow rate = 0.5 mL/min): t_R = 16.4 min (88.9%), t_R = 24.8 min (11.1%); IR (KBr): 3055, 1736, 1489, 1358, 1242, 1165, 741, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.38–6.98 (m, 13H), 7.01 (d, *J* = 6.8 Hz, 2H), 6.85–6.71 (m, 3H), 6.71–6.62 (m, 1H), 6.08 (d, *J* = 3.6 Hz, 1H), 5.38–5.24 (m, 1H), 4.99 (s, 1H), 2.61–2.38 (m, 2H), 2.12–1.89 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 172.1, 147.6, 147.4, 141.1, 138.6, 138.5, 128.96, 128.94, 128.8, 128.7, 128.6, 127.7, 127.5, 126.4, 121.94, 121.92, 109.4, 108.8, 108.7, 72.9, 57.4, 31.4, 30.5; HR MS: calcd for $C_{30}H_{26}O_4Na$ ($M+Na^+$) 473.1723, found 473.1743.

(*R*)-1-(1,3-Dioxan-2-yl)-3-phenylpropyl 2,2-diphenylacetate ((*R*)-2e) [Table 1, Entry 5, 76% ee, *s* = 14]: Mp 88.3 °C; HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/9, flow rate = 0.7 mL/min): t_R = 36.0 min (88.0%), t_R = 42.8 min (12.0%); IR (KBr): 2970, 1728, 1188, 1149, 1088, 1057, 1011, 741, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.45–7.17 (m, 12H), 7.17–7.09 (m, 1H), 7.00 (d, *J* = 7.2 Hz, 2H), 5.10 (s, 1H), 5.01 (dt, *J* = 9.2, 4.0 Hz, 1H), 4.55 (d, *J* = 4.0 Hz, 1H), 4.07 (dd, *J* = 11.6, 4.0 Hz, 2H), 3.67 (dt, *J* = 12.4, 2.0 Hz, 2H), 2.50–2.37 (m, 2H), 2.13–1.82 (m, 3H), 1.27 (dt, *J* = 12.4, 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 172.2, 141.8, 139.1, 138.9, 129.09, 129.07, 128.84, 128.67, 128.62, 128.57, 127.6, 127.4, 126.1, 100.7, 74.2, 67.1, 67.1, 57.5, 31.6, 30.6, 25.9; HR MS: calcd for $C_{27}H_{28}O_4Na$ ($M+Na^+$) 439.1880, found 439.1860.

(*R*)-1-(1',3'-Dithiolan-2'-yl)-3-phenylpropyl 2,2-diphenylacetate ((*R*)-2f) [Table 1, Entry 6, 75% ee, *s* = 11]: HPLC (CHIRALPAK IA-3, *i*-PrOH/hexane = 1/9, flow rate = 0.5 mL/min): t_R = 20.1 min (87.6%), t_R = 23.8 min (12.4%); IR (neat): 2924, 1736, 1142, 741, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.42–7.19 (m, 12H), 7.19–7.11 (m, 1H), 7.01 (d, *J* = 6.8 Hz, 2H), 5.12–4.97 (m, 2H), 4.55 (d, *J* = 7.2 Hz, 1H), 3.15–2.94

(m, 4H), 2.54–2.37 (m, 2H), 2.14–2.00 (m, 1H), 2.00–1.86 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 172.2, 141.4, 138.7, 129.2, 129.1, 128.9, 128.8, 128.7, 128.6, 127.7, 127.6, 126.3, 77.0, 57.7, 56.0, 39.2, 38.4, 34.8, 31.8; HR MS: calcd for $C_{26}H_{26}O_2S_2Na$ ($M+Na^+$) 457.1266, found 457.1285.

(*R*)-1-(1',3'-Dithian-2'-yl)-3-phenylpropyl 2,2-diphenylacetate ((*R*)-2g) [Table 1, Entry 7, 42% ee, *s* = 3]: HPLC (CHIRALPAK IA-3, *i*-PrOH/hexane = 1/9, flow rate = 0.5 mL/min): t_R = 27.5 min (71.2%), t_R = 40.4 min (28.8%); IR (neat): 2924, 1736, 1188, 1149, 741, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.45–7.18 (m, 12H), 7.18–7.11 (m, 1H), 6.99 (d, *J* = 7.2 Hz, 2H), 5.26 (ddd, *J* = 10.0, 6.4, 3.4 Hz, 1H), 5.11 (s, 1H), 4.03 (d, *J* = 6.4 Hz, 1H), 2.90 (ddd, *J* = 14.2, 7.2, 3.2 Hz, 1H), 2.81 (ddd, *J* = 14.2, 7.2, 3.2 Hz, 1H), 2.74–2.58 (m, 2H), 2.52–2.32 (m, 2H), 2.17 (dddd, *J* = 14.0, 10.4, 6.9, 3.4 Hz, 1H), 2.09–1.79 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 172.4, 141.3, 138.9, 138.7, 134.1, 129.2, 129.1, 129.0, 128.72, 128.65, 127.7, 127.5, 126.3, 74.4, 57.5, 49.3, 33.9, 31.7, 29.0, 28.6, 25.9; HR MS: calcd for $C_{27}H_{28}O_2S_2Na$ ($M+Na^+$) 471.1423, found 471.1428.

(*R*)-1-(1',3'-Dioxolan-2'-yl)butyl 2,2-diphenylacetate ((*R*)-4a) [Table 3, Entry 1, 94% ee, *s* = 72]: HPLC (CHIRALPAK IA-3, *i*-PrOH/hexane = 1/9, flow rate = 0.5 mL/min): t_R = 17.8 min (97.1%), t_R = 20.4 min (2.9%); IR (neat): 2962, 2877, 1736, 1157, 1111, 1034, 741, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.38–7.18 (m, 10H), 5.12–5.00 (m, 2H), 4.91 (d, *J* = 3.2 Hz, 1H), 3.87–3.61 (m, 4H), 1.68–1.47 (m, 2H), 1.36–1.11 (m, 2H), 0.84 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 172.0, 138.7, 138.6, 128.70, 128.69, 128.5, 128.4, 127.2, 127.1, 103.4, 73.2, 65.4, 65.0, 57.3, 31.3, 18.3, 13.8; HR MS: calcd for $C_{21}H_{24}O_4Na$ ($M+Na^+$) 363.1567, found 356.1549.

(*R*)-1-(1',3'-Dioxolan-2'-yl)-2-methylpropyl 2,2-diphenylacetate ((*R*)-4b) [Table 3, Entry 2, 98% ee, *s* = 117]: HPLC (CHIRALPAK IA-3, *i*-PrOH/hexane = 1/9, flow rate = 0.5 mL/min): t_R = 16.9 min (98.9%), t_R = 20.1 min (1.1%); IR (neat): 2962, 1736, 1149, 1111, 1034, 741, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.39–7.19 (m, 10H), 5.08 (s, 1H), 5.03 (d, *J* = 4.0 Hz, 1H), 4.86 (dd, *J* = 6.0, 4.0 Hz, 1H), 3.89–3.58 (m, 4H), 2.02 (dqq, *J* = 6.0, 6.8, 6.8 Hz, 1H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H, 3-H); ^{13}C NMR ($CDCl_3$): δ 172.0, 138.8, 138.7, 128.80, 128.76, 128.44, 128.40, 127.2, 127.1, 102.4, 77.0, 65.2, 65.0, 57.4, 28.8, 19.0, 17.6; HR MS: calcd for $C_{21}H_{24}O_4Na$ ($M+Na^+$) 363.1567, found 356.1558.

(*R*)-1-(1',3'-Dioxolan-2'-yl)pentyl 2,2-diphenylacetate ((*R*)-4c) [Table 3, Entry 3, 93% ee, *s* = 49]: HPLC (CHIRALPAK IA-3, *i*-PrOH/hexane = 1/99, flow rate = 0.5 mL/min): t_R = 40.9 min (3.7%), t_R = 45.2 min (96.3%); IR (neat): 2954, 2924, 1959, 1736, 1381, 1149, 1111, 1034, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.38–7.20 (m, 10H), 5.12–4.99 (m, 2H), 4.92 (d, *J* = 3.6 Hz, 1H), 3.88–3.61 (m, 4H), 1.69–1.54 (m, 2H), 1.37–1.08 (m, 4H), 0.80 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 172.0, 138.7, 138.6, 128.73, 128.71, 128.5, 128.4, 127.2, 127.1, 103.5, 73.4, 65.4, 65.1, 57.3, 29.0, 27.1, 22.4, 13.8; HR MS: calcd for $C_{22}H_{26}O_4Na$ ($M+Na^+$) 377.1723, found 377.1716.

(*R*)-1-(1',3'-Dioxolan-2'-yl)-2-phenylethyl 2,2-diphenylacetate ((*R*)-4d) [Table 3, Entry 4, 34% ee, *s* =

2]: Mp 62.0 °C; HPLC (CHIRALPAK IB-3, *i*-PrOH/hexane = 1/9, flow rate = 0.5 mL/min): t_R = 18.1 min (33.2%), t_R = 23.9 min (66.8%); IR (KBr): 3032, 2885, 1736, 1358, 1196, 1157, 1034, 741, 702 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.34–7.14 (m, 11H), 7.14–7.04 (m, 4H), 5.31 (ddd, *J* = 8.8, 5.0, 3.6 Hz, 1H), 4.98 (s, 1H), 4.95 (d, *J* = 3.6 Hz, 1H), 3.90–3.67 (m, 4H), 2.98 (dd, *J* = 14.0, 5.0 Hz, 1H), 2.89 (dd, *J* = 14.0, 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 171.9, 138.9, 138.8, 136.8, 129.7, 129.1, 129.0, 128.8, 128.72, 128.69, 127.45, 127.36, 126.8, 103.1, 74.2, 65.9, 65.5, 57.5, 35.9; HR MS: calcd for $C_{25}H_{24}O_4Na$ ($M+Na^+$) 411.1567, found 411.1561.

(*R*)-1-(1',3'-Dioxolan-2'-yl)-4-phenylbutyl 2,2-diphenylacetate ((*R*)-4f) [Table 3, Entry 6, 88% ee, *s* = 26]: HPLC (CHIRALPAK IA-3, *i*-PrOH/hexane = 1/9, flow rate = 0.5 mL/min): t_R = 27.4 min (6.2%), t_R = 30.2 min (93.8%); IR (neat): 2924, 1736, 1149, 1080, 1034, 741, 702 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.40–7.21 (m, 12H), 7.21–7.13 (m, 1H), 7.04 (d, *J* = 6.8 Hz, 2H), 5.10 (dt, *J* = 4.0, 6.4 Hz, 1H), 5.07 (s, 1H), 4.91 (d, *J* = 4.0 Hz, 1H), 3.88–3.64 (m, 4H), 2.64–2.42 (m, 2H), 1.74–1.60 (m, 2H), 1.60–1.45 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 172.3, 142.2, 138.92, 138.90, 129.02, 129.00, 128.84, 128.78, 128.7, 128.5, 127.54, 127.48, 126.0, 103.7, 73.4, 65.7, 65.4, 57.6, 35.8, 29.2, 27.1; HR MS: calcd for $C_{27}H_{28}O_4Na$ ($M+Na^+$) 439.1880, found 439.1881.

Spectroscopic data of all compounds, and Cartesian coordinates and absolute energies for all calculated structures have been provided in the Supporting Information.

ACKNOWLEDGEMENTS

This study was partly supported by a Research Grant from the Center for Chirality.

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