Supplementary Information

Redesign of enzyme for improving catalytic activity and enantioselectivity
toward poor substrates: manipulation of the transition state

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[A] Methods--------------------------------------------------S2
[B] Site-directed mutagenesis----------------------------------S2
[C] Synthesis of racemic alcohols-----------------------------S2
[D] Determination of enantiomeric purities and absolute configurations------S6
[E] Lipase-catalyzed kinetic resolution-------------------------S7
[F] NMR spectra---------------------------------------------S14
All the DNA manipulations and bacterial transformation were carried out according to the standard protocols or manufacturers’ instructions unless otherwise stated. The computational design, overexpression, refolding, purification, and immobilization of the recombinant lipases were done as reported previously. The method for the determination of kinetic constants has been reported. Racemic alcohols 1a–d were synthesized as described previously, while 1n–q were purchased.

Site-directed mutagenesis.

The mutations were introduced by the overlap-extension PCR method as reported previously. The mutagenic oligonucleotides used as primers and the plasmids used as templates are shown in Table S1.

Table S1 Primers and templates used for site-directed mutagenesis

<table>
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<tr>
<th>Mutant</th>
<th>Primer</th>
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<td>BC-I287F-1F</td>
<td>5’-CTACAAGTGGAACCATTTCGACGAG-3’</td>
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<td>pELIP(I287F/ I290A)</td>
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Synthesis of racemic alcohols.

2-Methoxymethoxy-1-phenylethanol (1e). To a solution of 2-methoxymethoxy-1-phenylethanone (1.68 g, 9.32 mmol) in dry EtOH (20 mL) was added NaBH₄ (177 mg, 4.67 mmol) in an ice bath. The mixture was stirred at room temperature overnight. The solution was adjusted to pH 6. After EtOH had been removed under reduced pressure, brine (9 mL) was added. The solution was neutralized, and the product was extracted with EtOAc (15 mL × 3). The mixture was dried over MgSO₄, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (3:1)) to afford 1e as a colorless oil (1.23 g, 72%): ¹H NMR (CDCl₃, 400 MHz) δ 3.04 (d, J = 2.6 Hz, 1H), 3.39 (s, 3H), 3.59 (dd, J = 8.7, 10.7 Hz, 1H), 3.79 (dd, J = 3.1, 10.6 Hz, 1H), 4.70 (d, J = 6.6 Hz, 1H), 4.72 (d, J = 6.6 Hz, 1H), 4.89–4.92 (m, 1H), 7.28–7.41 (m, 5H); ¹³C NMR (CDCl₃, 100 MHz) δ 55.4, 72.9, 74.1, 96.8, 126.1, 127.7, 128.3, 140.3; IR (neat) 3433, 3063, 3032, 2932, 2889, 2824, 2781, 1605, 1493, 1454, 1404, 1327, 1211, 1034, 918, 829, 760, 702 cm⁻¹;
HRMS (EI) calcd for C_{10}H_{14}O_{3} 182.0943, found 182.0943 (M').

1-Phenyl-5-hexen-1-ol (1f). To a mixture of Mg (260 mg, 10.7 mmol) in dry THF (3 mL) under Ar was added dropwise a solution of 5-bromo-1-pentene (1.1 mL, 9.5 mmol) and Br(CH\_2)\_2Br (a few drops) in dry THF (7 mL) over 30 min at room temperature. The mixture was stirred for 2 h. To the slurry was added dropwise a solution of benzaldehyde (0.91 mL, 9.0 mmol) in dry THF (5 mL) over 8 min in an ice bath, and the mixture was stirred at room temperature overnight. The reaction was quenched with saturated aqueous NH\_4Cl, and the solution was adjusted to pH 4. The mixture was extracted with EtOAc (10 mL \times 4), dried over MgSO\_4, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (5:1)) to afford **1f** as a colorless oil (1.39 g, 88%): ¹H NMR (CDCl\_3, 400 MHz) δ 1.36–1.42 (m, 1H), 1.50–1.57 (m, 1H), 1.70–1.83 (m, 3H), 2.05–2.11 (m, 2H), 4.66–4.71 (m, 1H), 4.93–5.02 (m, 2H), 5.73–5.83 (m, 1H), 7.28–7.35 (m, 5H); ¹³C NMR (CDCl\_3, 100 MHz) δ 25.0, 33.5, 38.4, 74.4, 114.6, 125.8, 127.5, 128.4, 138.5, 144.8; IR (neat) 3348, 3063, 3028, 2977, 2936, 2858, 1639, 1605, 1493, 1454, 1416, 1277, 1200, 995, 910, 760, 702 cm\(^{-1}\); HRMS (EI) calcd for C\_12H\_16O 176.1201, found 176.1186 (M').

5-Methoxymethoxy-1-phenyl-1-pentanol (1g). To a mixture of Mg (205 mg, 8.43 mmol) in dry THF (3 mL) under Ar was added dropwise a solution of 1-bromo-4-methoxymethoxybutane \(^7\) (1.54 g, 7.81 mmol) and Br(CH\_2)\_2Br (a few drops) in dry THF (7 mL) over 20 min at room temperature. The mixture was stirred for 2 h. To the slurry was added dropwise a solution of benzaldehyde (0.81 mL, 8.0 mmol) in dry THF (5 mL) over 10 min in an ice bath, and the mixture was stirred at room temperature for 3 h. The reaction was quenched with saturated aqueous NH\_4Cl, and the solution was adjusted to pH 7. The mixture was extracted with EtOAc (15 mL \times 4), dried over MgSO\_4, and concentrated. The product was purified by silica gel column chromatography (CH\_2Cl\_2/THF (20:1)) to afford **1g** as a colorless oil (1.14 g, 65%): ¹H NMR (CDCl\_3, 400 MHz) δ 1.35–1.43 (m, 1H), 1.48–1.57 (m, 1H), 1.60–1.67 (m, 2H), 1.70–1.86 (m, 3H), 3.34 (s, 3H), 3.51 (t, J = 6.5 Hz, 2H), 4.60 (s, 2H), 4.67–4.71 (m, 1H), 7.27–7.35 (m, 5H); ¹³C NMR (CDCl\_3, 100 MHz) δ 22.4, 29.4, 38.7, 55.0, 67.5, 74.3, 96.2, 125.8, 127.4, 128.3, 144.8; IR (neat) 3433, 3063, 3028, 2939, 2870, 1493, 1454, 1389, 1308, 1211, 1146, 1111, 1042, 918, 760, 702 cm\(^{-1}\); HRMS (EI) calcd for C\_13H\_20O\_3 224.1412, found 224.1399 (M').

1,6-Diphenyl-1-hexanol (1h). To a mixture of Mg (256 mg, 10.5 mmol) in dry THF (3 mL) under Ar was added dropwise a solution of (5-bromopentyl)benzene (1.9 mL, 10 mmol) and Br(CH\_2)\_2Br (a few drops) in dry THF (7 mL) over 30 min at room temperature. The mixture was stirred for 2 h. To the slurry was added dropwise a solution of benzaldehyde (0.92 mL, 9.1 mmol) in dry THF (5 mL) over 12 min in an ice bath, and the mixture was stirred at room temperature for 2.5 h. The reaction was quenched with saturated aqueous NH\_4Cl, and the solution was adjusted to pH 4. The mixture was extracted with EtOAc (15 mL \times 4), dried over MgSO\_4, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc/CH\_2Cl\_2 (20:1:5) to (10:1:5)) to afford **1h** as a colorless oil (1.24 g, 54%): ¹H NMR (CDCl\_3, 400 MHz) δ 1.31–1.48 (m, 4H), 1.48–1.57 (m, 2H), 1.67–1.82 (m, 3H), 2.58 (t, J = 7.6 Hz, 2H), 4.64–4.68 (m, 1H), 7.14–7.18 (m, 3H) 7.25–7.37 (m, 7H); ¹³C NMR (CDCl\_3, 100 MHz) δ 25.6, 29.1, 31.3, 35.8, 38.9, 74.5, 125.5, 125.8, 127.4, 128.2, 128.3, 128.4, 142.6, 144.8; IR (neat) 3352, 3063, 3028, 2932, 2855, 1948, 1605,
1493, 1454, 1312, 1200, 1030, 910, 748, 698 cm⁻¹; HRMS (EI) calcd for C₁₈H₂₂O 254.1671, found 254.1680 (M⁺).

5-Methyl-1-phenyl-1-hexanol (1i). To a mixture of Mg (269 mg, 11.1 mmol) in dry THF (3 mL) under Ar was added dropwise a solution of 1-bromo-4-methylpentane (1.6 mL, 11 mmol) and Br(CH₂)₂Br (a few drops) in dry THF (7 mL) over 30 min at room temperature. The mixture was stirred for 2.5 h. To the slurry was added dropwise a solution of benzaldehyde (1.1 mL, 10 mmol) in dry THF (5 mL) over 15 min in an ice bath, and the mixture was stirred at room temperature for 3 h. The reaction was quenched with saturated aqueous NH₄Cl, and the solution was adjusted to pH 4. The mixture was extracted with EtOAc (20 mL × 3), dried over MgSO₄, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (7:1)) to afford 1i as a colorless oil (1.06 g, 53%): ¹H NMR (CDCl₃, 400 MHz) δ 0.85 (d, J = 6.6 Hz, 6H), 1.16–1.22 (m, 2H), 1.24–1.31 (m, 1H), 1.39–1.47 (m, 1H), 1.49–1.54 (m, 1H), 1.64–1.82 (m, 3H), 4.66–4.69 (m, 1H), 7.27–7.35 (m, 5H); ¹³C NMR (CDCl₃, 100 MHz) δ 22.5, 22.6, 23.6, 27.8, 38.8, 39.3, 74.6, 125.8, 127.4, 128.4, 144.9; IR (neat) 3348, 3028, 2870, 1605, 1493, 1454, 1385, 1366, 1200, 1126, 1045, 760, 702, 552 cm⁻¹; HRMS (EI) calcd for C₁₃H₂₀O 192.1514, found 192.1513 (M⁺).

1-(4-Trifluoromethylphenyl)-1-hexanol (1j). To a mixture of Mg (243 mg, 10.0 mmol) in dry THF (3 mL) under Ar was added dropwise a solution of 1-bromopentane (1.2 mL, 9.7 mmol) and Br(CH₂)₂Br (a few drops) in dry THF (7 mL) over 20 min at room temperature. The mixture was stirred for 2.5 h. To the slurry was added dropwise a solution of 4-trifluoromethylbenzaldehyde (1.3 mL, 9.7 mmol) in dry THF (5 mL) over 10 min in an ice bath, and the mixture was stirred at room temperature for 5 h. The reaction was quenched with saturated aqueous NH₄Cl, and the solution was adjusted to pH 4. The mixture was extracted with EtOAc (15 mL × 3), dried over MgSO₄, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (5:1)) to afford 1j as a colorless oil (1.22 g, 51%): ¹H NMR (CDCl₃, 400 MHz) δ 0.86–0.89 (m, 3H), 1.29–1.46 (m, 6H), 1.65–1.80 (m, 2H), 1.89 (d, J = 3.4 Hz, 1H), 4.73–4.77 (m, 1H), 7.46 (d, J = 8.1 Hz, 2H), 7.60 (d, J = 8.1 Hz, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ 13.9, 22.5, 25.3, 31.6, 39.1, 74.0, 124.2 (q, J_CF = 270.2 Hz), 125.3 (q, J_CF = 3.8 Hz), 126.1, 129.5 (q, J_CF = 34.1 Hz), 148.8; ¹⁹F NMR (CDCl₃, 376 MHz) δ −63.6 (s, 3F); IR (neat) 3341, 2959, 2932, 2862, 1921, 1682, 1620, 1466, 1420, 1327, 1126, 1069, 1018, 840 cm⁻¹; HRMS (EI) calcd for C₁₃H₁₇F₃O 246.1231, found 246.1227 (M⁺).

1-(4-Methoxyphenyl)-1-hexanol (1k). To a mixture of Mg (294 mg, 12.1 mmol) in dry THF (3 mL) under Ar was added dropwise a solution of 1-bromopentane (1.5 mL, 9.7 mmol) and Br(CH₂)₂Br (a few drops) in dry THF (7 mL) over 20 min at room temperature. The mixture was stirred for 2 h. To the slurry was added dropwise a solution of 4-methoxybenzaldehyde (1.3 mL, 9.7 mmol) in dry THF (5 mL) over 10 min in an ice bath, and the mixture was stirred at room temperature overnight. The reaction was quenched with saturated aqueous NH₄Cl, and the solution was adjusted to pH 4. The mixture was extracted with EtOAc (15 mL × 3), dried over MgSO₄, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (5:1)) to afford 1k as a colorless oil (1.88 g, 85%): ¹H NMR (CDCl₃, 400 MHz) δ 0.87 (t, J = 7.0 Hz, 3H), 1.28–1.42 (m, 6H), 1.66–1.70 (m, 1H), 1.72 (d, J = 3.2 Hz, 1H), 1.75–1.84 (m, 1H), 3.81 (s, 3H), 4.59–4.63 (m, 1H), 6.86–6.90 (m, 2H), 7.25–7.29 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ 14.0,
22.5, 25.5, 31.7, 38.9, 55.2, 74.2, 113.7, 127.1, 137.1, 158.9; IR (neat) 3368, 2997, 2955, 2932, 2858, 1612, 1585, 1512, 1462, 1300, 1250, 1177, 1115, 1038, 926, 833, 733 cm⁻¹; HRMS (EI) calcd for C₁₃H₂₀O₂ 208.1463, found 208.1452 (M⁺).

**1-(3-Methoxymethoxyphenyl)-1-hexanol (1l).**

To a mixture of Mg (258 mg, 10.6 mmol) in dry THF (3 mL) under Ar was added dropwise a solution of 1-bromopentane (1.3 mL, 11 mmol) and Br(CH₂)₂Br (a few drops) in dry THF (7 mL) over 20 min at room temperature. The mixture was stirred for 2.5 h. To the slurry was added dropwise a solution of 3-methoxymethoxybenzaldehyde (1.51 g, 9.09 mmol) in dry THF (5 mL) over 10 min in an ice bath, and the mixture was stirred at room temperature for 4 h. The reaction was quenched with saturated aqueous NH₄Cl, and the solution was adjusted to pH 7. The mixture was extracted with EtOAc (15 mL × 4), dried over MgSO₄, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (3:1)) to afford 1l as a colorless oil (1.50 g, 70%): ¹H NMR (CDCl₃, 400 MHz) δ 0.86–0.89 (m, 3H), 1.29–1.47 (m, 6H), 1.66–1.81 (m, 3H), 3.48 (s, 3H), 4.62–4.66 (m, 1H), 5.18 (s, 2H), 6.94–7.03 (m, 3H), 7.24–7.28 (m, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 14.0, 22.5, 25.4, 31.6, 38.9, 55.9, 74.3, 94.3, 113.8, 115.0, 119.4, 129.3, 146.8, 157.2; IR (neat) 3410, 2955, 2932, 2858, 1589, 1485, 1454, 1246, 1153, 1080, 1018, 926, 791, 702 cm⁻¹; HRMS (EI) calcd for C₁₄H₂₂O₃ 238.1569, found 238.1556 (M⁺).

**1-(2-Naphthyl)-1-hexanol (1m).**

To a mixture of Mg (244 mg, 10.0 mmol) in dry THF (3 mL) under Ar was added dropwise a solution of 1-bromopentane (1.2 mL, 9.7 mmol) and Br(CH₂)₂Br (a few drops) in dry THF (7 mL) over 25 min at room temperature. The mixture was stirred for 2.5 h. To the slurry was added dropwise a solution of 2-naphthaldehyde (1.40 g, 8.96 mmol) in dry THF (5 mL) over 10 min in an ice bath, and the mixture was stirred at room temperature for 4 h. The reaction was quenched with saturated aqueous NH₄Cl, and the solution was adjusted to pH 4. The mixture was extracted with EtOAc (15 mL × 4), dried over MgSO₄, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (4:1)) to afford 1m as a white solid (1.65 g, 82%): mp 57–58 °C; ¹H NMR (CDCl₃, 400 MHz) δ 0.85–0.89 (m, 3H), 1.27–1.35 (m, 5H), 1.40–1.49 (m, 1H), 1.76–1.92 (m, 3H), 4.82–4.86 (m, 1H), 7.44–7.50 (m, 3H), 7.78–7.85 (m, 4H); ¹³C NMR (CDCl₃, 100 MHz) δ 14.0, 22.6, 25.5, 31.7, 38.9, 74.8, 124.1, 124.6, 125.7, 126.1, 127.6, 127.9, 128.2, 132.9, 133.2, 142.2; IR (KBr) 3271, 3055, 3020, 2955, 2928, 2855, 1601, 1466, 1369, 1315, 1173, 1103, 1034, 895, 860, 826, 748 cm⁻¹; Anal. Calcd for C₁₆H₂₀O: C, 84.16; H, 8.83. Found: C, 84.40; H, 8.97; HRMS (EI) calcd for C₁₆H₂₀O 228.1514, found 228.1514 (M⁺).
| Determination of enantiomeric purities and absolute configurations. | This journal is © The Royal Society of Chemistry 2012 | Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry | This journal is © The Royal Society of Chemistry 2012 | S6 | Determination of enantiomeric purities and absolute configurations. | The enantiomeric purities of 1a–f, 1h–p, and 2e–p were determined by HPLC using chiral columns (Daicel Chemical Industries), and those of 2a–d and 1g were determined after conversion to the corresponding alcohols and acetate, respectively. Those of 1q and 2q were determined by chiral GC. HPLC for 1a: Chiralcel OB-H, hexane/i-PrOH = 9:1, 0.5 mL/min, 254 nm, (S) 10.6 min, (R) 12.2 min. HPLC for 1b: Chiralcel OD-H, hexane/i-PrOH = 98:2, 0.5 mL/min, 254 nm, (R) 29.3 min, (S) 35.3 min. HPLC for 1c: Chiralcel OB-H, hexane/i-PrOH = 9:1, 0.5 mL/min, 254 nm, (R) 12.2 min, (S) 14.3 min. HPLC for 1d: Chiralcel OB-H, hexane/i-PrOH = 98:2, 0.5 mL/min, 254 nm, (S) 15.1 min, (R) 29.9 min. HPLC for 1e: Chiralpak IC, hexane/i-PrOH = 9:1, 0.5 mL/min, 254 nm, (R) 17.6 min, (S) 22.8 min. HPLC for 2e: Chiralpak IC, hexane/i-PrOH = 20:1, 0.5 mL/min, 254 nm, (S) 19.7 min, (R) 21.7 min. HPLC for 1f: Chiralpak IC, hexane/i-PrOH = 100:1, 0.5 mL/min, 254 nm, (R) 29.7 min, (S) 31.3 min. HPLC for 2f: Chiralpak IC, hexane/i-PrOH = 100:1, 0.5 mL/min, 254 nm, (R) 13.8 min, (S) 17.2 min. HPLC for 2g: Chiralpak IA, hexane/i-PrOH = 200:1, 0.5 mL/min, 254 nm, (S) 27.5 min, (R) 30.4 min. HPLC for 1h: Chiralpak IA, hexane/i-PrOH = 98:2, 0.5 mL/min, 254 nm, (S) 47.3 min, (R) 49.1 min. HPLC for 2h: Chiralpak IC, hexane/i-PrOH = 98:2, 0.5 mL/min, 254 nm, (R) 16.5 min, (S) 21.7 min. HPLC for 1i: Chiralpak IC, hexane/i-PrOH = 200:1, 0.5 mL/min, 254 nm, (R) 42.2 min, (S) 45.4 min. HPLC for 2i: Chiralpak IC, hexane/i-PrOH = 100:1, 0.5 mL/min, 254 nm, (R) 14.5 min, (S) 17.4 min. HPLC for 1j: Chiralpak IC, hexane/i-PrOH = 100:1, 0.5 mL/min, 254 nm, (R) 24.1 min, (S) 29.3 min. HPLC for 2j: Chiralpak IA, hexane/i-PrOH = 30:1, 0.5 mL/min, 254 nm, (R) 9.1 min, (S) 10.2 min. HPLC for 1k: Chiralcel OB-H, hexane/i-PrOH = 9:1, 0.5 mL/min, 254 nm, (S) 24.6 min, (R) 28.2 min. HPLC for 2k: Chiralpak IA, hexane/i-PrOH = 30:1, 0.5 mL/min, 254 nm, (R) 10.5 min, (S) 12.1 min. HPLC for 1l: Chiralpak IC, hexane/i-PrOH = 98:2, 0.5 mL/min, 254 nm, (S) 45.1 min, (R) 47.9 min. HPLC for 2l: Chiralpak IC, hexane/i-PrOH = 9:1, 0.5 mL/min, 254 nm, (R) 11.1 min, (S) 12.3 min. HPLC for 1m: Chiralpak IB, hexane/i-PrOH = 20:1, 0.5 mL/min, 254 nm, (S) 23.5 min, (R) 25.3 min. HPLC for 2m: Chiralpak IB, hexane/i-PrOH = 98:2, 0.5 mL/min, 254 nm, (R) 10.0 min, (S) 11.2 min. HPLC for 1n: Chiralcel OD-H, hexane/i-PrOH = 98:2, 1.0 mL/min, 254 nm, (R) 11.8 min, (S) 13.7 min. HPLC for 2n: Chiralcel OB-H, hexane/i-PrOH = 97:3, 0.5 mL/min, 254 nm, (S) 10.0 min, (R) 12.3 min. HPLC for 1o: Chiralpak IC, hexane/i-PrOH = 100:1, 0.5 mL/min, 254 nm, (R) 25.4 min, (S) 27.0 min. HPLC for 2o: Chiralpak IC, hexane/i-PrOH = 20:1, 0.5 mL/min, 254 nm, (R) 9.7 min, (S) 10.5 min. HPLC for 1p: Chiralcel OD-H, hexane/i-PrOH = 99:1, 0.5 mL/min, 254 nm, (R) 45.8 min, (S) 59.5 min. HPLC for 2p: Chiralcel OD-H, hexane/i-PrOH = 99:1, 0.5 mL/min, 254 nm, (R) 11.2 min, (S) 12.2 min. GC for 1q: Inj. 250 °C, Col. 95 °C, Det. 220 °C, (R) 29.3 min, (S) 32.0 min. GC for 2q: Inj. 250 °C, Col. 95 °C, Det. 220 °C, (S) 24.9 min, (R) 27.7 min. The absolute configurations of 1a, 1b, 1e, 1f, 1k, and 1m–q were determined by comparison with the signs of the reported optical rotation, and those of 1c, 1d, 1g–j, and 1l were determined by the Mosher method with MTPA. | |
**[E] Lipase-catalyzed kinetic resolution.**

**General procedure.** A mixture of alcohol **1** (0.50 mmol), immobilized lipase (700 mg for **1a–e** and 200 mg for **1f–q**, 0.5% (w/w) enzyme/Toyonite-200M), and molecular sieves 3A (three pieces) in dry i-Pr2O (5.0 mL) in a test tube with a rubber septum was stirred at 30 °C for 30 min. The reaction was started by addition of vinyl acetate (93 μL, 1.0 mmol) via a syringe. The progress of the reaction was monitored by TLC. The reaction was stopped by filtration at an appropriate conversion, and the filtrate was concentrated under reduced pressure. Alcohol **1** and ester **2** were separated by silica gel column chromatography.

**Kinetic resolution of 1-phenyl-1-hexanol (1a).** (S)-**1a**: Colorless oil; [α]$_D^{28}$ +6.4 (c 1.18, CHCl$_3$), 18.2% ee, lit.$^{13}$ [α]$_D^{18}$ +35.3 (c 1.04, CHCl$_3$) for **(R)-1a** with 94% ee. (R)-**2a**: Colorless oil; [α]$_D^{24}$ +44.1 (c 0.673, CHCl$_3$), 61.3% ee; $^1$H NMR (CDCl$_3$, 600 MHz) δ 0.86 (t, J = 7.1 Hz, 3H), 1.22–1.32 (m, 6H), 1.73–1.78 (m, 1H), 1.86–1.91 (m, 1H), 2.07 (s, 3H), 5.72 (dd, J = 6.5, 7.6 Hz, 1H), 7.27–7.35 (m, 5H).

**Kinetic resolution of 1-phenyl-1-heptanol (1b).** (S)-**1b**: Colorless oil; [α]$_D^{23}$ +16.1 (c 1.05, CHCl$_3$), 44.9% ee, lit.$^{15}$ [α]$_D^{10}$ +32.0 (c 1.02, CHCl$_3$) for **(R)-1b** with 93% ee. (R)-**2b**: Colorless oil; [α]$_D^{23}$ +48.1 (c 1.19, CHCl$_3$), 70.8% ee; $^1$H NMR (CDCl$_3$, 600 MHz) δ 0.86 (t, J = 7.0 Hz, 3H), 1.21–1.31 (m, 8H), 1.74–1.78 (m, 1H), 1.87–1.91 (m, 1H), 2.07 (s, 3H), 5.72 (dd, J = 6.5, 7.5 Hz, 1H), 7.27–7.35 (m, 5H).

**Kinetic resolution of 6,6,6-trifluoro-1-phenyl-1-hexanol (1c).** (S)-**1c**: Colorless oil; [α]$_D^{35}$ +17.0 (c 1.07, CHCl$_3$), 41.5% ee. (R)-**2c**: Colorless oil; [α]$_D^{24}$ +48.2 (c 1.22, CHCl$_3$), 80.8% ee; $^1$H NMR (CDCl$_3$, 600 MHz) δ 1.29–1.33 (m, 1H), 1.39–1.43 (m, 1H), 1.54–1.59 (m, 2H), 1.76–1.82 (m, 1H), 1.90–1.96 (m, 1H), 2.00–2.06 (m, 2H), 2.07 (s, 3H), 5.73 (dd, J = 6.4, 7.4 Hz, 1H), 7.28–7.36 (m, 5H); $^{13}$C NMR (CDCl$_3$, 150 MHz) δ 21.2, 21.6 (q, J$_{CF} = 2.1$ Hz), 24.6, 33.5 (q, J$_{CF} = 28.3$ Hz), 35.9, 75.7, 126.4, 127.0 (q, J$_{CF} = 275.0$ Hz), 128.0, 128.5, 140.3, 170.3; $^{19}$F NMR (CDCl$_3$, 565 MHz) δ –67.5 (t, J$_{FH} = 11.0$ Hz, 3F); IR (neat) 3034, 2949, 2874, 1736, 1497, 1437, 1375, 1240, 1140, 1040, 837, 761, 700 cm$^{-1}$; HRMS (EI) calcd for C$_{14}$H$_{17}$F$_3$O$_2$ 274.1181, found 274.1179 (M$^+$).

**Kinetic resolution of 4,4,4,5,5,6,6,6-heptafluoro-1-phenyl-1-hexanol (1d).** (S)-**1d**: White solid; [α]$_D^{27}$ –4.5 (c 0.97, CHCl$_3$), 18.6% ee. (R)-**2d**: Colorless oil; $^1$H NMR (CDCl$_3$, 600 MHz) δ 2.04–2.21 (m, 4H), 2.12 (s, 3H), 5.79 (dd, J = 4.8, 7.8 Hz, 1H), 7.31–7.39 (m, 5H); $^{13}$C NMR (CDCl$_3$, 150 MHz) δ 21.0, 27.02 (t, J$_{CF} = 21.8$ Hz), 27.04 (t, J$_{CF} = 3.5$ Hz), 74.4 (t, J$_{CF} = 10.9$ Hz), 108.7 (t of sextet, J$_{CF} = 36.5, 262.1$ Hz), 117.4 (tt, J$_{CF} = 31.2, 251.8$ Hz), 117.8 (qt, J$_{CF} = 33.7, 285.7$ Hz), 126.2, 128.4, 128.7, 139.2, 170.1; $^{19}$F NMR (CDCl$_3$, 565 MHz) δ –128.8 (s, 2F), –116.4 (m, 2F), –81.8 (t, J = 9.3 Hz, 3F); IR (neat) 3068, 3037, 2951, 1747, 1454, 1354, 1227, 1173, 1115, 1026, 702 cm$^{-1}$; HRMS (EI) calcd for C$_{14}$H$_{17}$F$_3$O$_2$ 346.0804, found 346.0810 (M$^+$).

**Kinetic resolution of 2-methoxymethoxy-1-phenylethanol (1e).** (R)-**1e**: Colorless oil; [α]$_D^{25}$ –37.3 (c 1.03, CHCl$_3$), 73.7% ee, lit.$^{15}$ [α]$_D^{22}$ +24.9 (c 4.25, cyclohexane) for **(S)-1e** with 70% ee. (S)-**2e**: Colorless oil; [α]$_D^{25}$ +74.8 (c 1.05, CHCl$_3$), 99.2% ee; $^1$H NMR (CDCl$_3$, 400 MHz) δ 2.12 (s, 3H), 3.30 (s, 3H), 3.75 (dd, J = 4.0, 11.0 Hz, 1H), 3.85 (dd, J = 7.9, 11.0 Hz, 1H), 4.62 (d, J = 6.7
Hz, 1H), 4.64 (d, J = 6.7 Hz, 1H), 5.96 (dd, J = 4.0, 7.9 Hz, 1H), 7.30–7.38 (m, 5H); 13C NMR (CDCl₃, 100 MHz) δ 21.1, 55.2, 69.9, 74.5, 96.3, 126.7, 128.3, 128.4, 137.4, 170.1; IR (neat) 3036, 2939, 2889, 1739, 1497, 1454, 1373, 1234, 1153, 1111, 1042, 949, 918, 860, 760, 702 cm⁻¹; HRMS (EI) calcd for C₁₂H₁₇O₄ 225.1127, found 225.1111 ([M + H]+).

Kinetic resolution of 1-phenyl-5-hexen-1-ol (1f). ([S]-1f): Colorless oil; [α]ᵢ₀°D –28.0 (c 0.976, CHCl₃), 64.0% ee, lit. [α]ᵢ₀°D –35.1 (c 1.74, CHCl₃) for ([S]-1f) with 92% ee. ([R]-2f): Colorless oil; [α]ᵢ₀°D +69.8 (c 0.979, CHCl₃), 98.9% ee; ¹H NMR (CDCl₃, 400 MHz) δ 1.31–1.37 (m, 1H), 1.38–1.48 (m, 1H), 1.73–1.82 (m, 1H), 1.87–1.96 (m, 1H), 2.06 (q, J = 7.2 Hz, 2H), 2.07 (s, 3H), 4.93–5.01 (m, 2H), 5.70–5.80 (m, 2H), 7.28–7.36 (m, 5H); 13C NMR (CDCl₃, 100 MHz) δ 21.2, 24.7, 25.3, 29.3, 36.0, 55.0, 67.3, 75.9, 96.3, 126.4, 127.8, 128.3, 140.6, 170.3; IR (neat) 3067, 3034, 2941, 2870, 1738, 1456, 1371, 1236, 1022, 910, 760, 698 cm⁻¹; HRMS (EI) calcd for C₁₄H₁₈O₂ 218.1307, found 218.1298 (M+).

Kinetic resolution of 1,6-diphenyl-1-hexanol (1h). ([S]-1h): Colorless oil; [α]ᵢ₀°D –15.7 (c 1.03, CHCl₃), 69.1% ee. ([R]-2h): Colorless oil; [α]ᵢ₀°D +51.8 (c 1.04, CHCl₃), >99.5% ee; ¹H NMR (CDCl₃, 100 MHz) δ 1.25–1.36 (m, 4H), 1.57–1.60 (m, 2H), 1.74–1.78 (m, 1H), 1.85–1.90 (m, 1H), 2.06 (s, 3H), 2.57 (t, J = 7.8 Hz, 2H), 5.71 (t, J = 6.8 Hz, 1H), 7.13–7.18 (m, 3H), 7.24–7.35 (m, 7H); ¹³C NMR (CDCl₃, 100 MHz) δ 21.2, 25.3, 28.9, 31.2, 35.7, 36.1, 76.0, 125.6, 126.4, 127.8, 128.1, 128.30, 128.33, 140.7, 142.5, 170.3; IR (neat) 3086, 3063, 3028, 2934, 2856, 1736, 1603, 1495, 1454, 1371, 1236, 1022, 964, 750, 700 cm⁻¹; HRMS (EI) calcd for C₁₈H₂₁ 237.1643, found 237.1575 ([M – OAc]+).

Kinetic resolution of 5-methyl-1-phenyl-1-hexanol (1i). ([S]-1i): White solid; [α]ᵢ₀°D –15.5 (c 1.15, CHCl₃), 53.4% ee. ([R]-2i): Colorless oil; [α]ᵢ₀°D +66.8 (c 1.14, CHCl₃), 97.7% ee; ¹H NMR (CDCl₃, 400 MHz) δ 0.83 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H), 1.14–1.35 (m, 4H), 1.46–1.53 (m, 1H), 1.69–1.77 (m, 1H), 1.84–1.91 (m, 1H), 2.07 (s, 3H), 5.72 (t, J = 7.0 Hz, 1H), 7.28–7.36 (m, 5H); ¹³C NMR (CDCl₃, 100 MHz) δ 21.2, 22.46, 22.48, 23.2, 27.7, 36.4, 38.5, 76.1, 126.5, 127.7, 128.3, 140.8, 170.3; IR (neat) 3067, 3032, 2955, 2870, 1740, 1493, 1458, 1369, 1242, 1123, 1022, 961, 899, 760, 698, 552 cm⁻¹; HRMS (EI) calcd for C₁₅H₂₂O₂ 234.1620, found 234.1609 (M+).

Kinetic resolution of 1-(4-trifluoromethylphenyl)-1-hexanol (1j). ([S]-1j): Colorless oil; [α]ᵢ₀°D –20.9 (c 1.07, CHCl₃), 80.7% ee. ([R]-2j): Colorless oil; [α]ᵢ₀°D +48.9 (c 0.991, CHCl₃), 97.8% ee; ¹H NMR (CDCl₃, 400 MHz) δ 0.85–0.88 (m, 3H), 1.27–1.29 (m, 6H), 1.73–1.77 (m, 1H), 1.86–1.90

S8
(m, 1H), 2.08 (s, 3H), 5.74 (t, J = 6.4 Hz, 1H), 7.43 (d, J = 8.2 Hz, 2H), 7.60 (d, J = 8.2 Hz, 2H); 
13C NMR (CDCl₃, 100 MHz) δ 13.9, 21.1, 22.4, 25.0, 31.4, 36.2, 75.4, 124.0 (q, JCF = 270.6 Hz), 
125.4 (q, JCF = 3.7 Hz), 126.7, 129.9 (q, JCF = 32.2 Hz), 144.9, 170.2; 19F NMR (CDCl₃, 376 MHz) δ 
–63.6 (s, 3F); IR (neat) 2959, 2934, 2862, 1742, 1622, 1373, 1327, 1238, 1167, 1128, 1069, 1018, 
837 cm⁻¹; HRMS (EI) calcd for C₁₃H₁₉F₃O₂ 288.1337, found 288.1323 (M⁺).

Kinetic resolution of 1-(4-methoxylphenyl)-1-hexanol (1k). (S)-1k: Colorless oil; [α]²⁶D –18.1 (c 
0.818, CHCl₃), 69.1% ee, lit.¹⁰ [α]²³D –17.8 (c 1.13, MeOH) for (S)-1k with 88% ee. (R)-2k: Colorless oil; [α]²⁶D +85.4 (c 1.11, CHCl₃), 99.3% ee; ¹H NMR (CDCl₃, 400 MHz) δ 0.85–0.87 (m, 3H), 1.27–1.29 (m, 6H), 1.69–1.76 (m, 1H), 1.82–1.91 (m, 1H), 2.04 (s, 3H), 3.48 (s, 3H), 5.16 (d, J = 6.9 Hz, 1H), 5.18 (d, J = 6.9 Hz, 1H), 5.69 (dd, J = 6.4, 7.5 Hz, 1H), 6.95–6.98 (m, 3H), 7.23–7.26 (m, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 
13.9, 21.2, 22.4, 25.1, 31.4, 36.2, 56.0, 75.9, 94.5, 114.5, 115.2, 119.9, 129.4, 142.6, 157.3, 170.3; IR (neat) 
2955, 2934, 2860, 2827, 1736, 1587, 1489, 1456, 1371, 1236, 1151, 1080, 1018, 995, 876, 789, 
700 cm⁻¹; HRMS (EI) calcd for C₁₆H₂₄O₄ 280.1675, found 280.1664 (M⁺).

Kinetic resolution of 1-(3-methoxymethoxyphenyl)-1-hexanol (1l). (S)-1l: Colorless oil; [α]²⁴D –19.1 (c 
1.01, CHCl₃), 73.2% ee. (R)-2l: Colorless oil; [α]²⁴D +61.1 (c 1.02, CHCl₃), 99.2% ee; ¹H NMR (CDCl₃, 400 MHz) δ 0.84–0.88 (m, 3H), 1.27–1.30 (m, 6H), 1.73–1.78 (m, 1H), 1.82–1.89 (m, 1H), 2.07 (s, 3H), 3.48 (s, 3H), 5.16 (d, J = 6.9 Hz, 1H), 5.18 (d, J = 6.9 Hz, 1H), 5.69 (dd, J = 6.4, 7.5 Hz, 1H), 7.44–7.49 (m, 3H), 7.78–7.84 (m, 4H); ¹³C NMR (CDCl₃, 100 MHz) δ 
13.9, 21.2, 22.4, 25.2, 31.4, 35.9, 55.1, 75.8, 113.7, 127.9, 132.8, 159.1, 170.3; IR (neat) 3055, 2955, 
2934, 2858, 1736, 1612, 1585, 1516, 1462, 1373, 1242, 1177, 1107, 1034, 949, 829 cm⁻¹; HRMS (EI) calcd for C₁₆H₂₂O₃ 250.1569, found 250.1567 (M⁺).

Kinetic resolution of 1-(2-naphthyl)-1-hexanol (1m). (S)-1m: White solid; [α]³⁵D –25.4 (c 1.00, 
CHCl₃), 68.0% ee, lit.¹⁰ [α]³³D –18 (c 1, MeOH) for (S)-1m with 82% ee. (R)-2m: Colorless oil; [α]²⁴D 
+79.3 (c 1.04, CHCl₃), 98.0% ee, lit.¹⁰ [α]³³D +76.7 (c 1.01, CHCl₃) for (R)-2m with 90.1% ee; ¹H NMR (CDCl₃, 400 MHz) δ 0.85–0.89 (m, 3H), 1.18–1.35 (m, 4H), 1.72–1.81 (m, 1H), 1.86–1.95 (m, 1H), 2.07 (s, 3H), 5.70–5.74 (m, 1H), 7.28–7.36 (m, 5H); ¹³C NMR (CDCl₃, 100 MHz) δ 13.9, 21.2, 22.4, 27.6, 36.0, 76.1, 126.5, 127.7, 128.3, 140.8, 170.4; IR (neat) 3088, 3065, 3034, 2957, 
2936, 2862, 1738, 1605, 1587, 1495, 1456, 1371, 1240, 1109, 1074, 1020, 964, 760, 700, 550 cm⁻¹; HRMS (EI) calcd for C₁₃H₁₈O₂ 206.1307, found 206.1286 (M⁺).
Kinetic resolution of 1-phenyl-1-butanol (1o). (S)-1o: White solid; [α]$^D_{31}$ $\approx$ -34.4 (c 1.06, CHCl$_3$), 72.0% ee, lit.$^{18}$ [α]$^{24}_D$ $\approx$ -44.9 (c 0.45, CHCl$_3$) for (S)-1o with 92% ee. (R)-2o: Colorless oil; [α]$^D_{31}$ $\approx$ +86.6 (c 1.04, CHCl$_3$), 98.6% ee, lit.$^{20}$ [α]$^{22}_D$ +78.2 (c 0.9, CHCl$_3$) for (R)-2o with 93% ee; $^1$H NMR (CDCl$_3$, 400 MHz) δ 0.91 (t, $J$ = 7.4 Hz, 3H), 1.23–1.39 (m, 2H), 1.69–1.78 (m, 1H), 1.85–1.94 (m, 1H), 2.07 (s, 3H), 5.74 (dd, $J$ = 6.3, 7.7 Hz, 1H), 7.27–7.36 (m, 5H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 13.7, 18.7, 21.2, 38.4, 75.9, 126.5, 127.7, 128.3, 140.8, 170.4; IR (neat) 3088, 3065, 3034, 2961, 2936, 2874, 1728, 1605, 1587, 1495, 1456, 1371, 1236, 1180, 1103, 1055, 1024, 957, 845, 762, 700, 544 cm$^{-1}$; HRMS (EI) calcd for C$_{12}$H$_{16}$O$_2$ 192.1150, found 192.1145 (M$^+$).

Kinetic resolution of 1-phenyl-1-propanol (1p). (S)-1p: Colorless oil; [α]$^{28}_D$ $\approx$ -27.3 (c 0.973, CHCl$_3$), 56.6% ee, lit.$^{18}$ [α]$^{24}_D$ $\approx$ -44.4 (c 0.63, CHCl$_3$) for (S)-1p with 80% ee. (R)-2p: Colorless oil; [α]$^{26}_D$ +100.3 (c 1.10, CHCl$_3$), >99.5% ee, lit.$^{21}$ [α]$^{20}_D$ +98.2 (c 1.308, CHCl$_3$) for (R)-2p with 99% ee; $^1$H NMR (CDCl$_3$, 400 MHz) δ 0.88 (t, $J$ = 7.4 Hz, 3H), 1.76–1.85 (m, 1H), 1.87–1.98 (m, 1H), 2.08 (s, 3H), 5.66 (t, $J$ = 7.0 Hz, 1H), 7.27–7.36 (m, 5H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 9.9, 21.2, 29.2, 77.3, 126.5, 127.8, 128.3, 140.5, 170.4; IR (neat) 3090, 3065, 3034, 2970, 2937, 2880, 1736, 1495, 1454, 1371, 1236, 1086, 1042, 1020, 966, 893, 839, 754, 700, 548 cm$^{-1}$; HRMS (EI) calcd for C$_{11}$H$_{14}$O$_2$ 178.0994, found 178.0968 (M$^+$).

Kinetic resolution of 1-phenylethanol (1q). (S)-1q: Colorless oil; [α]$^{25}_D$ $\approx$ -56.9 (c 0.686, CHCl$_3$), 99.8% ee, lit.$^{18}$ [α]$^{23}_D$ $\approx$ -43.7 (c 0.90, CHCl$_3$) for (S)-1q with 69% ee. (R)-2q: Colorless oil; [α]$^{26}_D$ +110.6 (c 1.02, CHCl$_3$), 99.1% ee, lit.$^{19}$ [α]$^{25}_D$ +112 (c 1.00, CHCl$_3$) for (R)-2q with 99.9% ee; $^1$H NMR (CDCl$_3$, 400 MHz) δ 1.54 (d, $J$ = 6.6 Hz, 3H), 2.07 (s, 3H), 5.88 (q, $J$ = 6.6 Hz, 1H), 7.28–7.36 (m, 5H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 21.2, 22.1, 72.2, 126.0, 127.8, 128.4, 141.6, 170.2; IR (neat) 3088, 3065, 3034, 2982, 2934, 2872, 1732, 1605, 1585, 1495, 1454, 1371, 1209, 1242, 1067, 1030, 943, 854, 762, 700, 621, 540 cm$^{-1}$.
## Table S2  Kinetic resolution of 1 with wild-type and mutant enzymes<sup>a</sup>

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<th>Time (h)</th>
<th>c (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>% Yield&lt;sup&gt;c&lt;/sup&gt; (%) (ee)</th>
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<th>(S)-1</th>
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<td>45</td>
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<td>I287F</td>
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<td>73.7</td>
<td>&gt;200&lt;sup&gt;e&lt;/sup&gt;</td>
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<sup>a</sup> Conditions: immobilized lipase (700 mg, 0.5% (w/w) enzyme/Toyonite-200M), 1 (0.50 mmol), vinyl acetate (1.0 mmol), molecular sieves 3A (three pieces), dry i-Pr₂O (5 mL), 30 °C.<br>
<sup>b</sup> Conversion calculated from c = ee(1)/(ee(1) + ee(2)).<br>
<sup>c</sup> Isolated yield.<br>
<sup>d</sup> Calculated from E = ln[1 - c(1 + ee(2))]/ln[1 - c(1 - ee(2))].<br>
<sup>e</sup> (S)-2e and (R)-1e were obtained.
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</table>

$^a$ Conditions: immobilized lipase (200 mg, 0.5% (w/w) enzyme/Toyonite-200M), 1 (0.50 mmol), vinyl acetate (1.0 mmol), molecular sieves 3A (three pieces), dry $i$-Pr$_2$O (5 mL), 30 °C.  
$^b$ Conversion calculated from $c = ee(1)/(ee(1) + ee(2))$.  
$^c$ Isolated yield.  
$^d$ Calculated from $E = \ln[1 - c(1 + ee(2))]/\ln[1 - c(1 - ee(2))]$.  
$^e$ Conversion calculated from $^1$H NMR.
References
[F] NMR spectra.

400 MHz $^1\text{H}$ NMR of 1e in CDCl$_3$. 

\[
\text{MOMO} \quad \text{OH} \\
\text{1e}
\]
100 MHz $^{13}$C NMR of 1e in CDCl$_3$. 

S15
400 MHz $^1$H NMR of 1f in CDCl$_3$. 
100 MHz $^{13}$C NMR of 1f in CDCl$_3$. 
400 MHz $^1$H NMR of 1g in CDCl$_3$. 
100 MHz $^{13}$C NMR of 1g in CDCl$_3$. 

S19
400 MHz $^1$H NMR of 1h in CDCl$_3$. 

S20
100 MHz $^{13}$C NMR of 1h in CDCl$_3$. 

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400 MHz $^1$H NMR of 1i in CDCl$_3$. 
100 MHz $^{13}$C NMR of ii in CDCl$_3$. 

S23
400 MHz $^1$H NMR of 1j in CDCl$_3$. 

OH

1j

CF$_3$
100 MHz $^{13}$C NMR of 1j in CDCl$_3$. 

S25
400 MHz $^1$H NMR of 1k in CDCl$_3$. 
100 MHz $^{13}$C NMR of 1k in CDCl$_3$. 
400 MHz $^1$H NMR of 11 in CDCl$_3$. 

S28
$^{13}$C NMR of II in CDCl$_3$. 
400 MHz $^1$H NMR of $1m$ in CDCl$_3$. 
100 MHz $^{13}$C NMR of 1m in CDCl$_3$. 
400 MHz $^1$H NMR of 2e in CDCl$_3$. 
100 MHz $^{13}$C NMR of 2e in CDCl$_3$. 

S33
400 MHz $^1$H NMR of 2f in CDCl$_3$. 
100 MHz $^{13}$C NMR of 2f in CDCl$_3$. 
400 MHz $^1$H NMR of 2g in CDCl$_3$. 
100 MHz $^{13}$C NMR of 2g in CDCl$_3$. 
400 MHz $^1$H NMR of 2h in CDCl$_3$. 
100 MHz $^{13}$C NMR of 2h in CDCl$_3$. 

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400 MHz $^1$H NMR of 2i in CDCl$_3$. 

S40
100 MHz $^{13}$C NMR of 2i in CDCl$_3$. 
400 MHz $^1$H NMR of $2j$ in CDCl$_3$. 

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100 MHz $^{13}$C NMR of 2j in CDCl$_3$. 

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400 MHz $^1$H NMR of 2k in CDCl$_3$. 

Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry
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100 MHz $^{13}$C NMR of 2k in CDCl$_3$. 
400 MHz $^1$H NMR of 2l in CDCl$_3$. 
100 MHz $^{13}$C NMR of 2l in CDCl$_3$. 
400 MHz $^1$H NMR of **2m** in CDCl$_3$. 

$OAc$
100 MHz $^{13}$C NMR of 2m in CDCl$_3$. 

S49
400 MHz $^1$H NMR of 2n in CDCl$_3$. 

S50
100 MHz $^{13}$C NMR of 2n in CDCl$_3$. 
400 MHz $^1$H NMR of 2o in CDCl$_3$. 

![NMR spectrum of 2o](image)
100 MHz $^{13}$C NMR of 2o in CDCl$_3$. 
400 MHz $^1$H NMR of 2p in CDCl$_3$. 
100 MHz $^{13}$C NMR of 2p in CDCl$_3$. 
400 MHz $^1$H NMR of 2q in CDCl$_3$. 
100 MHz $^{13}$C NMR of 2q in CDCl$_3$. 