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Asymmetric Cycloetherification by Bifunctional Organocatalyst

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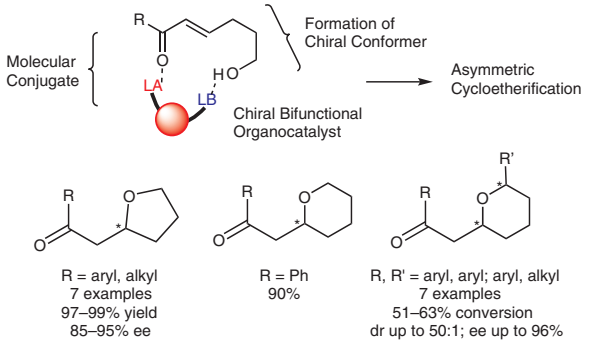

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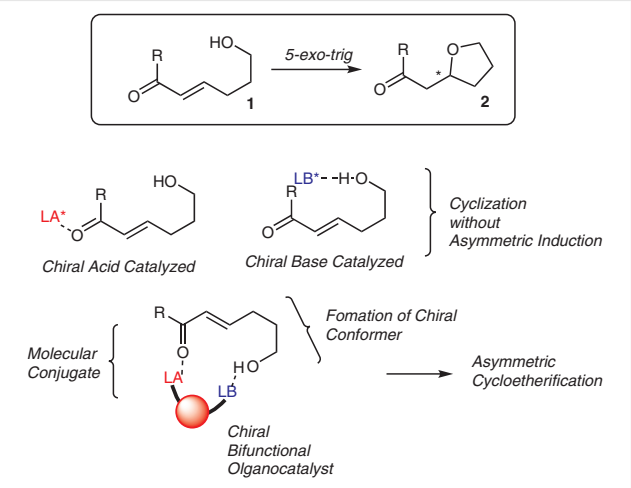
Abstract Attempts to obtain enantiomerically enriched tetrahydrofuran derivatives via an intramolecular *oxy*-Michael addition reaction of ε-hydroxyenone is discussed. Despite previous difficulties associated with the asymmetric induction of this reaction, which can proceed even without a catalyst, a highly efficient asymmetric induction was realized using a bifunctional organocatalyst derived from a cinchona alkaloid. The reaction could be extended to ζ-hydroxyenone to yield an optically active tetrahydropyran derivative with a high ee. In these reactions, it is important for the gentle acidic and basic sites in the bifunctional organocatalyst to be arranged properly within the molecular skeleton of the catalyst. The high performance asymmetric induction relied on the affinity of the catalyst for the substrate, which played an important role. A disubstituted tetrahydropyran synthesis could be effectively performed via kinetic resolution using ζ-hydroxyenone containing a secondary alcohol moiety using a chiral phosphoric acid catalyst.

Key words organocatalyst, bifunctional catalyst, asymmetric synthesis, oxy-Michael reaction, tetrahydrofuran, tetrahydropyran, kinetic resolution

Catalysts play an important role in synthesizing organic compounds, and a variety of compounds ranging from the smallest proton to very high molecular weight peptides are used for this purpose.[1] While stabilizing the rate-determining transition state to accelerate the reaction is the fundamental role of catalysts, catalysts improve the selectivity of the desired reaction. Catalysts that incorporate a variety of functions require artful design. Metal-centered catalysts, which have been studied broadly and deeply, exhibit selectivities that depend on the metal's inherent properties. Certain ligand combinations convey appropriate steric and electronic functions that enable highly selective reactions. Additives to a ligand-coordinated metal-centered catalyst can be used to achieve more elaborate selectivities. Recently, organocatalysts without any metal have been actively studied. A major feature of organocatalysts is the ease with which multiple active sites may be positioned within a single molecule, despite providing opposite properties, for example, acidic and basic sites.[2,3] In other words, the asymmetric arrangement of sites within a molecule can realize effective asymmetric induction and efficiently facilitate a reaction by recognizing the specific conformation of the substrate.

We studied the synthesis of the optically active tetrahydrofurans and tetrahydropyrans using a bifunctional organocatalyst[4] that is obtained readily from the cinchona alkaloid.[5] The asymmetric intramolecular *oxy*-Michael addition reaction of ε-hydroxyenone is a direct synthetic method that gives an optically active tetrahydrofuran ring, a substructure of many useful bioactive compounds.[6] Several reports have also described other catalytic methods.[7] In general, a discrimination of routes to form each enantiomer is subtle, when the activation energy is quite small. This tetrahydrofuran formation proceeds via entropically and enthalpically favorable 5-*exo*-trigonal intramolecular cyclization. We had focused on specific interactions between a catalyst and the substrate, which can induce this 5-*exo*-trigonal cyclization and also contain some crucial role for distinguishing the enantioface. In this sense, the use of a bifunctional organocatalyst possessing weak acidic and basic sites might be ideal for controlling this asymmetric cyclization reaction.[8] Because both interactions are indispensable for promoting the reaction, the substrate could be converted into the corresponding cyclized product via a molecular conjugate through them, in which the substrate assumes a specific chiral conformation (Scheme 1).[9]

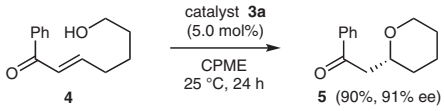


Scheme 1 Strategy for achieving the catalytic asymmetric cycloetherification of **1** to form tetrahydrofuran **2** using a bifunctional organocatalyst

Table 1 shows the results of the intramolecular *oxy*-Michael addition of ε-hydroxyenone **1a** using the typical thiourea-amine bifunctional organocatalyst **3** derived from the cinchona alkaloid. All reactions starting from ε-hydroxyenone **1a** were examined at 25 °C over 24 hours in the presence of various solvents. The catalyst **3a**, derived from quinidine, and **3b**, derived from cinchonine, gave the *R*-form of **2a**. The catalyst **3c**, derived from quinine, and **3d**, derived from cinchonidine, gave (*S*)-**2a** enantioselectively. Among these catalysts, **3a** and **3c** in cyclopentyl methyl ether (CPME) quantitatively gave both enantiomers of **2a** at over 95% ee (Table 1, entries 5 and 8). CPME, a poorly basic ether, was suitable as a solvent for these reactions.[10]

Based on the reaction conditions reported in Table 1, several substrates were examined to obtain optically active THF derivatives (Table 2). Even if the substituent R in the enone moiety in **1** was a benzene ring substituted with an electron-donating/-withdrawing group (Table 2, entries 2–5), a bulky 2-naphthyl (entry 6) or alkyl group (entry 7), the cyclization reaction proceeded in high yield and with high enantioselectivity.

This method was applied to ζ-hydroxyenone **4**, as shown in Equation 1, to obtain an optically active tetrahydropyran derivative **5** with high ee. The reaction progressed as described in the case of tetrahydrofuran, shown above.



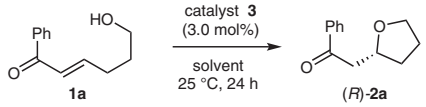
Equation 1 Asymmetric cycloetherification of **4** into tetrahydropyran **5** via the bifunctional organocatalyst **3a**

Biographical Sketches

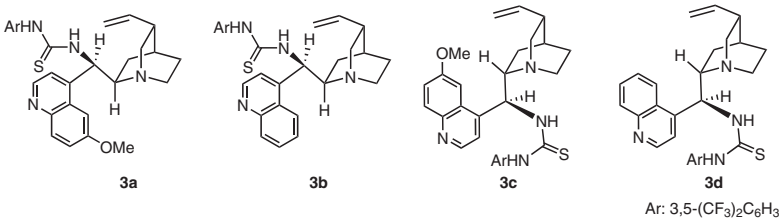
Keisuke Asano was born in 1984 and raised in Kobe. He completed his Ph.D. at Kyoto University (Japan) in 2012 under the supervision of Professor Seijiro Matsubara. He was appointed as an Assistant Professor at Kyoto University in 2012 and joined the group of Professor Jun-ichi Yoshida before moving back to the group of Professor Seijiro Matsubara in 2013. He received the 30th Inoue Research Award for Young Scientists (2014), the Eisai Award in Synthetic Organic Chemistry, Japan (2014), and was a Special Young Lecturer in the 95th CSJ Annual Meeting (2015).

Seijiro Matsubara was born in 1959 and raised in Kobe. He was educated in chemistry at Kyoto University (Japan), completing his Ph.D. in 1986 with Professors Hitosi Nozaki and Kiitiro Utimoto, and at the Université de Lausanne (Switzerland) where he was a Ph.D. course student with Professor Manfred Schlosser. He was appointed as an Assistant Professor at Kyoto University in 1986. After postdoctoral research with Professor Barry M. Trost at Stanford University (USA) in 1988–1989, he became an Associate Professor at Kyoto University in 1995. In 2006, he became a Full Professor at Kyoto University. He received The 3rd Inoue Research Award for Young Scientists (1987), the Incentive Award in Synthetic Organic Chemistry, Japan (1998), the Asian Core Program Lectureship Award, Korea and Malaysia (2014), and The 34th Chemical Society of Japan Award for Creative Work (2017).

Table 1 Optimizing the Conditions of the Asymmetric Cycloetherification of **1a** by the Bifunctional Organocatalyst **3**[a]

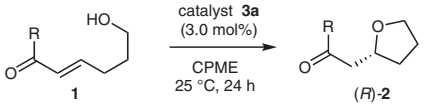


Entry	Catalyst **3**	Solvent	Yield (%)[b]	ee (%)
1	**3a**	CH_2Cl_2	99	92
2	**3a**	benzene	97	94
3	**3a**	THF	73	90
4	**3a**	Et_2O	99	94
5	**3a**	CPME	99	95
6[c]	**3a**	CPME	95	96
7	**3b**	CPME	99	89
8[d]	**3c**	CPME	99	–96
9[d]	**3d**	CPME	99	–94



[a] Reaction conditions: Substrate **1a** (0.25 mmol) and the catalyst **3** (0.0075 mmol) in solvent (0.5 mL).
[b] Isolated yields.
[c] Catalyst **3a** used: 1.0 mol%.
[d] (*S*)-**2a** was formed enantioselectively.

Table 2 Preparation of the Tetrahydrofurans via Asymmetric Cycloetherification of **1** by Bifunctional Organocatalyst **3a**[a]



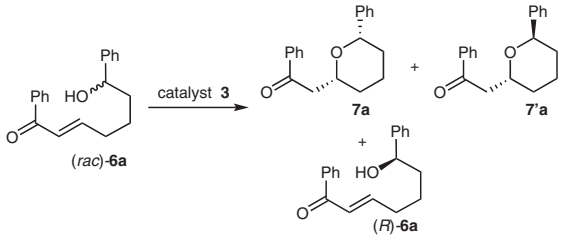
Entry	R		(*R*)-**2** Yield (%)[b]		ee (%)
1	Ph	**1a**	99	(*R*)-**2a**	95
2	*p*-$MeOC_6H_4$	**1b**	99	(*R*)-**2b**	94
3	*p*-$F_3CC_6H_4$	**1c**	93	(*R*)-**2c**	85
4	*p*-MeC_6H_4	**1d**	99	(*R*)-**2d**	93
5	*p*-BrC_6H_4	**1e**	99	(*R*)-**2e**	92
6	2-naphthyl	**1f**	98	(*R*)-**2f**	91
7[c]	$PhCH_2CH_2$	**1g**	97	(*R*)-**2g**	90

[a] Reaction conditions: Substrate **1** (0.25 mmol) and **3a** (0.0075 mmol) in CPME (0.5 mL).
[b] Isolated yields.
[c] Reaction time: 120 h.

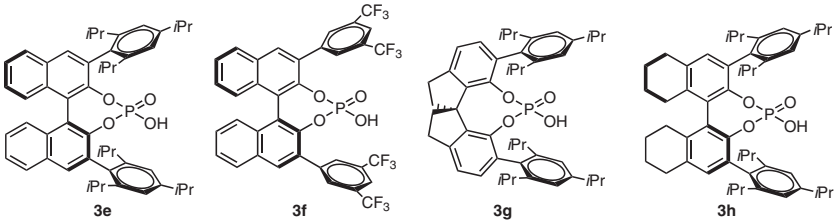
In these intramolecular cyclization reactions, the amine and thiourea groups in catalyst **3** play important roles in the asymmetric induction by interacting favorably with the acidic and basic sites of the substrate, that is, the hydroxyl and carbonyl groups. Each interaction is not strong enough for reaction activation, and the reaction is initiated only once both interactions form cooperatively. The substrate and catalyst must form an advantageous conjugate in the transition state. Formation of the conjugate increases the possibility of kinetically resolving the chiral substrate.[11,12]

As shown in Table 3, the reaction of the racemic (*E*)-7-hydroxy-1,7-diphenylhept-2-en-1-one [(*rac*)-**6a**] was performed at 0 °C using the bifunctional aminothiourea catalysts **3a–d**. The observed selectivity factors were not satisfactory (Table 3, entries 1–4). We next focused on the chiral phosphoric acid catalysts **3e–h**.[13,14] These catalysts possess both acidic and basic sites, allowing for the multipoint recognition of substrates via hydrogen bonding. Other sterically bulky substituents near the catalytic sites play a crucial role for the recognition of a substrate. In this context, we envisioned that these chiral phosphoric acid catalysts would be suitable for the kinetic resolution strategy (entries 5–8). In fact, the phosphoric acid catalyst **3e** performed significantly better than the aminothiourea catalysts **3a–d** (entry 5). Dichloromethane, diethyl ether, or ethyl acetate solvents were examined but were found to produce low *s*-factors compare to the reaction in toluene (entries 9–11). Although the stereoselectivity was not improved by performing the reaction at –20 °C in toluene (entry 12), the use of molecular sieves (MS) 4A as an additive

Table 3 Asymmetric Cycloetherification of (*rac*)-**6a** via Kinetic Resolution[a]



Entry	**3** (mol%)	Solvent	Temp (°C)	Time (h)	Conv. (%)	**7a**/**7′a** (% ee)	(*R*)-**6a** (% ee)	*s*[b]
1	**3a** (30)	CPME (0.5 M)	25	48	58	4.3/1 (70, 28)	72	6.5
2	**3b** (30)	CPME (0.5 M)	25	48	55	5.3/1 (71, 27)	69	7.0
3	**3c** (30)	CPME (0.5 M)	25	48	68	2.1/1 (–69, –7)	–93	8.0
4	**3d** (30)	CPME (0.5 M)	25	48	63	3.0/1 (–72, 0)	–91	10
5	**3e** (1.0)	toluene (0.01 M)	0	2	55	16/1 (80, 80)	85	15
6	**3f** (0.1)	toluene (0.01 M)	0	15	43	24/1 (4, 0)	3	1.1
7	**3g** (1.0)	toluene (0.01 M)	0	24	28	24/1 (62, 31)	23	4.7
8	**3h** (1.0)	toluene (0.01 M)	0	9	47	13/1 (86, 68)	66	14
9	**3e** (1.0)	CH_2Cl_2 (0.01 M)	0	2.5	60	16/1 (51, 67)	66	4.9
10	**3e** (1.0)	Et_2O (0.01 M)	0	24	9.6	6.7/1 (55, 9)	5	2.9
11	**3e** (5.0)	EtOAc (0.01 M)	0	24	31	13/1 (66, 39)	26	4.9
12	**3e** (1.0)	toluene (0.01 M)	–20	12	44	19/1 (87, 61)	62	16
13	**3e** (1.0)	toluene (0.01 M + MS 4A)	–20	2	44	19/1 (88, 79)	62	16
14	**3e** (5.0)	toluene (0.01 M + MS 4A)	–40	4	51	24/1 (89, 87)	85	27

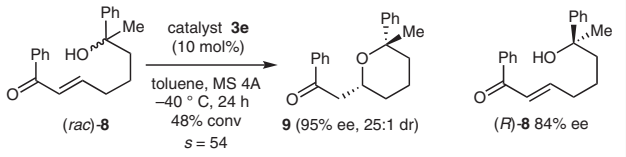


[a] Substrate (*rac*)-**6a** (0.15 mmol) was used.
[b] Selectivity factors (*s*) were calculated from the conversion (%) and ee values of the recovered (*R*)-**6a**. See ref. 11: $s = k_{fast}/k_{slow} = \ln[(1 - \text{Conv}\%/100)(1 - (R)\text{-}\mathbf{6a}\%\text{ee}/100)]/\ln[(1 - \text{Conv}\%/100)(1 + (R)\text{-}\mathbf{6a}\%\text{ee}/100)]$.

was found to dramatically accelerate the reaction (entry 13). In the presence of MS 4A, the reaction could be performed even at –40 °C, and the *s*-factor was significantly improved (entry 14).

With the conditions optimized, several substrates were examined as shown in Table 4. Although the substrate bearing a *p*-methoxyphenyl group in R^2 gave the corresponding products in a poor stereoselectivity (Table 4, entry 1), an electron-deficient aryl carbinol **6c** and the huge aryl carbinols **6d**, **6e** were converted into the optically active **7** with high selectivities (entries 2–4). The alkyl carbinol **6f** (R^1 = *n*-C_4H_9) also gave the disubstituted THP with reasonable selectivity (entry 5). The methoxy and trifluoromethyl groups on the aryl enone did not affect the selectivity (entries 6, 7).

As shown in equation 2, the asymmetric cyclization of **8** using **3e** as the catalyst gave **9** in 95% ee at 48% conversion. The catalyst-controlled cyclization induced chirality at the bond-forming β-position; the intermediary formed chair-like conformation of **8** dominated the kinetic resolution. Within the obtained product **9**, the two large substituents, were arranged in a *cis*-configuration, which allow them to take equatorial positions.



Equation 2 Asymmetric cycloetherification of the tertiary alcohol (*rac*)-**8** via kinetic resolution

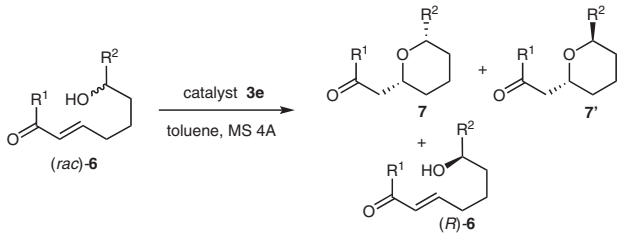
In summary, the asymmetric intramolecular Michael addition of hydroxyenone by a bifunctional organocatalyst was shown to be useful as a method for synthesizing optically active THF and THP derivatives. The reaction proceeds via formation of a molecular conjugate consisting of the substrate and the catalyst. In this conjugate, two acid-base interactions and the affinity of the preferable chiral conformer of the substrate with the organocatalyst's molecular skeleton assist the selective formation of the corresponding enantiomer of the product. This control enables the transformation of secondary ζ-hydroxyenones into THP derivatives via kinetic resolution.

^{1}H and ^{13}C NMR spectra were taken on a Varian Unity Inova 500 (^{1}H, 500 MHz; ^{13}C, 125.7 MHz) spectrometer using TMS as an internal standard for ^{1}H NMR (δ = 0) and $CDCl_3$ as an internal standard for ^{13}C NMR (δ = 77.0). When a ^{13}C NMR spectrum was measured using C_6D_6 as a solvent, C_6D_6 was used as an internal standard (δ = 128.06). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (standard abbreviations), coupling constants (Hz), integration. ^{19}F NMR spectra were measured on a Varian Mercury 200 (^{19}F, 188 MHz) spectrometer with C_6F_6 as an internal standard (δ = 0). GC-MS analyses and high-resolution mass spectra were obtained with a Jeol JMS-700 spectrometer by electron ionization at 70 eV. High-performance liquid chromatography (HPLC) was performed with a Shimadzu Prominence apparatus. IR spectra were determined on a Shimadzu IR Affinity-1 spectrophotometer. Melting points were determined using a Yanako MP-500D apparatus. Optical rotations were measured on a Horiba SEPA-200 polarimeter. TLC analyses were performed by means of Merck Kieselgel 60 F_{254} (0.25 mm) Plates. Visualization was accomplished with UV light (254 nm) and/or such as an aqueous alkaline $KMnO_4$ solution followed by heating. Flash column chromatography was carried out using Kanto Chemical silica gel (spherical, 40–50 μm). Unless otherwise noted, commercially available reagents were used without purification. The chiral phosphoric acids **3e–f** are commercially available.

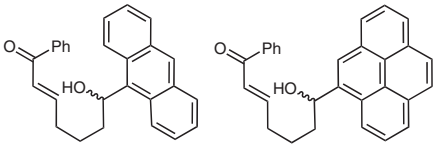
Asymmetric Synthesis of 2-Substituted Tetrahydrofurans 2; General Procedure

To a 5 mL vial were added ε-hydroxy-α,β-unsaturated ketone **1** (0.25 mmol), cyclopentyl methyl ether (0.5 mL), and quinidine-derived bifunctional catalyst **3a** (0.0075 mmol) sequentially. The mixture was stirred in an oil bath maintained at 25 °C for 24 h. The mixture was diluted with hexane/EtOAc (1:1 v/v), passed through a short silica gel column to remove **3a**, and concentrated in vacuo. Purification of the

Table 4 Substrate Scope of the Asymmetric Cycloetherification of (*rac*)-**6** via Kinetic Resolution[a]



Entry	R^1, R^2 (*rac*)-**6**	**3e** (mol%)	Time (h)	Temp (°C)	Conv (%)	**7**/**7**′ (% ee)	(*R*)-**6** (% ee)	*s*
1	Ph, *p*-$MeOC_6H_4$ (**6b**)	5	36	–40	63	4.3/1 (58, 96)	50	1.8
2	Ph, *p*-$F_3CC_6H_4$ (**6c**)	5	4	–40	52	16/1 (90, 90)	87	26
3	Ph, 9-anthracenyl (**6d**)	1	2	0	49	50/1 (90, 83)	84	39
4	Ph, 4-pyrenyl (**6e**)	1	1	0	58	17/1 (79, 71)	98	26
5	Ph, *n*-C_4H_9 (**6f**)	5	2.5	–40	53	14/1 (82, 84)	81	15
6	*p*-$MeOC_6H_4$ Ph, (**6g**)	5	4	–40	52	19/1 (90, 85)	89	30
7	*p*-$F_3CC_6H_4$, Ph (**6h**)	5	7	–40	57	12/1 (86, 88)	97	26



[a] Substrate (*rac*)-**6** (0.15 mmol) was used. See experimental section.

mixture by flash silica gel column chromatography using hexane/EtOAc (3:1 v/v) as an eluent afforded the corresponding 2-substituted tetrahydrofuran **2**.

(*R*)-1-Phenyl-2-(tetrahydrofuran-2-yl)ethanone (2a)

[CAS Reg. No. 1337999-50-4]

Yield: 47.0 mg (99%); 95% ee; colorless oil; R_f = 0.26 (hexane/EtOAc 3:1); $[\alpha]_D^{23}$ –3.5 (*c* 4.98, CH_2Cl_2).

HPLC: Daicel Chiralcel OD-H; hexane/*i*-PrOH (99.9:0.1), flow rate = 5.0 mL/min, λ = 254 nm, 40 °C); t_R = 15.4 min (minor), t_R = 17.1 min (major).

IR (neat): 3351, 2973, 2873, 1682, 1598, 1581, 1449, 1382, 1300, 1280, 1210, 1181, 1067, 1002, 928, 754, 691, 498 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.97 (m, 2 H), 7.56 (m, 1 H), 7.46 (m, 2 H), 4.41 (dddd, *J* = 7.0, 6.5, 6.5, 6.0 Hz, 1 H), 3.89 (ddd, *J* = 8.5, 7.0, 6.5 Hz, 1 H), 3.75 (m, 1 H), 3.40 (dd, *J* = 16.0, 6.0 Hz, 1 H), 3.06 (dd, *J* = 16.0, 6.5 Hz, 1 H), 2.20 (m, 1 H), 1.93 (m, 2 H), 1.57 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 198.4, 137.1, 133.1, 128.6, 128.2, 75.4, 67.8, 44.7, 31.6, 25.6. HRMS: *m*/*z* calcd for $C_{12}H_{15}O_2$ $[M + H]^+$: 191.1072; found: 191.1067.

(*R*)-1-(4-Methoxyphenyl)-2-(tetrahydrofuran-2-yl)ethanone (2b)

[CAS Reg. No. 1337999-51-5]

Yield: 54.0 mg (99%); 94% ee; colorless oil; R_f = 0.15 (hexane/EtOAc 3:1); $[\alpha]_D^{23}$ –2.5 (*c* 4.02, CH_2Cl_2).

HPLC: Daicel Chiralcel OD-H; hexane/*i*-PrOH (99.9:0.1), flow rate = 5.0 mL/min, λ = 254 nm, 40 °C); t_R = 34.1 min (minor), t_R = 41.1 min (major).

IR (neat): 3474, 2957, 2872, 2360, 1677, 1601, 1576, 1510, 1458, 1419, 1381, 1309, 1261, 1216, 1170, 1066, 1030, 990, 847, 488 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.95 (m, 2 H), 6.93 (m, 2 H), 4.38 (dddd, *J* = 7.0, 6.5, 6.5, 6.0 Hz, 1 H), 3.89 (m, 1 H), 3.86 (s, 3 H), 3.74 (m, 1 H), 3.35 (dd, *J* = 16.0, 6.0 Hz, 1 H), 3.00 (dd, *J* = 16.0, 7.0 Hz, 1 H), 2.18 (m, 1 H), 1.92 (m, 2 H), 1.56 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 196.9, 163.5, 130.5, 130.3, 113.7, 75.6, 67.8, 55.4, 44.3, 31.6, 25.6.

HRMS: *m*/*z* calcd for $C_{13}H_{17}O_3$ $[M + H]^+$: 221.1178; found: 221.1172.

(*R*)-2-(Tetrahydrofuran-2-yl)-1-[4-(trifluoromethyl)phenyl]ethanone (2c)

[CAS Reg. No. 1337999-52-6]

Reaction was run on 0.125 mmol scale; yield: 60.0 mg (93%); 85% ee; white solid; mp 82.0–82.3 °C; R_f = 0.30 (hexane/EtOAc 3:1); $[\alpha]_D^{23}$ –7.1 (*c* 3.18, CH_2Cl_2).

HPLC: Daicel Chiralcel OD-H; hexane/*i*-PrOH (99:1), flow rate = 1.0 mL/min, λ = 254 nm, 40 °C; t_R = 11.8 min (minor), t_R = 13.6 min (major).

IR (KBr): 3428, 2987, 2881, 2366, 1685, 1513, 1411, 1387, 1330, 1209, 1159, 1127, 1110, 1060, 1017, 995, 830, 760, 687, 607, 511 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.07 (d, *J* = 8.0 Hz, 2 H), 7.73 (d, *J* = 8.0 Hz, 2 H), 4.40 (dddd, *J* = 7.0, 6.5, 6.5, 6.0 Hz, 1 H), 3.89 (ddd, *J* = 8.5, 7.0, 6.5 Hz, 1 H), 3.76 (m, 1 H), 3.39 (dd, *J* = 16.0, 6.5 Hz, 1 H), 3.08 (dd, *J* = 16.0, 6.0 Hz, 1 H), 2.21 (m, 1 H), 1.94 (m, 2 H), 1.58 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 197.5, 139.7, 134.4 (q, *J* = 32.7 Hz), 128.5, 125.6 (q, *J* = 3.8 Hz), 123.6 (q, *J* = 272.6 Hz), 75.2, 67.9, 44.9, 31.6, 25.6.

^{19}F NMR ($CDCl_3$): δ = 98.0.

HRMS: *m*/*z* calcd for $C_{13}H_{13}F_3O_2$ (M^+): 258.0868; found: 258.0863.

(*R*)-1-(4-Methylphenyl)-2-(tetrahydrofuran-2-yl)ethanone (2d)

[CAS Reg. No. 1337999-54-8]

Yield: 50.5 mg (99%); 93% ee; colorless oil; R_f = 0.29 (hexane/EtOAc 3:1); $[\alpha]_D^{23}$ –1.7 (*c* 5.75, CH_2Cl_2).

HPLC: Daicel Chiralcel OD-H; hexane/*i*-PrOH (99:1), flow rate = 0.5 mL/min, λ = 254 nm, 40 °C; t_R = 29.7 min (minor), t_R = 31.9 min (major).

IR (neat): 3584, 2970, 2870, 2360, 1681, 1607, 1574, 1449, 1408, 1380, 1301, 1221, 1206, 1181, 1067, 1013, 844, 807, 761, 464 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.86 (d, *J* = 8.0 Hz, 2 H), 7.25 (d, *J* = 8.0 Hz, 2 H), 4.39 (dddd, *J* = 7.0, 6.5, 6.5, 6.0 Hz, 1 H), 3.89 (m, 1 H), 3.75 (m, 1 H), 3.37 (dd, *J* = 16.0, 5.0 Hz, 1 H), 3.03 (dd, *J* = 16.0, 7.0 Hz, 1 H), 2.41 (s, 3 H), 2.19 (m, 1 H), 1.92 (m, 2 H), 1.56 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 198.0, 143.9, 134.7, 129.2, 128.3, 75.5, 67.8, 44.6, 31.6, 25.7, 21.6.

HRMS: *m*/*z* calcd for $C_{13}H_{16}O_2$ (M^+): 204.1150; found: 204.1154.

(*R*)-1-(4-Bromophenyl)-2-(tetrahydrofuran-2-yl)ethanone (2e)

[CAS Reg. No. 1337999-55-9]

Yield: 66.8 mg (99%); 92% ee; white solid; mp 59.2–59.5 °C; R_f = 0.29 (hexane/EtOAc 3:1); $[\alpha]_D^{28}$ –6.7 (*c* 6.39, CH_2Cl_2).

HPLC: Daicel Chiralcel OD-H; hexane/*i*-PrOH (99:1), flow rate = 2.0 mL/min, λ = 254 nm, 40 °C; t_R = 7.9 min (minor), t_R = 9.1 min (major).

IR (KBr): 3459, 2928, 2878, 2366, 1679, 1587, 1485, 1397, 1343, 1301, 1209, 1179, 1062, 991, 814, 791, 668, 574 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.83 (m, 2 H), 7.60 (m, 2 H), 4.38 (dddd, *J* = 7.0, 6.5, 6.5, 6.0 Hz, 1 H), 3.88 (ddd, *J* = 8.0, 7.0, 6.5 Hz, 1 H), 3.75 (ddd, *J* = 8.0, 7.5, 7.0 Hz, 1 H), 3.33 (dd, *J* = 16.0, 6.0 Hz, 1 H), 3.02 (dd, *J* = 16.0, 6.5 Hz, 1 H), 2.19 (m, 1 H), 1.93 (m, 2 H), 1.56 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 197.4, 135.8, 131.9, 129.8, 128.3, 75.3, 67.9, 44.6, 31.6, 25.6.

HRMS: *m*/*z* calcd for $C_{12}H_{14}BrO_2$ $[M + H]^+$: 269.0177; found: 269.0172.

(*R*)-1-(Naphthalen-2-yl)-2-(tetrahydrofuran-2-yl)ethanone (2f)

[CAS Reg. No. 1337999-53-7]

Yield: 58.8 mg (98%); 91% ee; colorless oil; R_f = 0.27 (hexane/EtOAc 3:1); $[\alpha]_D^{23}$ –0.3 (*c* 7.36, CH_2Cl_2).

HPLC: Daicel Chiralcel OD-H; hexane/*i*-PrOH (99:1), flow rate = 2.0 mL/min; λ = 254 nm, 40 °C; t_R = 14.2 min (major), t_R = 15.8 min (minor).

IR (neat): 3058, 2971, 2871, 2368, 1681, 1628, 1597, 1469, 1385, 1359, 1297, 1279, 1210, 1186, 1126, 1065, 1026, 991, 943, 918, 865, 820, 754, 464 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.49 (s, 1 H), 8.04 (d, *J* = 9.0 Hz, 1 H), 7.97 (d, *J* = 8.0 Hz, 1 H), 7.90 (d, *J* = 9.0 Hz, 1 H), 7.88 (d, *J* = 8.5 Hz, 1 H), 7.60 (dd, *J* = 8.0, 7.0 Hz, 1 H), 7.56 (dd, *J* = 8.5, 7.0 Hz), 4.47 (dddd, *J* = 7.0, 6.5, 6.5, 6.0 Hz, 1 H), 3.92 (m, 1 H), 3.78 (m, 1 H), 3.54 (dd, *J* = 16.0, 6.0 Hz, 1 H), 3.19 (dd, *J* = 16.0, 6.5 Hz, 1 H), 2.23 (m, 1 H), 1.95 (m, 2 H), 1.63 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 198.3, 135.6, 134.5, 132.5, 130.0, 129.6, 128.5, 128.4, 127.8, 126.7, 123.9, 75.6, 67.9, 44.8, 31.7, 25.7.

HRMS: *m*/*z* calcd for $C_{16}H_{16}O_2$ (M^+): 240.1150; found: 240.1144.

(*R*)-4-Phenyl-1-(tetrahydrofuran-2-yl)butan-2-one (2g)

[CAS Reg. No. 1337999-56-0]

Yield: 52.9 mg (97%); 90% ee; colorless oil; R_f = 0.33 (hexane/EtOAc 3:1); $[\alpha]_D^{28}$ –4.8 (*c* 6.14, CH_2Cl_2).

HPLC: Daicel Chiralcel OD-H; hexane/*i*-PrOH (99:1), flow rate = 2.0 mL/min, λ = 254 nm, 40 °C; t_R = 10.6 min (major), t_R = 15.5 min (minor).

IR (neat): 3027, 2955, 2870, 1713, 1604, 1498, 1453, 1409, 1383, 1296, 1182, 1126, 1056, 1017, 919, 749, 700, 492 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.27 (m, 2 H), 7.18 (m, 3 H), 4.21 (m, 1 H), 3.84 (ddd, *J* = 8.5, 7.0, 7.0 Hz, 1 H), 3.71 (ddd, *J* = 8.5, 7.0, 7.0 Hz, 1 H), 2.90 (t, *J* = 8.0 Hz, 2 H), 2.79 (m, 2 H), 2.72 (dd, *J* = 16.0, 7.0 Hz, 1 H), 2.51 (dd, *J* = 16.0, 6.0 Hz, 1 H), 2.07 (m, 1 H), 1.88 (m, 2 H), 1.44 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 208.3, 141.1, 128.5, 128.3, 126.0, 75.1, 67.8, 48.9, 45.0, 31.5, 29.5, 25.5.

HRMS: *m*/*z* calcd for $C_{14}H_{18}O_2$ (M^+): 218.1307; found: 218.1304.

(*R*)-1-Phenyl-2-(tetrahydro-2*H*-pyran-2-yl)ethanone (5)

[CAS Reg. No. 1337999-57-1]

To a 5 mL vial, ζ-hydroxy-α,β-unsaturated ketone **4** (0.15 mmol), cyclopentyl methyl ether (0.3 mL), and quinidine-derived bifunctional catalyst **3a** (0.0075 mmol) were added sequentially. The mixture was stirred in an oil bath maintained at 25 °C for 24 h. The mixture was subsequently diluted with hexane/EtOAc (1:1 v/v), passed through a short silica gel pad to remove **3a**, and concentrated in vacuo. Purification of the residue by flash silica gel column chromatography using hexane/EtOAc (3:1 v/v) as an eluent afforded tetrahydropyran **5**; yield: 27.6 mg (90%); 91% ee; colorless oil; R_f = 0.45 (hexane/EtOAc 3:1); $[\alpha]_D^{26}$ +16.8 (*c* 2.53, CH_2Cl_2).

HPLC; Daicel Chiralcel OD-H; hexane/*i*-PrOH (99:1), flow rate = 2.0 mL/min, λ = 254 nm, 40 °C; t_R = 6.1 min (minor), t_R = 8.0 min (major).

IR (neat): 3060, 2936, 2849, 1686, 1597, 1581, 1449, 1379, 1357, 1325, 1292, 1273, 1208, 1194, 1175, 1088, 1045, 1003, 971, 904, 810, 777, 751, 692, 661, 471 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.97 (m, 2 H), 7.56 (m, 1 H), 7.46 (m, 2 H), 3.96 (m, 2 H), 3.48 (m, 1 H), 3.29 (dd, *J* = 16.0, 6.5 Hz, 1 H), 2.92 (dd, *J* = 16.0, 5.5 Hz, 1 H), 1.84 (m, 1 H), 1.75 (m, 1 H), 1.57 (m, 2 H), 1.52 (m, 1 H), 1.36 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 198.4, 137.4, 133.0, 128.5, 128.3, 74.4, 68.7, 45.4, 32.0, 25.9, 23.4.

HRMS: *m*/*z* calcd for $C_{13}H_{17}O_2$ $[M + H]^+$: 205.1229; found: 205.1227.

Kinetic Resolution of 6 and 8; General Procedure

A solution of **3e** (5.6 mg, 0.0075 mmol) in anhyd toluene (1 mL) was added to a mixture of (*rac*)-**6** (0.15 mmol), anhyd toluene (14 mL), and MS 4A (300 mg) at –40 °C. The resulting mixture was stirred at the same temperature. When the approximate conversion was 50% (monitored via TLC), the mixture was quenched with a drop of Et_3N, passed through a short silica gel column with hexane/Et_2O (1:2 v/v) to remove **3e**, and concentrated in vacuo. Purification of the residue by flash silica gel column chromatography using hexane/Et_2O (1:1 v/v) as an eluent afforded the corresponding cycloether product **7** and unreacted starting material **6**. The recovered **6**, after the kinetic resolution in the reaction using **3e**, contained the *R*-isomer as a major component. For (*rac*)-**8**, the same procedure was applied. Conversions in Tables 3 and 4 and Equation 2 were calculated based on the obtained ee values. See ref. 11.

(*R*,*E*)-7-Hydroxy-1,7-diphenylhept-2-en-1-one (6a)

[CAS Reg. No. 2087909-34-8]

White solid; yield: 49% (calcd by conversion; isolated: 16.8 mg); mp 42.8–43.3 °C; R_f = 0.25 (hexane/EtOAc 3:1); $[\alpha]_D^{18}$ +15.4 (*c* 0.56, CH_2Cl_2) [for (*R*)-**6a**, 85% ee].

HPLC: Daicel Chiralpak IB-H; hexane/*i*-PrOH (90.0:10.0), flow rate = 2.0 mL/min, λ = 254 nm, 40 °C; t_R = 6.6 min (minor), t_R = 13.3 min (major).

IR (KBr): 3509, 2950, 2929, 2909, 2883, 2360, 1962, 1895, 1813, 1663, 1609, 1578, 1491, 1447, 1417, 1336, 1297, 1256, 1232, 1216, 1174, 1062, 1038, 1025, 1001, 987, 936, 869, 847, 811, 759, 720, 700, 688 cm^{-1}.

^1H NMR (C_6D_6): δ = 7.87 (m, 2 H), 7.20–7.02 (m, 9 H), 6.63 (dt, *J* = 15.0, 1.5 Hz, 1 H), 4.28 (m, 1 H), 1.85 (m, 2 H), 1.58 (m, 1 H), 1.46 (m, 1 H), 1.38 (m, 1 H), 1.26 (d, *J* = 3.5 Hz, 1 H), 1.23 (m, 1 H).

^{13}C NMR (C_6D_6): δ = 189.5, 149.0, 145.7, 138.7, 132.4, 128.8, 128.65, 128.59, 127.6, 126.1, 126.0, 74.1, 39.1, 32.7, 24.6.

HRMS: *m*/*z* calcd for $C_{19}H_{21}O_2$ $[M + H]^+$: 281.1536; found: 281.1532.

(*R*,*E*)-7-Hydroxy-7-(4-methoxyphenyl)-1-phenylhept-2-en-1-one (6b)

[CAS Reg. No. 2087909-35-9]

White solid; yield: 37% (calcd by conversion; isolated: 14.4 mg); mp 89.0–89.5 °C; R_f = 0.17 (hexane/EtOAc 3:1); $[\alpha]_D^{18}$ +8.0 (*c* 0.46, CH_2Cl_2) [for (*R*)-**6b**, 50% ee].

HPLC: Daicel Chiralpak IB-H; hexane/*i*-PrOH (87.5:12.5), flow rate = 2.0 mL/min, λ = 254 nm, 40 °C; t_R = 7.3 min (minor), t_R = 10.4 min (major).

IR (KBr): 3490, 3063, 3005, 2960, 2926, 2906, 2864, 2838, 2054, 1983, 1894, 1833, 1773, 1654, 1594, 1576, 1511, 1462, 1404, 1339, 1300, 1249, 1217, 1170, 1061, 1033, 988, 936, 874, 843, 831, 773, 725, 692 cm^{-1}.

^1H NMR (C_6D_6): δ = 7.90 (m, 2 H), 7.16–7.05 (m, 6 H), 6.82 (m, 2 H), 6.68 (dt, *J* = 15.5, 1.5 Hz, 1 H), 4.33 (m, 1 H), 3.33 (s, 3 H), 1.92 (m, 2 H), 1.66 (m, 1 H), 1.53 (m, 1 H), 1.44 (m, 1 H), 1.282 (m, 1 H), 1.281 (d, *J* = 3.5 Hz, 1 H).

^{13}C NMR (C_6D_6): δ = 189.5, 159.6, 149.0, 138.7, 137.7, 132.4, 128.8, 128.6, 127.4, 126.0, 114.1, 73.8, 54.8, 39.2, 32.7, 24.7.

HRMS: *m*/*z* calcd for $C_{20}H_{23}O_3$ $[M + H]^+$: 311.1642; found: 311.1632.

(*R*,*E*)-7-Hydroxy-1-phenyl-7-[4-(trifluoromethyl)phenyl]hept-2-en-1-one (6c)

[CAS Reg. No. 2087909-36-0]

White solid; yield: 48% (calcd by conversion; isolated: 20.9 mg); mp 53.0–53.5 °C; R_f = 0.22 (hexane/EtOAc 3:1); $[\alpha]_D^{18}$ +12.4 (*c* 0.29, CH_2Cl_2); [for (*R*)-**6c**, 87% ee].

HPLC: Daicel Chiralpak IB-H; hexane/*i*-PrOH (90.0:10.0), flow rate = 2.0 mL/min, λ = 254 nm, 40 °C; t_R = 6.0 min (minor), t_R = 11.6 min (major).

IR (KBr): 3459, 2918, 2864, 1929, 1655, 1601, 1575, 1450, 1411, 1330, 1312, 1225, 1168, 1154, 1113, 1070, 1011, 903, 870, 828, 774, 718, 688 cm^{-1}.

^1H NMR (C_6D_6): δ = 7.90 (m, 2 H), 7.38 (d, *J* = 8.5 Hz, 2 H), 7.13–7.03 (m, 6 H), 6.70 (dt, *J* = 15.5, 1.5 Hz, 1 H), 4.20 (m, 1 H), 1.90 (m, 2 H), 1.57 (br s, 1 H), 1.45 (m, 1 H), 1.39–1.32 (m, 2 H), 1.23 (m, 1 H).

^{13}C NMR (C_6D_6): δ = 189.5, 149.6, 148.7, 138.5, 132.6, 129.5 (q, *J* = 32.6 Hz), 128.8, 128.7, 126.3, 126.1, 125.5 (q, *J* = 3.9 Hz), 125.1 (q, *J* = 271.3 Hz), 73.3, 38.9, 32.6, 24.4.

^{19}F NMR (C_6D_6): δ = 100.8.

HRMS: *m*/*z* calcd for $C_{20}H_{20}F_3O_2$ [M + H]$^+$: 349.1410; found: 349.1399.

(*R*,*E*)-7-(Anthracen-9-yl)-7-hydroxy-1-phenylhept-2-en-1-one (6d)

[CAS Reg. No. 2087909-37-1]

Yellow solid; yield: 51% (calcd by conversion; isolated: 24.5 mg); mp 145.0–145.5 °C; R_f = 0.36 (hexane/EtOAc 3:1); $[\alpha]_D^{18}$ –13.6 (*c* 0.95, CH_2Cl_2) [for (*R*)-**6d**, 84% ee].

HPLC: Daicel Chiralpak IB-H; hexane/*i*-PrOH (80.0:20.0), flow rate = 2.0 mL/min, λ = 254 nm, 40 °C; t_R = 5.9 min (minor), t_R = 9.0 min (major).

IR (KBr): 3497, 3446, 3057, 2933, 2861, 2363, 1654, 1610, 1577, 1523, 1459, 1447, 1347, 1299, 1284, 1232, 1212, 1182, 1158, 1056, 1020, 975, 921, 890, 872, 844, 792, 772, 736, 698, 662 cm^{-1}.

^{1}H NMR (C_6D_6): δ = 8.75 (br, 2 H), 8.18 (s, 1 H), 7.87–7.83 (m, 4 H), 7.33 (m, 2 H), 7.27 (m, 2 H), 7.13 (m, 1 H), 7.06 (m, 2 H), 7.02 (dt, *J* = 15.5, 7.0 Hz, 1 H), 6.61 (dt, *J* = 15.5, 1.5 Hz, 1 H), 5.85 (m, 1 H), 2.32 (m, 1 H), 1.95–1.82 (m, 3 H), 1.63 (m, 1 H), 1.58 (br s, 1 H), 1.28 (m, 1 H).

^{13}C NMR (C_6D_6): δ = 189.4, 148.9, 138.6, 136.0, 132.3, 129.8, 129.6, 128.8, 128.6, 128.3, 126.0, 125.6, 125.0, 70.7, 37.4, 32.6, 30.0, 25.6.

HRMS: *m*/*z* calcd for $C_{27}H_{25}O_2$ [M + H]$^+$: 381.1849; found: 381.1840.

(*R*,*E*)-7-Hydroxy-1-phenyl-7-(pyren-4-yl)hept-2-en-1-one (6e)

[CAS Reg. No. 2087909-38-2]

Pale yellow oil; yield: 42% (calcd by conversion; isolated 21.2 mg); R_f = 0.15 (hexane/EtOAc 3:1); $[\alpha]_D^{18}$ +81.0 (*c* 0.83, CH_2Cl_2) [for (*R*)-**6e**, 98% ee].

HPLC: Daicel Chiralpak IB-H; hexane/*i*-PrOH (85.0:15.0), flow rate = 2.0 mL/min, λ = 254 nm, 40 °C; t_R = 10.0 min (minor), t_R = 13.6 min (major).

IR (neat): 3421, 3048, 2944, 2862, 2347, 1669, 1617, 1507, 1448, 1340, 1297, 1224, 1182, 1072, 1018, 978, 848, 760, 719, 693 cm^{-1}.

^{1}H NMR (C_6D_6): δ = 8.22 (d, *J* = 9.5 Hz, 1 H), 8.16 (d, *J* = 8.0 Hz, 1 H), 8.00–7.91 (m, 4 H), 7.87–7.82 (m, 4 H), 7.78 (m, 1 H), 7.12–7.00 (m, 4 H), 6.66 (dt, *J* = 15.5, 1.5 Hz, 1 H), 5.36 (m, 1 H), 1.95 (br s, 1 H), 1.91–1.79 (m, 4 H), 1.56 (m, 1 H), 1.43 (m, 1 H).

^{13}C NMR (C_6D_6): δ = 189.4, 148.9, 139.2, 138.5, 132.3, 131.8, 131.1, 130.9, 128.7, 128.5, 128.2, 127.9, 127.84, 127.79, 127.4, 126.1, 126.0, 125.5, 125.34, 125.27, 125.22, 123.7, 122.9, 70.9, 38.8, 32.5, 24.8.

HRMS: *m*/*z* calcd for $C_{29}H_{25}O_2$ [M + H]$^+$: 405.1849; found: 405.1836.

(*R*,*E*)-7-Hydroxy-1-phenylundec-2-en-1-one (6f)

[CAS Reg. No. 2087909-39-3]

Colorless oil; yield: 47% (calcd by conversion; isolated: 15.6 mg); R_f = 0.29 (hexane/EtOAc 3:1); $[\alpha]_D^{18}$ +2.2 (*c* 0.58, CH_2Cl_2) [for (*R*)-**6f**, 81% ee].

HPLC: Daicel Chiralpak IB-H; hexane/*i*-PrOH (98.0:2.0), flow rate = 2.0 mL/min, λ = 254 nm, 40 °C; t_R = 14.3 min (minor), t_R = 20.6 min (major).

IR (neat): 3422, 3059, 2931, 2869, 1668, 1621, 1579, 1448, 1345, 1296, 1228, 1180, 1128, 1002, 855, 770, 692, 671 cm^{-1}.

^{1}H NMR (C_6D_6): δ = 7.94 (m, 2 H), 7.18–7.07 (m, 4 H), 6.76 (dt, *J* = 15.5, 1.5 Hz, 1 H), 3.29 (br s, 1 H), 1.97 (m, 2 H), 1.44 (m, 1 H), 1.36–1.16 (m, 10 H), 0.90 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (C_6D_6): δ = 189.5, 149.1, 138.6, 132.4, 128.8, 128.6, 126.0, 71.2, 37.7, 37.2, 32.8, 28.2, 24.5, 23.1, 14.3.

HRMS: *m*/*z* calcd for $C_{17}H_{25}O_2$ [M + H]$^+$: 261.1849; found: 261.1840.

(*R*,*E*)-7-Hydroxy-1-(4-methoxyphenyl)-7-phenylhept-2-en-1-one (6g)

[CAS Reg. No. 2087909-40-6]

Pale yellow oil; yield: 48% (calcd by conversion; isolated 19.1 mg); R_f = 0.16 (hexane/EtOAc 3:1); $[\alpha]_D^{18}$ +13.9 (*c* 0.72, CH_2Cl_2) [for (*R*)-**6g**, 89% ee].

HPLC: Daicel Chiralpak IB-H; hexane/*i*-PrOH (80.0:20.0), flow rate = 2.0 mL/min, λ = 254 nm, 40 °C; t_R = 5.0 min (minor), t_R = 7.0 min (major).

IR (neat): 3445, 3061, 3028, 2937, 2861, 1665, 1609, 1575, 1511, 1494, 1455, 1419, 1345, 1307, 1260, 1235, 1172, 1114, 1063, 1027, 982, 915, 843, 793, 702, 677 cm^{-1}.

^{1}H NMR (C_6D_6): δ = 7.97 (m, 2 H), 7.22–7.17 (m, 4 H), 7.14–7.08 (m, 2 H), 6.76 (dt, *J* = 15.5, 1.5 Hz, 1 H), 6.67 (m, 2 H), 4.32 (m, 1 H), 3.17 (s, 3 H), 1.93 (m, 2 H), 1.63 (m, 1 H), 1.55–1.38 (m, 2 H), 1.34–1.25 (m, 2 H).

^{13}C NMR (C_6D_6): δ = 187.8, 163.5, 148.0, 145.7, 131.6, 131.1, 128.6, 127.5, 126.2, 125.8, 114.0, 74.2, 54.9, 39.2, 32.7, 24.7.

HRMS: *m*/*z* calcd for $C_{20}H_{23}O_3$ [M + H]$^+$: 311.1642; found: 311.1642.

(*R*,*E*)-7-Hydroxy-7-phenyl-1-[4-(trifluoromethyl)phenyl]hept-2-en-1-one (6h)

[CAS Reg. No. 2087909-41-7]

White solid; yield: 43% (calcd by conversion; isolated: 18.3 mg); mp 49.0–49.5 °C; R_f = 0.17 (hexane/EtOAc 3:1); $[\alpha]_D^{18}$ +19.0 (*c* 0.69, CH_2Cl_2) [for (*R*)-**6h**, 97% ee].

HPLC: Daicel Chiralpak IC-H; hexane/*i*-PrOH (97.5:2.5), flow rate = 2.0 mL/min, λ = 254 nm, 40 °C; t_R = 30.8 min (minor), t_R = 35.4 min (major).

IR (KBr): 3483, 2931, 2869, 2363, 1660, 1603, 1577, 1507, 1456, 1411, 1319, 1226, 1169, 1120, 1069, 1015, 838, 798, 767, 746, 700, 659 cm^{-1}.

^{1}H NMR (C_6D_6): δ = 7.60 (d, *J* = 8.0 Hz, 2 H), 7.25 (d, *J* = 8.0 Hz, 2 H), 7.21–7.17 (m, 4 H), 7.10 (m, 1 H), 6.98 (dt, *J* = 15.5, 7.0 Hz, 1 H), 6.47 (dt, *J* = 15.5, 1.5 Hz, 1 H), 4.31 (m, 1 H), 1.87 (m, 2 H), 1.62 (m, 1 H), 1.54–1.38 (m, 2 H), 1.31–1.22 (m, 2 H).

^{13}C NMR (C_6D_6): δ = 188.7, 150.3, 145.6, 141.2, 133.5 (q, *J* = 32.2 Hz), 129.0, 128.6, 127.7, 126.1, 125.7, 125.6 (q, *J* = 3.9 Hz), 124.5 (q, *J* = 273.1 Hz), 74.1, 39.1, 32.7, 24.5.

^{19}F NMR (C_6D_6): δ = 100.1.

HRMS: *m*/*z* calcd for $C_{20}H_{20}F_3O_2$ [M + H]$^+$: 349.1410; found: 349.1398.

1-Phenyl-2-[(2*R*,6*S*)-6-phenyltetrahydro-2*H*-pyran-2-yl]ethan-1-one (7a)

[CAS Reg. No. 2087909-42-8]

The ratio of diastereomers was determined by ^{1}H NMR analysis. The diastereomers were further separated by flash silica gel column chromatography using hexane/EtOAc (10:1 v/v) as an eluent. Conversion: 51% (isolated: 15 mg); dr = 24:1; 89% ee; colorless oil; R_f = 0.62 (hexane/EtOAc 3:1); $[\alpha]_D^{18}$ –33.2 (*c* 0.53, CH_2Cl_2).

HPLC: Daicel Chiralpak IA; hexane/*i*-PrOH (99.0:1.0), flow rate = 1.0 mL/min, λ = 254 nm, 40 °C; t_R = 9.9 min (minor), t_R = 11.9 min (major).

IR (neat): 3356, 3062, 3029, 2936, 2859, 1683, 1597, 1581, 1496, 1449, 1388, 1343, 1308, 1286, 1071, 1045, 1001, 923, 752, 698 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.00 (m, 2 H), 7.56 (m, 1 H), 7.46 (m, 2 H), 7.31–7.27 (m, 4 H), 7.23 (m, 1 H), 4.44 (dd, *J* = 11.0, 2.0 Hz, 1 H), 4.18 (dddd, *J* = 8.0, 6.5, 6.0, 6.0 Hz, 1 H), 3.42 (dd, *J* = 16.0, 6.0 Hz, 1 H), 3.07 (dd, *J* = 16.0, 6.5 Hz, 1 H), 1.96 (m, 1 H), 1.89–1.83 (m, 2 H), 1.76 (m, 1 H), 1.52 (m, 1 H), 1.40 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 198.6, 143.1, 137.3, 133.0, 128.5, 128.3, 128.2, 127.1, 125.7, 79.8, 75.0, 45.5, 33.2, 31.3, 23.8.

HRMS: *m*/*z* calcd for $C_{19}H_{21}O_2$ $[M + H]^+$: 281.1536; found: 281.1532.

2-[(2*R*,6*S*)-6-(4-Methoxyphenyl)tetrahydro-2*H*-pyran-2-yl]-1-phenylethan-1-one (7b)

[CAS Reg. No. 2087909-43-9]

The ratio of diastereomers was determined by ^1H NMR analysis. The diastereomers were further separated by flash silica gel column chromatography using hexane/EtOAc (10:1 v/v) as an eluent. Conversion: 63% (isolated: 18.0 mg); dr = 4.3:1; 58% ee; colorless oil; R_f = 0.44 (hexane/EtOAc 3:1); $[\alpha]_D^{18}$ –22.8 (*c* 0.83, CH_2Cl_2).

IR (neat): 3421, 3061, 2999, 2935, 2858, 1682, 1614, 1581, 1449, 1342, 1304, 1285, 1247, 1207, 1179, 1078, 1036, 1001, 921, 831, 752, 691 cm^{-1}.

HPLC: Daicel Chiralpak IA; hexane/*i*-PrOH (99.0:1.0), flow rate = 1.7 mL/min, λ = 254 nm, 40 °C; t_R = 11.9 min (minor), t_R = 13.5 min (major).

^1H NMR ($CDCl_3$): δ = 7.99 (m, 2 H), 7.56 (m, 1 H), 7.45 (m, 2 H), 7.23 (m, 2 H), 6.84 (m, 2 H), 4.38 (dd, *J* = 11.5, 2.0 Hz, 1 H), 4.17 (dddd, *J* = 8.0, 6.5, 6.5, 5.5 Hz, 1 H), 3.78 (s, 3 H), 3.40 (dd, *J* = 16.0, 5.5 Hz, 1 H), 3.06 (dd, *J* = 16.0, 6.5 Hz, 1 H), 1.96 (m, 1 H), 1.85–1.82 (m, 2 H), 1.74 (m, 1 H), 1.53 (m, 1 H), 1.38 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 198.5, 158.7, 137.3, 135.3, 133.0, 128.5, 128.3, 127.1, 113.5, 79.4, 74.9, 55.2, 45.5, 33.0, 31.3, 23.8.

HRMS: *m*/*z* calcd for $C_{20}H_{23}O_3$ $[M + H]^+$: 311.1642: found: 311.1634.

1-Phenyl-2-{(2*R*,6*S*)-6-[4-(trifluoromethyl)phenyl]tetrahydro-2*H*-pyran-2-yl}ethan-1-one (7c)

[CAS Reg. No. 2087909-44-0]

The ratio of diastereomers was determined by ^1H NMR analysis. The diastereomers were further separated by flash silica gel column chromatography using hexane/EtOAc (10:1 v/v) as an eluent. Conversion: 52% (isolated: 20.1 mg); dr = 16:1; 90% ee; white solid; mp 75.0–75.5 °C; R_f = 0.61 (hexane/EtOAc 3:1); $[\alpha]_D^{18}$ –40.2 (*c* 0.54, CH_2Cl_2).

HPLC: Daicel Chiralpak IA; hexane/*i*-PrOH (99.5:0.5), flow rate = 2.0 mL/min, λ = 254 nm, 40 °C; t_R = 7.7 min (minor), t_R = 11.1 min (major).

IR (KBr): 3503, 3043, 2957, 2906, 2862, 2354, 1942, 1683, 1620, 1597, 1582, 1452, 1420, 1394, 1356, 1331, 1208, 1185, 1161, 1118, 1087, 1063, 1001, 924, 846, 818, 790, 757, 691 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.00 (m, 2 H), 7.57 (m, 1 H), 7.53 (d, *J* = 8.0 Hz, 2 H), 7.47 (m, 2 H), 7.38 (m, 2 H), 4.48 (dd, *J* = 11.5, 1.5 Hz, 1 H), 4.19 (dddd, *J* = 8.0, 7.0, 6.5, 6.0 Hz, 1 H), 3.42 (dd, *J* = 16.0, 6.5 Hz, 1 H), 3.05 (dd, *J* = 16.0, 6.0 Hz, 1 H), 1.98 (m, 1 H), 1.91–1.84 (m, 2 H), 1.78 (m, 1 H), 1.50–1.37 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 198.5, 147.0, 137.3, 133.1, 129.2 (q, *J* = 33.3 Hz), 128.5, 128.3, 125.9, 125.1 (q, *J* = 3.8 Hz), 126.4 (q, *J* = 272.6 Hz), 79.0, 75.0, 45.3, 33.3, 31.2, 23.7.

^{19}F NMR ($CDCl_3$): δ = 99.3.

HRMS: *m*/*z* calcd for $C_{20}H_{20}F_3O_2$ $[M + H]^+$: 349.1410; found: 349.1401.

2-[(2*R*,6*S*)-6-(Anthracen-9-yl)tetrahydro-2*H*-pyran-2-yl]-1-phenylethan-1-one (7d)

[CAS Reg. No. 2087909-45-1]

The ratio of diastereomers was determined by ^1H NMR analysis. The diastereomers were further separated by flash silica gel column chromatography using hexane/EtOAc (10:1 v/v) as an eluent. Conversion: 49% (isolated: 17.9 mg); dr = 50:1; 90% ee; pale yellow solid; mp 50.5–51.0 °C; R_f = 0.63 (hexane/EtOAc 3:1); $[\alpha]_D^{18}$ –42.1 (*c* 0.68, CH_2Cl_2).

HPLC: Daicel Chiralpak IB; hexane/*i*-PrOH (98.0:2.0), flow rate = 2.0 mL/min, λ = 254 nm, 40 °C; t_R = 6.9 min (minor), t_R = 9.1 min (major).

IR (KBr): 3432, 3052, 2938, 2857, 2363, 1676, 1449, 1345, 1286, 1210, 1197, 1158, 1075, 1057, 1001, 936, 888, 848, 789, 752, 733, 691, 668 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.70 (br s, 2 H), 8.38 (s, 1 H), 7.99–7.96 (m, 4 H), 7.51–7.42 (m, 5 H), 7.36 (m, 2 H), 5.97 (dd, *J* = 12.0, 2.5 Hz, 1 H), 4.36 (dddd, *J* = 7.5, 7.0, 5.5, 5.0 Hz, 1 H), 3.51 (dd, *J* = 16.0, 5.5 Hz, 1 H), 3.24 (dd, *J* = 16.0, 7.0 Hz, 1 H), 2.39 (m, 1 H), 2.14–1.95 (m, 3 H), 1.88 (m, 1 H), 1.75 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 198.5, 137.2, 133.5, 133.0, 131.7, 129.2, 129.0, 128.4, 128.3, 127.9, 125.2, 124.6, 78.0, 76.1, 45.6, 31.5, 31.2, 24.4.

HRMS: *m*/*z* calcd for $C_{27}H_{25}O_2$ $[M + H]^+$: 381.1849; found: 381.1835.

1-Phenyl-2-[(2*R*,6*S*)-6-(pyren-1-yl)tetrahydro-2*H*-pyran-2-yl]ethan-1-one (7e)

[CAS Reg. No. 2087909-46-2]

The ratio of diastereomers was determined by ^1H NMR analysis. The diastereomers were further separated by flash silica gel column chromatography using hexane/EtOAc (10:1 v/v) as an eluent. Conversion: 58% (isolated: 25.1 mg); dr = 17:1; 79% ee; white solid; mp 124.0–124.5 °C; R_f = 0.50 (hexane/EtOAc 3:1); $[\alpha]_D^{18}$ +24.6 (*c* 0.57, CH_2Cl_2).

HPLC: Daicel Chiralpak IA; hexane/*i*-PrOH (98.0:2.0), flow rate = 2.0 mL/min, λ = 254 nm, 40 °C; t_R = 9.1 min (minor), t_R = 11.2 min (major).

IR (KBr): 3039, 2934, 2857, 2328, 1685, 1596, 1507, 1449, 1354, 1288, 1209, 1195, 1080, 1051, 1039, 1001, 921, 841, 828, 751, 717, 689 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.30 (d, *J* = 9.5 Hz, 1 H), 8.18–8.15 (m, 2 H), 8.14 (d, *J* = 2.0 Hz, 2 H), 8.09 (d, *J* = 9.5 Hz, 1 H), 8.03 (s, 2 H), 8.02–7.97 (m, 3 H), 7.53 (dddd, *J* = 7.5, 7.5, 1.5, 1.5 Hz, 1 H), 7.45–7.42 (m, 2 H), 5.45 (dd, *J* = 11.0, 2.0 Hz, 1 H), 4.47 (ddd, *J* = 6.0, 6.0, 2.0 Hz, 1 H), 3.51 (dd, *J* = 16.0, 6.0 Hz, 1 H), 3.17 (dd, *J* = 16.0, 6.0 Hz, 1 H), 2.17–2.07 (m, 2 H), 2.04–1.95 (m, 2 H), 1.86 (m, 1 H), 1.58 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 198.5, 147.0, 137.3, 136.3, 133.0, 131.3, 130.7, 130.5, 128.5, 128.3, 127.6, 127.4, 127.3, 127.0, 125.7, 125.0, 124.91, 124.86, 124.76, 123.3, 123.1, 77.4, 75.4, 45.6, 32.8, 31.5, 24.2.

HRMS: *m*/*z* calcd for $C_{29}H_{25}O_2$ $[M + H]^+$: 405.1849; found: 405.1834.

2-[(2*R*,6*S*)-6-Butyltetrahydro-2*H*-pyran-2-yl]-1-phenylethan-1-one (7f)

[CAS Reg. No. 2087909-47-3]

The ratio of diastereomers was determined by ^{1}H NMR analysis. The diastereomers were further separated by flash silica gel column chromatography using hexane/EtOAc (10:1 v/v) as an eluent. Conversion: 53% (isolated: 17.7 mg); dr = 14:1; 82% ee; colorless oil; R_f = 0.72 (hexane/EtOAc 3:1); $[\alpha]_D^{18}$ +10.4 (*c* 0.45, CH_2Cl_2).

HPLC: Daicel Chiralpak IF; hexane/*i*-PrOH (99.0:1.0), flow rate = 1.0 mL/min, λ = 254 nm, 40 °C; t_R = 7.8 min (minor), t_R = 8.6 min (major).

IR (neat): 3375, 3064, 2933, 2860, 1684, 1598, 1581, 1449, 1373, 1347, 1285, 1210, 1195, 1088, 1074, 1049, 1002, 896, 751, 691, 667 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.97 (m, 2 H), 7.55 (m, 1 H), 7.45 (m, 2 H), 3.93 (dddd, *J* = 9.0, 6.5, 6.5, 6.5 Hz, 1 H), 3.31 (dd, *J* = 16.0, 6.5 Hz, 1 H), 3.28 (m, 1 H), 2.94 (dd, *J* = 16.0, 6.5 Hz, 1 H), 1.83 (m, 1 H), 1.74 (m, 1 H), 1.61–1.51 (m, 2 H), 1.45 (m, 1 H), 1.38–1.13 (m, 7 H), 0.83 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 198.9, 137.4, 132.9, 128.4, 128.3, 78.1, 74.6, 45.6, 36.2, 31.8, 31.4, 27.6, 23.6, 22.7, 14.0.

HRMS: *m*/*z* calcd for $C_{17}H_{25}O_2$ [M + H]$^+$: 261.1849; found: 261.1841.

1-(4-Methoxyphenyl)-2-[(2*R*,6*S*)-6-phenyltetrahydro-2*H*-pyran-2-yl]ethan-1-one (7g)

[CAS Reg. No. 2087909-48-4]

The ratio of diastereomers was determined by ^{1}H NMR analysis. The diastereomers were further separated by flash silica gel column chromatography using hexane/EtOAc (10:1 v/v) as an eluent. Conversion: 52% (isolated: 20.1 mg); dr = 19:1; 90% ee; white solid; mp 88.2–88.7 °C; R_f = 0.51 (hexane/EtOAc 3:1); $[\alpha]_D^{18}$ –13.9 (*c* 0.74, CH_2Cl_2).

HPLC: Daicel Chiralpak IA; hexane/*i*-PrOH (98.5:1.5), flow rate = 2.0 mL/min, λ = 254 nm, 40 °C; t_R = 9.1 min (minor), t_R = 11.5 min (major).

IR (KBr): 3478, 3028, 2933, 2908, 2874, 2859, 2840, 2369, 1674, 1606, 1576, 1510, 1458, 1415, 1390, 1359, 1343, 1314, 1260, 1217, 1176, 1126, 1085, 1069, 1027, 993, 970, 925, 846, 816, 754, 703 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.98 (m, 2 H), 7.31–7.28 (m, 4 H), 7.23 (m, 1 H), 6.93 (m, 2 H), 4.43 (dd, *J* = 11.5, 2.5 Hz, 1 H), 4.16 (dddd, *J* = 8.0, 7.0, 6.5, 6.0 Hz, 1 H), 3.87 (s, 3 H), 3.37 (dd, *J* = 15.5, 6.0 Hz, 1 H), 3.01 (dd, *J* = 15.5, 6.5 Hz, 1 H), 1.95 (m, 1 H), 1.89–1.82 (m, 2 H), 1.75 (m, 1 H), 1.51 (m, 1 H), 1.37 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 197.1, 163.4, 143.1, 130.6, 130.5, 128.1, 127.1, 125.8, 113.6, 79.8, 75.1, 55.4, 45.2, 33.2, 31.4, 23.8.

HRMS: *m*/*z* calcd for $C_{20}H_{23}O_3$ [M + H]$^+$: 311.1642; found: 311.1633.

2-[(2*R*,6*S*)-6-Phenyltetrahydro-2*H*-pyran-2-yl]-1-[4-(trifluoromethyl)phenyl]ethan-1-one (7h)

[CAS Reg. No. 2087909-49-5]

The ratio of diastereomers was determined by ^{1}H NMR analysis. The diastereomers were further separated by flash silica gel column chromatography using hexane/EtOAc (10:1 v/v) as an eluent. Conversion: 57% (isolated: 25.7 mg); dr = 12:1; 86% ee; colorless oil; R_f = 0.52 (hexane/EtOAc 3:1); $[\alpha]_D^{18}$ –28.8 (*c* 0.64, CH_2Cl_2).

HPLC: Daicel Chiralpak IA; hexane/*i*-PrOH (99.0:1.0), flow rate = 1.0 mL/min, λ = 254 nm, 40 °C; t_R = 9.1 min (minor), t_R = 11.3 min (major).

IR (neat): 3369, 3082, 3032, 2938, 2860, 1691, 1582, 1510, 1491, 1452, 1441, 1410, 1325, 1286, 1207, 1169, 1128, 1067, 1045, 1017, 997, 925, 855, 828, 755, 698 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.09 (dd, *J* = 9.0, 1.0 Hz, 2 H), 7.72 (m, 2 H), 7.28 (m, 2 H), 7.25–7.20 (m, 3 H), 4.41 (dd, *J* = 11.5, 2.0 Hz, 1 H), 4.16 (dddd, *J* = 8.5, 7.0, 6.5, 6.0 Hz, 1 H), 3.42 (dd, *J* = 15.5, 6.5 Hz, 1 H), 3.06 (dd, *J* = 15.5, 6.0 Hz, 1 H), 1.98 (m, 1 H), 1.89–1.82 (m, 2 H), 1.76 (m, 1 H), 1.51 (m, 1 H), 1.42 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 197.9, 142.9, 140.1, 134.2 (q, *J* = 32.1 Hz), 128.7, 128.2, 127.2, 125.6, 125.5 (q, *J* = 3.8 Hz), 123.6 (q, *J* = 272.6 Hz), 79.8, 75.0, 45.7, 33.1, 31.3, 23.8.

^{19}F NMR ($CDCl_3$): δ = 98.7.

HRMS: *m*/*z* calcd for $C_{20}H_{20}F_3O_2$ [M + H]$^+$: 349.1410; found: 349.1399.

2-[(2*R*,6*S*)-6-Methyl-6-phenyltetrahydro-2*H*-pyran-2-yl]-1-phenylethan-1-one (9)

[CAS Reg. No. 2087909-65-5]

The ratio of diastereomers was determined by ^{1}H NMR analysis. The diastereomers were further separated by flash silica gel column chromatography using benzene as an eluent. Conversion: 48% (isolated: 17.1 mg); dr = 25:1; 95% ee; colorless oil; R_f = 0.53 (benzene); $[\alpha]_D^{18}$ –53.9 (*c* 0.18, CH_2Cl_2, 90% ee).

HPLC: Daicel Chiralpak IA; hexane/*i*-PrOH (99.4:0.6), flow rate = 0.8 mL/min, λ = 254 nm, 40 °C; t_R = 11.8 min (minor), t_R = 15.8 min (major).

IR (neat): 3087, 3058, 2977, 2936, 2850, 1688, 1598, 1581, 1494, 1370, 1288, 1260, 1202, 1171, 1065, 1030, 993, 962, 898, 763, 715, 698, 665 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.02 (m, 2 H), 7.58 (m, 1 H), 7.48 (m, 2 H), 7.33 (m, 2 H), 7.25 (m, 2 H), 7.18 (m, 1 H), 4.45 (dddd, *J* = 7.0, 7.0, 5.5, 5.0 Hz, 1 H), 3.40 (dd, *J* = 15.5, 7.0 Hz, 1 H), 2.97 (dd, *J* = 15.5, 5.5 Hz, 1 H), 1.95 (m, 1 H), 1.91–1.78 (m, 3 H), 1.62 (m, 1 H), 1.47 (s, 3 H), 1.32 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 199.3, 149.9, 137.6, 132.9, 128.5, 128.4, 127.9, 126.2, 124.1, 75.2, 68.1, 45.8, 35.7, 31.6, 23.1, 20.0.

HRMS: *m*/*z* calcd for $C_{20}H_{23}O_2$ [M + H]$^+$: 295.1693; found: 295.1687.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591592. Included are the preparation of starting substrates (**1a–g**, **6**, and **8**) and the derivatization of **2b** into (*R*)-2-(tetrahydrofuran-2-yl)ethanol].

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