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Enantioselective Friedel–Crafts reactions of ethenetricarboxylates and substituted pyrroles and furans and intramolecular reaction of benzene derivatives

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ABSTRACT

Compared to enantioselective Friedel–Crafts reactions of indoles, reactions of alkylidene malonates with monocyclic aromatic compounds generally proceed with low enantioselectivity. The Friedel–Crafts reactions of ethenetricarboxylates **1** and monocyclic heteroaromatic compounds, such as substituted pyrroles and furans were investigated. The reaction of **1** with 2,4-dimethylpyrrole in the presence of a chiral bisoxazoline–copper(II) complex (10 mol %) in tetrahydrofuran at room temperature gave alkylated products in up to 72% ee. The reaction of **1** with 2-substituted furans gave alkylated products in 46–62% ee. The absolute stereochemistry of the furan Friedel–Crafts product **7e** was determined by transformation to the known 2,3-dimethylbutyric acid. The intramolecular reaction of benzene derivatives gave cyclized products up to 56% ee.

1. Introduction

The development of new catalytic asymmetric bond-forming reactions is important. We have recently studied various Lewis acid-promoted reactions of ethenetricarboxylate derivatives **1** and reported that they function as highly electrophilic Michael acceptors.[1] For example, catalytic enantioselective Friedel–Crafts reactions of ethenetricarboxylates with indoles in the presence of catalytic amounts of the chiral bisoxazoline–copper(II) complex have been shown to proceed with high enantioselectivity.[2]

Compared to enantioselective Friedel–Crafts reactions with indoles, the reported reactions of alkylidene malonates with monocyclic aromatic compounds generally proceed with low enantioselectivity.[3,2] Longer distances between the ligand (bisoxazoline) chirality in the alkylidene malonate–Cu complex and the reacting center are also suggested.[3c] The high enantioselectivity in the Friedel–Crafts reactions of alkylidene malonates **1** was limited to indoles, probably because of the steric interaction with the benzannelated structure.

Some enantioselective conjugate addition/Friedel–Crafts reactions of monocyclic aromatic compounds are already known, such as the reported enantioselective Friedel–Crafts reactions with pyrroles.[4–6] These reactions involve electrophilic olefins such as α′-hydroxy enones[4] and α,β-unsaturated 2-acyl imidazoles,[5] or α,β-unsaturated aldehydes catalyzed by organocatalysts.[6] In order to find enantioselective reactions of ethenetricarboxylates and related compounds, an approach to increase the steric interaction between the substituents of monocyclic aromatic rings and chiral-ligand-coordinated electrophilic olefins was envisioned. Therefore, Friedel–Crafts reactions of ethenetricarboxylates **1** and substituted pyrroles, furans, and intramolecular reaction with substituted benzene derivatives were investigated.

The reaction of **1** with substituted pyrroles and furans in the presence of a catalytic amount of chiral bisoxazoline–Cu(II) complex gave alkylated products with better enantioselectivities than those previously reported for alkylidene malonates with pyrroles and furans.[3,2] The results of the new enantioselective cyclization reaction of the benzene derivatives are also presented.

2. Results and discussion

2.1. Friedel–Crafts reactions with pyrroles

Pyrroles are an important class of electron-rich heteroaromatic compounds that are incorporated into biologically active compounds and are also of synthetic interest.[7] The Friedel–Crafts reaction of benzylidenemalonate with pyrroles using bisoxazoline/$Cu(OTf)_2$ yielded products with 28–36% ee.[3a,e] The reaction of ethenetricarboxylate with *N*-methylpyrrole gave a product with

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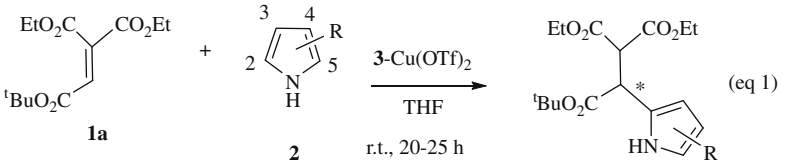
18% ee.[2] Evans et al. reported the enantioselective Friedel–Crafts reaction of α,β-unsaturated 2-acyl imidazoles with pyrroles.[5] In these examples, N-substituents and 2,5-dimethyl substituents of pyrrole decrease the ee when compared to the parent and 2-ethyl pyrroles. Herein, substitution effects were investigated to attempt to improve the selectivity for ethenetricarboxylates **1** and to determine the substituent dependency on ee.

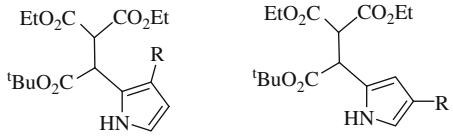
Bisoxazoline–Cu(II) complexes have been shown to be effective catalysts for reactions between alkylidene malonates or ethenetricarboxylates **1** and indoles.[3,2] Thus, the reaction conditions for pyrroles involving the readily available bisoxazoline **3**–Cu(II) complexes were examined (Table 1, Eq. 1). The reaction of **1a** with a parent pyrrole and *N*-ethyl, phenyl, and benzyl pyrroles **2a**–**d** in the presence of a catalytic amount of chiral bisoxazoline [(*S*,*S*)-2,2′-isopropylidenebis-(4-*t*-butyl-2-oxazoline) **3a**] copper(II) complex, **3a**-Cu(OTf)$_2$ (10 mol %) in THF at room temperature gave products **4a**–**d** with 10–29% ee (entries 1–3,7). Several chiral ligands for the catalysts were also examined (Scheme 1). However, both ee and yields were not significantly improved with these ligands. In general, ligand **3a** gave the best ee, as shown in Table 1. The reaction of **1a** with 2-substituted pyrrole, 2-ethylpyrrole **2e** gave 5-alkylated product **4e** in 45% ee and 84% yield (entry 8). The reaction of **1a** with 3-methylpyrrole **2g** gave 2-alkylated product **4g**-**2** in 69% ee and 56% yield as a main regioisomer (entry 12). The reaction of **1a** with 2,4-dimethylpyrrole **2j** gave alkylated products in 72% ee and 72% yield (entry 20).[8] Contrary to the reported tendency of

Table 1
Reaction of **1** and substituted pyrroles **2**



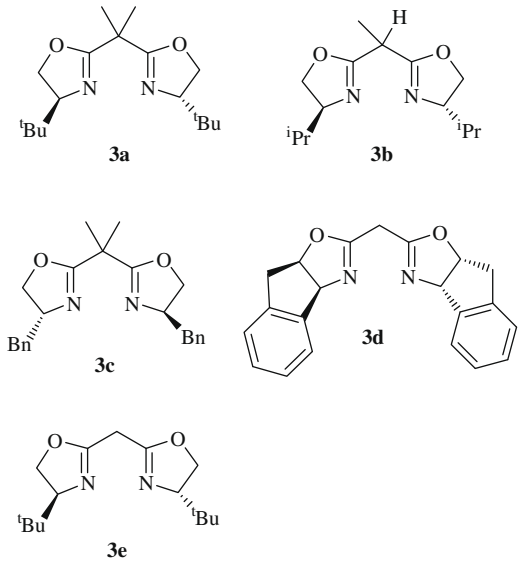
Entry	Pyrrole	R	Ligand	Product	Yield (%)	ee[a] (%)	$[\alpha]_D$[b]
1	**2a**	None	**3a**	**4a**	76[c]	29	−20
2	**2b**	*N*-Et	**3a**	**4b**	87[c]	10	−15
3	**2c**	*N*-Ph	**3a**	**4c**	87	10	+10
4	**2c**	*N*-Ph	**3b**	**4c**	67[c]	26	−35
5	**2c**	*N*-Ph	**3c**	**4c**	38[c]	38	+70
6	**2c**	*N*-Ph	**3d**	**4c**	68	11	−17
7	**2d**	*N*-CH_2Ph	**3a**	**4d**	78	12	nd
8	**2e**	2-Et	**3a**	**4e**	84	45	−40
9	**2e**	2-Et	**3b**	**4e**	79	2	nd
10	**2e**	2-Et	**3d**	**4e**	70	27	−23
11	**2f**	2-CH_2Ph	**3a**	**4f**	84	41	−37
12	**2g**	3-Me	**3a**	**4g**-2[d]	56[d]	69[d]	−73[d]
				4g-5[d]	10[d]	40[d]	
13	**2g**	3-Me	**3b**	**4g**-2[d]	41[d]	25[d]	−48[d]
				4g-5[d]	14[d]	2[d]	
14	**2g**	3-Me	**3d**	**4g**-2[d]	32[d]	38[d]	nd
				4g-5[d]	14[d]	10[d]	
15	**2h**	3-Ph	**3a**	**4h**-2	79	66	−99
16	**2h**	3-Ph	**3b**	**4h**-2[d]	29[d]	59[d]	nd
				4h-5[d]	29[d]	9	
17	**2h**	3-Ph	**3c**	**4h**-2[d]	31[d]	39[d]	nd
				4h-5[d,e]	31[d,e]	12	11
18	**2i**	3-C_6H_4-4′–Cl	**3a**	**4i**-2	64	50	−77
				4i-5	9	28	−13
19	**2i**	3-C_6H_4-4′–Cl	**3c**	**4i**-2	11	28	+61
				4i-5	86	9	+5
20	**2j**	2,4-DiMe	**3a**	**4j**[f,g]	72	72	−75
21	**2j**	2,4-DiMe	**3b**	**4j**	83	12	−28
22	**2j**	2,4-DiMe	**3d**	**4j**	80	35	−38
23	**2j**	2,4-DiMe	**3e**	**4j**	81	5	−5

[a] Determined by chiral HPLC.
[b] In $CHCl_3$ solution.
[c] 3-Alkylated regioisomers (**4a**-3; 5% for entry 1, **4b**-3; 9% for entry 2, **4c**-3; 9% for entry 4 and **4c**-3; 13% for entry 5) were also formed.
[d] Obtained as a mixture.
[e] 14% of **4h**-5 was isolated.
[f] When the reaction was carried out at −20 and −78 °C, **4j** was obtained with 52% ee/80% yield and 28% ee/80% yield, respectively.
[g] The reaction of **1a** and **2j** in CH_2Cl_2 at rt gave **4j** in 19% ee and 51% yield.



4g-2 (R = Me)
4h-2 (R = Ph)
4i-2 (R = C_6H_4-4'-Cl)

4g-5 (R = Me)
4h-5 (R = Ph)
4i-5 (R = C_6H_4-4'-Cl)



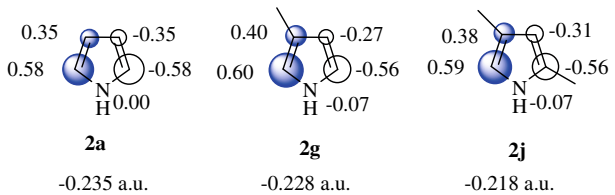
Scheme 1.

the enantioselectivity in the Friedel–Crafts reaction of α,β-unsaturated 2-acyl imidazoles,[5] 2,4-dimethylpyrrole **2j** gave better ee than the parent pyrrole **2a**.

When the reaction was carried out at lower temperatures (−20 and −78 °C), the enantioselectivity of **4j** was lowered (footnote f of entry 20). The solvent effect was also examined. The reaction of **1a** with **2j** in CH_2Cl_2 gave **4j** in lower ee (19% ee) than that in THF (footnote g of entry 20). The use of ^{i}PrOH and EtOH resulted in contamination with possible solvent alcohol adducts of **1a**. The reaction of α-dibenzyl ester analogue ($^{t}BuO_2C$–HC=C(CO_2CH_2Ph)$_2$) **1az** with **2j** in the presence of **3a**-Cu(OTf)$_2$ gave the corresponding alkylated product **4jz** with lower ee (38% ee, 73% yield) than that for the α-diethyl ester **1a**.

The ligands also had an effect on the regioselectivity for 3-substituted pyrroles **2g**, **2h**, and **2i**. Thus, the use of **3a** gave higher regioselectivity for 2- versus 5-alkylations (entries 12–18). Interestingly, the use of **3c** gave the opposite regioselectivity in the reaction of **2i** (entry 19).

The commonly observed 2-alkylation selectivity of unsubstituted and 3-substituted pyrroles can be rationalized by the HOMO of pyrroles as shown in Scheme 2.[9] The regioselectivity of 2-alkylation versus 5-alkylation of 3-methylpyrrole **2g** is shown by the comparison between the HOMO coefficients of 2-C (0.60) and 5-C (−0.56). Successive methyl alkylations also increase the reactivities of pyrroles, which are suggested by the higher HOMO energy levels.



Scheme 2. HOMOs and energy levels of pyrroles, **2a**, **2g**, and **2j** calculated using STO-3G//B3LYP/6-31G*.

The reaction of 2,4-dimethylpyrrole **2j** with various β-substituents of α-diethyl esters was also examined (Table 2). Ethyl and 4-bromobenzyl esters and *N*-piperidinyl amide and phenyl ketone groups using ligand **3a** gave alkylated product **5** in 73–100% yield and 41–71% ee (entries 1, 4, 5 and 7). Contrary to the results given in footnote f of entry 20 in Table 1, the enantioselectivities increased slightly at lower temperatures for the reaction of **1d** with **2j** in the presence of **3a** (entry 5). The reaction of diethyl benzylidenemalonate **1** (Y = Ph) and **2j** in the presence of ligand **3a** gave 2-alkylated product **5** (Y = Ph) with 47% ee (37% yield); however, the product was unstable and partially decomposed by column chromatography or standing in $CDCl_3$.

Several conditions were then tested to crystallize the enantioenriched products, in order to increase the ee and determine the absolute configuration. However, most of the products crystallized in a racemic form and the remaining filtrate had an increased ee.[10]

2.2. Friedel–Crafts reactions with furans

The chemistry of furans has also been a field of active research for a long time.[11] Friedel–Crafts alkylation reactions of furans at C=O or C=N groups to afford optically active furans have been developed.[12] Asymmetric conjugate addition-type reactions of reactive furan derivatives have also been reported,[5b,13] but the furan substituents have not been examined in detail. An example of the Friedel–Crafts reaction of a benzylidenemalonate with 2-methylfuran in the presence of chiral bisoxazoline–copper(II) complex gave an alkylated product in low ee (12%).[3a] Herein, the reaction of **1** with substituted furans **6** was investigated, in order to examine the effects of the substituents.

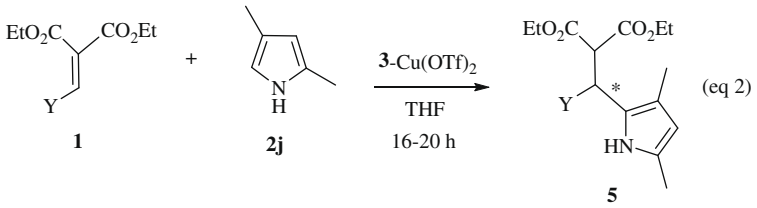
The parent furan **6a** gave the Friedel–Crafts product **7a** in satisfactory yield (Table 3, entry 1) when Cu(OTf)$_2$ was used as the catalyst. However, the reaction with the chiral catalyst **3a**-Cu(OTf)$_2$ gave a complex mixture. The reaction of **6a** with **3b** and **3d**-Cu(OTf)$_2$ gave only **7a** in 29% and 18% yields with low ee of 5% and 9%, respectively. The readily available 2-alkyl-substituted furans **6b–e** were then examined. They were found to give Friedel–Crafts products **7b–e** in good yields and modest ee (46–62% ee) using ligand **3d**. Use of ligand **3e** in the reaction of **6e** gave **7e** in racemic form in 82% yield. The reaction of **6e** with **3d**-Cu(OTf)$_2$ in CH_2Cl_2 instead of THF gave a lower ee (43%, footnote f of entry 12). The reaction of **6e** with **3d**-Cu(ClO_4)$_2$·6H_2O instead of **3d**-Cu(OTf)$_2$ in THF also gave **7e** in lower ee% (42% ee, footnote g of entry 12). Unlike pyrroles, ligand **3d** gave better ee% than **3a** for furans, and the reaction of 3- and 2,3-substituted furans **6f-g** gave low ee (entries 13–18).

With respect to the regioselectivity, 2-alkylation of furans is preferred, similar to that of pyrroles. The selectivity can be rationalized by the HOMO of the furans, as shown in Scheme 3,[9] as well as that for pyrroles. 3-Alkylation of furans has not been detected, while the formation of 3-alkylated products of pyrroles was observed sometimes in small amounts (for example, Table 1, entries 1–2 and 4–5). This is probably because the total reactivity of furans as nucleophiles may be lower than that of pyrroles, as suggested by comparison of the HOMO energy levels.

Compared to its nitrogen analogue indole, benzofuran is less reactive toward Friedel–Crafts reaction; the reaction of **1** with benzofuran did not yield alkylated products under the conditions examined in this study.

The absolute stereochemistry of the furan Friedel–Crafts product **7e** was determined by transformation to a literature compound (Scheme 4). The ethyl and *t*-butyl ester groups of **7e** (62% ee) were reduced to triol **8** by $LiAlH_4$. Transformation of **8** to the trimesylate was performed with methanesulfonyl chloride in dichloromethane in the presence of triethylamine. Treatment of the crude trimesylate with lithium triethylborohydride in THF gave 2-butyl-5-(1,2-dimethylpropyl)furan **9** in 79% yield from **8**. Compound **9** was oxidized to 2,3-dimethylbutyric acid **10** and valeric acid **11** by $RuCl_3$–$NaIO_4$.[14] HPLC analysis of the anilide of **10** (compound **12**) was compared with the reported data and **10** was determined to have an (*R*)-configuration.[15,16]

Table 2
Reaction of **1** and **2j**

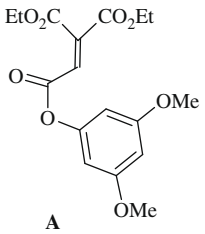


Entry	Substrate	Y	Ligand	Product	Yield[a] (%)	ee[a,b] (%)	$[\alpha]_D$[c]
1	**1b**	CO_2Et	**3a**	**5b**	77	63	−96
2	**1b**	CO_2Et	**3b**	**5b**	70	5	nd
3	**1b**	CO_2Et	**3c**	**5b**	74	10	+10
4	**1c**	$CO_2CH_2C_6H_4$-4-Br	**3a**	**5c**	73	48	−38
5	**1d**	$CON(CH_2)_5$–	**3a**	**5d**	100[d]	71[d]	−118
6	**1d**	$CON(CH_2)_5$–	**3b**	**5d**	93	65	−100
7	**1e**	COPh	**3a**	**5e**	97	41	−83

[a] Reactions were carried out at rt unless otherwise stated.
[b] Determined by chiral HPLC.
[c] In $CHCl_3$.
[d] The reaction was carried out at −78 °C. (rt, 94% yield/64% ee; −20 °C, 93% yield/65% ee).

2.3. Intramolecular Friedel–Crafts reactions of benzene derivatives

Monocyclic aromatic systems, such as simple benzene derivatives that are electron-deficient relative to pyrroles and furans, were found to be poor substrates for these alkylation reactions. More efficient intramolecular Friedel–Crafts cyclization was examined. However, five-membered ring formations such as the reaction of **A**, for which we have previously reported racemic product formation,[1c,17] was found to lead to almost no asymmetric induction under similar reaction conditions.



A

Thus, reactions of ethenetricarboxylate analogous benzene derivatives **13** to form six-membered rings were examined in the presence of a catalytic amount of chiral bisoxazoline **3** (Table 4, Eq. 4). The reaction of **13a–b** using **3a** at room temperature gave benzoannelated products, tetraline **14a** and chromane **14b** in low ee. The reaction of **13a** using **3c** increased the ee to 48% ee. The reaction of dibenzoxy derivative **13c** and **3c** gave **14c** in 63% yield with the best ee% (56%).

Evans et al. have proposed a mechanism for the bisoxazoline–Cu(II)-catalyzed asymmetric Mukaiyama–Michael reaction of arylidene malonates.[18] However, the proposed facial selectivity is opposite to the Friedel–Crafts/Michael reaction of arylidene malonate and ethenetricarboxylates **1** with indoles (Scheme 5).[3,2,19] The observed facial selectivity for the furan derivative **7e** was the same as the Friedel–Crafts/Michael reaction for arylidene malonate and ethenetricarboxylates **1** with indoles. The present modest facial selectivity of the furan system with a bisoxazoline–Cu(II)-coordinated complex of **1** together with the previous results[2] could be described as follows; the favored si-face of **1** may arise from secondary orbital interactions of the aromatic π systems. However, the detailed steric interaction is still not clear and the difference between suitable ligands for pyrroles and furans is difficult to explain. The enantioselectivity in the intramolecular reaction may not be straightforward due to steric restrictions. The diastereomeric interaction of the two faces for monocyclic systems with substituents will be further investigated.

3. Conclusion

In conclusion, we have shown the reaction of **1** with substituted pyrroles **2** in the presence of catalytic amounts of the chiral bisoxazoline **3**–Cu(II) complex to give alkylated products **4** in moderate to good (up to 72%) ee. The reaction of **1** with 2-substituted furans gave alkylated products in 46–62% ee. The absolute stereochemistry of the alkylated furan **7e** was determined by transformation into a known compound. The intramolecular reaction of benzene derivatives gave the cyclized product in up to 56% ee. The present results reveal improvements in the enantioselective Friedel–Crafts alkylation of pyrroles and furans by the use of diversely substituted compounds. The highly functionalized products are expected to be useful for further elaboration to important compounds and the development of other catalytic asymmetric reactions of ethenetricarboxylates is currently under investigation.

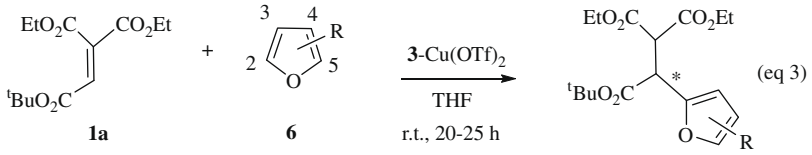
4. Experimental

4.1. General methods

Melting points are uncorrected. IR spectra were recorded in the FT-mode. ^1H NMR spectra were recorded at 400 MHz. ^{13}C NMR spectra were recorded at 100.6 MHz. Chemical shifts are reported in ppm relative to Me_4Si or residual nondeuterated solvent. ^{13}C multiplicities were determined by DEPT and HSQC. Mass spectra were recorded at an ionizing voltage of 70 eV by EI or FAB. HPLC analysis was performed with a JASCO LC system using a UV detector (detection, 254 and 238 nm light) and flow rate of 1.0 mL/min using a CHIRALPAK AS-H, CHIRALPAK AD-H, CHIRALCEL OD-H or CHIRALCEL OD (0.46 cm × 250 mm) column at 30 °C. Optical rotations were measured with a 1 cm i.d. × 10 cm cell. All reactions were carried out under a nitrogen atmosphere.

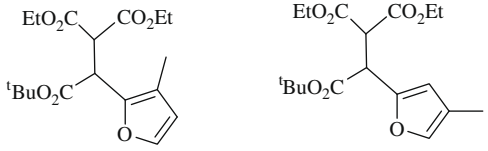
Pyrroles **2h**,**i**[20], and **2f**[21] were prepared according to the literature. Ligand **3b** was prepared according to the literature.[3b]

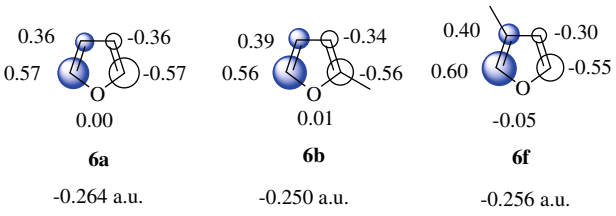
Table 3
Reaction of **1a** and substituted furans **6**



Entry	Furan	R	Ligand	Product	Yield (%)	ee (%)[a]	$[\alpha]_D$[b]
1	**6a**	None	None	**7a**	79		
2	**6a**	None	**3b**	**7a**	29	5	−5
3	**6a**	None	**3d**	**7a**	18	9	−8
4	**6b**	2-Me	**3a**	**7b**	17	16	nd
5	**6b**	2-Me	**3b**	**7b**	58	13	−15
6	**6b**	2-Me	**3d**	**7b**	80	46	−52
7	**6c**	2-Et	**3d**	**7c**	86	60	−63
8	**6d**	2-*n*-Pr	**3a**	**7d**	40	17	−13
9	**6d**	2-*n*-Pr	**3d**	**7d**	76	57	−62
10	**6e**	2-*n*-Bu	**3a**	**7e**	80	16	−17
11	**6e**	2-*n*-Bu	**3b**	**7e**	81	16	−15
12[f,g]	**6e**	2-*n*-Bu	**3d**	**7e**	84–93[d]	58–62[d]	−59[e]
13	**6f**	3-Me	**3a**	**7f**-2[c]	74[c]	38[c]	−28[c]
				7f-5[c]	8[c]	nd[c]	
14	**6f**	3-Me	**3b**	**7f**-2[c]	69[c]	33[c]	−1[c]
				7f-5[c]	23[c]	nd[c]	
15	**6f**	3-Me	**3d**	**7f**-2[c]	73[c]	31[c]	−17[c]
				7f-5[c]	12[c]	nd[c]	
16	**6g**	2,3-DiMe	**3a**	**7g**	83	27	−29
17	**6g**	2,3-DiMe	**3b**	**7g**	85	6	−7
18	**6g**	2,3-DiMe	**3d**	**7g**	91	25	−28

[a] Determined by chiral HPLC.
[b] In $CHCl_3$.
[c] Obtained as a mixture.
[d] Experiments for entry 12 were repeated several times and all the results showed good reproducibility of the yields and ee%.
[e] Measured for the product with 58% ee.
[f] The reaction of **6e** with **3d**-$Cu(OTf)_2$ in CH_2Cl_2 gave **7e** in 43% ee and 73% yield.
[g] The reaction of **6e** with **3d**-$Cu(ClO_4)_2{\cdot}6H_2O$ in THF gave **7e** in 42% ee and 96% yield.



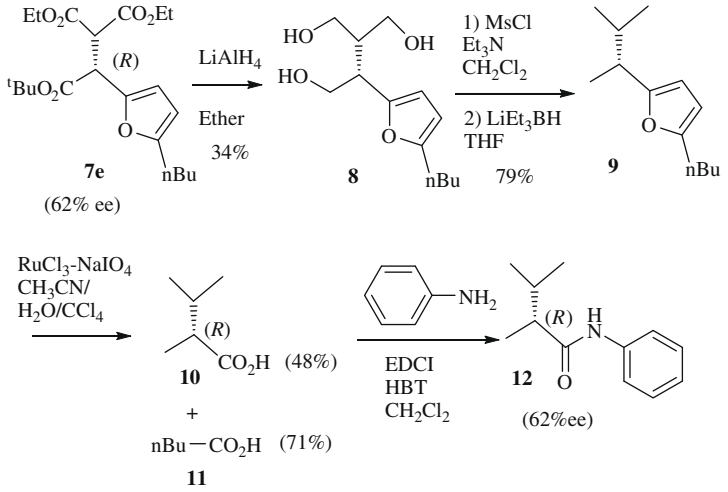


Scheme 3. HOMOs and energy levels of furans **6a**, **6b**, and **6f** calculated using STO-3G//B3LYP/6-31G*.

4.2. Typical procedure (Table 1, entry 20)

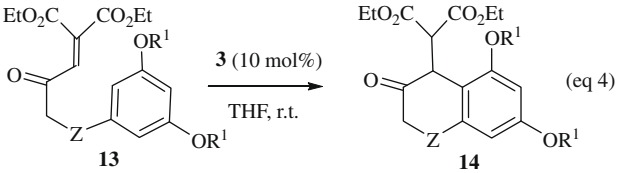
A powdered mixture of $Cu(OTf)_2$ (18 mg, 0.05 mmol) and **3a** (16 mg, 0.054 mmol) was dried under vacuum for 1 h. Next, THF (1 mL) was added under N_2 and the solution stirred for 1 h. Compound **1a** (0.136 g, 0.5 mmol) in THF (0.5 mL) was added and stirred for 15 min, followed by addition of **2j** (52.3 mg, 0.55 mmol). After 22 h the reaction mixture was filtered through a plug of silica gel, washed with Et_2O, dried ($MgSO_4$), and the solvent removed. The residue was purified by column chromatography over silica gel eluting with CH_2Cl_2 to give **4j** (135 mg, 72%). **4j** (R_f = 0.3 (CH_2Cl_2)): brown solid; HPLC (CHIRALPAK AS-H, hexane–^{i}PrOH = 9:1) major peak t_{R1} 3.8 min, minor peak t_{R2} 6.7 min, 72% ee; $[\alpha]_D^{30} = -75$ (*c* 1.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.21 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.42 (s, 9H), 1.97 (s, 3H), 2.16 (s, 3H), 3.98–4.24 (m, 4H), 4.04 (d, *J* = 10.4 Hz, 1H), 4.25 (d, *J* = 10.4 Hz, 1H), 5.58 (br s, 1H), 7.96 (br s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 10.82 (q), 13.09 (q), 13.89 (q), 14.05 (q), 27.95 (q), 43.15 (d), 54.83 (d), 61.57 (t), 61.79 (t), 81.84 (s), 108.09 (d), 117.59 (s), 118.33 (s), 127.33 (s), 167.90 (s), 167.98 (s), 170.94 (s); IR (KBr) 3372, 2976, 1741, 1733, 1701, 1464, 1370, 1303, 1258, 1147 cm^{-1}; MS (FAB) *m*/*z* 368 $(M+H)^+$; HRMS $(M+H)^+$ 368.2054 (calcd for $C_{19}H_{30}NO_6$ 368.2073); Anal. Calcd for $C_{19}H_{29}NO_6$: C, 62.11; H, 7.96; N, 3.81. Found: C, 62.28; H, 8.16; N, 3.76.

Compound **4a** (Table 1, entry 1) (R_f = 0.2 (CH_2Cl_2)): yellow oil; HPLC (CHIRALPAK AS-H, hexane–^{i}PrOH = 19:1) major peak t_{R1} 6.8 min, minor peak t_{R2} 15.2 min, 29% ee; $[\alpha]_D^{32} = -20$ (*c* 0.96, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.14 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.42 (s, 9H), 4.06–4.11 (m, 2H), 4.08 (d, *J* = 10.5 Hz, 1H), 4.15–4.22 (m, 2H), 4.30 (d, *J* = 10.5 Hz, 1H), 6.01–6.03 (m, 1H), 6.06–6.09 (m, 1H), 6.68–6.70 (m, 1H), 8.62 (br s,



Scheme 4.

Table 4
Reaction of benzene derivatives **13**



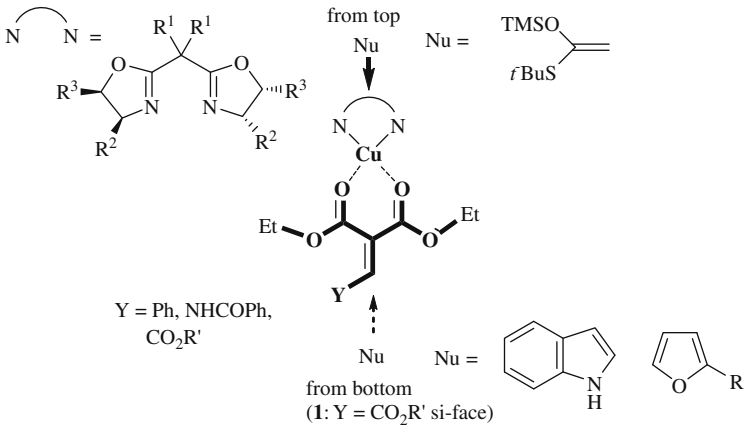
Z = CH_2, O; R^1 = CH_3, CH_2Ph

Entry	Substrate	Z	R^1	Ligand	Product	Yield (%)	ee (%)
1	**13a**	CH_2	Me	**3a**	**14a**	87	14
2	**13b**	O	Me	**3a**	**14b**	65	20
3	**13a**	CH_2	Me	**3c**	**14a**	78	48
4	**13c**	CH_2	CH_2Ph	**3c**	**14c**	63	56

1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.92 (q), 14.02 (q), 27.83 (q), 45.20 (d), 55.05 (d), 61.71 (t), 61.87 (t), 82.02 (s), 107.67 (d), 108.32 (d), 118.18 (d), 124.65 (s), 167.75 (s), 167.98 (s), 170.25 (s); IR (neat) 3390, 2981, 1734, 1564, 1466, 1394, 1370, 1304, 1151, 1096, 1031 cm^{-1}; MS (FAB) *m/z* 340 $(M+H)^+$; HRMS $(M+H)^+$ 340.1752 (calcd for $C_{17}H_{26}NO_6$ 340.1760); Anal. Calcd for $C_{17}H_{25}NO_6$: C, 60.16; H, 7.42; N, 4.13. Found: C, 59.93; H, 7.68; N, 4.04.

Compound **4a-3** (Table 1, entry 1) (R_f = 0.1 (CH_2Cl_2)): yellow oil; ee and $[\alpha]_D$ were not determined.; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.09 (t, *J* = 7.1 Hz, 3H), 1.27 (*J* = 7.1 Hz, 3H), 1.41 (s, 9H), 4.00–4.06 (m, 2H), 4.03 (d, *J* = 11.6 Hz, 1H), 4.17 (d, *J* = 11.6 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 6.12–6.14 (m, 1H), 6.66–6.69 (m, 2H), 8.13 (br s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.92 (q), 14.12 (q), 27.91 (q), 44.69 (d), 56.05 (d), 61.30 (t), 61.68 (t), 81.00 (s), 108.02 (d), 116.42 (d), 117.75 (s), 118.02 (d), 167.91 (s), 168.25 (s), 171.69 (s); IR (neat) 3403, 2981, 1732, 1466, 1393, 1369, 1302, 1151, 1034 cm^{-1}; MS (EI) *m/z* 339 (M^+, 11), 265 (56), 238 (74), 120 (100%); HRMS M^+ 339.1682 (calcd for $C_{17}H_{25}NO_6$ 339.1682).

Compound **4b** (Table 1, entry 2) (R_f = 0.6 (hexane–ether = 1:1)): colorless oil; HPLC (CHIRALPAK AS-H, hexane–EtOH = 49:1) minor peak t_{R1} 4.2 min, major peak t_{R2} 4.6 min, 10% ee; $[\alpha]_D^{23} = -15$ (c 1.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.40 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.37 (s, 9H), 1.41 (t, *J* = 7.3 Hz, 3H), 3.97–4.06 (m, 4H), 4.18 (d, *J* = 11.9 Hz, 1H), 4.20–4.26 (m, 2H), 4.30 (d, *J* = 11.9 Hz, 1H), 6.01–6.04 (m, 2H), 6.57 (dd, *J* = 2.7, 1.8 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.83 (q), 14.05 (q), 16.74 (q), 27.78 (q), 41.31 (t), 42.83 (d), 54.79 (d), 61.47 (t), 61.84 (t), 81.54 (s), 107.14 (d), 107.40 (d), 120.45 (d), 125.42 (s), 167.38 (s), 168.02 (s), 169.81 (s); IR (neat) 2980, 1751, 1732, 1369, 1299, 1153 cm^{-1}; MS (EI) *m/z* 367 (M^+, 57), 266 (100%); HRMS M^+ 367.1995 (calcd for $C_{19}H_{29}NO_6$ 367.1995).



Scheme 5.

Compound **4b-3** (Table 1, entry 2) (R_f = 0.4 (hexane–ether = 1:1)): yellow oil; ee% and $[\alpha]_D$ were not determined.; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.09 (t, J = 7.1 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.35 (t, J = 7.3 Hz, 3H), 1.41 (s, 9H), 3.83 (q, J = 7.3 Hz, 2H), 4.00 (d, J = 11.7 Hz, 1H), 3.99–4.07 (m, 2H), 4.11 (d, J = 11.7 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 6.00 (dd, J = 2.7, 1.8 Hz, 1H), 6.51 (t-like, J = 2.6 Hz, 1H), 6.54 (t-like, J = 2.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.94 (q), 14.13 (q), 16.56 (q), 27.92 (q), 44.24 (t), 44.88 (d), 56.15 (d), 61.24 (t), 61.63 (t), 80.88 (s), 107.55 (d), 118.59 (d), 120.03 (d), 167.97 (s), 168.29 (s), 171.75 (s); IR (neat) 2980, 1752, 1733, 1368, 1302, 1149 cm^{-1}; MS (EI) m/z 367 (M^+, 56), 293 (86), 266 (100%); HRMS M^+ 367.1993 (calcd for $C_{19}H_{29}NO_6$ 367.1995).

Compound **4c** (Table 1, entry 3) (R_f = 0.3 (CH_2Cl_2)): pale yellow oil; HPLC (CHIRALPAK AD-H, hexane–^{i}PrOH = 19:1) minor peak t_{R1} 4.8 min, major peak t_{R2} 5.3 min, 10% ee; $[\alpha]_D^{21} = +10$ (c 1.80, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.05 (t, J = 7.1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H), 1.34 (s, 9H), 3.90–3.98 (m, 1H), 4.00–4.08 (m, 1H), 4.10–4.22 (m, 2H), 4.19 (d, J = 11.7 Hz, 1H), 4.31 (d, J = 11.7 Hz, 1H), 6.19–6.21 (m, 1H), 6.23 (dd, J = 3.7, 1.8 Hz, 1H), 6.72 (dd, J = 2.7, 1.8 Hz, 1H), 7.36–7.41 (m, 1H), 7.42–7.49 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.92 (q), 14.05 (q), 27.82 (q), 42.54 (d), 55.00 (d), 61.50 (t), 61.80 (t), 81.55 (s), 108.45 (d), 108.69 (d), 123.02 (d), 126.87 (d), 126.95 (s), 127.52 (d), 129.15 (d), 139.66 (s), 167.29 (s), 167.89 (s), 169.90 (s); IR (neat) 2980, 1758, 1732, 1600, 1501, 1466, 1369, 1301, 1152, 1096, 1035 cm^{-1}; MS (FAB) m/z 416 $(M+H)^+$; HRMS $(M+H)^+$ 416.2045 (calcd for $C_{23}H_{30}NO_6$ 416.2073).

Compound **4c-3** (Table 1, entry 4) (R_f = 0.2 (CH_2Cl_2)): colorless oil; HPLC (CHIRALPAK AD-H, hexane–^{i}PrOH = 19:1) minor peak t_{R1} 17.0 min, major peak t_{R2} 18.2 min, 66% ee; $[\alpha]_D^{14} = -76$ (c 0.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.08 (t, J = 7.1 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.43 (s, 9H), 3.99–4.11 (m, 2H), 4.07 (d, J = 11.5 Hz, 1H), 4.20 (d, J = 11.5 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 6.24 (dd, J = 2.8, 1.7 Hz, 1H), 6.97–7.00 (m, 2H), 7.21–7.25 (m, 1H), 7.32–7.34 (m, 2H), 7.38–7.43 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.94 (q), 14.13 (q), 27.91 (q), 44.77 (d), 55.83 (d), 61.40 (t), 61.77 (t), 81.21 (s), 110.13 (d), 117.77 (d), 119.36 (d), 119.90 (s), 120.13 (d), 125.66 (d), 129.62 (d), 140.47 (s), 167.86 (s), 168.15 (s), 171.42 (s); IR (neat) 2980, 1733, 1602, 1511, 1368, 1304, 1148, 1035 cm^{-1}; MS (EI) m/z 415 (34, M^+), 341 (61), 314 (100%); HRMS M^+ 415.1997 (calcd for $C_{23}H_{29}NO_6$ 415.1995).

Compound **4d** (Table 1, entry 7) (R_f = 0.6 (CH_2Cl_2)): brown solid; HPLC (CHIRALPAK AD-H, hexane–^{i}PrOH = 99:1) minor peak t_{R1} 12.0 min, major peak t_{R2} 23.3 min, 12% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.04 (t, J = 7.1 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.32 (s, 9H), 3.89–4.06 (m, 2H), 4.18–4.23 (m, 2H), 4.19 (d, J = 11.7 Hz, 1H), 4.31 (d, J = 11.7 Hz, 1H), 5.19 (d, J = 16.0 Hz, 1H), 5.22 (d, J = 16.0 Hz, 1H), 6.09–6.10 (m, 1H), 6.11–6.13 (m, 1H), 6.53 (dd, J = 2.7, 1.8 Hz, 1H), 7.06–7.09 (m, 2H), 7.23–7.33 (m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.92 (q), 14.10 (q), 27.82 (q), 42.96 (d), 50.14 (t), 55.01 (d), 61.59 (t), 61.90 (t), 81.70 (s), 107.77 (d), 108.08 (d), 122.21 (d), 126.43 (s), 127.05 (d), 127.45 (d), 128.65 (d), 138.27 (s), 167.52 (s), 167.99 (s), 169.93 (s); IR (KBr) 2984, 1747, 1729, 1477, 1369, 1296, 1149, 1031 cm^{-1}; MS (FAB) m/z 430 $(M+H)^+$; HRMS $(M+H)^+$ 430.2182 (calcd for $C_{24}H_{32}NO_6$ 430.2230); Anal. Calcd for $C_{24}H_{31}NO_6$: C, 67.11; H, 7.27; N, 3.26. Found: C, 67.06; H, 7.36; N, 3.22.

Compound **4e** (Table 1, entry 8) (R_f = 0.1 (CH_2Cl_2)): pale yellow solid; HPLC (CHIRALPAK AS-H, hexane–^{i}PrOH = 9:1) major peak t_{R1} 4.4 min, minor peak t_{R2} 7.6 min, 45% ee; $[\alpha]_D^{26} = -40$ (c 0.99, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.16 (t, J = 7.1 Hz, 3H), 1.19 (t, J = 7.5 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H), 1.42 (s, 9H), 2.56 (qd, J = 7.5, 0.5 Hz, 2H), 4.04 (d, J = 10.4 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 4.16–4.22 (m, 2H), 4.23 (d, J = 10.4 Hz, 1H), 5.74–5.75 (m, 1H), 5.88 (t, J = 2.9 Hz, 1H), 8.15 (br s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.59 (q), 13.98 (q), 14.08 (q), 20.92 (t), 27.89 (q), 45.31 (d), 55.17 (d), 61.71 (t), 61.87 (t), 81.93 (s), 104.35 (d), 107.52 (d), 122.98 (s), 134.63 (s), 167.84 (s), 168.04 (s), 170.42 (s); IR (KBr) 3354, 2981, 2936, 1750, 1725, 1706, 1589, 1371, 1297, 1185, 1150 cm^{-1}; MS (EI) m/z 367 (M^+, 33), 293 (31), 266 (94), 265 (96), 57 (100); HRMS M^+ 367.1998 (calcd for $C_{19}H_{29}NO_6$ 367.1995); Anal. Calcd for $C_{19}H_{29}NO_6$: C, 62.11; H, 7.96; N, 3.81. Found: C, 62.24; H, 8.25; N, 3.77.

Compound **4f** (Table 1, entry 11) (R_f = 0.6 (hexane–ether = 1:1)): brown oil; HPLC (CHIRALPAK AD-H, hexane–^{i}PrOH = 9:1) major peak t_{R1} 18.2 min, minor peak t_{R2} 20.8 min, 41% ee; $[\alpha]_D^{24} = -37$ (c 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.12 (t, J = 7.1 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H), 1.35 (s, 9H), 3.90 (s, 2H), 3.99–4.07 (m, 2H), 4.01 (d, J = 10.7 Hz, 1H), 4.13–4.19 (m, 2H), 4.20 (d, J = 10.7 Hz, 1H), 5.83 (dd, J = 3.3, 2.7 Hz, 1H), 5.91 (t, J = 3.0 Hz, 1H), 7.13–7.29 (m, 5H), 8.05 (br s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.95 (q), 14.03 (q), 27.77 (q), 34.14 (t), 45.28 (d), 54.89 (d), 61.68 (t), 61.84 (t), 81.87 (s), 106.77 (d), 107.63 (d), 124.00 (s), 126.36 (d), 128.54 (d), 128.57 (d), 131.01 (s), 139.66 (s), 167.73 (s), 167.86 (s), 170.16 (s); IR (neat) 3380, 2980, 1738, 1732, 1495, 1455, 1369, 1303, 1150, 1032 cm^{-1}; MS (EI) m/z 429 (M^+, 20), 328 (100); HRMS M^+ 429.2164 (calcd for $C_{24}H_{31}NO_6$ 429.2151).

Compounds **4g-2/4g-5** as a mixture (Table 1, entry 12) (R_f = 0.5 (CH_2Cl_2–ether = 19:1)): brown oil; HPLC (CHIRALPAK AS-H, hexane–^{i}PrOH = 19:1) major peak t_{R1} 5.5 min, minor peak t_{R2} 17.8 min, 69% ee for **4g-2**; major peak t_{R1} 6.1 min, minor peak t_{R2} 14.1 min, 40% ee for **4g-5**; $[\alpha]_D^{23} = -73$ (c 1.19, $CHCl_3$) for the mixture; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **4g-2**, 1.11 (t, J = 7.1 Hz, 3H), 1.23 (t, J = 7.5 Hz, 3H), 1.41 (s, 9H), 2.032 (s, 3H), 3.98–4.24 (m, 5H), 4.31 (d, J = 10.3 Hz, 1H), 5.92 (t, J = 2.7 Hz, 1H), 6.61 (t, J = 2.7 Hz, 1H), 8.40 (br s, 1H), separate peaks for **4g-5**, 1.15 (t, J = 7.1 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H), 1.42 (s, 9H), 2.027 (s, 3H), 5.84 (d, J = 2.6 Hz, 1H), 6.44 (br s, 1H), 8.21 (br s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) peaks for **4g-2**, 10.84 (q), 13.89 (q), 14.02 (q), 27.91 (q), 43.11 (d), 54.64 (d), 61.69 (t), 61.84 (t), 81.98 (s), 110.03 (d), 117.30 (s), 117.38 (d), 120.16 (s), 167.90 (s), 167.97 (s), 170.69 (s); IR (neat) 3390, 2981, 2936, 1733, 1456, 1370, 1304, 1149, 1034 cm^{-1}; MS (FAB) m/z 354 $(M+H)^+$; HRMS $(M+H)^+$ 354.1919 (calcd for $C_{18}H_{28}NO_6$ 354.1917).

Compound **4h-2** (Table 1, entry 15) (R_f = 0.6 (hexane–hexane–ether = 1:1)): yellow crystals; mp = 120–121 °C; HPLC (CHIRALPAK AS-H, hexane–^{i}PrOH = 19:1) major peak t_{R1} 6.5 min, minor peak t_{R2} 36.6 min, 66% ee; $[\alpha]_D^{23} = -99$ (c 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.973 (t, J = 7.1 Hz, 3H), 1.11 (t, J = 7.1 Hz, 3H), 1.45 (s, 9H), 3.79–3.87 (m, 1H), 3.96–4.06 (m, 2H), 4.10–4.18 (m, 1H), 4.11 (d, J = 9.6 Hz, 1H), 4.63 (d, J = 9.6 Hz, 1H), 6.22 (t, J = 2.7 Hz, 1H), 6.75–6.77 (m, 1H), 7.21–7.26 (m, 1H), 7.34–7.39 (m, 2H), 7.44–7.46 (m, 2H), 9.00 (br s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.64 (q), 13.86 (q), 27.89 (q), 42.76 (d), 54.84 (d), 61.69 (t), 61.83 (t), 82.30 (s), 109.06 (d), 118.38 (d), 120.20 (s), 124.80 (s), 125.86 (d), 128.43 (d), 128.46 (d), 136.41 (s), 167.73 (s), 167.93 (s), 170.70 (s); IR (KBr) 3369, 2992, 1726, 1142 cm^{-1}; MS (EI) m/z 415 (M^+, 21), 314 (32), 168 (70), 154 (86), 57 (100%); HRMS M^+ 415.1997 (calcd for $C_{23}H_{29}NO_6$ 415.1995); Anal. Calcd for $C_{23}H_{29}NO_6$: C, 66.49; H, 7.04; N, 3.37. Found: C, 66.39; H, 7.08; N, 3.38.

Compound **4h-5** (Table 1, entry 17) (R_f = 0.5 (hexane–ether = 1:1)): pale yellow oil; HPLC (CHIRALPAK AS-H, hexane–hexane–^{i}PrOH = 19:1) major peak t_{R1} 9.8 min, minor peak t_{R2} 30.7 min, 12% ee; $[\alpha]_D^{27} = +11$ (c 0.22, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.14 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.43 (s, 9H), 4.10 (q, J = 7.1 Hz, 2H), 4.12 (d, J = 10.3 Hz, 1H), 4.16–4.22 (m, 2H), 4.31 (d, J = 10.3 Hz, 1H), 6.34–6.35 (m, 1H), 6.99–7.01 (m, 1H), 7.12–7.16 (m, 1H), 7.28–7.33 (m, 2H), 7.45–7.48 (m,

2H), 8.67 (br s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.99 (q), 14.06 (q), 27.88 (q), 45.25 (d), 54.95 (d), 61.87 (t), 61.99 (t), 82.26 (s), 106.02 (d), 115.01 (d), 124.86 (s), 124.96 (d), 125.46 (d), 125.90 (s), 128.63 (d), 135.73 (s), 167.73 (s), 168.10 (s), 170.12 (s); IR (neat) 3373, 2981, 1733, 1605, 1370, 1152, 1033 cm^{-1}; MS (EI) *m/z* 415 (M^+, 13), 315 (21), 314 (38), 313 (38), 173 (67), 105 (100%); HRMS M^+ 415.1997 (calcd for $C_{23}H_{29}NO_6$ 415.1995).

Compound **4i-2** (Table 1, entry 18) (R_f = 0.5 (hexane–ether = 1:1)): pale yellow crystals; mp = 115–119 °C; HPLC (CHIRALPAK AD-H, hexane–^{i}PrOH = 7:1) major peak t_{R1} 4.4 min, minor peak t_{R2} 8.4 min, 50% ee; $[\alpha]_D^{22} = -77$ (*c* 1.23, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.03 (t, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.44 (s, 9H), 3.84–3.92 (m, 1H), 3.99–4.18 (m, 3H), 4.09 (d, *J* = 9.5 Hz, 1H), 4.53 (d, *J* = 9.5 Hz, 1H), 6.19 (t, *J* = 2.7 Hz, 1H), 6.77 (t, *J* = 2.7 Hz, 1H), 7.32–7.40 (m, 4H), 8.97 (br s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.75 (q), 13.91 (q), 27.92 (q), 42.74 (d), 54.72 (d), 61.81 (t), 61.95 (t), 82.53 (s), 109.00 (d), 118.56 (d), 120.48 (s), 123.70 (s), 128.65 (d), 129.69 (d), 131.76 (s), 134.94 (s), 167.63 (s), 168.06 (s), 170.43 (s); IR (KBr) 3396, 3354, 2986, 1746, 1732, 1717, 1700, 1502, 1369, 1313, 1143 cm^{-1}; MS (EI) *m/z* 451 (M^+, 20), 449 (M^+, 53), 348 (100%); HRMS M^+ 449.1606 (calcd for $C_{23}H_{28}{}^{35}ClNO_6$ 449.1605), 451.1606 (calcd for $C_{23}H_{28}{}^{37}ClNO_6$ 451.1576); Anal. Calcd for $C_{23}H_{28}ClNO_6$: C, 61.40; H, 6.27; N, 3.11. Found: C, 60.95; H, 6.20; N, 3.05.

Compound **4i-5** (Table 1, entry 18) (R_f = 0.3 (hexane–ether = 1:1)): yellow oil; HPLC (CHIRALPAK AD-H, hexane–^{i}PrOH = 7:3) major peak t_{R1} 11.2 min, minor peak t_{R2} 17.5 min, 28% ee; $[\alpha]_D^{26} = -13$ (*c* 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.15 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.43 (s, 9H), 4.10 (d, *J* = 10.0 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 4.15–4.21 (m, 2H), 4.30 (d, *J* = 10.0 Hz, 1H), 6.29 (dd, *J* = 2.2, 1.8 Hz, 1H), 6.98 (dd, *J* = 2.7, 1.8 Hz, 1H), 7.25–7.28 (m, 2H), 7.36–7.39 (m, 2H), 8.69 (br s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.02 (q), 14.08 (q), 27.90 (q), 45.17 (d), 54.94 (d), 61.91 (t), 62.04 (t), 82.40 (s), 106.05 (d), 115.16 (d), 123.78 (s), 126.17 (d), 126.23 (s), 128.71 (d), 130.90 (s), 134.28 (s), 167.68 (s), 168.15 (s), 170.01 (s); IR (neat) 3375, 2981, 1733, 1520, 1492, 1033 cm^{-1}; MS (EI) *m/z* 451 (M^+, 8), 449 (M^+, 23), 347 (67), 139 (92), 57 (100%); HRMS M^+ 449.1602 (calcd for $C_{23}H_{28}{}^{35}ClNO_6$ 449.1605), 451.1578 (calcd for $C_{23}H_{28}{}^{37}ClNO_6$ 451.1576).

Compound **4jz** (1-*tert*-Butyl 2,2-dibenzyl 1-(3,5-dimethyl-1*H*-pyrrol-2-yl)ethane-1,2,2-tricarboxylate) R_f = 0.6 (hexane–ether = 1:1): brown oil; HPLC (CHIRALPAK AS-H, hexane–^{i}PrOH = 9:1) major peak t_{R1} 5.3 min, minor peak t_{R2} 9.0 min, 38% ee; $[\alpha]_D^{26} = -35$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.37 (s, 9H), 1.92 (s, 3H), 2.12 (d, *J* = 0.7 Hz, 3H), 4.18 (d, *J* = 10.4 Hz, 1H), 4.30 (d, *J* = 10.4 Hz, 1H), 4.95 (d, *J* = 12.3 Hz, 1H), 4.99 (d, *J* = 12.3 Hz, 1H), 5.11 (d, *J* = 12.4 Hz, 1H), 5.14 (d, *J* = 12.4 Hz, 1H), 5.59 (d, *J* = 2.7 Hz, 1H), 7.09–7.12 (m, 2H), 7.24–7.35 (m, 8H), 7.92 (br s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 10.81 (q), 13.07 (q), 27.88 (q), 43.21 (d), 54.79 (d), 67.38 (t), 67.43 (t), 81.96 (s), 108.28 (d), 117.72 (s), 118.15 (s), 127.39 (s), 128.14 (d), 128.16 (d), 128.30 (d), 128.36 (d), 128.52 (d), 128.58 (d), 135.11 (s), 135.25 (s), 167.63 (s), 167.68 (s), 170.75 (s); IR (neat) 3382, 2978, 1733, 1456, 1370, 1298, 1150 cm^{-1}; MS (EI) *m/z* 491 (M^+, 26), 390 (22), 114 (67), 91 (100); HRMS M^+ 491.2311 (calcd for $C_{29}H_{33}NO_6$ 491.2308).

Compound **5b** (Table 2, entry 1) (R_f = 0.2 (CH_2Cl_2)): brown oil; HPLC (CHIRALPAK AD-H, hexane–^{i}PrOH = 9:1) major peak t_{R1} 11.6 min, minor peak t_{R2} 15.0 min, 63% ee; $[\alpha]_D^{21} = -96$ (*c* 1.24, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.11 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.98 (s, 3H), 2.16 (d, *J* = 0.7 Hz, 3H), 3.97–4.27 (m, 6H), 4.11 (d, *J* = 10.6 Hz, 1H), 4.35 (d, *J* = 10.6 Hz, 1H), 5.59 (d, *J* = 2.7 Hz, 1H), 8.02 (br s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 10.74 (q), 13.02 (q), 13.83 (q), 13.98 (q), 14.05 (q), 42.12 (d), 54.79 (d), 61.59 (t), 61.62 (t), 61.88 (t), 108.13 (d), 117.77 (s), 117.78 (s), 127.61 (s), 167.67 (s), 167.92 (s), 172.10 (s); IR (neat) 3389, 2982, 1733, 1369, 1301, 1174, 1030 cm^{-1}; MS (EI) *m/z* 339 (M^+, 98), 266 (100%); HRMS M^+ 339.1681 (calcd for $C_{17}H_{25}NO_6$ 339.1682).

Compound **5c** (Table 2, entry 4) (R_f = 0.4 (hexane–ether = 1:1)): yellow oil; HPLC (CHIRALPAK AD-H, hexane–^{i}PrOH = 9:1) major peak t_{R1} 17.8 min, minor peak t_{R2} 19.9 min, 48% ee; $[\alpha]_D^{23} = -38$ (*c* 0.54, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.10 (t, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.97 (s, 3H), 2.14 (d, *J* = 0.7 Hz, 3H), 3.96–4.22 (m, 4H), 4.11 (d, *J* = 10.5 Hz, 1H), 4.42 (d, *J* = 10.5 Hz, 1H), 5.03 (d, *J* = 12.7 Hz, 1H), 5.14 (d, *J* = 12.7 Hz, 1H), 5.60 (d, *J* = 2.7 Hz, 1H), 7.10 (d-like, *J* = 8.5 Hz, 1H), 7.43 (d-like, *J* = 8.5 Hz, 1H), 7.93 (br s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 10.79 (q), 13.04 (q), 13.84 (q), 13.98 (q), 42.13 (d), 54.51 (d), 61.71 (t), 61.99 (t), 66.15 (t), 108.27 (d), 117.39 (s), 118.17 (s), 122.13 (s), 127.78 (s), 129.40 (d), 131.62 (d), 134.78 (s), 167.56 (s), 167.83 (s), 171.71 (s); IR (neat) 3390, 2981, 2937, 1732, 1597, 1489, 1370, 1294, 1159 cm^{-1}; MS (EI) *m/z* 481 (M^+, 20), 479 (M^+, 20), 310 (34), 266 (100%); HRMS M^+ 479.0929 (calcd for $C_{22}H_{26}{}^{79}BrNO_6$ 479.0944), 481.0909 (calcd for $C_{22}H_{26}{}^{81}BrNO_6$ 481.0909); Anal. Calcd for $C_{22}H_{26}BrNO_6$: C, 55.01; H, 5.46; N, 2.92. Found: C, 54.79; H, 5.26; N, 2.89.

Compound **5d** (Table 2, entry 5) (R_f = 0.2 (CH_2Cl_2–ether = 9:1)): brown solid; HPLC (CHIRALPAK AD-H, hexane–^{i}PrOH = 19:1) major peak t_{R1} 20.1 min, minor peak t_{R2} 26.0 min, 71% ee; $[\alpha]_D^{27} = -118$ (*c* 1.08, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.06 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.20–1.30 (m, 1H), 1.40–1.70 (m, 5H), 1.96 (s, 3H), 2.14 (d, *J* = 0.5 Hz, 3H), 3.37–3.48 (m, 2H), 3.54–3.62 (m, 2H), 3.88–3.96 (m, 2H), 3.98–4.06 (m, 2H), 4.10–4.26 (m, 4H), 4.29 (d, *J* = 11.0 Hz, 1H), 4.64 (d, *J* = 11.0 Hz, 1H), 5.54 (d, *J* = 2.7 Hz, 1H), 8.00 (br s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 10.73 (q), 13.02 (q), 13.83 (q), 14.06 (q), 24.61 (t), 25.66 (t), 25.99 (t), 38.89 (d), 43.66 (t), 47.12 (t), 55.56 (d), 61.40 (t), 61.60 (t), 107.70 (d), 116.07 (s), 118.53 (s), 127.74 (s), 168.30 (s), 168.45 (s), 169.41 (s); IR (KBr) 3301, 2938, 1751, 1620, 1267 cm^{-1}; MS (EI) *m/z* 378 (M^+, 19), 266 (100%); HRMS M^+ 378.2145 (calcd for $C_{20}H_{30}N_2O_5$ 378.2155); Anal. Calcd for $C_{20}H_{30}N_2O_5$: C, 63.47; H, 7.99; N, 7.40. Found: C, 63.14; H, 7.90; N, 7.30.

Compound **5e** (Table 2, entry 7) (R_f = 0.2 (CH_2Cl_2)): yellow crystals, HPLC (CHIRALPAK AD-H, hexane–EtOH = 7:3) major peak t_{R1} 6.0 min, minor peak t_{R2} 12.3 min, 41% ee; $[\alpha]_D^{22} = -83$ (*c* 1.68, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.10 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H), 2.06 (s, 3H), 2.11 (d, *J* = 0.7 Hz, 3H), 3.95–4.21 (m, 4H), 4.39 (d, *J* = 11.3 Hz, 1H), 5.40 (d, *J* = 11.3 Hz, 1H), 5.56 (d, *J* = 2.7 Hz, 1H), 7.41–7.45 (m, 2H), 7.51–7.55 (m, 1H), 7.69 (br s, 1H), 7.99–8.02 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 10.99 (q), 13.07 (q), 13.89 (q), 13.98 (q), 43.75 (d), 54.98 (d), 61.60 (t), 61.92 (t), 108.67 (d), 117.05 (s), 117.99 (s), 128.62 (s), 128.71 (d), 128.75 (d), 133.43 (d), 136.01 (s), 168.13 (s), 168.24 (s), 197.91 (s); IR (KBr) 3372, 2986, 2938, 1745, 1721, 1663, 1596, 1446, 1317, 1288, 1254, 1149, 1037 cm^{-1}; MS (EI) *m/z* 371 (M^+, 13), 266 (100%); HRMS M^+ 371.1738 (calcd for $C_{21}H_{25}NO_5$ 371.1733); Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77. Found: C, 67.91; H, 6.78; N, 3.75.

Compound **5** (Y = Ph) (37% yield); (R_f = 0.3 (CH_2Cl_2)): brown crystals, HPLC (CHIRALPAK AS-H, hexane–^{i}PrOH = 9:1) major peak t_{R1} 4.6 min, minor peak t_{R2} 6.6 min, 47% ee; $[\alpha]_D^{19} = -10$ (*c* 0.56, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.05 (t, *J* = 7.1 Hz, 3H), 1.11 (t, *J* = 7.1 Hz, 3H), 1.97 (s, 3H), 2.18 (d, *J* = 0.7 Hz, 3H), 3.96–4.10 (m, 4H), 4.26 (d, *J* = 8.6 Hz, 1H), 4.86 (d, *J* = 8.6 Hz, 1H), 5.59 (d, *J* = 2.7 Hz, 1H), 7.15–7.21 (m, 3H), 7.24–7.28 (m, 2H), 8.54 (br s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 11.05 (q), 13.23 (q), 13.84 (q), 13.92 (q), 41.58 (d), 56.81 (d), 61.65 (t), 61.66 (t), 107.62 (d), 116.33 (s), 123.42 (s), 126.61 (s), 126.68 (d), 127.45 (d), 128.60 (d), 140.95 (s), 167.98 (s), 169.01 (s); IR (KBr) 3393, 2989, 2925, 1743, 1718, 1603, 1455, 1370, 1306, 1175,

1028 cm^{-1}; MS (EI) *m/z* 343 (M^+, 18), 184 (100%); HRMS M^+ 343.1794 (calcd for $C_{20}H_{25}NO_4$ 343.1784); Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.81; H, 7.29; N, 4.15.

Compound **7a** (Table 3, entry 3) (R_f = 0.4 (CH_2Cl_2)): colorless oil; HPLC (CHIRALPAK AD-H, hexane–^{i}PrOH = 19:1) major peak t_{R1} 5.4 min, minor peak t_{R2} 5.9 min, 9% ee; $[\alpha]_D^{28} = -8$ (*c* 0.31, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.12 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.41 (s, 9H), 4.059 (q, *J* = 7.1 Hz, 1H), 4.062 (q, *J* = 7.1 Hz, 1H), 4.14 (d, *J* = 11.4 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.39 (d, *J* = 11.4 Hz, 1H), 6.21–6.22 (m, 1H), 6.29–6.31 (m, 1H), 7.34 (dd, *J* = 1.8, 0.9 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.95 (q), 14.08 (q), 27.85 (q), 45.76 (d), 53.57 (d), 61.68 (t), 61.95 (t), 82.15 (s), 108.27 (d), 110.55 (d), 142.52 (d), 148.97 (s), 167.30 (s), 167.60 (s), 168.53 (s); IR (neat) 2982, 1733, 1504, 1394, 1370, 1150, 1034, 1014 cm^{-1}; MS (EI) *m/z* 340 (M^+); HRMS M^+ 340.1522 (calcd for $C_{17}H_{24}O_7$ 340.1522); Anal. Calcd for $C_{17}H_{24}O_7$: C, 59.99; H, 7.11. Found: C, 59.75; H, 7.07.

Compound **7b** (Table 3, entry 6) (R_f = 0.2 (CH_2Cl_2)): pale yellow oil; HPLC (CHIRALPAK AD-H, hexane–^{i}PrOH = 49:1) major peak t_{R1} 6.3 min, minor peak t_{R2} 7.0 min, 46% ee; $[\alpha]_D^{24} = -52$ (*c* 0.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.14 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.42 (s, 9H), 2.23 (d, *J* = 0.9 Hz, 3H), 4.07 (q, *J* = 7.1 Hz, 1H), 4.08 (q, *J* = 7.1 Hz, 1H), 4.11 (d, *J* = 11.4 Hz, 1H), 4.22 (d, *J* = 7.1 Hz, 2H), 4.32 (d, *J* = 11.4 Hz, 1H), 5.86 (dq, *J* = 3.1, 0.9 Hz, 1H), 6.07 (d, *J* = 3.1 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.53 (q), 13.92 (q), 14.05 (q), 27.82 (q), 45.82 (d), 53.68 (d), 61.61 (t), 61.87 (t), 81.96 (s), 106.44 (d), 108.92 (d), 146.93 (s), 152.10 (s), 167.39 (s), 167.68 (s), 168.80 (s); IR (neat) 2981, 1738, 1563, 1456, 1370, 1300, 1150 cm^{-1}; MS (EI) *m/z* 354 (M^+, 5.4), 298 (30), 280 (68), 253 (82), 180 (99), 135 (100%); HRMS M^+ 354.1690 (calcd for $C_{18}H_{26}O_7$ 354.1679).

Compound **7c** (Table 3, entry 7) (R_f = 0.4 (CH_2Cl_2)): pale yellow oil; HPLC (CHIRALPAK AD-H, hexane–^{i}PrOH = 49:1) major peak t_{R1} 8.8 min, minor peak t_{R2} 9.6 min, 60% ee; $[\alpha]_D^{30} = -63$ (*c* 1.07, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.13 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.5 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.41 (s, 9H), 2.58 (qd, *J* = 7.5, 0.9 Hz, 2H), 4.03–4.10 (m, 2H), 4.11 (d, *J* = 11.4 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.33 (d, *J* = 11.4 Hz, 1H), 5.87 (dt, *J* = 3.1, 0.9 Hz, 1H), 6.08 (d, *J* = 3.1 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 12.18 (q), 13.97 (q), 14.09 (q), 21.40 (t), 27.87 (q), 45.89 (d), 53.65 (d), 61.61 (t), 61.88 (t), 81.91 (s), 104.86 (d), 108.69 (d), 146.85 (s), 157.77 (s), 167.42 (s), 167.70 (s), 168.77 (s); IR (neat) 2979, 1737, 1561, 1464, 1369, 1300, 1148 cm^{-1}; MS (EI) *m/z* 368 (M^+, 6.3), 312 (32), 294 (75), 267 (83), 194 (83), 149 (88), 57 (100%); HRMS M^+ 368.1835 (calcd for $C_{19}H_{28}O_7$ 368.1835); Anal. Calcd for $C_{19}H_{28}O_7$: C, 61.94; H, 7.66. Found: C, 61.79; H, 7.56.

Compound **7d** (Table 3, entry 9) (R_f = 0.5 (CH_2Cl_2)): pale yellow oil; HPLC (CHIRALPAK AD-H, hexane–^{i}PrOH = 49:1) major peak t_{R1} 8.1 min, minor peak t_{R2} 8.8 min, 57% ee; $[\alpha]_D^{28} = -62$ (*c* 1.48, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.912 (t, *J* = 7.4 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.41 (s, 9H), 1.57–1.63 (m, 2H), 2.53 (t-like, *J* = 7.4 Hz, 2H), 4.00–4.12 (m, 2H), 4.12 (d, *J* = 11.5 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.32 (d, *J* = 11.5 Hz, 1H), 5.87 (d-like, *J* = 3.1 Hz, 1H), 6.08 (d, *J* = 3.1 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.66 (q), 13.98 (q), 14.09 (q), 21.40 (t), 27.86 (q), 30.02 (t), 45.89 (d), 53.60 (d), 61.60 (t), 61.87 (t), 81.87 (s), 105.82 (d), 108.71 (d), 146.84 (s), 156.37 (s), 167.39 (s), 167.70 (s), 168.77 (s); IR (neat) 2980, 1737, 1561, 1465, 1369, 1300, 1148, 1035, 1015 cm^{-1}; MS (EI) *m/z* 382 (M^+, 10). 326 (60), 308 (98), 281 (100%); HRMS M^+ 382.1992 (calcd for $C_{20}H_{30}O_7$ 382.1992); Anal. Calcd for $C_{20}H_{30}O_7$: C, 62.81; H, 7.91. Found: C, 62.53; H, 7.81.

Compound **7e** (Table 3, entry 12) (R_f = 0.2 (CH_2Cl_2)): pale yellow oil; HPLC (CHIRALPAK AD-H, hexane–^{i}PrOH = 49:1) major peak t_{R1} 7.5 min, minor peak t_{R2} 8.1 min, 58% ee; $[\alpha]_D^{22} = -59$ (*c* 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.902 (t, *J* = 7.3 Hz, 1H), 1.13 (t, *J* = 7.1 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 1H), 1.28–1.37 (m, 2H), 1.41 (s, 9H), 1.53–1.61 (m, 2H), 2.55 (t, *J* = 7.3 Hz, 2H), 4.02–4.09 (m, 2H), 4.12 (d, *J* = 11.5 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.32 (d, *J* = 11.5 Hz, 1H), 5.86 (d-like, *J* = 3.1 Hz, 1H), 6.08 (d, *J* = 3.1 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.87 (q), 13.98 (q), 14.09 (q), 22.18 (t), 27.72 (t), 27.85 (q), 30.16 (t), 45.86 (d), 53.58 (d), 61.61 (t), 61.88 (t), 81.87 (s), 105.65 (d), 108.70 (d), 146.77 (s), 156.54 (s), 167.39 (s), 167.70 (s), 168.77 (s); IR (neat) 2980, 2935, 1737, 1561, 1467, 1369, 1280, 1148, 1016 cm^{-1}; MS (EI) *m/z* 396 (M^+, 3.8), 375 (18), 322 (46), 295 (74), 57 (100%); HRMS M^+ 396.2149 (calcd for $C_{21}H_{32}O_7$ 396.2148).

Compounds **7f-2/7f-5** as a mixture (Table 3, entry 13) (R_f = 0.3 (CH_2Cl_2): colorless oil; HPLC (CHIRALCEL OD-H, hexane–^{i}PrOH = 49:1) major peak t_{R1} 5.3 min, minor peak t_{R2} 5.7 min, 38% ee for **7f-2**; peaks for **7f-5** were not determined.; $[\alpha]_D^{21} = -28$ (*c* 1.00, $CHCl_3$) for the mixture; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **7f-2**, 1.08 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.39 (s, 9H), 2.02 (s, 3H), 3.97–4.05 (m, 2H), 4.19–4.27 (m, 2H), 4.26 (d, *J* = 11.7 Hz, 1H), 4.38 (d, *J* = 11.7 Hz, 1H), 6.16 (d, *J* = 2.0 Hz, 1H), 7.26 (d, *J* = 1.9 Hz, 1H), separate peaks for **7f-5**, 1.13 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.42 (s, 9H), 1.97 (d-like, *J* = 1.3 Hz, 3H), 4.11 (d, *J* = 11.4 Hz, 1H), 4.32 (dd, *J* = 11.4, 0.5 Hz, 1H), 6.069–6.071 (m, 1H), 7.09–7.10 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) peaks for **7f-2**, 9.72 (q), 13.89 (q), 14.08 (q), 27.90 (q), 43.80 (d), 52.66 (d), 61.54 (t), 61.88 (t), 81.95 (s), 113.08 (d), 118.04 (s), 141.63 (d), 143.86 (s), 167.36 (s), 167.89 (s), 168.64 (s); IR (neat) 2981, 1738, 1509, 1457, 1394, 1370, 1300, 1149, 1034 cm^{-1}; MS (FAB) *m/z* 355 $(M+H)^+$; HRMS $(M+H)^+$ 355.1746 (calcd for $C_{18}H_{27}O_7$ 355.1757).

Compound **7g** (Table 3, entry 16) (R_f = 0.2 (CH_2Cl_2)): pale yellow oil; HPLC (CHIRALPAK AD-H, hexane–^{i}PrOH = 19:1) major peak t_{R1} 4.6 min, minor peak t_{R2} 5.4 min, 27% ee; $[\alpha]_D^{22} = -29$ (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.14 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.42 (s, 9H), 1.87 (br s, 3H), 2.13 (s, 3H), 4.08 (d, *J* = 11.4 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.27 (d, *J* = 11.4 Hz, 1H), 5.96 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 9.91 (q), 11.35 (q), 13.94 (q), 14.08 (q), 27.85 (q), 45.76 (d), 53.70 (d), 61.57 (t), 61.85 (t), 81.86 (s), 111.27 (d), 114.73 (s), 145.61 (s), 147.33 (s), 167.42 (s), 167.72 (s), 168.87 (s); IR (neat) 2981, 1738, 1571, 1456, 1393, 1369, 1301, 1149, 1035 cm^{-1}; MS (EI) *m/z* 368 (M^+, 2.4), 312 (12), 294 (39), 267 (57), 194 (58), 149 (75), 57 (100%); HRMS M^+ 368.1837 (calcd for $C_{19}H_{28}O_7$ 368.1835).

4.3. 2-(5-Butylfuran-2-yl)-3-(hydroxymethyl)butane-1,4-diol 8

At first, $LiAlH_4$ (394 mg, 10.7 mmol) was slowly added to a solution of **7e** (655 mg, 1.65 mmol) in anhydrous diethyl ether (15.5 mL) with stirring at 0 °C. The mixture was allowed to warm to room temperature and stirred for 15 h. Saturated aqueous Na_2SO_4 (10 mL) was added to the stirred mixture with ice-cooling. The mixture was extracted with ether (×5), and the organic phase was dried ($MgSO_4$) and evaporated in vacuo. Column chromatography (silica gel, ether–MeOH = 10:1) of the residue gave **8** (135 mg, 34%).

Compound **8** (R_f = 0.6 (ether–MeOH = 10:1)): colorless oil; $[\alpha]_D^{17} = -5.8$ (*c* 1.35, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.915 (t, *J* = 7.4 Hz, 3H), 1.30–1.39 (m, 2H), 1.54–1.61 (m, 2H), 2.13 (quintet d, *J* = 5.6, 5.6 Hz, 1H), 2.55 (t, *J* = 7.6 Hz, 2H), 3.10 (td, *J* = 6.2 Hz, 1H), 3.45 (br s, 3H), 3.56 (dd, *J* = 11.0, 6.0 Hz, 1H), 3.73 (dd, *J* = 11.0, 4.3 Hz, 1H), 3.80 (d, *J* = 5.1 Hz, 2H), 3.83–3.91 (m, 2H), 5.87 (d, *J* = 3.1 Hz, 1H), 6.01 (d, *J* = 3.1 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.86 (q), 22.30 (t), 27.72 (t), 30.15 (t), 40.76 (d), 43.66 (d), 62.90 (t), 62.96 (t), 63.30 (t), 105.14 (d),

107.45 (d), 152.42 (s), 155.69 (s); IR (neat) 3347, 2957, 2931, 1562, 1467, 1379, 1036 cm^{-1}; MS (EI) *m/z* 242 (M^+, 13), 224 (26), 163 (100%); HRMS M^+ 242.1520 (calcd for $C_{13}H_{22}O_4$ 242.1518).

4.4. 2-Butyl-5-(1,2-dimethypropyl)furan 9

To an ice-cooled solution of **8** (63 mg, 0.26 mmol) in dichloromethane (6 mL) was added triethylamine (0.16 mL, 117 mg, 1.15 mmol). After 15 min, methanesulfonyl chloride (0.060 mL, 89 mg, 0.78 mmnol) was added. The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was poured into the mixture of saturated aqueous $NaHCO_3$ and dichloromethane, extracted, washed with water, and dried. The solvent was removed in vacuo to give crude trimesylate (137 mg) as a pale brown oil. A solution of the crude trimesylate in THF (11.3 mL) was added slowly to 1.0 M lithium triethylborohydride in THF (4.5 mL, 4.5 mmol) at 0 °C. After addition was complete, the reaction was refluxed for 18 h, cooled, and quenched with water. The mixture was extracted with ether, and the organic phase was washed with saturated aqueous NaCl, dried ($MgSO_4$), and evaporated in vacuo. The residue was purified by column chromatography over silica gel, eluting with hexane to give **9** (40 mg, 79%).

Compound **9**: (R_f = 0.9 (hexane)): colorless oil; $[\alpha]_D^{16} = -6.3$ (*c* 0.66, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.850 (d, *J* = 6.8 Hz, 6H), 0.918 (t, *J* = 7.3 Hz, 3H), 1.15 (d, *J* = 7.1 Hz, 3H), 1.31–1.40 (m, 2H), 1.56–1.63 (m, 2H), 1.83–1.95 (m, 1H), 2.57 (t, *J* = 7.8 Hz, 2H), 2.57–2.64 (m, 1H), 5.83 (d, *J* = 2.9 Hz, 1H), 5.84 (d, *J* = 2.9 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.92 (q), 15.07 (q), 19.35 (q), 20.20 (q), 22.34 (t), 27.84 (t), 30.36 (t), 32.43 (d), 39.42 (d), 104.59 (d), 104.66 (d), 154.42 (s), 158.15 (s); IR (neat) 2959, 2932, 2873, 1563, 1466, 1376, 1230, 1180, 1013 cm^{-1}; MS (EI) *m/z* 194 (M^+, 9.2), 151 (100%); HRMS M^+ 194.1674 (calcd for $C_{13}H_{22}O$ 194.1671); Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.55; H,11.37.

4.5. 2,3-Dimethylbutyric acid 10 and valeric acid 11

Compound **9** (66 mg, 0.34 mmol) was dissolved in a mixture of CH_3CN (2.0 mL), CCl_4 (2.0 mL), and H_2O (2.8 mL). Then $NaIO_4$ (291 mg, 1.36 mmol) was added followed by $RuCl_3 \times H_2O$ (6 mg, ca. 0.029 mmol). After 15 h of stirring at room temperature, the solution was diluted with CH_2Cl_2, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 three times. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography over silica gel, eluting with hexane–ether to give the mixtures of **10** and **11** (total 44 mg, **10** (48% yield): **11** (71% yield) by NMR). Also, 11 mg of 2,3-dimethylbutyric acid **10** was isolated.

^1H NMR spectra of 2,3-dimethylbutyric acid **10** were in accordance with the reported data.[22]

To a solution of 2,3-dimethylbutyric acid **10** (11 mg, 0.095 mmol) in CH_2Cl_2 (0.6 mL) were added aniline (10 mg, 0.11 mmol), EDCI (1-[3-dimethylaminopropyl]-3-ethylcarbodiimide hydrochloride) (20 mg, 0.1 mmol) and HOBt (1-hydroxybenzotriazole) (14 mg, 0.1 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was extracted with CH_2Cl_2. The organic phase was washed with saturated aqueous $NaHCO_3$ solution, 2 M aqueous citric acid, saturated aqueous $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel eluting with ether to give *N*-phenyl-2,3-dimethylbutanamide (10 mg, 55%). The enantiomeric excess [62%, (*R*)] of the anilide of **10** (*N*-phenyl-2,3-dimethylbutanamide **12**) was determined by HPLC analysis. HPLC (Chiralcel OD, hexane–^{i}PrOH = 98:2; flow rate, 1.0 mL/min) minor peak t_{R1} 34 (*S*) min, major peak t_{R2} 41 (*R*), 62% ee.

For HPLC calibration purposes, racemic 2,3-dimethylbutyric acid **10** was prepared by alkaline hydrolysis of ethyl 2,3-dimethyl-2-butenoate[23] and subsequent hydrogenation with 10% Pd/C according to the literature procedure.[15] The product was condensed with aniline in the presence of EDCI and HOBt in CH_2Cl_2 to afford racemic *N*-phenyl-2,3-dimethylbutanamide **12**. HPLC (Chiralcel OD, hexane–^{i}PrOH = 98:2; flow rate, 1.0 mL/min) t_{R1} 34 (*S*) min, t_{R2} 41 (*R*) min.

Compound **12** (*N*-Phenyl-2,3-dimethylbutanamide) R_f = 0.5 (CH_2Cl_2–MeOH = 30:1): pale brown crystals; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.968 (d, *J* = 6.8 Hz, 3H), 0.989 (d, *J* = 6.6 Hz, 3H), 1.21 (d, *J* = 6.8 Hz, 3H), 1.88–2.00 (m, 1H), 2.01–2.09 (m, 1H), 7.10 (t-like, *J* = 7.4 Hz, 1H), 7.31 (t-like, *J* = 8.0 Hz, 2H), 7.54 (d-like, *J* = 8.4 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 15.08 (q), 19.64 (q), 21.20 (q), 31.74 (d), 49.67 (d), 119.94 (d), 124.22 (d), 129.03 (d), 138.02 (s), 174.84 (s); IR (KBr) 3280, 2965, 1647, 1598, 1544, 1446, 1377, 1296, 1250, 1200, 1152, 758 cm^{-1}; MS (EI) *m/z* 191 (M^+, 54), 149 (17), 120 (13), 93 (100%); HRMS M^+ 191.1311 (calcd for $C_{12}H_{17}NO$ 191.1310); Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 18.96; N, 7.32. Found: C, 75.11; H,8.86; N, 7.20.

4.6. Compounds 13 and 14

Compounds **13a–c** were prepared by the reaction of diethyl ketomalonate with carbonylmethylenetriphenylphosphoranes.[1] The corresponding carbonylmethylenetriphenyl-phosphoranes for **13a,c** were prepared from the reaction of acetomethylene-triphenylphosphorane, n-BuLi, and 3,5-dimethoxy- or 3,5-dibenzyloxybenzyl bromide. The carbonylmethylenetriphenylphosphorane for **13b** was prepared by the reaction of α-chloroacetomethylenetriphenylphosphorane, NaH, and 3,5-dimethoxyphenol in DMF.[24]

Compound **13a** (54%): (R_f = 0.1 (hexane–ether = 2:1)): yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.32 (t, *J* = 7.1 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 2.86–2.96 (m, 4H), 3.77 (s, 6H), 4.29 (q, *J* = 7.1 Hz, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 6.31 (t, *J* = 2.2 Hz, 1H), 6.33 (d, *J* = 2.2 Hz, 2H), 7.11 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.92 (q), 14.02 (q), 29.64 (t), 45.19 (t), 55.34 (q), 62.12 (t), 62.55 (t), 98.32 (d), 106.42 (d), 135.26 (d), 135.70 (s), 142.68 (s), 161.00 (s), 162.78 (s), 164.74 (s), 197.63 (s); IR (neat) 2983, 1733, 1597, 1464, 1374, 1253, 1153, 1099, 1061 cm^{-1}; MS (EI) *m/z* 364 (M^+, 4.1), 272 (36), 199 (55), 169 (76), 143 (100%); HRMS M^+ 364.1529 (calcd for $C_{19}H_{24}O_7$ 364.1522).

Compound **14a** (Table 4, entry 3) (R_f = 0.2 (CH_2Cl_2)): yellow oil; HPLC (CHIRALPAK AS-H, hexane–^{i}PrOH = 19:1) minor peak t_{R1} 14.2 min, major peak t_{R2} 14.9 min, 48% ee; $[\alpha]_D^{31} = +90$ (*c* 0.75, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.15 (t, *J* = 7.1 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H), 2.54 (ddd, *J* = 14.5, 14.5, 6.3 Hz, 1H), 2.73 (ddd, *J* = 14.9, 4.3, 2.2 Hz, 1H), 2.83 (ddd, *J* = 15.7 Hz, 6.2, 2.2 Hz, 1H), 3.44 (dddd, *J* = 14.8, 14.8, 4.3, 0.8 Hz, 1H), 3.80 (s, 3H), 3.84 (s, 3H), 3.91–3.99 (m, 1H), 4.09–4.17 (m, 1H), 4.24 (d, *J* = 3.7 Hz, 1H), 4.24–4.37 (m, 3H), 6.33 (d, *J* = 2.2 Hz, 1H), 6.35 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.91 (q), 14.00 (q), 28.96 (t), 39.90 (t), 46.02 (d), 53.90 (d), 55.31 (q), 55.49 (q), 61.19 (t), 61.56 (t), 96.57 (d), 104.47 (d), 115.60 (s), 140.14 (s), 158.15 (s), 159.77 (s), 168.58 (s), 169.18 (s), 209.45 (s); IR (neat) 2980, 1732, 1608, 1492, 1464, 1371, 1339, 1207, 1152, 1096 cm^{-1}; MS (EI) *m/z* 364 (M^+, 24), 318 (29), 272 (100%); HRMS M^+ 364.1527 (calcd for $C_{19}H_{24}O_7$ 364.1522).

Compound **13b** (82%): (R_f = 0.3 (hexane–ether = 1:1)): yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.32 (t, *J* = 7.1 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H), 3.75 (s, 6H), 4.30 (q, *J* = 7.1 Hz, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.67 (s, 2H), 6.06 (d, *J* = 2.1 Hz, 2H), 6.12 (t, *J* = 2.1 Hz, 1H), 7.38 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.72 (q), 13.86 (q), 55.30 (q), 62.10 (t), 62.53 (t), 72.58 (t), 93.49 (d), 94.11 (d), 131.47 (d), 137.26 (s), 159.19 (s), 161.60 (s),

162.41 (s), 164.36 (s), 195.05 (s); IR (neat) 2982, 2842, 1733, 1598, 1477, 1374, 1258, 1155, 1067 cm^{-1}; MS (EI) *m/z* 366 (M^+, 30), 320 (26), 274 (85), 207 (66), 154 (99), 125 (100%); HRMS M^+ 366.1316 (calcd for $C_{18}H_{22}O_8$ 366.1315).

Compound **14b** (Table 4, entry 2) (R_f = 0.2 (CH_2Cl_2)): yellow oil; HPLC (CHIRALPAK AS-H, hexane–^{i}PrOH = 9:1) minor peak t_{R1} 11.2 min, major peak t_{R2} 12.0 min, 20% ee; $[\alpha]_D^{26} = +38$ (*c* 1.19, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.18 (t, *J* = 7.1 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H), 3.77 (s, 3H), 3.84 (s, 3H), 3.99–4.07 (m, 1H), 4.12–4.20 (m, 1H), 4.18 (d, *J* = 3.8 Hz, 1H), 4.22–4.37 (m, 4H), 4.67 (d, *J* = 17.2 Hz, 1H), 6.15 (d, *J* = 2.3 Hz, 1H), 6.18 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.80 (q), 14.01 (q), 42.71 (d), 54.95 (d), 55.42 (q), 55.72 (q), 61.75 (t), 61.85 (t), 72.82 (t), 93.19 (d), 94.50 (d), 102.24 (s), 155.99 (s), 158.46 (s), 160.97 (s), 167.95 (s), 168.22 (s), 205.11 (s); IR (neat) 2982, 1742, 1621, 1593, 1498, 1467, 1372, 1339, 1204, 1152, 1113, 1055 cm^{-1}; MS (EI) *m/z* 366 (M^+, 40), 320 (31), 274 (100), 207 (91), 84 (77%); HRMS M^+ 366.1319 (calcd for $C_{18}H_{22}O_8$ 366.1315).

Compound **13c** (51%): (R_f = 0.3 (hexane–ether = 1:1)): yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.29 (t, *J* = 7.1 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H), 2.86–2.89 (m, 4H), 4.27 (q, *J* = 7.1 Hz, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.99 (s, 4H), 6.42 (d, *J* = 2.4 Hz, 2H), 6.47 (t, *J* = 2.4 Hz, 1H), 7.08 (s, 1H), 7.28–7.41 (m, 10H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.86 (q), 13.95 (q), 29.46 (t), 44.99 (t), 62.03 (t), 62.46 (t), 69.98 (t), 99.87 (d), 107.52 (d), 127.53 (d), 127.98 (d), 128.57 (d), 135.16 (d), 135.58 (s), 136.84 (s), 142.64 (s), 160.05 (s), 162.67 (s), 164.67 (s), 197.51 (s); IR (neat) 2983, 1733, 1704, 1594, 1453, 1376, 1253, 1159, 1057 cm^{-1}; MS (EI) *m/z* 516 (M^+, 19), 470 (27), 333 (82), 181 (49), 91 (100%); HRMS M^+ 516.2148 (calcd for $C_{31}H_{32}O_7$ 516.2148).

Compound **14c** (Table 4, entry 4) (R_f = 0.6 (CH_2Cl_2–ether = 9:1)): pale yellow crystals; HPLC (CHIRALPAK AS-H, hexane–^{i}PrOH = 19:1) minor peak t_{R1} 15.6 min, major peak t_{R2} 17.9 min, 56% ee; $[\alpha]_D^{30} = +109$ (*c* 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.13 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 2.54 (ddd, *J* = 14.6, 14.6, 6.3 Hz, 1H), 2.75–2.85 (m, 2H), 3.48 (ddd, *J* = 14.9, 14.9, 4.1 Hz, 1H), 3.91–3.99 (m, 1H), 4.08–4.17 (m, 1H), 4.23–4.30 (m, 2H), 4.32 (d, *J* = 3.6 Hz, 1H), 4.41 (d, *J* = 3.6 Hz, 1H), 5.03 (br s, 2H), 5.07 (d, *J* = 12.1 Hz, 1H), 5.10 (d, *J* = 12.1 Hz, 1H), 6.44 (d, *J* = 2.1 Hz, 1H), 6.52 (d, *J* = 2.1 Hz, 1H), 7.30–7.47 (m, 10H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.92 (q), 13.99 (q), 28.94 (t), 39.92 (t), 45.96 (d), 54.14 (d), 61.28 (t), 61.50 (t), 69.89 (t), 70.11 (t), 98.53 (d), 105.84 (d), 116.20 (s), 126.71 (d), 127.58 (d), 127.89 (d), 128.12 (d), 128.58 (d), 128.65 (d), 136.43 (s), 136.72 (s), 140.30 (s), 157.09 (s), 158.89 (s), 168.61 (s), 169.03 (s), 209.42 (s); IR (neat) 2981, 1735, 1608, 1498, 1454, 1373, 1341, 1155, 1039 cm^{-1}; MS (EI) *m/z* 516 (M^+, 14), 333 (54), 91 (100%); HRMS M^+ 516.2150 (calcd for $C_{31}H_{32}O_7$ 516.2148); Anal. Calcd for $C_{31}H_{32}O_7$: C, 72.08; H, 6.24. Found: C, 71.91; H, 6.33.

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9. The calculations were performed at the STO-3G//B3LYP/6–31G* level with GAUSSIAN 03.
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