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Rhodium-catalyzed asymmetric 1,4-addition of arylboron reagents to α,β-unsaturated esters

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Abstract

Reaction of arylboron reagents, arylboronic acids or arylborates, which are readily accessible by lithiation of aryl bromides followed by treatment with trimethoxyborane, with α,β-unsaturated esters in the presence of rhodium/(*S*)-binap catalyst proceeded with high enantioselectivity to give high yields of optically active β-aryl esters of up to 98% ee. The enantioselectivity depends on the steric bulkiness of the ester moiety.

1. Introduction

The conjugate addition of organometallic reagents to α,β-unsaturated esters is one of the most useful processes for carbon–carbon bond formation giving β-substituted esters which are versatile synthons to further organic transformations. Although considerable efforts have been made to develop asymmetric synthesis by conjugate addition reactions,[1,2] only a few successful examples have been reported on the reaction by asymmetric catalysis.[3] In 1997, Miyaura et al. showed that organoboronic acids could be used for conjugate addition to α,β-unsaturated ketones under the catalysis by a rhodium(I)–phosphine complex in an aqueous solution.[4] Based on this finding, we have succeeded in applying the rhodium-catalyzed reaction to catalytic asymmetric synthesis by carrying out the reaction in the presence of $Rh(acac)(C_2H_4)_2$/(*S*)-binap as a catalyst in dioxane:H_2O (10:1) at 100°C.[5] We have also reported the successful application of 2-alkenyl-1,3-2-benzodioxaboroles, readily accessible by hydroboration of alkynes with catecholborane, to the catalytic asymmetric 1,4-addition.[6] Very recently, we have developed a new one-pot reaction system starting from aryl bromides, which involves lithium arylborates generated in situ by lithiation of aryl bromides followed by treatment of the resulting aryllithiums with trimethoxyborane.[7] The 1,4-addition of the arylborates to α,β-unsaturated ketones usually proceeds in

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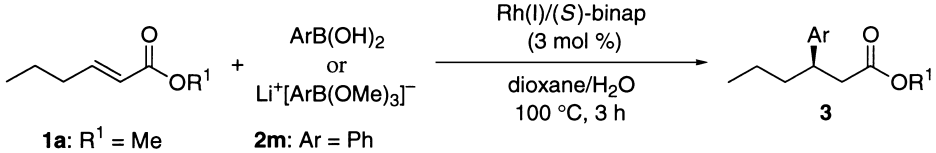
higher yields than that of arylboronic acids. Here we report the application of the rhodium-catalyzed asymmetric 1,4-addition to α,β-unsaturated esters.

2. Results and discussion

We started our studies on the catalytic asymmetric 1,4-addition to α,β-unsaturated esters with the phenylation of (*E*)-2-hexenoate esters **1a**–**1d** (Scheme 1). The reaction of methyl ester **1a** with phenylboronic acid (5 equiv. to ester) in the presence of 3 mol% of Rh(acac)$(C_2H_4)_2$/(*S*)-binap in dioxane:H_2O (10:1) at 100°C for 3 h (method A)[5] gave a 94% yield of methyl 3-phenylhexanoate (**3am**) which is 86% enantiomerically pure (entry 1 in Table 1). Under the same reaction conditions, ethyl ester **1b** gave a quantitative yield of the corresponding phenylation product **3bm**, but the yields were much lower in the reaction of isopropyl ester **1c** (42% yield) and *tert*-butyl ester **1d** (21% yield) (entries 5 and 7). The low yield is ascribed to the competing hydrolysis of the boronic acid giving benzene before completion of the rhodium-catalyzed 1,4-addition. The yields were greatly improved by use of the new one-pot method. Thus, the reaction of the *tert*-butyl ester **1d** with lithium phenylborate (2.5 equiv. to ester) generated in situ from bromobenzene, *n*-butyllithium and trimethoxyborane in the presence of 3 mol% of Rh(acac)$(C_2H_4)_2$/(*S*)-binap and 1 equiv. (to phenylborate) of water in dioxane at 100°C for 3 h (method B)[7] gave a 92% yield of *tert*-butyl 3-phenylhexanoate **3dm** (entry 8). It was found that the enantioselectivity increases as the steric bulkiness of the ester moiety increases. The enantiomeric purities of the phenylation products are 89%, 91%, 95%, and 96% ee for methyl **3am**, ethyl **3bm**, isopropyl **3cm** and *tert*-butyl **3dm** esters, respectively (entries 2, 4, 6 and 8). Interestingly, the phenylation of ester **1d** containing 3% of the (*Z*)-isomer gave **3dm** of significantly lower enantiomeric purity (93% ee, entry 9), suggesting that asymmetric phenylation of the (*Z*)-isomer gave the product which has an absolute configuration opposite to that obtained from the (*E*)-isomer. Several aryl groups, 4-ClC_6H_4 **2n**, 4-MeC_6H_4 **2o**, 4-$CF_3C_6H_4$ **2p**, 3-$MeOC_6H_4$ **2q**, and 2-naphthyl **2r**, were also introduced into α,β-unsaturated ester **1c** with high enantioselectivity, ranging between 93% and 97% ee, in high yields by method B (entries 10–14).



1a: R^1 = Me
1b: R^1 = Et
1c: R^1 = *i*-Pr
1d: R^1 = *t*-Bu

2m: Ar = Ph
2n: Ar = 4-ClC_6H_4
2o: Ar = 4-MeC_6H_4
2p: Ar = 4-$CF_3C_6H_4$
2q: Ar = 3-$MeOC_6H_4$
2r: Ar = 2-naphthyl

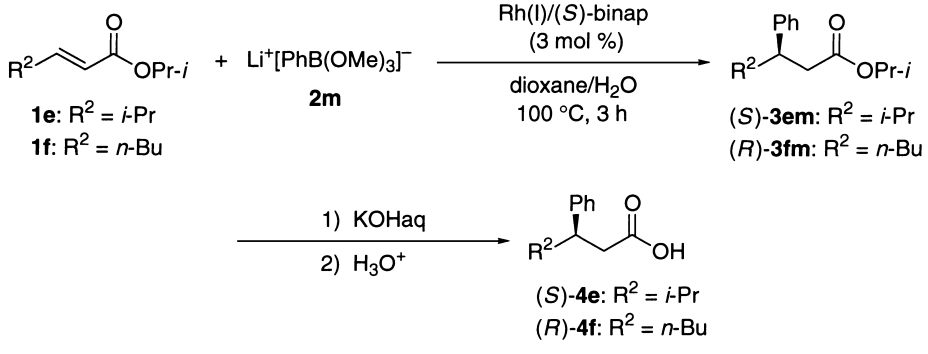
Scheme 1.

The reaction of isopropyl 4-methyl-2-pentenoate **1e** proceeded with the highest enantioselectivity (98% ee), though the chemical yield was somewhat lower (entry 15). The absolute configuration of isopropyl esters **3em** and **3fm** was determined by hydrolysis to known β-phenyl substituted carboxylic acids **4e** and **4f**, respectively (Scheme 2). A sample of (−)-**3em** ($[\alpha]_D^{20}$ −23 (*c* 1.19, chloroform)) was hydrolyzed (40% KOH/methanol) to give (*S*)-(−)-3-phenyl-4-methylpentanoic acid **4e** ($[\alpha]_D^{20}$ −38 (*c* 0.65, benzene))[8] in 90% yield. Similarly, (*R*)-(−)-3-phenylheptanoic acid **4f** ($[\alpha]_D^{20}$ −32 (*c* 0.81, benzene))[8] was obtained quantitatively from (−)-**3fm** ($[\alpha]_D^{20}$ −8.3 (*c* 0.92, chloroform)).

Table 1
Rhodium-catalyzed asymmetric arylation of α,β-unsaturated esters **1**[a]

entry	ester **1**	Ar **2**	method[b]	yield (%)[c] of **3**	% ee[d] of **3**	$[\alpha]_D^{20}$ (*c* in $CHCl_3$)
1	(*E*)-*n*-PrCH=CHCOOMe (**1a**)	Ph (**2m**)	A	94 (**3am**)	86	
2	(*E*)-*n*-PrCH=CHCOOMe (**1a**)	Ph (**2m**)	B	>99 (**3am**)	89	–20 (0.90)
3	(*E*)-*n*-PrCH=CHCOOEt (**1b**)	Ph (**2m**)	A	>99 (**3bm**)	90	
4	(*E*)-*n*-PrCH=CHCOOEt (**1b**)	Ph (**2m**)	B	>99 (**3bm**)	91	–18 (0.95)
5	(*E*)-*n*-PrCH=CHCOOPr-*i* (**1c**)	Ph (**2m**)	A	42 (**3cm**)	94	
6	(*E*)-*n*-PrCH=CHCOOPr-*i* (**1c**)	Ph (**2m**)	B	96 (**3cm**)	95	–18 (1.09)
7	(*E*)-*n*-PrCH=CHCOOBu-*t* (**1d**)	Ph (**2m**)	A	21 (**3dm**)	95	
8	(*E*)-*n*-PrCH=CHCOOBu-*t* (**1d**)	Ph (**2m**)	B	92 (**3dm**)	96	–15 (0.97)
9[e]	(*E*)-*n*-PrCH=CHCOOBu-*t* (**1d**)	Ph (**2m**)	B	86 (**3dm**)	93	
10	(*E*)-*n*-PrCH=CHCOOPr-*i* (**1c**)	4-ClC_6H_4 (**2n**)	B	95 (**3cn**)	97	–18 (0.93)
11	(*E*)-*n*-PrCH=CHCOOPr-*i* (**1c**)	4-MeC_6H_4 (**2o**)	B	88 (**3co**)	97	–19 (1.22)
12	(*E*)-*n*-PrCH=CHCOOPr-*i* (**1c**)	4-$CF_3C_6H_4$ (**2p**)	B	98 (**3cp**)	96	–14 (1.00)
13	(*E*)-*n*-PrCH=CHCOOPr-*i* (**1c**)	3-$MeOC_6H_4$ (**2q**)	B	83 (**3cq**)	94	–13 (1.14)
14	(*E*)-*n*-PrCH=CHCOOPr-*i* (**1c**)	2-naphthyl (**2r**)	B	96 (**3cr**)	93	–16 (0.94)
15	(*E*)-*i*-PrCH=CHCOOPr-*i* (**1e**)	Ph (**2m**)	B	64 (**3em**)	98 (*S*)[f]	–23 (1.19)
16	(*E*)-*n*-BuCH=CHCOOPr-*i* (**1f**)	Ph (**2m**)	B	91 (**3fm**)	95 (*R*)[f]	–8.3 (0.92)

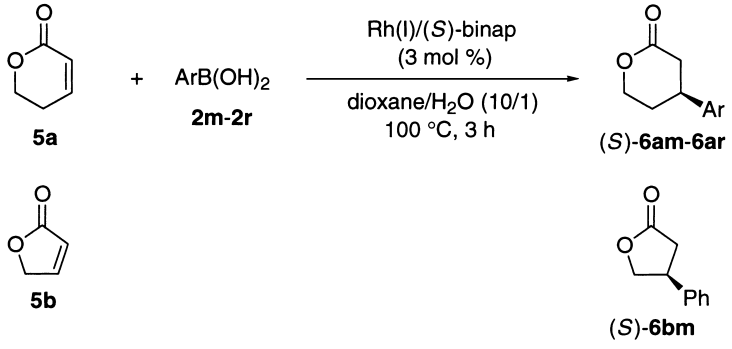
[a] The reactions were carried out in dioxane/H_2O at 100 °C for 3 h with arylboronic acids or arylborates generated *in situ*, in the presence of 3 mol % of the catalyst generated from $Rh(acac)(C_2H_4)_2$ and (*S*)-binap. [b] Method A employs arylboronic acid (5 equiv to **1**) in dioxane/H_2O (10/1); method B employs arylborate (2.5 equiv to **1**) generated from aryl bromide, n-butyllithium and trimethoxyborane in the presence of 1 equiv (to arylborate) of H_2O. [c] Isolated yield by silica gel chromatography. [d] Determined by HPLC analysis with chiral stationary phase columns: Daicel Chiralcel OD-H (**3am**, **3bm**) (eluent, hexane/2-propanol = 90/10), OD-H (**3cm**, **3cn**, **3cp**, **3cq**, **3dm**, **3em**, **3fm**) (eluent, hexane/2-propanol = 200/1), OJ (**3co**, **3cr**) (eluent, hexane/2-propanol = 100/1. [e] Used ester (**1d**) was the mixture of *E*/*Z* (97/3). [f] See text.



Scheme 2.

The asymmetric arylation was also successful for cyclic α,β-unsaturated esters (Scheme 3, Table 2). Studies on the reaction conditions in the asymmetric phenylation of 5,6-dihydro-2*H*-pyran-2-one **5a** revealed that method A is much better for this reaction than method B with respect to the chemical yield. Thus, the reaction of **5a** with phenylboronic acid (method A) proceeded smoothly to give a 94% yield of phenylated lactone (*S*)-**6am**[9] of 98% ee (entry 1), while the reaction with phenylborate (method B) gave only a 38% yield of **6am** (entry 2). This is in striking contrast to the reaction of linear esters where method B gave higher yields of the phenylation products than method A. Several aryl groups were also introduced into **5a** with high enantioselectivity in high yields by method A to give arylated lactones

6am–**6ar** of over 97% ee (entries 3–7). The enantioselectivity was also high (96% ee (*S*))[9] for 2(5*H*)-furanone **5b**, though neither method A nor method B gave a sufficiently high yield. At this moment, we cannot rationalize the difference of the reactivity between linear esters and cyclic esters.



Scheme 3.

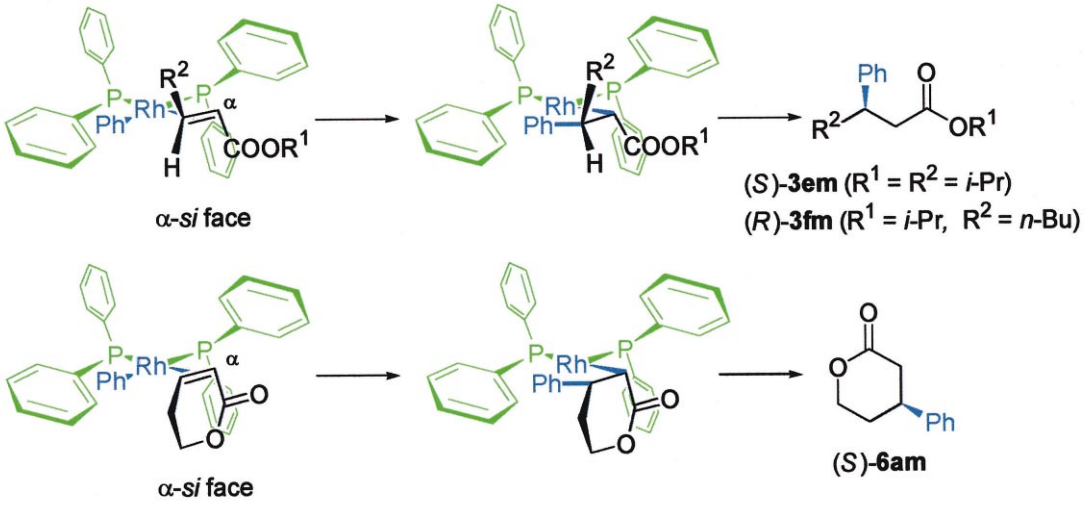
Although the catalytic cycle of the rhodium-catalyzed 1,4-addition has not been established, we believe that it involves the insertion of a carbon–carbon double bond into a rhodium–aryl bond as a key step. The absolute configurations of the 1,4-addition products obtained with the (*S*)-binap/rhodium catalyst show that α,β-unsaturated esters underwent the arylation on their α*si* face irrespective of the *E*,*Z* geometry of the double bond (Scheme 4). Thus, an aryl-rhodium species coordinated with (*S*)-binap, which has an open space at the lower part of the vacant coordination site, attacks linear esters on their α*si* face to give the (*S*)-isomer for R^2=*i*-Pr (**3em**) and the (*R*)-isomer for R^2=*n*-Bu (**3fm**) preferentially. Attack on the α*re* face is less favored because of steric repulsion between the ester moiety and one of the binap phenyl groups located on the upper part of the coordination site.[10] Similarly, the arylation takes place on the α*si* face of cyclic α,β-unsaturated esters to give (*S*)-**6am** and (*S*)-**6bm**. The (*S*)-binap/rhodium catalyst recognizes the enantioface of α,β-unsaturated esters by the steric bulkiness of the ester moiety,

Table 2
Rhodium-catalyzed asymmetric arylation of cyclic esters **5**[a]

entry	ester **5**	Ar **2**	method[b]	yield (%)[c] of **6**	% ee[d] of **6**	$[\alpha]_D^{20}$ (*c* in $CHCl_3$)
1	**5a**	Ph (**2m**)	A	94 (**6am**)	98 (*S*)[e]	+4.0 (2.70)
2	**5a**	Ph (**2m**)	B	38 (**6am**)	98 (*S*)[e]	
3	**5a**	4-ClC_6H_4 (**2n**)	A	95 (**6an**)	97	+8.4 (1.38)
4	**5a**	4-MeC_6H_4 (**2o**)	A	91 (**6ao**)	97	+6.3 (1.56)
5	**5a**	4-$CF_3C_6H_4$ (**2p**)	A	75 (**6ap**)	97	+3.5 (0.85)
6	**5a**	3-$MeOC_6H_4$ (**2q**)	A	91 (**6aq**)	98	+7.2 (1.12)
7	**5a**	2-naphthyl (**2r**)	A	93 (**6ar**)	98	+21 (0.98)
8	**5b**	Ph (**2m**)	A	33 (**6bm**)	96 (*S*)[e]	+46 (0.95)

[a] The reactions were carried out in dioxane/H_2O at 100 °C for 3 h with arylboronic acids or arylborates generated *in situ*, in the presence of 3 mol % of the catalyst generated from Rh(acac)$(C_2H_4)_2$ and (*S*)-binap. [b] Method A employs arylboronic acid (5 equiv to **1**) in dioxane/H_2O (10/1); method B employs arylborate (2.5 equiv to **1**) generated from aryl bromide, n-butyllithium and trimethoxyborane in the presence of 1 equiv (to arylborate) of H_2O. [c] Isolated yield by silica gel chromatography. [d] Determined by HPLC analysis with chiral stationary phase column: Daicel Chiralcel OG (**6am**, **6an**, **6ao**, **6ap**, **6aq**, **6ar**) (eluent, hexane/2-propanol = 80/20), OG (**6bm**) (eluent, hexane/2-propanol = 90/10). [e] See ref. 7.

not by the steric bulkiness of the β-substituents. This is consistent with the results that sterically more bulky ester groups brought about higher enantioselectivity.



Scheme 4. The binaphthylene moiety in (*S*)-binap is omitted for clarity

In summary, we have shown that the rhodium-catalyzed asymmetric 1,4-addition of arylboron reagents can be successfully applied to α,β-unsaturated esters. The enantioselectivity was high, usually over 95% ee, for both linear and cyclic esters. High chemical yields were attained by use of either arylboronic acids (method A) or arylborates (method B) depending on the structure of the esters.

3. Experimental

3.1. General

All manipulations were carried out under a nitrogen atmosphere. Nitrogen gas was dried by passage through P_2O_5. Optical rotations were measured with a JASCO DIP-370 polarimeter. NMR spectra were recorded on a JEOL JNM LA500 spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C). Chemical shifts are reported in δ ppm referenced to an internal tetramethylsilane standard for ^{1}H NMR and residual chloroform (δ 77.0) for ^{13}C. HPLC analysis was performed on a Shimadzu LC-9A and a JASCO PU-980, with a JASCO UV-970 UV detector, liquid chromatographic system with chiral stationary phase columns, Daicel Chemical Co., Ltd, Chiralcel OD-H, OJ and OG.

3.2. Materials

1,4-Dioxane and diethyl ether were distilled from sodium benzophenone ketyl under nitrogen. Rhodium complex Rh(acac)$(C_2H_4)_2$[11] and the chiral phosphine ligand (*S*)-binap[12] were prepared according to the literature. α,β-Unsaturated esters **1a**–**1f** were obtained by esterification of *trans*-2-hexenoic acid, 4-methyl-*trans*-2-pentenoic acid, and *trans*-2-heptenoic acid with corresponding alcohols, respectively. 5,6-Dihydro-2*H*-pyran-2-one **5a** and 2(5*H*)-furanone **5b** were purchased from Aldrich Chemical Company Inc., phenylboronic acid **2m** was purchased from Tokyo Kasei Kogyo Co., Ltd, hexane solution of *n*-butyllithium was purchased from Kanto Chemical Co., Inc., and used without further purification.

Several arylboronic acids (**2n**–**2r**) were synthesized from the corresponding aryl bromides in a similar manner to the reported procedures.[13] 4-Bromochlorobenzene (for **2n**) and 4-bromobenzotrifluoride (for **2p**) were purchased from Aldrich Chemical Company Inc., 4-bromotoluene (for **2o**) was purchased from Wako Pure Chemical Industries Ltd, 3-bromoanisole (for **2q**) and 2-bromonaphthalene (for **2r**) were purchased from Tokyo Kasei Kogyo Co., Ltd, and used without further purification.

3.3. Method A

A typical procedure is given for the preparation of 4-(phenyl)tetrahydro-2*H*-pyran-2-one (**6am**) (entry 1 in Table 2): 1,4-Dioxane (2.0 mL) was added to a flask charged with Rh(acac)(C_2H_4)$_2$ (3.1 mg, 12 μmol), (*S*)-binap (9.0 mg, 14 μmol), and phenylboronic acid (244 mg, 2.00 mmol; **2m**) and flushed with nitrogen, which was followed by addition of water (0.2 mL) and 5,6-dihydro-2*H*-pyran-2-one (39 mg, 0.40 mmol; **5a**). The resulting mixture was then stirred at 100°C for 3 h. After evaporation of the solvent, the residue was dissolved in ethyl acetate. The solution was washed with saturated aqueous sodium bicarbonate and dried over anhydrous Na_2SO_4. Chromatography on silica gel (hexane:AcOEt 1:1) gave 4-(phenyl)tetrahydro-2*H*-pyran-2-one (66 mg, 94% yield; **6am**) as a colorless oil.

3.4. Method B

A typical procedure is given for the preparation of isopropyl 3-phenylhexanoate (**3cm**) (entry 6 in Table 1): Under a nitrogen atmosphere, a hexane solution of butyllithium (650 μL, 1.00 mmol) was added to bromobenzene (157 mg, 1.00 mmol; **2m**) in Et_2O (0.5 mL) at 0°C. The mixture was stirred at room temperature for 1 h and cooled to −78°C. Trimethoxyborane (104 mg, 1.00 mmol) was added to the reaction mixture. The mixture was stirred at −78°C for 30 min and at room temperature for 1 h. To the mixture were added H_2O (18 mg, 1.00 mmol), isopropyl *trans*-2-hexenoate (62 mg, 0.40 mmol; **1c**) and a solution of Rh(acac)(C_2H_4)$_4$ (3.1 mg, 12 μmol) and (*S*)-binap (9.0 mg, 14 μmol) in dioxane (2.0 mL). The whole mixture was heated at 100°C for 3 h. Addition of saturated aqueous sodium bicarbonate followed by ethyl acetate extraction and silica gel chromatography (hexane:ethyl acetate 10:1) gave 90 mg (96% yield) of isopropyl 3-phenylhexanoate **3cm** as a colorless oil.

3.5. Methyl 3-phenylhexanoate ***3am***

^{1}H NMR ($CDCl_3$) δ 0.85 (t, *J*=7.4 Hz, 3H), 1.11–1.26 (m, 2H), 1.56–1.65 (m, 2H), 2.57 (dd, *J*=15.2 and 8.3 Hz, 1H), 2.62 (dd, *J*=15.2 and 7.4 Hz, 1H), 3.10 (br quint, *J*=7.5Hz, 1H), 3.57 (s, 3H), 7.16–7.20 (m, 3H), 7.28 (t, *J*=7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.96, 20.47, 38.39, 41.65, 41.93, 51.43, 126.39, 127.42, 128.40, 144.15, 172.93. Anal. calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.62; H, 8.67.

3.6. Ethyl 3-phenylhexanoate ***3bm***

^{1}H NMR ($CDCl_3$) δ 0.85 (t, *J*=7.3 Hz, 3H), 1.12 (t, *J*=7.4 Hz, 3H), 1.14–1.22 (m, 2H), 1.56–1.66 (m, 2H), 2.54 (dd, *J*=15.2 and 8.3 Hz, 1H), 2.61 (dd, *J*=15.2 and 7.4 Hz, 1H), 3.10 (br quint, *J*=7.6 Hz, 1H), 4.02 (q, *J*=7.3 Hz, 2H), 7.17–7.19 (m, 3H), 7.27 (t, *J*=7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.90, 14.06, 20.40, 38.40, 41.84, 41.97, 60.11, 126.30, 127.44, 128.29, 144.13, 172.41. Anal. calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.61; H, 9.38.

3.7. Isopropyl 3-phenylhexanoate **3cm**

^{1}H NMR ($CDCl_3$) δ 0.85 (t, *J*=7.3 Hz, 3H), 1.05 (d, *J*=6.4 Hz, 3H), 1.13 (d, *J*=6.4 Hz, 3H), 1.15–1.22 (m, 2H), 1.57–1.62 (m, 2H), 2.52 (dd, *J*=14.7 and 8.3 Hz, 1H), 2.58 (dd, *J*=14.7 and 7.4 Hz, 1H), 3.08 (br quint, *J*=7.5 Hz, 1H), 4.89 (sept, *J*=6.4 Hz, 1H), 7.17–7.19 (m, 3H), 7.27 (t, *J*=7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.92, 20.39, 21.60, 21.68, 38.49, 42.11, 42.13, 67.37, 126.28, 127.51, 128.25, 144.10, 171.96. Anal. calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.11; H, 9.70.

3.8. Isopropyl 3-(4-chlorophenyl)hexanoate **3cn**

^{1}H NMR ($CDCl_3$) δ 0.85 (t, *J*=7.4 Hz, 3H), 1.06 (d, *J*=6.4 Hz, 3H), 1.13 (d, *J*=6.4 Hz, 3H), 1.13–1.19 (m, 2H), 1.51–1.64 (m, 2H), 2.48 (dd, *J*=15.0 and 8.8 Hz, 1H), 2.57 (dd, *J*=15.0 and 6.6 Hz, 1H), 3.07 (tt, *J*=8.8 and 6.1 Hz, 1H), 4.89 (sept, *J*=6.4 Hz, 1H), 7.11 (d, *J*=8.6 Hz, 2H), 7.25 (d, *J*=8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.86, 20.33, 21.63, 21.70, 38.45, 41.53, 41.97, 67.56, 128.42, 128.89, 131.96, 142.63, 171.65. Anal. calcd for $C_{15}H_{21}ClO_2$: C, 67.03; H, 7.88; Cl, 13.19. Found: C, 67.29; H, 7.86; Cl, 13.03.

3.9. Isopropyl 3-(4-methylphenyl)hexanoate **3co**

^{1}H NMR ($CDCl_3$) δ 0.84 (t, *J*=7.4 Hz, 3H), 1.07 (d, *J*=6.4 Hz, 3H), 1.14 (d, *J*=6.4 Hz, 3H), 1.14–1.21 (m, 2H), 1.53–1.64 (m, 2H), 2.30 (s, 3H), 2.49 (dd, *J*=14.7 and 8.3 Hz, 1H), 2.56 (dd, *J*=14.7 and 7.4 Hz, 1H), 3.05 (br quint, *J*=7.5 Hz, 1H), 4.90 (sept, *J*=6.4 Hz, 1H), 7.05–7.09 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 13.96, 20.45, 21.00, 21.67, 21.76, 38.55, 41.71, 42.28, 67.38, 127.41, 128.99, 135.72, 141.13, 172.07. Anal. calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.40; H, 9.87.

3.10. Isopropyl 3-(4-trifluoromethylphenyl)hexanoate **3cp**

^{1}H NMR ($CDCl_3$) δ 0.86 (t, *J*=7.4 Hz, 3H), 1.04 (d, *J*=6.4 Hz, 3H), 1.12 (d, *J*=6.4 Hz, 3H), 1.14–1.26 (m, 2H), 1.56–1.68 (m, 2H), 2.52 (dd, *J*=15.2 and 8.8 Hz, 1H), 2.61 (dd, *J*=15.2 and 6.4 Hz, 1H), 3.16 (tt, *J*=8.8 and 6.4 Hz, 1H), 4.88 (sept, *J*=6.4 Hz, 1H), 7.29 (d, *J*=8.3 Hz, 2H), 7.54 (d, *J*=8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.89, 20.40, 21.62, 21.72, 38.41, 41.81, 42.05, 67.72, 124.33 (q, *J*=270.9 Hz), 125.32 (q, *J*=4.1 Hz), 127.97, 128.79 (q, *J*=32.0 Hz), 148.42, 171.54. Anal. calcd for $C_{16}H_{21}F_3O_2$: C, 63.56; H, 7.00; F, 18.85. Found: C, 63.82; H, 7.01; F, 18.73.

3.11. Isopropyl 3-(3-methoxyphenyl)hexanoate **3cq**

^{1}H NMR ($CDCl_3$) δ 0.85 (t, *J*=7.4 Hz, 3H), 1.08 (d, *J*=6.1 Hz, 3H), 1.15 (d, *J*=6.1 Hz, 3H), 1.15–1.24 (m, 2H), 1.56–1.61 (m, 2H), 2.51 (dd, *J*=15.0 and 8.1 Hz, 1H), 2.56 (dd, *J*=15.0 and 7.3 Hz, 1H), 3.06 (br quint, *J*=7.6 Hz, 1H), 3.79 (s, 3H), 4.91 (sept, *J*=6.1 Hz, 1H), 6.72–6.74 (m, 2H), 6.78 (d, *J*=7.6 Hz, 1H), 7.17–7.21 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.98, 20.45, 21.68, 21.76, 38.45, 42.13, 42.19, 55.14, 67.44, 111.46, 113.53, 120.00, 129.25, 145.94, 159.63, 171.97. Anal. calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.87; H, 9.38.

3.12. Isopropyl 3-(2-naphthyl)hexanoate **3cr**

^{1}H NMR ($CDCl_3$) δ 0.86 (t, *J*=7.4 Hz, 3H), 1.01 (d, *J*=6.4 Hz, 3H), 1.11 (d, *J*=6.4 Hz, 3H), 1.13–1.26 (m, 2H), 1.69 (q, *J*=7.6 Hz, 2H), 2.62 (dd, *J*=14.9 and 8.3 Hz, 1H), 2.67 (dd, *J*=14.9 and 7.1 Hz, 1H),

3.27 (br quint, J=7.5 Hz, 1H), 4.87 (sept, J=6.4 Hz, 1H), 7.34 (dd, J=8.3 and 1.7 Hz, 1H), 7.43 (dquint, J=7.8 and 2.0 Hz, 2H), 7.62 (d, J=1.5 Hz, 1H), 7.77–7.80 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 13.97, 20.50, 21.64, 21.75, 38.40, 42.16, 42.25, 67.49, 125.28, 125.79, 125.87, 126.24, 127.59, 127.61, 128.01, 132.41, 133.51, 141.63, 171.95. Anal. calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.19; H, 8.61.

3.13. tert-*Butyl 3-phenylhexanoate* ***3dm***

^{1}H NMR ($CDCl_3$) δ 0.85 (t, J=7.3 Hz, 3H), 1.14–1.24 (m, 2H), 1.30 (s, 9H), 1.53–1.64 (m, 2H), 2.46 (dd, J=15.2 and 8.8 Hz, 1H), 2.53 (dd, J=15.2 and 6.9 Hz, 1H), 3.04 (br quint, J=7.6 Hz, 1H), 7.15–7.18 (m, 3H), 7.27 (t, J=7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.98, 20.45, 27.94, 38.66, 42.30, 43.00, 80.10, 126.24, 127.64, 128.23, 144.35, 171.83. Anal. calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.41; H, 9.90.

3.14. Isopropyl 3-phenyl-4-methylpentanoate ***3em***

^{1}H NMR ($CDCl_3$) δ 0.76 (d, J=6.9 Hz, 3H), 0.95 (d, J=6.9 Hz, 3H), 0.97 (d, J=6.4 Hz, 3H), 1.05 (d, J=6.4 Hz, 3H), 1.84 (oct, J=6.9 Hz, 1H), 2.55 (dd, J=14.7 and 10.3 Hz, 1H), 2.73 (dd, J=14.7 and 5.4 Hz, 1H), 2.84–2.89 (m, 1H), 4.81 (sept, J=6.4 Hz, 1H), 7.13–7.18 (m, 3H), 7.25 (t, J=7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 20.39, 20.60, 21.56, 21.60, 33.29, 38.95, 49.17, 67.31, 126.25, 127.97, 128.37, 142.87, 172.35. Anal. calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.92; H, 9.35.

3.15. Isopropyl 3-phenylheptanoate ***3fm***

^{1}H NMR ($CDCl_3$) δ 0.83 (t, J=7.4 Hz, 3H), 1.05 (d, J=6.4 Hz, 3H), 1.07–1.30 (m, 4H), 1.13 (d, J=6.4 Hz, 3H), 1.57–1.67 (m, 2H), 2.52 (dd, J=14.7 and 8.3 Hz, 1H), 2.59 (dd, J=14.7 and 7.1 Hz, 1H), 3.06 (br quint, J=7.6 Hz, 1H), 4.89 (sept, J=6.4 Hz, 1H), 7.17–7.20 (m, 3H), 7.27 (t, J=8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.93, 21.65, 21.73, 22.60, 29.51, 36.02, 42.21, 42.42, 67.40, 126.32, 127.55, 128.30, 144.23, 172.00. Anal. calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.68; H, 9.82.

*3.16. 4-(Phenyl)tetrahydro-2*H*-pyran-2-one* ***6am***

^{1}H NMR ($CDCl_3$) δ 2.00–2.08 (m, 1H), 2.15–2.21 (m, 1H), 2.63 (dd, J=17.6 and 10.8 Hz, 1H), 2.91 (ddd, J=17.6, 5.9 and 1.5 Hz, 1H), 3.24 (m, 1H), 4.39 (dt, J=11.1 and 3.7 Hz, 1H), 4.50 (ddd, J=11.1, 4.9, 3.9 Hz, 1H), 7.21 (d, J=7.3 Hz, 2H), 7.27 (t, J=7.4 Hz, 1H), 7.36 (t, J=7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 30.31, 37.44, 37.50, 68.62, 126.47, 127.23, 129.00, 142.82, 170.66.

*3.17. 4-(4-Chlorophenyl)tetrahydro-2*H*-pyran-2-one* ***6an***

^{1}H NMR ($CDCl_3$) δ 1.97–2.05 (m, 1H), 2.14–2.20 (m, 1H), 2.59 (dd, J=17.7 and 10.8 Hz, 1H), 2.91 (ddd, J=17.7, 5.9 and 1.5 Hz, 1H), 3.23 (m, 1H), 4.39 (dt, J=11.3 and 3.4 Hz, 1H), 4.50 (ddd, J=11.3, 4.9, 3.9 Hz, 1H), 7.15 (d, J=8.3 Hz, 2H), 7.33 (d, J=8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 30.19, 36.90, 37.39, 68.49, 127.85, 129.12, 132.99, 141.26, 170.28.

3.18. 4-(4-Methylphenyl)tetrahydro-2H-pyran-2-one **6ao**

^{1}H NMR ($CDCl_3$) δ 1.97–2.05 (m, 1H), 2.13–2.18 (m, 1H), 2.34 (s, 3H), 2.62 (dd, *J*=17.6 and 10.8 Hz, 1H), 2.90 (ddd, *J*=17.6, 5.9 and 1.5 Hz, 1H), 3.20 (m, 1H), 4.38 (dt, *J*=11.3 and 4.0 Hz, 1H), 4.49 (ddd, *J*=11.3, 4.9, 3.9 Hz, 1H), 7.10 (d, *J*=8.3 Hz, 2H), 7.16 (d, *J*=8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 20.99, 30.45, 37.07, 37.60, 68.66, 126.33, 129.63, 136.84, 139.96, 170.65. Anal. calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 76.05; H, 7.70.

3.19. 4-(4-Trifluoromethylphenyl)tetrahydro-2H-pyran-2-one **6ap**

^{1}H NMR ($CDCl_3$) δ 2.03–2.11 (m, 1H), 2.18–2.24 (m, 1H), 2.63 (dd, *J*=17.6 and 10.5 Hz, 1H), 2.94 (ddd, *J*=17.6, 6.2 and 1.7 Hz, 1H), 3.33 (m, 1H), 4.42 (dt, *J*=11.5 and 3.7 Hz, 1H), 4.53 (ddd, *J*=11.5, 4.9 and 3.7 Hz, 1H), 7.35 (d, *J*=8.1 Hz, 2H), 7.63 (d, *J*=8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 30.06, 37.18, 37.38, 68.45, 124.00 (q, *J*=270.9 Hz), 126.02 (q, *J*=4.1 Hz), 126.95, 129.67 (q, *J*=32.0 Hz), 146.73, 170.05. Anal. calcd for $C_{12}H_{11}F_3O_2$: C, 59.02; H, 4.54; F, 23.34. Found: C, 59.31; H, 4.81; F, 22.69.

3.20. 4-(3-Methoxyphenyl)tetrahydro-2H-pyran-2-one **6aq**

^{1}H NMR ($CDCl_3$) δ 1.98–2.06 (m, 1H), 2.14–2.19 (m, 1H), 2.62 (dd, *J*=17.6 and 10.8 Hz, 1H), 2.90 (ddd, *J*=17.6, 5.9 and 2.0 Hz, 1H), 3.20 (m, 1H), 3.81 (s, 3H), 4.38 (dt, *J*=11.3 and 4.0 Hz, 1H), 4.49 (ddd, *J*=11.3, 4.9 and 3.9 Hz, 1H), 6.75 (s, 1H), 6.79–6.82 (m, 2H), 7.27 (t, *J*=7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 30.23, 37.44, 37.46, 55.25, 68.61, 112.13, 112.70, 118.69, 130.03, 144.48, 160.05, 170.63. Anal. calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.04; H, 6.87.

3.21. 4-(2-Naphthyl)tetrahydro-2H-pyran-2-one **6ar**

^{1}H NMR ($CDCl_3$) δ 2.08–2.16 (m, 1H), 2.23–2.26 (m, 1H), 2.74 (dd, *J*=17.6 and 10.8 Hz, 1H), 2.99 (ddd, *J*=17.6, 5.9 and 1.1 Hz, 1H), 3.39 (m, 1H), 4.41 (dt, *J*=10.2 and 3.5 Hz, 1H), 4.50–4.54 (m, 1H), 7.33 (d, *J*=8.8 Hz, 1H), 7.47–7.51 (m, 2H), 7.63 (s, 1H), 7.80–7.85 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 30.18, 37.30, 37.43, 68.53, 124.76, 124.79, 125.95, 126.44, 127.61, 127.66, 128.80, 132.47, 133.40, 140.04, 170.59. Anal. calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.35; H, 6.38.

3.22. 4-(Phenyl)tetrahydro-2-furanone **6bm**

^{1}H NMR ($CDCl_3$) δ 2.68 (dd, *J*=17.6 and 9.1 Hz, 1H), 2.93 (dd, *J*=17.6 and 8.8 Hz, 1H), 3.79 (br quint, *J*=8.4 Hz, 1H), 4.27 (t, *J*=8.6 Hz, 1H), 4.67 (t, *J*=8.6 Hz, 1H), 7.23 (d, *J*=7.4 Hz, 2H), 7.30 (t, *J*=7.3 Hz, 1H), 7.37 (t, *J*=7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 35.65, 41.05, 73.99, 126.65, 127.67, 129.10, 139.38, 176.35.

3.23. Hydrolysis of **3em** and **3fm**

Methanol (1.5 mL) was added to a flask charged with a sample of **3em** (41 mg, 0.18 mmol) and flushed with nitrogen, which is followed by addition of 40% aq. KOH (0.3 mL). The resulting mixture was then stirred at 85°C for 16 h. To the reaction mixture was added 10% aq. HCl (15 mL). After evaporation of the solvent, the residue was dissolved in ethyl acetate. The solution was washed with saturated aqueous

sodium chloride and dried over anhydrous $MgSO_4$. By evaporation of the solvent, (*S*)-(−)-3-phenyl-4-methylpentanoic acid **4e** was obtained in 90% yield. (*R*)-(−)-3-Phenylheptanoic acid **4f** was obtained quantitatively from **3fm** in a similar manner. The specific rotation data for the esters and acids are shown in the text.

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