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Enantioselective Synthesis of Tertiary Alcohols through a Zirconium-Catalyzed Friedel−Crafts Alkylation of Pyrroles with α-Ketoesters

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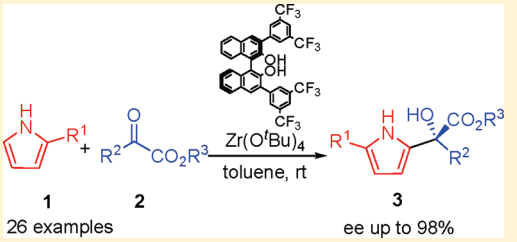
Supporting Information

ABSTRACT: Chiral complexes of 1,1′-bi-2-naphthol-based ligands with zirconium *tert*-butoxide catalyze the Friedel−Crafts alkylation of pyrroles with α-ketoesters to afford tertiary alcohols in good yields and ee up to 98%. The reaction is also of application to 4,7-dihydroindole to give C2-alkylated indoles after oxidation with *p*-benzoquinone.



INTRODUCTION

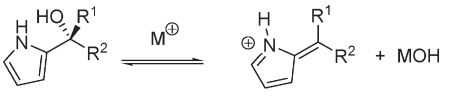
The catalytic enantioselective construction of stereogenic tetrasubstituted carbon centers is a very challenging goal in organic chemistry. The addition of carbon nucleophiles to ketones appears as an attractive procedure for this purpose, affording chiral tertiary alcohols which are versatile synthetic precursors for natural products and pharmaceutical drugs.[1]

The electron-rich nature of the indole and pyrrole rings allows enantioselective Friedel−Crafts (F−C) reactions with prochiral electrophiles to give enantiomerically enriched indole and pyrrole derivatives.[2] However, despite the prevalence of the pyrrole ring in biologically active compounds, the F−C reaction with pyrroles has been less explored, compared with the F−C reaction with indoles.[3] This is probably due to the tendency of pyrrole to undergo dialkylation at both the 2- and 5-positions and to its instability toward acids, which make the development of enantioselective F−C alkylations with pyrroles more challenging.

Several enantioselective F−C alkylations of pyrroles through the 1,4-addition to α,β-unsaturated carbonyl compounds have been reported.[4] However, the asymmetric F−C alkylation of pyrroles involving the 1,2-addition to carbonyl compounds, which would lead to pyrroles bearing a substituent with a chiral tertiary alcohol in the α-position, is more troublesome because of the tendency of this moiety to undergo racemization through azafulvenium intermediates (Scheme 1).[5]

In fact, only two methods for the enantioselective F−C alkylation of pyrroles with carbonyl compounds have been reported to date. Jørgensen described the first catalytic F−C reaction of pyrroles with ethyl trifluoropyruvate catalyzed by a bisoxazoline−copper(II) complex as a Lewis acid.[6] On the other hand, our group has carried out the first enantioselective F−C alkylation of pyrrole with 2,2,2-trifluoroacetophenones using a zirconium-based Lewis acid catalyst (zirconium 3,3′-dibromo-1,1′-bi-2-naphthol).[7] In both cases the presence of the strong electron-withdrawing CF_3 group (and an additional ethyl carboxylate for the copper-catalyzed reaction) attached to the stereogenic carbon seems to destabilize the azafulvenium cation intermediate, precluding the loss of stereochemical integrity at the stereogenic center.[8] As a part of our research on the asymmetric F−C reaction, we report herein the first enantioselective F−C reaction of pyrroles with α-ketoesters to give tertiary alcohols. To the best of our knowledge, this is the first example of synthesis of this kind of pyrrole-substituted tertiary alcohols (via an F−C alkylation of pyrroles) in which the stereochemical integrity of the quaternary stereogenic center is not guaranteed by a CF_3 group.

Scheme 1. Racemization of α-Pyrrolyl Alcohols through Azafulvenium Ions



RESULTS AND DISCUSSION

Our investigation began with an examination of the reaction between pyrrole (**1a**) and ethyl phenyloxoacetate (**2a**) (Scheme 2)

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Scheme 2. Enantioselective F−C Reaction between Pyrrole (1a) and Ketoester 2a and Ligands Used in This Study

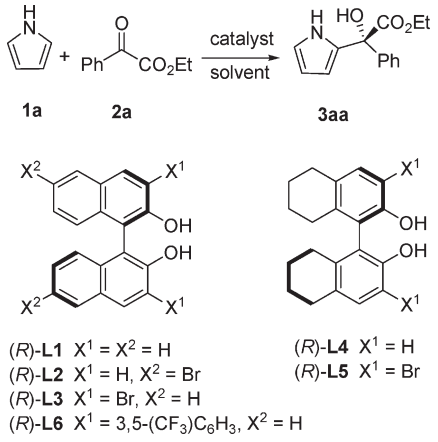

Table 1. Enantioselective F−C Reaction between Pyrrole (1a) and α-Ketoester 2a Catalyzed by Zr(IV)−BINOL Complexes: Optimization of the Reaction Conditions[a]

entry	L(concn, mol %)	$M(OR)_4$ (concn, mol %)	*t* (h)	yield[b] (%)	ee[c] (%)
1	**L1** (20)	$Zr(O^tBu)_4$ (20)	19	48	3
2	**L2** (20)	$Zr(O^tBu)_4$ (20)	19	52	−4
3	**L3** (20)	$Zr(O^tBu)_4$ (20)	21	78	−54
4	**L4** (20)	$Zr(O^tBu)_4$ (20)	20	27	1
5	**L5** (20)	$Zr(O^tBu)^4$ (20)	20	39	−9
6	**L6** (20)	$Zr(O^tBu)_4$ (20)	7	79	98
7	**L6** (20)	$Ti(O^iPr)_4$ (20)	24	20	5
8	**L6** (20)	$Hf(O^tBu)_4$ (20)	8	58	97
9[d]	**L6** (20)	$Zr(O^tBu)_4$ (20)	16	64	95
10	**L6** (10)	$Zr(O^tBu)_4$ (10)	8	58	92
11	**L6** (10)	$Zr(O^tBu)_4$ (20)	9	56	96
12[e]	**L6** (20)	$Zr(O^tBu)_4$ (20)	24	73	99

[a] All reactions performed with pyrrole (**1a**; 0.625 mmol) and ketoester **2a** (0.125 mmol) in toluene (1 mL) at rt unless otherwise stated. [b] Yield after flash chromatography. [c] Determined by HPLC on a chiral stationary-phase column. [d] Dichloromethane was used as the solvent. [e] The reaction temperature was 0 °C.

under the original optimized catalytic conditions described by our group for the F−C reaction of pyrrole with 2,2,2-trifluoroacetophenones.[7] However, when compound **2a** was reacted with pyrrole under those conditions, using **L3**−$Zr(O^tBu)_4$ as the catalyst in toluene (instead of benzene), conversion to the F−C adduct **3aa** occurred in good yield, although with moderate enantiomeric excess (Table 1, entry 3). Next we screened other 1,1′-bi-2-naphthol (BINOL)-type ligands which contained electron-withdrawing groups at the 6,6′-positions or a tetrahydrogenated ring (**L1**, **L2**, **L4**, **L5**), as well as the highly hindered 3,3′-diaryl-BINOL ligand **L6**. The best result was obtained with ligand **L6**, which allowed compound **3aa** to be obtained in 79% yield and 98% ee. The use of other group IV metal alkoxides was also tested. Performing the reaction with $Ti(O^iPr)_4$ and ligand **L6** resulted in a slow reaction rate, and product **3aa** was obtained with very low yield (entry 7). Also, by using $Hf(O^tBu)_4$ (entry 8), the reaction product was obtained with good enantioselectivity (97% ee), although with a lower yield (58%) than with $Zr(O^tBu)_4$.

The use of dichloromethane as the solvent resulted in a lower yield and enantioselectivity (entry 9). Decreasing the catalyst loading to 10 mol % resulted in a lower yield, although the enantioselectivity was still kept high (entries 10 and 11). Finally, lowering the temperature to 0 °C improved the enantioselectivity to 99% ee with a minor detriment to the yield (73%) of product **3aa** (entry 12).

With these optimized conditions, we next investigated the influence of the ester group in substrates **2** (Table 2, entries 1−6). The best results in terms of enantioselectivity and yield were obtained with ethyl and trichloroethyl esters, while other esters (methyl, isopropyl, or benzyl) gave the expected products with high ee (97−98%) but lower yields. Therefore, ethyl ketoesters were established as the best substrates for this reaction.

To explore the scope of the reaction, various substituted α-ketoesters **2g**−**m** were reacted with pyrrole (**1a**). In all the cases, the reaction provided the expected products **3ag**−**3am** with good to high enantiomeric excesses (up to 98%). The reaction with ethyl α-ketoesters containing weak electron-donating (−Me) or electron-withdrawing (−Cl) groups on the aromatic ring gave better results in terms of yields and enantioselectivities than those containing strong electron-donating (−OMe) or electron-withdrawing (−CN− or $-NO_2$) groups on the aromatic ring (entries 7 and 10 vs entries 9 and 11 and 12). The *ortho* substitution on the aromatic ring of the ethyl α-ketoester lowered the reaction rate, and the yield of the alkylation product dropped to 13% (65% ee), indicating the existence of a steric effect caused by the *ortho* substituent. In addition, the 2-naphthyl α-ketoester (**2n**) and heteroaromatic α-ketoesters **2o** and **2p** could also serve as substrates for this reaction, giving the corresponding alkylated pyrroles in acceptable yields and high enantioselectivities (entries 14 and 15). Finally, ethyl (3,5-difluorophenyl)oxoacetate (**2m**), bearing two additional substituents on the aromatic ring, gave the corresponding alkylated pyrrole **3am** with a good yield and enantioselectivity (entry 13). Unfortunately, the reaction with the aliphatic α-ketoester **2q** (entry 17) took place with a poor yield (30%) and enantioselectivity (46% ee).

The effects of pyrrole substitution were also evaluated. 2-Ethylpyrrole (**1b**) and 2-(3′-oxobutyl)pyrrole (**1c**) led to the C5 alkylation products with good yields (62−82%) and excellent enantioselectivities (up to 96%).

Interestingly, 4,7-dihydroindole (**4**), which can be considered as a disubstituted pyrrole, reacted with different aromatic and heteroaromatic α-ketoesters **2** to give the C2-alkylated indoles **5** with good yields and enantioselectivities (up to 92%) after oxidation with *p*-benzoquinone (Table 3).[9]

To determine the absolute stereochemistry of the F−C products, we subjected compound **3aj** to oxidative cleavage of the pyrrole ring with ozone followed by reductive treatment with Ph_3P, which provided imide **6** (Scheme 3). For this compound, we could obtain suitable crystals for X-ray analysis (see the Supporting Information),[10] which allowed determination of the absolute configuration of the stereogenic center in compound **6**, and hence in compound **3aj**, to be *R*. For the rest of the products **3** and **5**, it was assigned as *R* on the assumption of a uniform reaction mechanism.

To gain insight into the nature of the chiral zirconium catalyst, several ^1H NMR experiments were carried out. Equimolar mixtures

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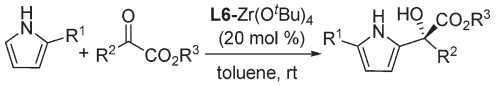
Table 2. Enantioselective F−C Reaction between Pyrroles 1 and α-Ketoesters 2 Catalyzed by L6−Zr(O^{t}Bu)$_4$: Substrate Scope[a]

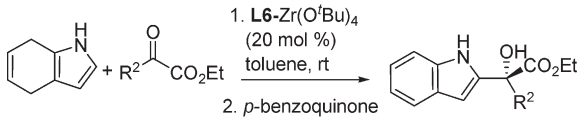


1 2 3

entry	1	R^1	2	R^2	R^3	t (h)	3	yield[b] (%)	ee[c] (%)
1	**1a**	H	**2a**	Ph	Et	7	**3aa**	79	98
2	**1a**	H	**2b**	Ph	Me	7	**3ab**	55	97
3	**1a**	H	**2c**	Ph	^{i}Pr	7	**3ac**	58	98
4	**1a**	H	**2d**	Ph	^{t}Bu	7	**3ad**	33	90
5	**1a**	H	**2e**	Ph	Bn	8	**3ae**	49	97
6	**1a**	H	**2f**	Ph	CH_2Cl_3	5	**3af**	79	97
7	**1a**	H	**2g**	4-MeC_6H_4	Et	18	**3ag**	56	97
8	**1a**	H	**2h**	2-MeC_6H_4	Et	22	**3ah**	13	65
9	**1a**	H	**2i**	4-$MeOC_6H_4$	Et	22	**3ai**	35	98
10	**1a**	H	**2j**	4-ClC_6H_4	Et	17	**3aj**	69	96
11	**1a**	H	**2k**	4-CNC_6H_4	Et	17	**3ak**	62	81
12	**1a**	H	**2l**	4-$NO_2C_6H_4$	Et	8	**3al**	77	60
13	**1a**	H	**2m**	3,5-$F_2C_6H_3$	Et	20	**3am**	72	77
14	**1a**	H	**2n**	2-naphthyl	Et	22	**3an**	63	98
15	**1a**	H	**2o**	2-thiophene-yl	Et	18	**3ao**	68	95
16	**1a**	H	**2p**	2-furanyl	Et	18	**3ap**	43	90
17	**1a**	H	**2q**	$PhCH_2CH_2$	Et	7	**3aq**	30	46
18	**1b**	Et	**2a**	Ph	Et	20	**3ba**	82	92
19	**1b**	Et	**2g**	4-MeC_6H_4	Et	19	**3bg**	62	93
20	**1b**	Et	**2j**	4-ClC_6H_4	Et	18	**3bj**	67	83
21	**1c**	$CH_3COCH_2CH_2$	**2a**	Ph	Et	16	**3ca**	71	96

[a] All reactions performed with pyrroles **1** (0.625 mmol), ketoester **2** (0.125 mmol), **L6** (0.025 mmol), and Zr(O^{t}Bu)$_4$ (0.025 mmol) in toluene (1 mL) at rt. [b] Yield after flash chromatography. [c] Determined by HPLC on chiral stationary-phase columns.

Table 3. Enantioselective F−C Reaction between 4,7-Dihydroindole (4) and α-Ketoesters 2 Catalyzed by L6−Zr(O^{t}Bu)$_4$[a]



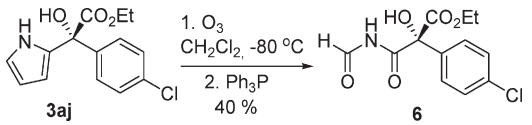
4 2 5

entry	2	R^2	t (h)	5	yield[b] (%)	ee[c] (ee)
1	**2a**	Ph	18	**5a**	76	91
2	**2g**	4-MeC_6H_4	18	**5g**	66	92
3	**2j**	4-ClC_6H_4	18	**5j**	85	83
4	**2n**	2-naphthyl	18	**5n**	74	90
5	**2o**	2-thiophene-yl	18	**5o**	51	84

[a] All reactions performed with 4,7-dihydroindole (**4**; 0.15 mmol), ketoester **2** (0.125 mmol), **L6** (0.025 mmol), and Zr(O^{t}Bu)$_4$ (0.025 mmol) in toluene (1.6 mL) at rt. [b] Yield after flash chromatography. [c] Determined by HPLC on chiral stationary-phase columns.

of Zr(O^{t}Bu)$_4$ and ligand **L6** in toluene-d_8 were stirred at room temperature for 1 h, and ^{1}H NMR spectra of the formed complexes were then measured. We also prepared the same catalyst in dichloromethane-d_2 since the enantioselectivities of the F−C reaction in both solvents were very similar (98% ee in toluene vs 95% ee in dichloromethane). In both solvents, the

Scheme 3. Ozonolysis of Compound 3aj



3aj 6

^{1}H NMR spectra of the formed complexes showed a single set of signals for the BINOLate ligands; that is, only five signals for the binaphthoxy moiety and two signals for the 3,3′-bis[3,5-bis-(trifluoromethyl)phenyl] substituents were observed (Table 4). These simple spectra support the formation of a C_2-symmetrical species and, hence, the monomeric nature of the zirconium complex (Figure 1), as has been previously reported for a related zirconium complex.[11]

The observed absolute stereochemistry of products **3** indicates the preference of the pyrrole to approach the α-ketoester from the *re* face of the ketone carbonyl group. Our working model to account for this stereoselectivity is shown in Figure 2. An octahedrical complex would result from the coordination of the ketoester to the initial monomeric complex in a bidentante fashion, with the ketone carbonyl group occupying one of the apical positions.[12] In this situation, the *si* face of the ketone carbonyl would be shielded by one of the substituted naphthyl moieties of ligand **L6** and the preferred attack of the pyrrole would take place on the *re* face oriented to the outer part of the complex to give compounds with an *R* configuration at the newly

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Table 4. Assignment of the ^{1}H NMR Spectral Signals for Ligand L6 and Its Zr(IV) Complexes

	δ (toluene-d_8)		δ (dichloromethane-d_2)	
signal	**L6**	Zr(O^{t}Bu)$_4$–**L6**	**L6**	Zr(O^{t}Bu)$_4$–**L6**
H1″	8.36	8.56	8.30	8.32
H3″	8.08	8.04	7.98	7.91
H4	7.85	7.87	8.18	7.86
H5	7.80	7.86	8.05	7.85
H6	7.37	7.28	7.51	7.24
H7	7.23	7.07	7.44	7.11
H8	7.28	7.32	7.25	6.87
OH	5.03		5.50	
^{t}BuOH		1.04		1.00
^{t}BuO		1.04		1.00

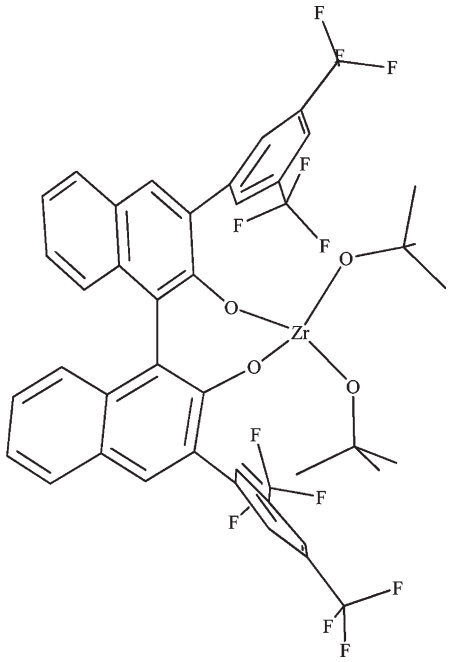

Figure 1. Structure for the C_2-symmetrical monomeric **L6**–Zr(O^{t}Bu)$_4$ complex.

formed stereogenic center. On the other hand, we cannot exclude the possibility that the pyrrole is activated by another zirconium molecule through the formation of a hydrogen bond. This may explain a small nonlinear effect observed (see the Supporting Information) and why *N*-methylpyrrole reacts with **2a** with a poor yield and enantioselectivity (13% yield, 20% ee).[13]

CONCLUSIONS

In summary, we have demonstrated the use of a zirconium(IV)/BINOL catalyst in a Friedel–Crafts reaction of unprotected pyrroles with a variety of differently substituted α-ketoesters to give pyrroles with a chiral substituted tertiary alcohol moiety. The reaction takes place with high enantioselectivities (up to 98%) and good isolated yields (up to 79%). The conditions are also of application to 4,7-dihydroindole, which gives C2-alkylated indoles after oxidation with *p*-benzoquinone. The use of ligands

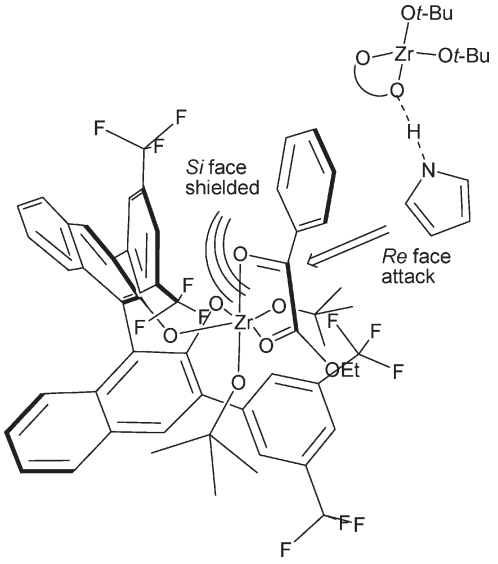

Figure 2. Working model for the Friedel–Crafts reaction of pyrroles with α-ketoesters catalyzed by **L6**–Zr(O^{t}Bu)$_4$.

that are commercially available in both enantiomeric forms (hence providing access to both enantiomeric products) and a simple experimental procedure at room temperature constitute additional advantages of this method. Furthermore, the avoidance of using *N*-protecting groups in this pyrrole alkylation also enhances the efficiency by which substituted pyrroles can be synthesized.

EXPERIMENTAL SECTION

General Experimental Methods. All catalytic reactions were carried out in glassware dried overnight at 120 °C. Reactions were monitored by TLC analysis using silica gel 60 thin layer plates. Flash column chromatography was performed on silica gel 60, 0.040–0.063 mm. Melting points were measured in a microscope instrument. NMR spectra were determined at 300 MHz for ^{1}H and at 50 MHz for ^{13}C NMR and referenced to the residual protic solvent as the internal standard. Chemical shifts are given in δ values (ppm). The carbon multiplicity was determined by DEPT experiments. Specific optical rotations were measured using sodium light (D line, 589 nm). Chiral HPLC analyses were performed in an instrument equipped with a diode-array detector using chiral stationary columns. Mass spectra (EI) were run at 70 eV. ESI mass spectra were recorded on a Q-TOF premier mass spectrometer with an electrospray source. The drying gas as well as the nebulizing gas was nitrogen. Toluene was freshly distilled from CaH_2 under nitrogen. All BINOL-type ligands, ethyl benzoylformate, methyl benzoylformate, ethyl (4-nitrophenyl)glyoxylate, ethyl (3,5-difluorobenzoyl)formate, ethyl (4-cyanobenzoyl)formate, and ethyl (2-oxo-4-phenyl)butyrate, were obtained from commercial sources and used without further purification. The remaining ethyl α-ketoesters were prepared according to known procedures.[14] Zr(O^{t}Bu)$_4$ (Puratrem, 99.99%) was obtained from a commercial supplier. Pyrrole and *N*-methylpyrrole were distilled prior to use. Dihydroindole was prepared by reduction of indole with Li–ammonia.[9]

General Procedure for the Catalytic Enantioselective Friedel–Crafts Reaction. Ligand **L6** (11.1 mg, 0.025 mmol) was introduced into a round-bottom flask provided with a septum, and the flask was purged with nitrogen. Toluene (1 mL) was added via syringe followed by Zr(O^{t}Bu)$_4$ (10 μL, 0.025 mmol), and the solution was stirred at rt for 1 h. After this time, α-ketoester **2** (0.125 mmol) and

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pyrrole **1a** (45 μL, 0.625 mmol) were added, and the mixture was stirred at rt until reaction completion (TLC). Then the mixture was filtered through a short pad of silica gel eluting with diethyl ether. After removal of the solvent, the products **3** were isolated by column chromatography eluting with hexane−EtOAc (95:5) mixtures.

Racemic Friedel−Crafts products for comparison were prepared following the same procedure by using racemic BINOL (±)-**L1.**

*Data for ethyl 2-hydroxy-2-phenyl-2-(1H-pyrrol-2-yl)acetate (**3aa**):* oil; $[\alpha]_D^{25}$ +59.8 (*c* = 1.00 in $CHCl_3$, 98% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.57 (br s, 1H), 7.43−7.40 (m, 2H), 7.34−7.30 (m, 3H), 6.77 (m, 1H), 6.31−6.30 (m, 1H), 6.21 (q, *J* = 3.0 Hz, 1H), 4.40−4.21 (m, 3H), 1.28 (d, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 173.3 (C), 141.2 (C), 130.4 (C), 128.21 (CH), 128.17 (CH), 126.6 (CH), 117.8 (CH), 108.6 (CH), 107.6 (CH), 77.0 (C), 63.4 (CH_2), 14.0 (CH_3) ppm; MS (EI) *m*/*z* (rel intens) 245 $[M]^+$ (4), 198 (33), 172 (100), 154 (85), 105 (84), 94 (43), 77 (46); HRMS *m*/*z* calcd for $C_{14}H_{15}NO_3$ $[M]^+$ 245.1052, found 245.1052.

Assay of enantiomeric excess: chiral HPLC analysis (Chiralcel OD-H, 10% 2-propanol−90% hexane, 1.0 mL/min) $(+)_{major}$ t_R = 10.0 min, $(-)_{minor}$ t_R = 8.8 min, ee = 98%.

*Data for methyl 2-hydroxy-2-phenyl-2-(1H-pyrrol-2-yl)acetate (**3ab**):* oil; $[\alpha]_D^{25}$ +10.5 (*c* = 0.55 in $CHCl_3$, 97% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.57 (br s, 1H), 7.44−7.40 (m, 2H), 7.36−7.32 (m, 3H), 6.79 (td, *J* = 2.6, 1.6 Hz, 1H), 6.29−6.26 (m, 1H), 6.22 (q, *J* = 3.0 Hz, 1H), 4.27 (s, 1H), 3.85 (s, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 173.9 (C), 141.0 (C), 130.2 (C), 128.4 (CH), 128.3 (CH), 126.6 (CH), 117.9 (CH), 108.5 (CH), 107.7 (CH), 77.2 (C), 53.8 (CH_3) ppm; MS (EI) *m*/*z* (rel intens) 231 $[M]^+$ (9), 184 (17), 172 (100), 171 (18), 105 (67), 94 (34), 77 (34); HRMS *m*/*z* calcd for $C_{13}H_{13}NO_3$ $[M]^+$ 231.0895, found 231.0895.

Assay of enantiomeric excess: chiral HPLC analysis (Chiralcel OD-H, 10% 2-propanol−90% hexane, 1.0 mL/min) $(+)_{major}$ t_R = 12.4 min, $(-)_{minor}$ t_R = 11.0 min, ee = 97%.

*Data for isopropyl 2-hydroxy-2-phenyl-2-(1H-pyrrol-2-yl)acetate (**3ac**):* oil; $[\alpha]_D^{25}$ +55.8 (*c* = 0.74 in $CHCl_3$, 98% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.59 (br s, 1H), 7.42−7.40 (m, 2H), 7.32−7.30 (m, 3H), 6.77 (td, *J* = 2.7, 1.5 Hz, 1H), 6.33−6.31 (m, 1H), 6.21 (q, *J* = 3.0 Hz, 1H), 5.14 (sept, *J* = 6.3 Hz, 1H), 4.38 (s, 1H), 1.32 (d, *J* = 6.3 Hz, 3H), 1.20 (d, *J* = 6.3 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 172.8 (C), 141.4 (C), 130.5 (C), 128.2 (CH), 128.1 (CH), 126.5 (CH), 117.7 (CH), 108.4 (CH), 107.5 (CH), 76.9 (C), 71.3 (CH), 21.5 (CH_3), 21.4 (CH_3) ppm; MS (EI) *m*/*z* (rel intens) 259 $[M]^+$ (5), 172 (100), 105 (74), 94 (37), 77 (40); HRMS *m*/*z* calcd for $C_{15}H_{17}NO_3$ $[M]^+$ 259.1208, found 259.1204.

Assay of enantiomeric excess: chiral HPLC analysis (Chiralcel OD-H, 10% 2-propanol−90% hexane, 1.0 mL/min) $(+)_{major}$ t_R = 8.7 min, $(-)_{minor}$ t_R = 7.5 min, ee = 98%.

*Data for tert-butyl 2-hydroxy-2-phenyl-2-(1H-pyrrol-2-yl)acetate (**3ad**):* oil; $[\alpha]_D^{25}$ +62.6 (*c* = 0.35 in $CHCl_3$, 90% ee); ^{1}H RMN (300 MHz, $CDCl_3$) δ = 8.57 (br s, 1H), 7.42−7.39 (m, 2H), 7.31−7.29 (m, 3H), 6.77 (td, *J* = 2.6, 1.5 Hz, 1H), 6.34−6.32 (m, 1H), 6.22 (q, *J* = 3.0 Hz, 1H), 4.42 (s, 1H), 1.46 (s, 9H) ppm; ^{13}C RMN (75.5 MHz, $CDCl_3$) δ = 172.2 (C), 141.8 (C), 130.7 (C), 128.0 (CH), 127.9 (CH), 126.5 (CH), 117.5 (CH), 108.4 (CH), 107.3 (CH), 84.1 (C), 77.0 (C), 27.7 (CH_3) ppm; MS (EI) *m*/*z* (rel intens) 273 $[M]^+$ (12), 173 (12), 172 (100), 105 (15); HRMS *m*/*z* calcd for $C_{16}H_{19}NO_3$ $[M]^+$ 273.1365, found 273.1361.

Assay of enantiomeric excess: chiral HPLC analysis (Chiralcel OD-H, 10% 2-propanol−90% hexane, 1.0 mL/min) $(+)_{major}$ t_R = 7.0 min, $(-)_{minor}$ t_R = 6.2 min, ee = 90%.

*Data for benzyl 2-hydroxy-2-phenyl-2-(1H-pyrrol-2-yl)acetate (**3ae**):* oil; $[\alpha]_D^{25}$ +50.6 (*c* = 0.77 in $CHCl_3$, 97% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.53 (br s, 1H), 7.42−7.38 (m, 2H), 7.34−7.30 (m, 6H), 7.23−7.20 (m, 2H), 6.76 (td, *J* = 2.6, 1.7 Hz, 1H), 6.26−6.23 (m, 1H), 6.18 (q, *J* = 3.0 Hz, 1H), 5.30 (d, *J* = 12.3 Hz, 1H), 5.24 (d, *J* = 12.3 Hz, 1H), 4.26 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 173.2 (C), 141.0 (C), 134.7 (C), 130.2 (C), 128.6 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 128.0 (CH), 126.6 (CH), 117.9 (CH), 108.5 (CH), 107.8 (CH), 77.2 (C), 68.5 (CH_2) ppm; MS (EI) *m*/*z* (rel intens) 307 $[M]^+$ (10), 172 (100); HRMS *m*/*z* calcd for $C_{19}H_{17}NO_3$ $[M]^+$ 307.1208, found 307.1200.

Assay of enantiomeric excess: chiral HPLC analysis (Chiralcel OD-H, 10% 2-propanol−90% hexane, 1.0 mL/min) $(+)_{major}$ t_R = 15.8 min, $(-)_{minor}$ t_R = 13.2 min, ee = 97%.

*Data for 2,2,2-trichloroethyl 2-hydroxy-2-phenyl-2-(1H-pyrrol-2-yl)acetate (**3af**):* oil; $[\alpha]_D^{25}$ +48.8 (*c* = 1.39 in $CHCl_3$, 97% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.58 (br s, 1H), 7.51−7.48 (m, 2H), 7.35−7.32 (m, 3H), 6.79 (td, *J* = 2.7, 1.5 Hz, 1H), 6.45 (ddd, *J* = 3.6, 2.7, 1.5 Hz, 1H), 6.23 (q, *J* = 3.0 Hz, 1H), 4.86 (d, *J* = 11.7 Hz, 1H), 4.81 (d, *J* = 12.0 Hz, 1H), 4.13 (s, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 171.8 (C), 140.1 (C), 129.4 (C), 128.6 (CH), 128.3 (CH), 126.7 (CH), 118.3 (CH), 108.6 (CH), 108.2 (CH), 93.8 (C), 77.4 (C), 75.5 (CH_2) ppm; MS (EI) *m*/*z* (rel intens) 347 $[M]^+$ (1), 198 (63), 172 (59), 154 (100), 127 (21), 105 (29), 77 (22); HRMS *m*/*z* calcd for $C_{14}H_{12}NO_3Cl_3$ $[M]^+$ 346.9883, found 346.9881.

Assay of enantiomeric excess: chiral HPLC analysis (Chiralcel OD-H, 10% 2-propanol−90% hexane, 1.0 mL/min) $(+)_{major}$ t_R = 13.0 min, $(-)_{minor}$ t_R = 11.0 min, ee = 97%.

*Data for ethyl 2-hydroxy-2-(1H-pyrrol-2-yl)-2-p-tolylacetate (**3ag**):* oil; $[\alpha]_D^{25}$ +51.7 (*c* = 0.67 in $CHCl_3$, 97% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.56 (br s, 1H), 7.29 (d, *J* = 8.1 Hz,2H), 7.13 (d, *J* = 7.8 Hz, 2H), 6.77 (td, *J* = 2.6, 1.6 Hz,1H), 6.29 (ddd, *J* = 3.3, 2.4, 1.5 Hz, 1H), 6.21 (q, *J* = 3.0 Hz, 1H), 4.41−4.21 (m, 3H), 2.34 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 173.5 (C), 138.4 (C), 138.0 (C), 130.6 (C), 128.9 (CH), 126.5 (CH), 117.7 (CH), 108.4 (CH), 107.5 (CH), 76.9 (C), 63.1 (CH_2), 21.2 (CH_3), 14.0 (CH_3) ppm; MS (EI) *m*/*z* (rel intens) 259 $[M]^+$ (4), 186 (100), 168 (28), 119 (70), 94 (55), 91 (35); HRMS *m*/*z* calcd for $C_{15}H_{17}NO_3$ $[M]^+$ 259.1208, found 259.1221.

Assay of enantiomeric excess: chiral HPLC analysis (Chiralcel OD-H, 10% 2-propanol−90% hexane, 1.0 mL/min) $(+)_{major}$ t_R = 18.2 min, $(-)_{minor}$ t_R = 19.6 min, ee = 97%.

*Data for ethyl 2-hydroxy-2-(1H-pyrrol-2-yl)-2-o-tolylacetate (**3ah**):* oil; $[\alpha]_D^{25}$ +11.5 (*c* = 0.23 in $CHCl_3$, 65% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.67 (br s, 1H), 7.24−7.15 (m, 2H), 7.06 (dd, *J* = 7.4, 1.6 Hz, 1H), 6.84 (td, *J* = 2.6, 1.7 Hz, 1H), 6.78 (td, *J* = 8.0, 1.1 Hz, 1H), 6.25−6.22 (m, 2H), 4.46−4.24 (m, 2H), 4.09 (s, 1H), 2.31 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 174.0 (C), 139.4 (C), 137.1 (C), 131.6 (CH), 130.3 (C), 128.6 (CH), 128.5 (CH), 125.6 (CH), 117.7 (CH), 108.8 (CH), 107.5 (CH), 78.1 (C), 63.1 (CH_2), 29.7 (CH_3), 14.0 (CH_3) ppm; MS (EI) *m*/*z* (rel intens) 259 $[M]^+$ (10), 186 (100), 168 (34), 119 (67), 94 (45), 91 (30); HRMS *m*/*z* calcd for $C_{15}H_{17}NO_3$ $[M]^+$ 259.1208, found 259.1216.

Assay of enantiomeric excess: chiral HPLC analysis (Chiralcel OD-H, 10% 2-propanol−90% hexane, 1.0 mL/min) $(+)_{major}$ t_R = 12.5 min, $(-)_{minor}$ t_R = 9.4 min, ee = 65%.

*Data for ethyl 2-hydroxy-2-(4-methoxyphenyl)-2-(1H-pyrrol-2-yl)acetate (**3ai**):* oil; $[\alpha]_D^{25}$ +55.6 (*c* = 0.47 in $CHCl_3$, 98% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.57 (br s, 1H), 7.32 (d, *J* = 9.0 Hz, 2H), 6.84 (d, *J* = 9.0 Hz, 2H), 6.77 (td, *J* = 2.6, 1.6 Hz, 1H), 6.29 (ddd, *J* = 3.6, 2.7, 1.8 Hz, 1H), 6.21 (q, *J* = 2.9 Hz, 1H), 4.40−4.21 (m, 3H), 3.79 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 173.6 (C), 159.4 (C), 133.5 (C), 130.7 (C), 127.9 (CH), 117.7 (CH), 113.5 (CH), 108.4 (CH), 107.4 (CH), 76.7 (C), 63.1 (CH_2), 55.3 (CH_3), 14.0 (CH_3) ppm; MS (EI) *m*/*z* (rel intens) 275 $[M]^+$ (1), 228 (17), 202 (18), 184 (62), 135 (100), 94 (14); HRMS *m*/*z* calcd for $C_{15}H_{17}NO_4$ $[M]^+$ 275.1158, found 275.1149.

Assay of enantiomeric excess: chiral HPLC analysis (Chiralcel OD-H, 10% 2-propanol−90% hexane, 1.0 mL/min) $(+)_{major}$ t_R = 12.3 min, $(-)_{minor}$ t_R = 13.8 min, ee = 98%.

*Data for ethyl 2-(4-chlorophenyl)-2-hydroxy-2-(1H-pyrrol-2-yl)acetate (**3aj**):* oil; $[\alpha]_D^{25}$ +67.6 (*c* = 0.70 in $CHCl_3$, 96% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.56 (br s, 1H), 7.38 (d, *J* = 8.7, 2H), 7.29 (d, *J* = 9.0 Hz, 2H), 6.78 (td, *J* = 2.7, 1.5 Hz, 1H), 6.30−6.27 (m, 1H), 6.21 (q, *J* = 3.0 Hz, 1H), 4.41−4.21 (m, 3H), 1.29 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 172.9 (C), 140.0 (C), 134.2 (C), 130.0 (C), 128.3 (CH), 128.1 (CH), 118.0 (CH), 108.6 (CH), 107.6 (CH), 76.5 (C), 63.3 (CH_2), 14.0 (CH_3) ppm; MS (EI) *m*/*z* (rel intens) 279 $[M]^+$ (9), 226 (16), 208 (34), 206 (100), 190 (48), 188 (24), 139 (28), 99 (19), 97 (20), 85 (35), 83 (19), 71 (42), 69 (26), 57 (56), 55 (24); HRMS *m*/*z* calcd for $C_{14}H_{14}NO_3Cl$ $[M]^+$ 279.0662, found 279.0664.

Assay of enantiomeric excess: chiral HPLC analysis (Chiralpack AD-H, 10% 2-propanol−90% hexane, 1.0 mL/min) $(+)_{major}$ t_R = 16.5 min, $(-)_{minor}$ t_R = 17.8 min, ee = 96%.

*Data for ethyl 2-(4-cyanophenyl)-2-hydroxy-2-(1H-pyrrol-2-yl)acetate (**3ak**):* oil; $[\alpha]_D^{25}$ +56.6 (*c* = 0.78 in $CHCl_3$, 81% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.59 (br s, 1H), 7.63−7.57 (m, 4H), 6.79 (td, *J* = 2.7, 1.5 Hz, 1H), 6.30 (ddd, *J* = 3.6, 2.7, 1.5 Hz, 1H), 6.21 (q, *J* = 2.9 Hz, 1H), 4.44 (s, 1H), 4.42−4.21 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 172.1 (C), 146.0 (C), 131.9 (CH), 129.3 (C), 127.5 (CH), 118.6 (C), 118.4 (CH), 112.0 (C), 108.7 (CH), 107.7 (CH), 76.6 (C), 63.6 (CH_2), 13.9 (CH_3) ppm; MS (EI) *m*/*z* (rel intens) 270 $[M]^+$ (16), 197 (100), 130 (23). HRMS *m*/*z* calcd for $C_{15}H_{14}N_2O_3$ $[M]^+$ 270.1004, found 270.1006.

Assay of enantiomeric excess: chiral HPLC analysis (Chiralcel OD-H, 10% 2-propanol−90% hexane, 1.0 mL/min) $(+)_{major}$ t_R = 16.5 min, $(-)_{minor}$ t_R = 15.3 min, ee = 81%.

*Data for ethyl 2-hydroxy-2-(4-nitrophenyl)-2-(1H-pyrrol-2-yl)acetate (**3al**):* oil; $[\alpha]_D^{25}$ +39.3 (*c* = 1.27 in $CHCl_3$, 60% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.60 (br s, 1H), 8.16 (d, *J* = 9.0 Hz, 2H), 7.66 (d, *J* = 9.0 Hz, 2H), 6.80 (td, *J* = 2.6, 1.7 Hz, 1H), 6.33−6.30 (m, 1H), 6.23 (q, *J* = 3.0 Hz, 1H), 4.47 (s, 1H), 4.43−4.22 (m, 2H), 1.30 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 172.0 (C), 147.8 (C), 147.6 (C), 129.3 (C), 127.8 (CH), 123.3 (CH), 118.5 (CH), 108.8 (CH), 107.8 (CH), 76.5 (C), 63.7 (CH_2), 13.9 (CH_3) ppm; MS (EI) *m*/*z* (rel intens) 290 $[M]^+$ (5), 217 (100), 150 (58), 104 (27), 94 (26); HRMS *m*/*z* calcd for $C_{14}H_{14}N_2O_5$ $[M]^+$ 290.0903, found 290.0902.

Assay of enantiomeric excess: chiral HPLC analysis (Chiralcel OD-H, 10% 2-propanol−90% hexane, 1.0 mL/min) $(+)_{major}$ t_R = 17.2 min, $(-)_{minor}$ t_R = 15.7 min, ee = 60%.

*Data for ethyl 2-(3,5-difluorophenyl)-2-hydroxy-2-(1H-pyrrol-2-yl)acetate (**3am**):* oil; $[\alpha]_D^{25}$ +57.6 (*c* = 1.02 in $CHCl_3$, 77% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.58 (br s, 1H), 7.07−7.00 (m, 2H), 6.78 (td, *J* = 2.7, 1.5 Hz, 1H), 6.74 (tt, *J* = 8.7, 2.4 Hz, 1H), 6.32−6.29 (m, 1H), 6.21 (q, *J* = 2.7 Hz, 1H), 4.43−4.23 (m, 3H), 1.32 (t, *J*(H,H) = 7.2 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 172.2 (C), 162.8 (d, *J*(C,F) = 246.9 Hz, CF), 162.6 (d, *J*(C,F) = 246.8 Hz, CF), 145.1 (t, *J*(C,F) = 8.6 Hz, C) 129.4 (C), 118.3 (CH), 110.1−109.8 (m, 2CH), 108.7 (CH), 107.7(CH), 103.6 (t, *J*(C,F) = 25.2 Hz, CH), 76.29 (t, *J*(C,F) = 2.2 Hz, C), 63.6 (CH_2), 13.9 (CH_3) ppm; MS (EI) *m*/*z* (rel intens) 281 $[M]^+$ (10), 208 (100), 141 (58), 113 (16); HRMS *m*/*z* calcd for $C_{14}H_{13}N_1O_3F_2$ $[M]^+$ 281.0864, found 281.0862.

Assay of enantiomeric excess: chiral HPLC analysis (Chiralpack AD-H, 10% 2-propanol−90% hexane, 1.0 mL/min) $(+)_{major}$ t_R = 10.3 min, $(-)_{minor}$ t_R = 11.2 min, ee = 77%.

*Data for ethyl 2-hydroxy-2-(naphthalen-2-yl)-2-(1H-pyrrol-2-yl)acetate (**3an**):* oil; $[\alpha]_D^{25}$ +49.3 (*c* = 1.15 in $CHCl_3$, 98% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.59 (br s, 1H), 7.87 (d, *J* = 1.8 Hz, 1H), 7.82−7.79 (m, 3H), 7.54 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.49−7.46 (m, 2H), 6.81 (td, *J* = 2.7, 1.5 Hz, 1H), 6.37 (ddd, *J* = 3.9, 2.7, 1.8 Hz, 1H), 6.25 (q, *J* = 3.0 Hz, 1H), 4.42−4.23 (m, 3H), 1.29 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 173.3 (C), 138.6 (C), 133.1 (C), 132.9 (C), 130.4 (C), 128.5 (CH), 128.0 (CH), 127.5 (CH), 126.4 (CH), 126.2 (CH), 125.7 (CH), 124.6 (CH), 117.9 (CH), 108.6 (CH), 107.7 (CH), 77.2 (C), 63.2 (CH_2), 14.0 (CH_3) ppm; MS (EI) *m*/*z* (rel intens) 295 $[M]^+$ (5), 277 (24), 222 (100), 204 (80), 155 (53), 127 (47), 94 (96); HRMS *m*/*z* calcd for $C_{18}H_{17}N_1O_3$ $[M]^+$ 295.1208, found 295.1209.

Assay of enantiomeric excess: chiral HPLC analysis (Chiralcel OD-H, 10% 2-propanol−90% hexane, 1.0 mL/min) $(+)_{major}$ t_R = 11.7 min, $(-)_{minor}$ t_R = 12.9 min, ee = 98%.

*Data for ethyl 2-hydroxy-2-(1H-pyrrol-2-yl)-2-(thiophene-2-yl)acetate (**3ao**):* oil; $[\alpha]_D^{25}$ +6.7 (*c* = 0.21 in $CHCl_3$, 95% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.61 (br s, 1H), 7.28 (d, *J* = 1.5 Hz, 1H), 7.07 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.96 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.76 (td, *J* = 2.6, 1.5 Hz, 1H), 6.33−6.31 (m, 1H), 6.19 (q, *J* = 3.0 Hz, 1H), 4.50 (s, 1H), 4.34 (dq, *J* = 7.1, 1.1 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 172.4 (C), 145.7 (C), 130.5 (C), 126.8 (CH), 125.9 (CH), 125.8 (CH), 117.8 (CH), 108.7 (CH), 107.1 (CH), 74.8 (C), 63.5 (CH_2), 14.0 (CH_3) ppm; MS (EI) *m*/*z* (rel intens) 251 $[M]^+$ (7), 178 (100), 160 (20), 110 (76), 94 (34); HRMS *m*/*z* calcd for $C_{12}H_{13}NO_3S$ $[M]^+$ 251.0616, found 251.0610.

Assay of enantiomeric excess: chiral HPLC analysis (Chiralcel OD-H, 10% 2-propanol−90% hexane, 1.0 mL/min) $(+)_{major}$ t_R = 12.0 min, $(-)_{minor}$ t_R = 10.5 min, ee = 90%.

*Data for ethyl 2-(furan-2-yl)-2-hydroxy-2-(1H-pyrrol-2-yl)acetate (**3ap**):* oil; $[\alpha]_D^{25}$ +11.5 (*c* = 0.30 in $CHCl_3$, 90% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.74 (br s, 1H), 7.40 (dd, *J* = 1.8, 0.9 Hz, 1H), 6.80 (td, *J* = 2.6, 1.4 Hz, 1H), 6.34−6.31 (m, 2H), 6.25−6.20 (m, 2H), 4.36−4.29 (m, 3H), 1.29 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 171.6 (C), 153.7 (C), 143.1 (CH), 127.8 (C), 117.7 (CH), 110.2 (CH), 109.2 (CH), 108.9 (CH), 107.3 (CH), 72.8 (C), 63.4 (CH_2), 14.0 (CH_3) ppm; MS (EI) *m*/*z* (rel intens) 235 $[M]^+$ (3), 162 (74), 97 (39), 95 (60), 83 (43), 71 (54), 57 (100); HRMS *m*/*z* calcd for $C_{12}H_{13}NO_4$ $[M]^+$ 235.0846, found 235.0843.

Assay of enantiomeric excess: chiral HPLC analysis (Chiralcel OD-H, 10% 2-propanol−90% hexane, 1.0 mL/min) $(+)_{major}$ t_R = 15.4 min, $(-)_{minor}$ t_R = 11.6 min, ee = 90%.

*Data for ethyl 2-hydroxy-4-phenyl-2-(1H-pyrrol-2-yl)butanoate (**3aq**):* oil; $[\alpha]_D^{25}$ −12.2 (*c* = 0.54 in $CHCl_3$, 46% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.64 (br s, 1H), 7.30−7.25 (m, 2H), 7.20−7.16 (m, 3H), 6.73 (q, *J* = 2.2 Hz, 1H), 6.20−6.18 (m, 2H), 4.28−4.17 (m, 2H), 3.94 (s, 1H), 2.78−2.68 (m, 1H), 2.62−2.52 (m, 1H), 2.43−2.24 (m, 2H), 1.31 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 174.5 (C), 141.4 (C), 131.1 (C), 128.41 (CH), 128.37 (CH), 125.9 (CH), 116.8 (CH), 109.1 (CH), 105.2 (CH), 75.2 (C), 62.8 (CH_2), 42.2 (CH_2), 29.9 (CH_2), 14.1 (CH_3) ppm; MS (EI) *m*/*z* (rel intens) 273 $[M]^+$ (10), 200 (96), 105 (48), 91 (100); HRMS *m*/*z* calcd for $C_{16}H_{19}NO_3$ $[M]^+$ 273.1365, found 273.1366.

Assay of enantiomeric excess: chiral HPLC analysis (Chiralcel OD-H, 10% 2-propanol−90% hexane, 1.0 mL/min) $(+)_{major}$ t_R = 9.0 min, $(-)_{minor}$ t_R = 8.4 min, ee = 90%.

*Data for ethyl 2-(5-ethyl-1H-pyrrol-2-yl)-2-hydroxy-2-phenylacetate (**3ba**):* oil; $[\alpha]_D^{25}$ +42.8 (*c* = 1.33 in $CHCl_3$, 92% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.25 (br s, 1H), 7.48−7.44 (m, 2H), 7.37−7.30 (m, 3H), 6.17 (d, *J* = 3.6 Hz, 1H), 5.89 (d, *J* = 3.3 Hz, 1H), 4.40−4.20 (m, 2H), 4.38 (s, 1H), 2.60 (q, *J* = 7.6 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.7 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 173.4 (C), 141.3 (C), 134.5 (C), 128.7 (C), 128.1 (2 × CH), 126.6 (CH), 107.6 (CH), 104.9 (CH), 77.2 (C), 63.0 (CH_2), 20.8 (CH_2), 14.0 (CH_3), 13.4 (CH_3) ppm; MS (EI) *m*/*z* (rel intens) 273 $[M]^+$ (10), 255 (26), 200 (100), 154 (85), 105 (29); HRMS *m*/*z* calcd for $C_{16}H_{19}NO_3$ $[M]^+$ 273.1365, found 273.1355.

Assay of enantiomeric excess: chiral HPLC analysis (Chiralpack AS-H, 10% 2-propanol−90% hexane, 1.0 mL/min) $(+)_{major}$ t_R = 10.2 min, $(-)_{minor}$ t_R = 14.5 min, ee = 92%.

*Data for ethyl 2-(5-ethyl-1H-pyrrol-2-yl)-2-hydroxy-2-p-tolylacetate (**3bg**):* oil; $[\alpha]_D^{25}$ +28.2 (*c* = 0.87 in $CHCl_3$, 93% ee); ^1H NMR (300 MHz, $CDCl_3$) δ = 8.21 (br s, 1H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 8.1 Hz, 2H), 6.15 (t, *J* = 3.0 Hz, 1H), 5.88 (t, *J* = 3.0 Hz, 1H), 4.40−4.15 (m, 3H), 2.59 (q, *J* = 7.6 Hz, 2H), 2.34 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.22 (t, *J* = 7.5 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 173.5 (C), 138.5 (C), 137.9 (C), 134.4 (C), 129.3 (C), 128.8 (CH), 126.6 (CH), 107.5 (CH), 104.3 (CH), 76.9 (C), 63.0 (CH_2), 21.1 (CH_3), 20.8 (CH_2), 14.0 (CH_3), 13.4 (CH_3) ppm; MS (EI) *m*/*z* (rel intens) 287 $[M]^+$ (3), 269 (44), 214 (47), 196 (74), 119 (44), 91 (25), 71 (52), 69 (48), 57 (100); HRMS *m*/*z* calcd for $C_{17}H_{21}NO_3$ $[M]^+$ 287.152, found 287.1514.

Assay of enantiomeric excess: chiral HPLC analysis (Chiralpack AS-H, 10% 2-propanol−90% hexane, 1.0 mL/min) $(+)_{major}$ t_R = 9.0 min, $(-)_{minor}$ t_R = 11.3 min, ee = 93%.

*Data for ethyl 2-(4-chlorophenyl)-2-(5-ethyl-1H-pyrrol-2-yl)-2-hydroxyacetate (**3bj**):* oil; $[\alpha]_D^{25}$ +26.0 (*c* = 1.25 in $CHCl_3$, 83% ee); ^1H NMR (300 MHz, $CDCl_3$) δ = 8.17 (br s, 1H), 7.41 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 8.7 Hz, 2H), 6.14 (t, *J* = 3.0 Hz, 1H), 5.88 (t, *J* = 3.2 Hz, 1H), 4.39−4.19 (m, 3H), 2.59 (q, *J* = 7.5 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.22 (t, *J* = 7.5 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 173.0 (C), 139.7 (C), 134.8 (C), 134.1 (C), 128.4 (C), 128.22 (CH), 128.21 (CH), 107.6 (CH), 104.5 (CH), 77.2 (C), 63.0 (CH_2), 20.8 (CH_2), 14.0 (CH_3), 13.4 (CH_3) ppm; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{18}ClNO_3Na$ $[M + Na]^+$ 330.0873, found 330.0879.

Assay of enantiomeric excess: chiral HPLC analysis (Chiralpack AD-H, 10% 2-propanol−90% hexane, 1.0 mL/min) $(+)_{major}$ t_R = 10.2 min, $(-)_{minor}$ t_R = 9.4 min, ee = 83%.

*Data for ethyl 2-hydroxy-2-(5-(3-oxobutyl)-1H-pyrrol-2-yl)-2-phenylacetate (**3da**):* oil; $[\alpha]_D^{25}$ +26.5 (*c* = 1.2 in $CHCl_3$, 96% ee); ^1H NMR (300 MHz, $CDCl_3$) δ = 8.60 (br s, 1H), 7.45−7.42 (m, 2H), 7.35−7.28 (m, 3H), 6.12 (t, *J* = 3.0 Hz, 1H), 5.84 (t, *J* = 3.0 Hz, 1H), 4.39−4.23 (m, 3H), 4.22 (1H, s), 2.84−2.73 (m, 4H), 2.13 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 208.7 (C), 173.4 (C), 141.3 (C), 131.6 (C), 129.5 (C), 128.1 (2 × CH), 126.6 (CH), 107.4 (CH), 105.5 (CH), 77.2 (C), 63.0 (CH_2), 43.7 (CH_2), 30.0 (CH_3), 21.5 (CH_2), 14.0 (CH_3) ppm; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{21}NO_4Na$ $[M + Na]^+$ 338.1368, found 338.1365.

Assay of enantiomeric excess: chiral HPLC analysis (Chiralcel OD-H, 10% 2-propanol−90% hexane, 1.0 mL/min) $(+)_{major}$ t_R = 17.8 min, $(-)_{minor}$ t_R = 12.7 min, ee = 96%.

General Procedure for the Catalytic Enantioselective Friedel−Crafts Reaction with Dihydroindole. $Zr(O^tBu)_4$ (10 μL, 0.025 mmol) was added via syringe to a solution of ligand **L6** (18.7 mg, 0.025 mmol) in toluene (1.0 mL) under a nitrogen atmosphere at rt. After 1 h, a solution of α-ketoester **2** (0.125 mmol) and 4,7-dihydroindole (**4**; 0.15 mmol) in toluene (0.8 mL) was added, stirring was continued until completion of the reaction (TLC), and *p*-benzoquinone (40 mg, 0.375 mmol) was added. After 2 h, the reaction mixture was diluted with diethyl ether (30 mL), washed with 0.5 M aqueous sodium thiosulfate (25 mL), 2 M aqueous NaOH (2 × 20 mL), and brine, and dried over $MgSO_4$. After removal of the solvents under reduced pressure, product **5** was obtained by column chromatography eluting with hexane−EtOAc (9:1).

*Data for ethyl 2-hydroxy-2-(1H-indol-2-yl)-2-phenylacetate (**5a**):* oil; $[\alpha]_D^{25}$ +46.3 (*c* = 1.19 in $CHCl_3$, 91% ee); ^1H NMR (300 MHz, $CDCl_3$) δ = 8.54 (br s, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.50−7.47 (m, 2H), 7.35−7.33 (m, 4H), 7.21 (td, *J* = 7.5, 1.2 Hz, 1H), 7.13 (td, *J* = 7.5, 1.1 Hz, 1H), 6.66 (dd, *J* = 2.1, 0.9 Hz, 1H), 4.48 (s, 1H), 4.34−4.31 (m, 2H), 1.34 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 172.9 (C), 140.5 (C), 137.2 (C), 135.7 (C), 128.5 (CH), 128.3 (CH), 127.9 (C), 126.6 (CH), 122.4 (CH), 120.7 (CH), 120.0 (CH), 111.1 (CH), 101.8 (CH), 77.3 (C), 63.5 (CH_2), 14.0 (CH_3) ppm; MS (EI) *m*/*z* (rel intens) 295 $[M]^+$ (53), 223 (18), 222 (100), 206 (30), 105 (49), 77 (12); HRMS *m*/*z* calcd for $C_{18}H_{17}NO_3$ $[M]^+$ 295.1208, found 295.1215.

Assay of enantiomeric excess: chiral HPLC analysis (Chiralcel OD-H, 10% 2-propanol−90% hexane, 1.0 mL/min) $(+)_{major}$ t_R = 13.6 min, $(-)_{minor}$ t_R = 17.6 min, ee = 91%.

*Data for ethyl 2-hydroxy-2-(1H-indol-2-yl)-2-p-tolylacetate (**5g**):* oil; $[\alpha]_D^{25}$ +40.5 (*c* = 1.05 in $CHCl_3$, 92% ee); ^1H NMR (300 MHz, $CDCl_3$) δ = 8.51 (br s, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.36−7.32 (m, 3H), 7.19 (td, *J* = 7.6, 1.3 Hz, 1H), 7.15−7.09 (m, 3H), 6.64 (dd, *J* = 2.1, 0.9 Hz, 1H), 4.43−4.30 (m, 3H), 2.34 (s, 3H),1.34 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 173.0 (C), 138.3 (C), 137.7 (C), 137.4 (C), 135.7 (C), 129.0 (CH), 128.0 (C), 126.5 (CH), 122.3 (CH), 120.8 (CH), 120.0 (CH), 111.1 (CH), 101.8 (CH), 77.2 (C), 63.4 (CH_2), 21.1 (CH_3), 14.1 (CH_3) ppm; MS (EI) *m*/*z* (rel intens) 309 $[M]^+$ (47), 237 (18), 236 (100), 119 (47); HRMS *m*/*z* calcd for $C_{19}H_{19}NO_3$ $[M]^+$ 309.1365, found 309.1354.

Assay of enantiomeric excess: chiral HPLC analysis (Chiralcel OD-H, 10% 2-propanol−90% hexane, 1.0 mL/min) $(+)_{major}$ t_R = 11.8 min, $(-)_{minor}$ t_R = 16.1 min, ee = 92%.

*Data for ethyl 2-(4-chlorophenyl)-2-hydroxy-2-(1H-indol-2-yl)acetate (**5j**):* oil; $[\alpha]_D^{25}$ +50.2 (*c* = 1.41 in $CHCl_3$, 83% ee); ^1H NMR (300 MHz, $CDCl_3$) δ = 8.52 (br s, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.44 (d, *J* = 8.7 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.21 (td, *J* = 7.6, 1.2 Hz, 1H), 7.14 (td, *J* = 7.4, 1.0 Hz, 1H), 6.64 (d, *J* = 1.5 Hz, 1H), 4.51 (s, 1H), 4.46−4.28 (m, 2H), 1.34 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 172.5 (C), 138.9 (C), 136.7 (C), 135.7 (C), 134.4 (C), 128.4 (CH), 128.1 (CH), 127.9 (C), 122.6 (CH), 120.8 (CH), 120.1 (CH), 111.1 (CH), 101.8 (CH), 76.8 (C), 63.7 (CH_2), 14.0 (CH_3) ppm; MS (EI) *m*/*z* (rel intens) 329 $[M]^+$ (44), 258 (33), 257 (19), 256 (100), 140 (17), 138 (52); HRMS *m*/*z* calcd for $C_{18}H_{16}NO_3Cl$ $[M]^+$ 329.0819, found 329.0811.

Assay of enantiomeric excess: chiral HPLC analysis (Chiralcel OD-H, 10% 2-propanol−90% hexane, 1.0 mL/min) $(+)_{major}$ t_R = 13.4 min, $(-)_{minor}$ t_R = 21.0 min, ee = 83%.

*Data for ethyl 2-hydroxy-2-(1H-indol-2-yl)-2-(naphthalen-2-yl)acetate (**5n**):* oil; $[\alpha]_D^{25}$ +68.5 (*c* = 1.43 in $CHCl_3$, 90% ee); ^1H NMR (300 MHz, $CDCl_3$) δ = 8.60 (br s, 1H), 7.94 (d, *J* = 1.5 Hz, 1H), 7.85−7.78 (m, 3H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 8.7, 1.8 Hz, 1H), 7.51−7.48 (m, 2H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.22 (td, *J* = 7.5, 1.4 Hz, 1H), 7.16 (td, *J* = 7.4, 1.2 Hz, 1H), 6.73 (dd, *J* = 2.1, 0.9 Hz, 1H), 4.60 (s, 1H), 4.48−4.30 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 172.9 (C), 137.8 (C), 137.1 (C), 135.8 (C), 133.1 (C), 132.8 (C), 128.4 (CH), 128.1 (CH), 128.0 (C), 127.5 (CH), 126.6 (CH), 126.3 (CH), 125.8 (CH), 124.5 (CH), 122.4 (CH), 120.8 (CH), 120.0 (CH), 111.1 (CH), 102.0 (CH), 77.5 (C), 63.5 (CH_2), 14.0 (CH_3) ppm; MS (EI) *m*/*z* (rel intens) 345 $[M]^+$ (50), 327 (57), 272 (100), 254 (54), 155 (22) ppm; HRMS *m*/*z* calcd for $C_{22}H_{19}NO_3$ $[M]^+$ 345.1365, found 345.1352.

Assay of enantiomeric excess: chiral HPLC analysis (Chiralcel OD-H, 10% 2-propanol−90% hexane, 1.0 mL/min) $(+)_{major}$ t_R = 17.6 min, $(-)_{minor}$ t_R = 24.6 min, ee = 90%.

*Data for ethyl 2-hydroxy-2-(1H-indol-2-yl)-2-(thiophene-2-yl)acetate (**5o**):* oil; $[\alpha]_D^{25}$ +16.7 (*c* = 0.5 in $CHCl_3$, 84% ee); ^1H NMR (300 MHz, $CDCl_3$) δ = 8.56 (br s, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.35 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.30 (dd, *J* = 5.1, 1.5 Hz, 1H), 7.19 (td, *J* = 7.6, 1.3 Hz, 1H), 7.15 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.11 (td, *J* = 7.4, 1.2 Hz, 1H), 6.97 (dd, *J* = 5.0, 3.8 Hz, 1H), 6.65 (dd, *J* = 2.1, 0.9 Hz, 1H), 4.65 (s, 1H), 4.38 (qd, *J* = 7.2, 0.5 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 172.0 (C), 144.8 (C), 137.2 (C), 135.6 (C), 128.0 (C), 126.8 (CH), 126.2 (CH), 126.1 (CH), 122.5 (CH), 120.9 (CH), 120.0 (CH), 111.1 (CH), 101.4 (CH), 75.0 (C), 63.8 (CH_2), 14.0 (CH_3) ppm; MS (EI) *m*/*z* (rel intens) 301 $[M]^+$ (14), 283 (29), 228 (69), 212 (43), 210 (50), 110 (100), 71 (48); HRMS *m*/*z* calcd for $C_{16}H_{15}NO_3S$ $[M]^+$ 301.0773, found 301.0775.

Assay of enantiomeric excess: chiral HPLC analysis (Chiralcel OD-H, 10% 2-propanol−90% hexane, 1.0 mL/min) $(+)_{major}$ t_R = 14.4 min, $(-)_{minor}$ t_R = 18.4 min, ee = 84%.

Determination of the Absolute Stereochemistry of Compound 3aj. (*R*)-Ethyl 2-(Formylcarbamoyl)-2-(4-chlorophenyl)-2-hydroxyacetate (6). Ozone-enriched oxygen was bubbled through a precooled solution of compound **3aj** (84 mg, 0.3 mmol) in dichloromethane (6 mL) at −78 °C until complete reaction of the starting material (TLC). The excess ozone was removed by bubbling nitrogen through the solution. Then triphenylphosphine (87 mg, 0.33 mmol) was added, and the mixture was allowed to reach room temperature and diluted with dichloromethane. The solution was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the concentrated sample was chromatographed on silica gel eluting with hexane−EtOAc (90:10 to 60:40) to afford product **6** (11.4 mg, 40%). Product **6** was recrystallized from hexane−dichloromethane to give suitable crystals for X-ray analysis. Data for **6**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.25 (br d, J = 9.9 Hz, 1H), 9.08 (d, J = 9.9 Hz, 1H), 7.70 (d, J = 9.0 Hz, 2H), 7.37 (d, J = 9.0 Hz, 2H), 4.81 (s, OH), 4.38 (m, 2H), 1.34 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 169.1 (C), 168.6(C), 161.4 (CH), 135.5 (C), 133.4 (C), 128.7 (CH), 127.5 (CH), 79.0 (C), 64.8 (CH_2), 13.9 (CH_3) ppm.

Characterization of the Chiral Zirconium Catalyst. *Data for (R)-3,3′-bis(3,5-bis(trifluoromethyl)phenyl)-1,1′-binaphthyl-2,2′-diol (**L6**):* ^{1}H NMR (400 MHz, CD_2Cl_2) δ = 8.30 (s, 4H), 8.18 (s, 2H), 8.05 (d, J = 8.0 Hz, 2H), 7.98 (s, 2H), 7.51 (ddd, J = 8.1, 6.9, 1.2 Hz, 2H), 7.44 (ddd, J = 8.3, 6.9, 1.4 Hz, 2H), 7.25 (dd, J = 8.4, 0.4 Hz, 2H), 5.50 (s, 2H, OH) ppm; ^{1}H NMR (400 MHz, toluene-d_8) δ = 8.36 (s, 4H), 8.08 (s, 2H), 7.85 (s, 2H), 7.80 (d, J = 8.1 Hz, 2H), 7.37 (ddd, J = 8.1, 6.7, 1.4 Hz, 2H), 7.28 (dd, J = 7.8, 0.6 Hz, 2H), 7.23 (ddd, J = 8.1, 6.7, 1.2 Hz, 2H), 5.03 (s, 2H, OH) ppm; ^{13}C NMR (100.1 MHz, CD_2Cl_2) δ = 150.8 (C), 140.6 (C), 134.2 (C), 133.2 (CH), 132.1 (q, J(C,F) = 33.2 Hz, C), 130.7 (CH), 130.3 (C), 129.6 (CH), 129.2 (CH), 128.5 (C), 125.8 (CH), 124.7 (CH), 125.4 (q, J(C,F) = 271.3 Hz, CF_3). 122.0 (C), 112.6 (CH) ppm.

Zr(O^{t}Bu)$_2$-[(R)-3,3′-(3,5-bis(trifluoromethyl)phenyl)$_2$-BINOL]. Zr(O^{t}Bu)$_4$ (10 μL, 0.025 mmol) was added via syringe to a solution of ligand **L6** (18.7 mg, 0.025 mmol) in CD_2Cl_2 or toluene-d_8 (0.5 mL) under a nitrogen atmosphere at rt. Data for the title compound: ^{1}H NMR (400 MHz, CD_2Cl_2) δ = 8.32 (s, 4H), 7.91 (s, 2H), 7.86 (s, 2H), 7.85 (d, J = 8.4 Hz, 2H), 7.24 (ddd, J = 8.0, 6.8, 1.2 Hz, 2H), 7.11 (ddd, J = 8.2, 6.8, 1.2 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 1.00 (s, 18H) ppm; ^{1}H NMR (400 MHz, toluene-d_8) δ = 8.56 (s, 4H), 8.04 (s, 2H), 7.87 (s, 2H), 7.86 (d, J = 6.8 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.28 (t, J = 7.2 Hz, 2H), 7.07 (t, J = 7.4 Hz, 2H), 1.04 (s, 18H) ppm; ^{13}C NMR (100.1 MHz, CD_2Cl_2) δ = 157.0 (C), 144.6 (C), 136.6 (C), 132.5 (q, J(C,F) = 32.6 Hz, C), 132.0 (C), 130.7 (CH), 130.4 (CH), 129.0 (C), 128.7 (CH), 126.7 (CH), 126.6 (CH), 124.4 (q, J(C,F) = 271.1 Hz, CF_3), 123.1 (CH), 121.2 (CH), 120.2 (C), 75.6 (C), 31.6 (CH_3) ppm.

■ ASSOCIATED CONTENT

Supporting Information. Copies of NMR spectra for compounds **3**, **5**, and **6**, and ligand **L6** and its Zr(IV) complexes, X-ray plot and CIF file for compound **6**, NLE plot, and chiral HPLC chromatograms for compounds **3** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Flack parameter 0.04(7). Crystallographic data: refined formula $C_{12}H_{12}ClNO_5$, formula weight M_r 285.68, crystal dimensions 0.02 × 0.04 × 0.06 mm, crystal system monoclinic, space group $P2_1$, unit-cell dimensions a = 8.6560(4) Å, b = 5.9190(2) Å, c = 13.1680(5) Å, and β = 104.521(2)°, volume 653.11(4) Å, number of formula units in the unit cell (Z) 2, calculated density (ρ_{calcd}) 1.453, linear absorption coefficient (μ) 0.308, radiation wavelength 0.71073 Å, temperature of measurement 293 K, $2\theta_{max}$ = 27.53, nnumber of measured and independent reflections 3005, R_{int} = 0.0104, R = 0.0347, R_w = 0.0970, residual electron density 0.189, −0.243. Diffraction data were collected with an Enraf-Nonius Kappa-CCD single-crystal diffractometer using Mo Kα radiation.

The structure was solved by direct methods using SHELXS-97 and refined by full-matrix least-squares on F^2 using SHELXL-97. CCDC 812138 contains the supplementary crystallographic data for compound **6**. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Rd., Cambridge CB2 1EZ, U.K. Fax.: +441223/336-033. E-mail: deposit@ccdc.cam.ac.uk.

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