Ytterbium(III) Trifluoromethanesulfonate Catalyzed Electrophilic Aromatic Substitution with Glyoxalate and Lipase-Mediated Product Resolution: A Convenient Route to Optically Active Aromatic α-Hydroxy Esters

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Electrophilic aromatic substitution with carbonyl compounds is the most efficient method for the carbon−carbon bond formation leading to a variety of arylated compounds that can be used as important synthetic intermediates. Acid-catalyzed reactions of aromatic heterocycles with *p*-(dimethylamino)benzaldehyde have been known as the Ehrlich test for electron-rich aromatic heterocyclic compounds such as pyrroles and indoles.[1] In recent years, Friedel−Crafts type hydroxyalkylation of phenol systems with α-keto esters have been studied by Citterio[2] and Bigi.[3−6] The stereoselective hydroxyalkylation using chiral glyoxalates[5] or chiral Lewis acids[6] have also been reported, although levels of chiral induction varied. However, these electrophilic reactions usually require stoichiometric use of $TiCl_4$, or $SnCl_4$ and a chiral reagent under strictly anhydrous condition at low temperatures. On the other hand, there has been no precedent in the literature that aromatic heterocycles can undergo the same reaction to yield α-hydroxy esters.

In our ongoing "green" chemistry research program, namely, the use of environmentally friendly reagents and processes for organic reactions, we have studied the activities of lanthanide(III) triflates in catalyzing a variety of organic transformations.[7−13] Lanthanide(III) triflates, a unique class of water stable and reusable Lewis acids, have been used in recent years by our group and other researchers to catalyze reactions both in organic and aqueous media.[14] $Ln(OTf)_3$ catalyzed Friedel−Crafts acylation of substituted benzenes was also reported by Kobayashi.[15] We have previously demonstrated that lanthanide triflates are especially effective in activating aldehydes and imines with great functionality and solvent tolerance. As a continuing effort, we report here the electrophilic substitution reactions of electron-rich aromatic systems including phenols, phenol ethers, and heterocyles, with ethyl glyoxalate in the presence of catalytic amount of $Yb(OTf)_3$. In addition, lipase-mediated stereoselective transesterification of the resulting products was carried out to obtain aromatic α-hydroxy acid derivatives in optically active forms.

In our initial studies, we found that, in the presence of 5% molar equivalent of a lanthanide triflate, aromatic substitution proceeded smoothly by simply mixing 1,4-dimethoxybenzene and ethyl glyoxalate in regular grade CH_2Cl_2 at room temperature. The reaction yielded 2,5-dimethoxymandelic acid ethyl ester with essentially no byproducts. We investigated the effectiveness of five lanthanide triflates (hydrated and/or anhydrous), $La(OTf)_3$, $Nd(OTf)_3$, $Dy(OTf)_3$, $Sc(OTf)_3$, and $Yb(OTf)_3$, in catalyzing the reaction shown in Scheme 1 (Table 1, Lewis acid loading all 5% equiv). We also examined several other commonly used Lewis acids as potential catalysts. The results indicated that there was no significant difference among the four lanthanide triflates in terms of product yield, while $Yb(OTf)_3$ seemed to offer a slight yield increase. In sharp contrast, in the absence of the lanthanide triflates the reaction did not take place, and no desired products were observed with $AlCl_3$, $MgCl_2$, and $ZnCl_2$. It is also worth mentioning that lanthanide triflates are reusable, and $Yb(OTf)_3$ recovered after the reaction exhibited the same level of catalytic activity.

The electrophilic reaction occurred at the most reactive position of the aromatic ring, and no disubstituted products were found for all the reactions shown in Table 2, catalyzed by $Yb(OTf)_3$ at room temperature. The reaction time and yield are primarily dependent on the susceptibility of the aromatic systems to electrophilic substitution. For phenols and phenol ethers examined, the reactions reached maximum conversion within 3−10 h. It appeared that the reaction could only proceed with activated aromatic systems such as phenols, while no reaction was observed under these conditions with alkylbenzenes. In addition, a strong electron-withdrawing group on the phenol ring (e.g., 4-nitrophenol, Table 2) significantly deactivated the system and prevented the reaction from happening.

Similar reaction conditions were applied to aromatic heterocyclic compounds including furan and thiophene

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Scheme 1

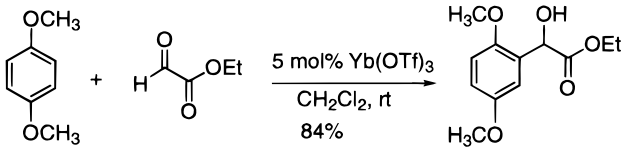


Table 1. Effectiveness of Lanthanide Triflates and Other Lewis Acids in Catalyzing the Reaction Shown in Scheme 1

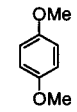
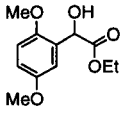
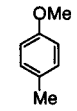
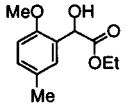
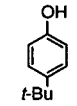
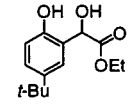
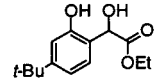
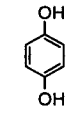
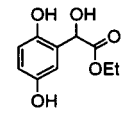
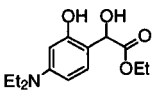
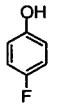
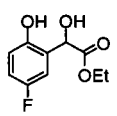
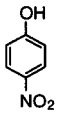
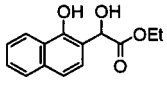
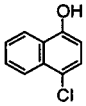
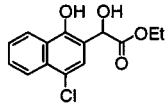
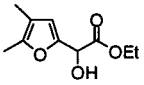
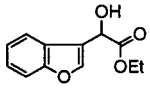
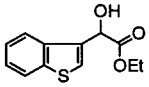
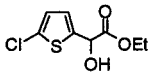
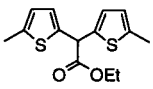
Lewis acid	yield, %
$Yb(OTF)_3$ anhydrous	84
$Yb(OTF)_3$ hydrate	80
$Nd(OTF)_3$ anhydrous	78
$Sc(OTF)_3$ anhydrous	80
$Dy(OTF)_3$ hydrate	78
$La(OTF)_3$ anhydrous	67
$AlCl_3$	0
$MgCl_2$	0
$ZnCl_2$	0
no Lewis acid	0

derivatives with satisfactory results. Although aromatic electrophilic substitution has been the major route to functionalized derivatives of heterocycles, such a type of direct hydroxyalkylation has not been reported. The general protocol of this reaction could be applied to derivatization of a variety of aromatic heterocyclic compounds under very mild conditions.

Interestingly, reaction of 2-chlorothiophene yielded predominantly α-hydroxy ester **13**, whereas 2-methylthiophene afforded bisthiophenyl derivative **14** as the major product. This suggests that the electronic density of the aromatic ring (affected by the electronic properties of the substituents) has a significant effect on the reaction outcome. The similar phenomenon was also observed with indole and some indole derivatives (not listed in Table 2). A possible mechanism to account for the different product formation of the thiophene derivatives is illustrated in Scheme 2. The aldehyde is first activated by the lanthanide, and an electrophilic substitution takes place via intermediate **15** to afford the α-hydroxy ester. If R is an electron-donating group, the resulting α-hydroxy ester will be further activated by the lanthanide and a cation intermediate is formed (stabilized by the methyl-substituted thiophene), which reacts with another thiophene molecule to yield the bisthiophenyl derivative **14**. It is worth noting that trace amounts of H_2O promote the reaction in both cases, which rationalizes the moisture-tolerant nature of the reaction.

Enzyme-assisted resolutions have gradually gained recognition as a clean, simple, and effective way to obtain optically active compounds.[16] We initially examined the possibility of using proteases and lipases to stereoselectively hydrolyze the α-hydroxy esters with limited success. Alternatively, we turned our attention to enzyme-mediated transesterification and screened a thermophilic lipase library (Diversa Inc) as well as other commercially available lipases isolated from different natural sources. The results indicated that lipases PS-C (*Pseudomonas cepacia*, Amano) and EC 3.1.1.3 (*Candida rugosa*, Sigma) catalyzed the transesterification of the aromatic α-hydroxy esters with high activities and good to excellent levels of stereoselectivity (Table 3). The enzymatic reactions also exhibited excellent regioselectivity. For substrates **3**, **4**, and **5**, acylation occurred only at the α-OH with the phenolic OH left intact.

Table 2. $Yb(OTf)_3$ Catalyzed Electrophilic Substitution

reactant		product	reaction time (hour)	yield %
	1		5	84
	2		24	80
	3		3	88
	4		3	90
	5		10	80
	6		2	68
	7		6	81
		no reaction		
	8		2	82
	9		5	86
	10		24	83
	11		24	76
	12		12	78
	13		12	81
	14		3	73

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Scheme 2

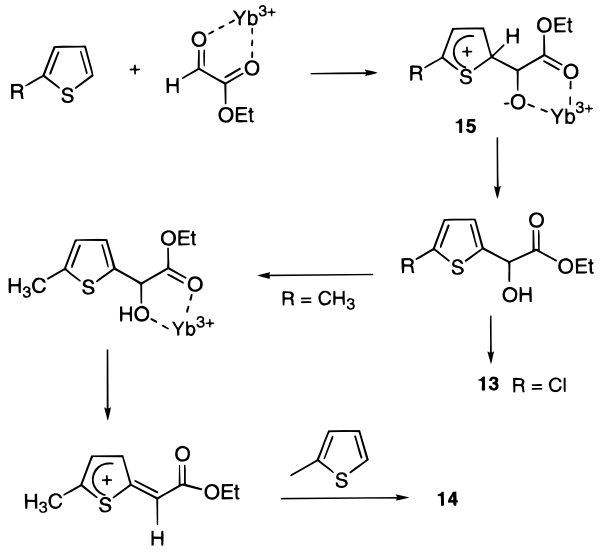
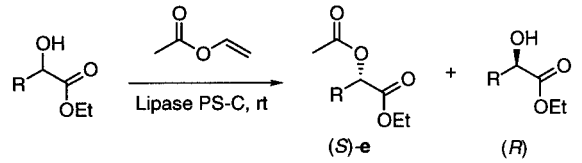


Table 3. Lipase-Mediated Stereoselective Transesterification



substrate	lipase[a]	time h	conversion %	product ester	ee[b] %	yield %
2	L1	72	48	(*S*)-**2e**	97	46
3	L2	300	45	(*R*)-**3e**	99	41
4	L1	72	47	(*S*)-**4e**	95	45
5	L2	36	51	(*R*)-**5e**	90	48
10	L1	72	46	(S)-**10e**	97	40

[a] L1 = PS-C (*pseudomonas cepacia*, Amano); L2 = EC 3.1.1.3 (*candida rugosa*, Sigma). [b] Determined by ^{1}H NMR using Eu(hfc)$_3$.

The absolute configurations of ester (*S*)-**4e** and alcohol (*R*)-**4** was determined by complete hydrolysis to (+)- and (−)-2-hydroxy-2-(2-hydroxy-4-*tert*-butylphenyl)ethanoic acids, which are known enantiomerically pure compounds.[5] The absolute configurations of the other compounds were assigned via polarimetric measurements and further confirmed by ^{1}H NMR experiments using chiral shifting reagents.

In conclusion, an efficient route to enantiomerically pure hydroxylated aromatic compounds has been developed using Yb(OTf)$_3$-catalyzed aromatic substitution reactions followed by lipase-mediated stereoselective transesterification. This process provides a clean, effective, and low-cost method for the preparation of a variety of aromatic α-hydroxy acid derivatives which are an important class of building blocks in organic synthesis.

Experimental Section

General Methods. All reagents and solvents were purchased from commercial sources and used directly without purification or treatment unless specified otherwise. ^{1}H and ^{13}C NMR spectra were recorded on a 300, or 400, or 500 MHz NMR spectrometer. Thin-layer chromatography was conducted on Baker Si$_{250F}$ silica gel TLC plates with a fluorescent indicator. Flash column chromatography was carried out on Silica Gel 60 (230−400 mesh) from E. Merck Co.

General Procedure for Aromatic Substitution Reaction with Ethyl Glyoxalate. To 2 mmol of an aromatic compound and 0.1 mmol of Yb(OTf)$_3$ in 3 mL of CH_2Cl_2 at room temperature was added 2.2 mmol of a freshly distilled ethyl glyoxalate toluene solution (Fluka). The reaction was stirred or shaken gently and monitored using TLC. If the starting aromatic compound is not consumed in 10 h, more ethyl glyoxalate may be added to obtain a higher yield. The solvent was evaporated, and the crude product was subjected to chromatographic purification with hexanes/EtOAc (3:1 to 2:1).

α-Hydroxy ester 1 (84%): pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 (m, 1 H), 6.83 (m, 2 H), 5.23 (s, 1 H), 4.25−4.17 (m, 2 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 2.16 (s, 1 H), 1.21 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz) δ 173.8, 153.9, 151.5, 128.2, 115.4, 114.6, 112.6, 70.4, 62.0, 56.4, 56.0, 14.3; HRMS calcd for $C_{12}H_{16}O_5$ 240.0998, found 240.0998.

α-Hydroxy ester 2 (80%): clear oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09−7.07 (m, 2 H), 6.79 (d, J = 8 Hz, 1 H), 5.22 (s, 1 H), 4.25−4.16 (m, 2 H), 3.79 (s, 3 H), 3.61 (s, 1 H), 2.27 (s, 3 H), 1.20 (t, J = 7.0 Hz, 1 H); ^{13}C NMR (125 MHz) δ 174.0, 155.3, 130.4, 130.3, 127.1, 111.3, 70.4, 61.9, 55.8, 20.6. 14.3; HRMS calcd for $C_{12}H_{16}O_4$ 224.1049, found 224.1046.

α-Hydroxy ester 3 (88%): clear viscous oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23−7.19 (m, 2 H), 6.79 (d, J = 8.5 Hz, 1 H), 4.27−4.19 (m, 2 H), 1.28 (s, 9 H), 1.23 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz) δ 173.6, 152.8, 143.4, 127.1, 126.0, 122.2, 116.9, 72.9, 62.6, 34.3, 31.7, 14.2; HRMS calcd for $C_{14}H_{20}O_4$ 252.1362, found 252.1361.

α-Hydroxy ester 4 (90%): clear viscous oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (s, 1 H), 7.11−7.09 (m, 1 H), 6.93−6.90 (m, 2 H), 5.28 (d, J = 4.0 Hz, 1 H), 4.32−4.17 (m, 2 H), 3.76 (d, J = 4.0 Hz, 1 H), 1.28 (s, 9 H), 1.25 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz) δ 173.5, 154.8, 154.0, 128.5, 119.7, 117.8, 114.8, 72.5, 62.8, 34.8, 31.4, 14.3; HRMS calcd for $C_{14}H_{20}O_4$ 252.1362, found 252.1363.

α-Hydroxy ester 5 (80%): white solid; mp 108−110 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 6.73 (d, J = 3.0 Hz, 1 H), 6.66−6.57 (m, 2 H), 5.36 (s, 1 H), 4.22−4.16 (m, 2 H), 1.20 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz) δ 173.7, 150.0, 148.0, 126.1, 116.1, 115.9, 114.6, 68.7, 61.0, 13.2; HRMS calcd for $C_{10}H_{12}O_5$ 212.0685, found 212.0684.

α-Hydroxy ester 6 (68%): brown viscous oil; ^{1}H NMR (400 MHz, CD_3OD) δ 6.96 (d, J = 10.0 Hz, 1 H), 6.21−6.18 (m, 2 H), 5.18 (s, 1 H), 4.31−4.12 (m, 2 H), 3.29 (q, J = 7.6 Hz, 4 H), 1.24 (t, J = 6.4 Hz, 3 H), 1.12 (t, J = 7.2 Hz, 6 H); ^{13}C NMR (75 MHz) δ 174.0, 156.5, 149.7, 129.9, 111.0, 104.3, 100.3, 72.6, 62.4, 44.6, 14.3, 14.2, 12.8.

α-Hydroxy ester 7 (81%): clear viscous oil; ^{1}H NMR (300 MHz, CD_3OD) δ 7.14 (s, 1 H), 6.96−6.90 (m, 2 H), 6.83−6.80 (m, 1 H), 5.27 (s, 1 H), 4.32−4.20 (m, 2 H), 3.83 (s, 1 H), 1.25 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz) δ 172.9, 158.1, 155.7, 151.1, 123.93, 123.86, 118.7, 118.6, 116.7, 116.5, 115.6, 115.3, 115.1, 71.9, 63.2, 14.2; HRMS calcd for $C_{10}H_{11}FO_4$ 214.0641, found 214.0644.

α-Hydroxy ester 8 (82%): pale yellow viscous oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.4 (s, 1 H), 8.29 (m, 1 H), 7.78 (m, 1 H). 7.50 (m, 2 H), 7.38 (d, J = 8.5 Hz, 1 H), 7.25 (d, J = 8.5 Hz, 1 H), 5.47 (s, 1 H), 4.29−4.22 (m, 2 H), 4.19−4.13 (m, 1 H), 1.20 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz) δ 173, 151.8, 134.7, 127.6, 127.1, 126.0, 125.8, 122.5, 120.0, 114.8, 73.7, 63.0, 14.2; HRMS calcd for C_{14}H14O4 246.0892, found 246.0890.

α-Hydroxy ester 9 (86%); purple viscous oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (s, 1 H), 8.28 (d, J = 7.5 Hz, 1 H), 8.18 (d, J = 7.5 Hz, 1 H), 7.60 (t, J = 7.0 Hz, 1 H), 7.53 (t, J = 7.0 Hz, 1 H), 7.36 (s, 1 H), 5.43 (s, 1 H), 4.31 (s, 1 H), 4.30−4.24 (m, 1 H), 4.22−4.16 (m, 1 H), 1.22 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz) δ 172.9, 150.9, 131.5, 128.1, 126.8, 126.4, 125.6, 124.3, 122.9, 114.9, 73.1, 63.3, 14.2; $C_{14}H_{20}ClO_4$ 280.0502, found 280.0500.

α-Hydroxy ester 10 (83%): clear oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.13 (s, 1 H), 5.06 (d, J = 7.0 Hz, 1 H), 4.33−4.22 (m, 2 H), 3.29 (d, J = 7.0 Hz, 1 H), 2.17 (s, 3 H), 1.90 (s, 3 H), 1.27 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz) δ 172.0, 148.5, 148.0,

115.1, 112. 2, 67.2, 62.6, 14.3, 11.6, 10.0; HRMS calcd for $C_{10}H_{14}O_4$ 198.0892, found 198.0896.

α-Hydroxy ester 11 (76%): clear oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J = 8.0 Hz, 1 H), 7.48 (d, J = 8.0 Hz, 1 H), 7.32−7.22 (m, 2 H), 6.78 (s, 1 H), 5.32 (d, J = 6.5 Hz, 1 H), 4.36−4.24 (m, 2 H), 3.59 (d, J = 6.5 Hz, 1 H), 1.27 (t, J = 7.0 Hz, 3 H). ^{13}C NMR (125 MHz) δ 171.4, 155.3, 153.5, 143.3, 125.0, 123.2, 121.6, 111.7, 105.7, 67.6, 63.1, 14.3; HRMS calcd for $C_{12}H_{12}O_4$ 220.0736, found 220.0736.

α-Hydroxy ester 12 (78%): pale yellow viscous oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J = 8.0 Hz, 1 H), 7.86 (d, J = 8.0, 1 Hz, 1 H), 7,48 (s, 1 H), 7.41−7.35 (m, 2 H), 5.53 (s, 1 H), 4.31−4.25 (m, 1 H), 4.21−4.16 (m, 1 H), 3.59 (s, 1 H), 1.20 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz) δ 173.3, 140.9, 137.2, 133.4, 125.5, 124.9, 124.4, 123.1, 122.7, 69.0, 62.7, 14.3; HRMS calcd for $C_{12}H_{12}O_3S$ 236.0507, found 236.0509.

α-Hydroxy ester 13 (81%): pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (d, J = 3.7 Hz, 1 H), 6.80 (d, J = 3.7 Hz, 1 H), 5.27 (d, J = 5.3 Hz, 1 H), 4.33−4.24 (m, 2 H), 3.57 (d, J = 5.3 Hz, 1 H), 1.30 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz) δ 172.2, 140.2, 130.5, 126.2, 124.8, 69.3, 63.1, 14.3; HRMS calcd for $C_8H_9ClO_3S$ 219.9961, found 219.9966.

Bisthiophenyl ester 14 (73%): pale yellow viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (d, J = 6.5 Hz, 2 H), 6.60 (d, J = 6.5 Hz, 2 H), 5.28 (s, 1 H), 4.24 (q, J = 7.5 Hz, 2 H), 2.44 (s, 3 H), 1.30 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz) δ 171.1, 140.2, 138.7, 126.2, 124.9, 70.0, 48.3, 15.5, 14.3; HRMS calcd for $C_{14}H_{16}O_2S_2$ 280.0592, found 280.0591.

General Procedure for Lipase-Catalyzed Transesterification. To 100 mg of an α-hydroxy ester in 2 mL of vinyl acetate was added the lipase (100 mg of PS−C, *Pseudomonas cepacia*, Amano; or 300 mg of EC 3.1.1.3, *Candida rugosa*, Sigma). The reaction mixture was stirred at room temperature, and the conversion was monitored by TLC and HPLC (EtOAc/hexanes = 1:3). The reaction was stopped at about 50% conversion by filtering off the solid material. The filtrate was then concentrated in vacuo and subjected to chromatographic separation with haxanes/EtOAc (3:1 to 2:1). The enantiomeric excesses of the ester products and unreacted alcohols were determined by ^{1}H NMR using Eu(hfc)$_3$.

Ester (*S*)-2e (46%): clear viscous oil; $[\alpha]^{25}_D$ 89.5° (c = 0.81, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15−7.13 (m, 2 H), 6.82 (d, J = 8.0 Hz, 1 H), 6.37 (s, 1 H), 4.24−4.15 (m, 2 H), 3.81 (s, 3 H), 2.28 (s, 3 H), 2,16 (s, 3 H), 1.22 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz) δ 170.7, 169.6, 155.5, 131.3, 130.3, 130.1, 122.6, 111.5, 69.2, 61.7, 56.1, 21.1, 20.6, 14.3.

Ester (*R*)-3e (41%): clear viscous oil; $[\alpha]^{25}_D$ −87.6° (c = 0.90, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (dd, J = 8.5, 2.5 Hz, 1 H), 7.24 (d, J = 2.5 Hz, 1 H), 6.88 (d, J = 8.5 Hz, 1 H), 6.81 (s, 1 H), 6.04 (s, 1 H), 2.20 (s, 3 H), 1.28 (s, 9 H), 1.26 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz) δ 170.9, 170.4, 153.0, 143.8, 128.4, 126.7, 118.7, 117.6, 73.2, 62.6, 34.4, 31.7, 20.9, 14.2; HRMS calcd for $C_{16}H_{22}O_5$ 294.1467, found 294.1469.

Ester (*S*)-4e (45%): clear viscous oil; $[\alpha]^{25}_D$ 98.6° (c = 0.63, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, J = 8 Hz, 1 H), 6.99−6.88 (m, 2 H), 6.89 (s, 1 H), 5.98 (s, 1 H), 4.33−4.14 (m, 2 H), 2.19 (s, 3 H), 1.29 (s, 9 H), 1.27 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz) δ 170.8, 170.5, 129.6, 118.3, 116.3, 115.4, 73.0, 62.7, 34.9, 31.4, 20.9, 14.2; HRMS calcd for $C_{16}H_{22}O_5$ 294.1467, found 294.1466.

Ester (*R*)-5e (49%): clear viscous oil; $[\alpha]^{25}_D$ −123.1° (c = 0.78, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82−6.81 (m, 2 H), 6.78−6.75 (m, 1 H), 6.45 (s, 1 H), 6.07 (s, 1 H), 5.35 (s, 1 H), 4.30−4.17 (m, 2 H), 2.17 (s, 3 H), 1.25 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz) δ 170.9, 170.2, 150.0, 148.6, 120.7, 119.1, 118.2, 115.6, 71.6, 62.8, 20.9, 14.1; HRMS calcd for $C_{12}H_{14}O_6$ 254.0790, found 254.0786.

Ester (*S*)-10e (40%): pale yellow viscous oil; $[\alpha]^{25}_D$ 18.2° (c = 0.44, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.25 (s, 1 H), 5.94 (s, 1 H), 4.28−4.21 (m, 2 H), 2.20 (s, 3 H), 2.17 (s, 3 H), 1.92 (s, 3 H), 1.27 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz) δ 170.5, 167.2, 149.6, 143.7, 115.5, 114.7, 68.2, 62.3, 20.9, 14.3, 11.7, 10.0.

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Supporting Information Available: NMR spectra for compounds **1**−**14**, **2e**−**5e**, and **10e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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