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Direct Asymmetric Allylic Alkenylation of *N*-Itaconimides with Morita–Baylis–Hillman Carbonates

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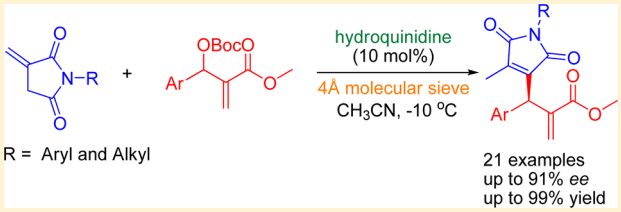
Supporting Information

ABSTRACT: The asymmetric allylic alkenylation of Morita–Baylis–Hillman (MBH) carbonates with *N*-itaconimides as nucleophiles has been developed using a commercially available *Cinchona* alkaloid catalyst. A variety of multifunctional chiral α-methylene-β-maleimide esters were attained in moderate to excellent yields (up to 99%) and good to excellent enantioselectivities (up to 91% *ee*). The origin of the regio- and stereoselectivity was verified by DFT methods. Calculated geometries and relative energies of various transition states strongly support the observed regio- and enantioselectivity.



INTRODUCTION

Succinimides are present in a variety of biologically interesting molecules and are studied as potential pharmacophores in drug discovery research.[1] In this context, many synthetic strategies have been developed in recent years for the asymmetric synthesis of succinimide derivatives. The application of *N*-maleimides as electrophiles has been largely recognized as a straightforward approach for their preparation.[2] Recently, *N*-itaconimides,[3] derived from *N*-maleimides, have been introduced by our group for the assembly of succinimide motifs owing to their dense functionalization. This functionalization exploits the activated exocyclic double bond and enolizable amide moiety.[4] For instance, we disclosed the first example of a highly enantioselective protonation of the *N*-itaconimides with secondary phosphine oxides[4a] or thiols[4b] to synthesize chiral succinimides. Later, we applied *N*-itaconimides as nucleophiles in a bicyclic-guanidine-catalyzed highly enantioselective allylic addition reaction to imines to produce various maleimides, which could be readily converted to succinimides.[4c] Despite this, the reaction scope of *N*-itaconimides used as nucleophiles is still limited due to their low reactivity.[4c]

Recently, Lewis base-catalyzed asymmetric allylic substitutions of MBH[5] adducts have become an alternative and viable option for accessing various chiral *C*-,[6] *N*-,[7] *O*-,[8] *P*-,[9] and *S*-,[10] allylic and spirocyclic[11] compounds. We have also demonstrated that modified *Cinchona* alkaloids are effective catalysts for the asymmetric allylic alkylation[6m] of bis(phenylsulfonyl)-methane (BSM), fluoro-bis(phenylsulfonyl)methane (FBSM) and allylic hydroxylation[8f] using water with MBH carbonates. Inspired by this progress and furthering our research interest, we herein report the first example of enantioselective allylic alkenylation[6p] of *N*-itaconimides with O-Boc-protected MBH carbonates to produce α-methylene-β-maleimide esters in high yields and good to excellent *ee* values. As shown in Scheme 1, we propose that the reaction between *N*-itaconimides **1** and MBH carbonates **2** should give an intermediate **A**, which could smoothly tautomerize to compound **3**.

RESULTS AND DISCUSSION

Our initial investigation was carried out with a series of *Cinchona* alkaloids as Lewis base organocatalysts[12] in the model reaction between *N*-phenyl itaconimide **1a** and MBH carbonate **2a** in 1,2-dichloroethane (DCE) at room temperature (Table 1, entries 1–11). The best enantioselectivity with 61% *ee* was achieved for hydroquinidine (HQD) resulting in the desired allylic alkenylation adduct **3aa** (entry 6). Furthermore, we screened the solvent effect with hydroquinidine as catalyst, and the results revealed that toluene was the best reaction solvent regarding the enantioselectivity (Table 1, entry 14). However, when the temperature was lowered to 0 °C, the enantioselectivity did not improve (Table 1, entry 17). When acetonitrile was used as solvent, the *ee* value of **3aa** was increased to 85% with 72% yield (Table 1, entry 19). Lowering the temperature to −20 °C showed a mild positive effect to the enantioselectivity (Table 1, entry 21). When 4 Å molecular

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Scheme 1. Postulated Mechanism for the Allylic Alkenylation of *N*-Itaconimides and MBH Carbonates Catalyzed by Lewis Base

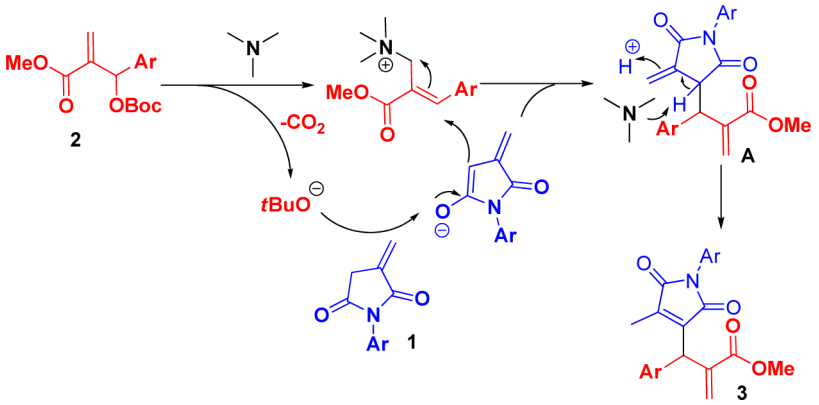
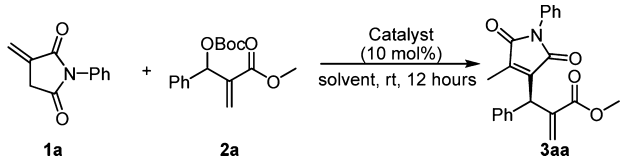


Table 1. Allylic Alkenylation of *N*-Phenyl Itaconimide 1a with MBH Carbonate 2a[a]



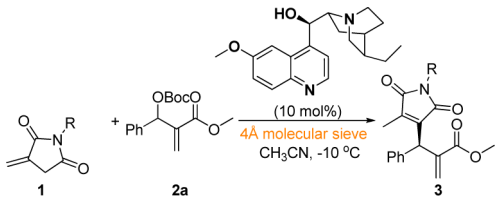
entry	catalyst	solvent	*T* (°C)	*t* (h)	yield (%)[b]	*ee* (%)[c]
1	QD	DCE	rt	12	61	52
2	QN	DCE	rt	12	59	−10
3	CN	DCE	rt	12	67	33
4	CND	DCE	rt	12	65	41
5	HQN	DCE	rt	12	63	17
6	HQD	DCE	rt	12	88	61
7	$(DHQ)_2PHAL$	DCE	rt	12	trace	27
8	$(DHQD)_2AQN$	DCE	rt	12	52	17
9	$(DHQD)_2PYR$	DCE	rt	12	47	10
10	$(DHQ)_2AQN$	DCE	rt	12	62	10
11	$(DHQD)_2PHAL$	DCE	rt	12	55	47
12	HQD	CH_2Cl_2	rt	12	90	66
13	HQD	CH_3CN	rt	12	94	65
14	HQD	Toluene	rt	12	89	80
15	HQD	THF	rt	12	66	62
16	HQD	Et_2O	rt	12	88	70
17	HQD	Toluene	0	24	91	79
18	HQD	Et_2O	0	24	68	72
19	HQD	CH_3CN	0	24	72	85
20	HQD	CH_3CN	−10	30	88	86
21	HQD	CH_3CN	−20	48	67	87
22[d]	HQD	CH_3CN	−10	68	97	89[e,f]
23[d]	HQD	CH_3CN	−20	80	84	87[e]

[a]Unless otherwise noted, the reaction was carried out with 0.04 mmol of **1a**, 0.02 mmol of **2a**, and 0.002 mol of catalyst in 0.2 mL of solvent. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC analysis. [d]4 Å molecular sieve (1:1, m/m) was added. [e]0.1 mmol scale in 1.0 mL of CH_3CN. [f]0.5 mmol scale in 5.0 mL of CH_3CN, yield = 90%, *ee* = 90%. DCE = 1,2-dichloroethane, QD = quinidine, QN = quinine, CN = cinchonine, CND = cinchonidine, HQN = hydroquinine, HQD = hydroquinidine, $(DHQ)_2PHAL$ = hydroquinine 1,4-phthalazinediyl diether, $(DHQD)_2AQN$ = hydroquinidine (anthraquinone-1,4-diyl) diether, $(DHQD)_2PYR$ = hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether, $(DHQ)_2AQN$ = hydroquinine anthraquinone-1,4-diyl diether, $(DHQD)_2PHAL$ = hydroquinidine 1,4-phthalazinediyl diether.

sieves were utilized as additive [1:1, m/m (**2a**: 4 Å molecular sieve)] in order to remove the trace amounts of water,[13] the allylic alkenylation reaction of *N*-phenyl itaconimide **1a** with MBH carbonate **2a** could be conducted at −10 °C, affording the adduct **3a** with 97% yield and 89% *ee* (Table 1, entry 22). When the reaction scale was increased from 0.1 to 0.5 mmol, no loss of *ee* was observed. It is worth noting that 4 Å molecular sieves did not increase the enantioselectivity when the reaction was conducted at −20 °C (Table 1, entry 23).

Under the established conditions, allylic alkenylations of different *N*-itaconimides (Table 2, **1b**–**h**) and MBH carbonate

Table 2. Allylic Alkenylation of *N*-Itaconimides 1 and MBH Carbonate 2a Catalyzed by Hydroquinidine[a]



entry	**1**, R	**3**	*t* (h)	yield (%)[b]	*ee* (%)[c]
1	**1b**, 4-BrC_6H_4	**3ba**	58	83	90
2	**1c**, 3-BrC_6H_4	**3ca**	54	99	90
3	**1d**, 3,5-$F_2C_6H_3$	**3da**	48	96	87
4	**1e**, 4-*t*BuC_6H_4	**3ea**	62	86	91
5	**1f**, 2-naphthyl	**3fa**	96	72	88
6	**1g**, 4-$MeOC_6H_4$	**3ga**	96	97	90
7	**1h**, *n*Bu	**3ha**	96	62	83

[a]Unless otherwise noted, the reaction was carried out with 0.2 mmol of **a**, 0.1 mmol of **2a**, and 0.01 mol of hydroquinidine in 1.0 mL of solvent. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC analysis.

2a afforded the products **3ba**–**ha** with good to excellent *ee* values (Table 2). *N*-Itaconimides (Table 2, **1b**–**d**) with electron-withdrawing groups on the aromatic rings were more active than those with electron-neutral and donating groups (Table 2, **1e**–**g**). However, the enantioselectivity slightly deviated from this trend, as the best *ee* value was achieved when **1e** with *para*-substituted *tert*-butyl group on the aromatic ring was utilized (91% *ee*, 86% yield, 62 h, Table 2, **1e**). Good enantioselectivity but moderate yield was achieved for *N*-itaconimide with *n*-butyl as aliphatic substituted group (83% *ee*, 62% yield, 96 h, Table 2, **1h**).

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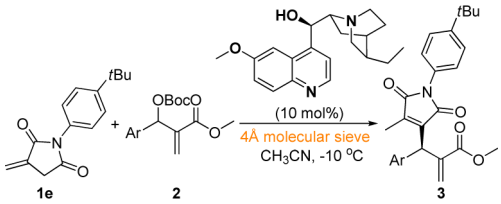
With *N*-itaconimide **1e** as the nucleophile, we investigated the scope of MBH carbonates in the presence of 10 mol % hydroquinidine in acetonitrile at −10 °C using 4 Å molecular sieve as additive (Table 3). All reactions proceeded smoothly with moderate to good yields (up to 86%) and good to excellent *ee* values (up to 91%). The trend of the electronic and steric effects of the substitutents on the aromatic ring of the MBH carbonates **2** did not have an observable effect on the outcome of the reaction. Unfortunately, this asymmetric allylic alkenylation reaction is not applicable to the aliphatic MBH carbonates due to many side reactions.[14]

Table 3. Allylic Alkenylation of *N*-Itaconimide 1e with MBH Carbonates 2 Catalyzed by Hydroquinidine[a]

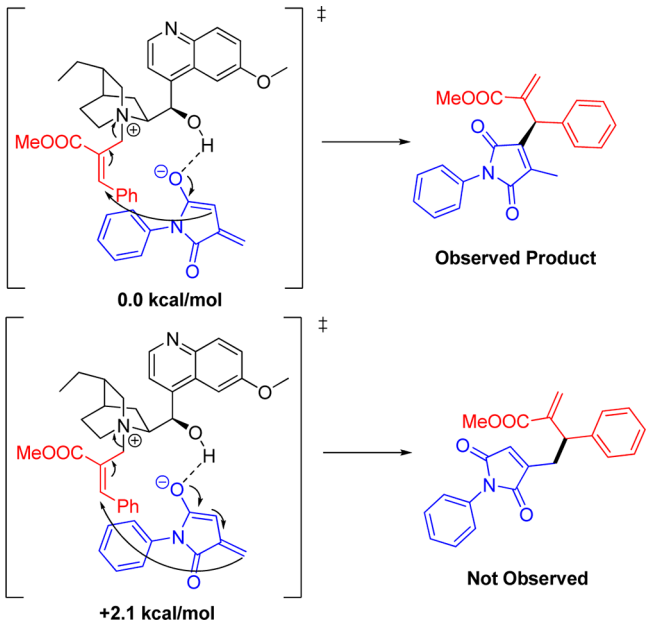


entry	2, Ar	3	*t* (h)	yield (%)[b]	*ee* (%)[c]
1	**2b**, 4-$NO_2C_6H_4$	**3eb**	48	85	79
2	**2c**, 4-$CF_3C_6H_4$	**3ec**	64	75	90
3	**2d**, 4-FC_6H_4	**3ed**	96	67	85
4	**2e**, 4-ClC_6H_4	**3ee**	32	85	91
5	**2f**, 4-BrC_6H_4	**3ef**	83	81	91
6	**2g**, 3-$CF_3C_6H_4$	**3eg**	74	86	85
7	**2h**, 3-ClC_6H_4	**3eh**	96	62	89
8	**2i**, 2-FC_6H_4	**3ei**	60	64	91
9	**2j**, 2-ClC_6H_4	**3ej**	70	72	91
10	**2k**, 4-MeC_6H_4	**3ek**	96	57	89
11	**2l**, 4-*i*PrC_6H_4	**3el**	96	40	90
12	**2m**, 4-$MeOC_6H_4$	**3em**	68	63	90
13	**2n**, 3-$MeOC_6H_4$	**3en**	60	67	90

[a]Unless otherwise noted, the reaction was carried out with 0.2 mmol of **1e**, 0.1 mmol of **2**, and 0.01 mol of hydroquinidine in 1.0 mL of solvent. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC analysis.

In order to fully comprehend the reaction mechanism and confirm our proposed transition state, we employed density functional theory (DFT) calculations using the Gaussian 09 program[15] and modeling experiments at the B3LYP/6-31G** level of theory[16] for the allylic alkenylation of MBH carbonate with *N*-itaconimide. Mechanistically, it is comprehensible that the *Cinchona* alkaloid moiety of the HQD catalyst is a strong tertiary amine nucleophile, which can attack to the *β* position of the *α*,*β* unsaturated MBH carbonate **2a**, which then subsequently undergoes a decarboxylation of the Boc moiety to extrude a molecule of CO_2 and *t*BuO^-. Subsequently, *t*BuO^- can abstract a proton from **1a** to generate an aromatic enolate intermediate that can be further stabilized by intermolecular H-bonding to the free hydroxyl group of the HQD-**2a** adduct, forming a pretransition state intermediate with a relative free energy of +6.5 kcal/mol with respect to the starting materials. The bifunctionality of the catalyst then allows it to bring the two substrates closer for the desired C−C bond formation, forming the *S*-enantiomer with an activation energy of +22.0 kcal/mol. Subsequent intramolecular proton rearrangement and decomplexation from the catalyst affords the product with an extremely stable relative free energy of −25.1 kcal/mol. DFT calculations also revealed that the activation barrier for the *R*-enantiomer was higher by +1.3 kcal/mol (refer to the Supporting Information). Upon closer inspection of the 3-D model of the transition state, we discovered that there is also a regioselectivity issue in this reaction: the alkenylation C−C bond can also occur at the *γ*-position of the nucleophile (Scheme 2), forming a totally different product. However, this product was not observed experimentally, and DFT calculations revealed that the activation barrier for the *S*-enantiomer of this product was much higher, by +3.4 kcal/mol. With these information in mind, we were able to formulate a possible catalytic cycle for this reaction (Scheme 3).

Scheme 2. Regioselectivity for the Formation of Different Alkenylation Products



In addition, we demonstrated that the chiral allylic alkenylation adducts can be easily converted to important biologically active intermediates,[17] which are shown in Scheme 4. A highly diastereoselective 1,3-dipolar cycloaddition between **3aa** and nitrile *N*-oxide, generated in situ from **4a**, occurred to deliver the desired product **5a** with vicinal quaternary−tertiary chiral centers without compromising the *ee* value. The protocol was readily extended to afford other 1,3-dipolar cycloaddition adducts with good results, such as **5b**. The absolute configurations of the allylic alkenylation products were assigned on the basis of X-ray crystallographic analysis of a single crystal of **5b**.[18]

CONCLUSION

In conclusion, we have developed an efficient allylic alkenylation of MBH carbonates with *N*-itaconimides. The reactions employed a commercially available *Cinchona* alkaloid as Lewis base catalyst and an experimentally simple protocol with mild reaction conditions. From this methodology, various synthetically valuable chiral *α*-methylene-*β*-maleimide esters were achieved in moderate to excellent yields (up to 99%) and good to excellent enantioselectivities (up to 91%). Several enantio-enriched compounds could be prepared from the allylic products. The origin of regio- and stereoselectivity were elucidated by DFT calculations. We believe this work should

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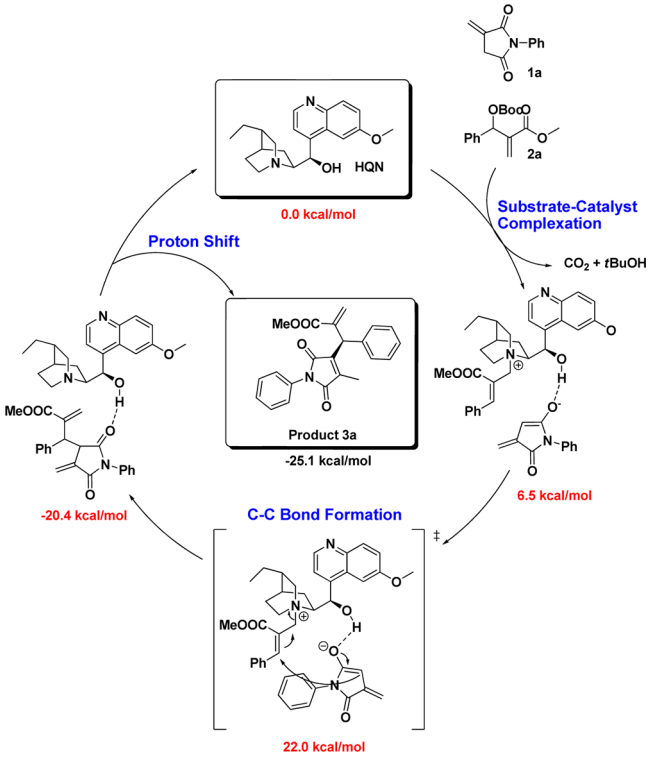
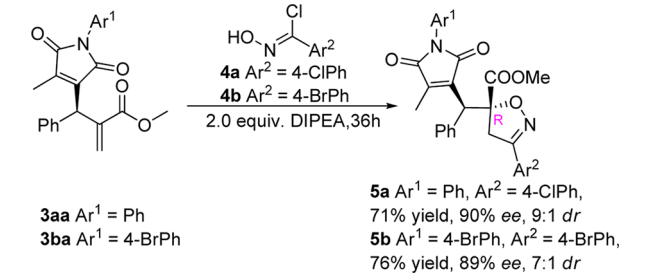
Scheme 3. Proposed Catalytic Cycle for the Asymmetric Allylic Alkenylation of *N*-Itaconimides with MBH Carbonates Catalyzed by HQD



Scheme 4. Synthetic Transformations of Multifunctional Adducts



potentially expand the synthetic utility of α-methylene-β-alkene esters in organic and medicinal chemistry.

EXPERIMENTAL SECTION

General Procedures and Methods. Experiments involving moisture and/or air sensitive components were performed under a positive pressure of nitrogen in oven-dried glassware equipped with a rubber septum inlet. Dried solvents and liquid reagents were transferred by oven-dried syringes or hypodermic syringe cooled to ambient temperature in a desiccator. Reactions mixtures were stirred in 4 mL sample vial with Teflon-coated magnetic stirring bars unless otherwise stated. Moisture in nonvolatile reagents/compounds was removed in high vacuo by means of an oil pump and subsequent purging with nitrogen. Solvents were removed in vacuo under ~30 mmHg and heated with a water bath at 30–35 °C using rotary evaporator with aspirator. The condenser was cooled with running water at 0 °C.

All experiments were monitored by analytical thin layer chromatography (TLC). TLC was performed on precoated plates, 60 F_{254}. After elution, plate was visualized under UV illumination at 254 nm for UV active material. Further visualization was achieved by staining $KMnO_4$, Ceric Ammonium Molybdate, or *para*-anisaldehyde solution. For those using the aqueous stains, the TLC plates were heated on a hot plate.

Columns for flash chromatography (FC) contained silica gel 200–300 mesh. Columns were packed as slurry of silica gel in petroleum ether (60–90 °C) and equilibrated using the appropriate solvent system. The elution was assisted by applying pressure of about 2 atm with an air pump.

Instrumentations. Proton nuclear magnetic resonance (^{1}H NMR) and carbon NMR (^{13}C NMR) spectra were recorded in $CDCl_3$ unless otherwise stated. ^{1}H (400 MHz) and ^{13}C (100 MHz) were performed on a 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm), using the residual solvent signal as an internal standard: $CDCl_3$ (^{1}H NMR: δ 7.26, singlet; ^{13}C NMR: δ 77.0, triplet). Low resolution mass spectra were obtained in EI or ESI mode. MS and HRMS (Analyzer: TOF) were reported in units of mass of charge ratio (m/z). Mass samples were dissolved in CH_3CN (HPLC grade) unless otherwise stated. Optical rotations were recorded with a sodium lamp of wavelength 589 nm and reported as follows; $[\alpha]_\lambda^{T\,°C}$ (c = g/100 mL, solvent).

Enantiomeric excesses were determined by chiral high performance liquid chromatography (HPLC) analysis with manual injection valve. HPLC samples were dissolved in HPLC grade isopropanol (IPA) unless otherwise stated.

Materials. All commercial reagents were purchased with the highest purity grade. They were used without further purification unless specified. All solvents used, mainly petroleum ether and ethyl acetate, were distilled. THF and toluene were freshly distilled from sodium/benzophenone before use. DCE and MeCN were distilled from CaH_2 and stored under N_2 atomosphere. All compounds synthesized were stored in a −20 °C freezer, and light-sensitive compounds were protected with aluminum foil.

General Procedure for the Asymmetric Allylic Alkenylation of *N*-Itaconimides 1 with Morita–Baylis–Hillman Carbonates 2 in the Presence of Hydroquinidine As Lewis Base. MBH carbonate **2** (0.1 mmol, 1.0 equiv), hydroquinidine (3.3 mg, 0.01 mmol, 0.1 equiv) and 4 Å molecular sieve [m/m (molecular sieve: **2**) = 1:1] were dissolved in acetonitrile (1.0 mL) in 4 mL sample vials and stirred at −10 °C for 30 min. Then *N*-itaconimides **1** (0.2 mmol, 2.0 equiv) was added. The reaction mixtures were stirred and maintained at −10 °C, and the reaction progress was monitored by TLC. Upon complete consumption of **2**, the reaction mixtures were loaded onto a short silica gel column, followed by separation with flash chromatography using gradient elution with petroleum ether/ethyl acetate (10:1 to 5:1). After removal of solvent under vacuum, the corresponding adducts **3** were obtained.

3aa, (*S*)-(+)-Methyl 2-((4-methyl-2,5-dioxo-1-phenyl-2,5-dihydro-1*H*-pyrrol-3-yl)(phenyl)methyl)acrylate. Yellow oil: 163.2 mg (0.5 mmol), 90% yield; 90% *ee*; $[\alpha]_D^{26}$ +27.4 (*c* 0.19, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42 (d, J = 7.4 Hz, 2H), 7.39–7.35 (m, 4H), 7.33–7.30 (m, 2H), 7.26–7.24 (m, 2H), 6.52 (s, 1H), 5.47 (d, J = 1.5 Hz, 1H), 5.35 (s, 1H), 3.77 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.7, 169.9, 166.6, 139.8, 139.6, 138.4, 137.6, 131.8, 129.0, 128.9, 128.8, 128.4, 127.6, 127.4, 125.6, 52.3, 43.3, 9.1; LRMS (ESI) m/z 383.9 (M + Na^+); HRMS (ESI) m/z 384.1218 (M + Na^+), calc. for $C_{22}H_{19}NNaO_4$ 384.1206. The *ee* was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 80/20; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time = 10.5 min (major) and 11.5 min (minor).

3ba, (*S*)-(+)-Methyl 2-((1-(4-bromophenyl)-4-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)(phenyl)methyl)acrylate. Colorless oil: 36.7 mg (0.1 mmol), 83% yield; 90% *ee*; $[\alpha]_D^{26}$ +16.4 (*c* 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.55 (d, J = 8.8 Hz, 2H), 7.36 (dd, J = 16.4, 8.8 Hz, 3H), 7.32–7.26 (m, 2H), 7.24 (d, J = 7.2 Hz, 2H), 6.51 (s, 1H), 5.46 (s, 1H), 5.32 (s, 1H), 3.77 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.4, 169.6, 166.6, 139.9, 139.7, 138.6, 137.5, 132.0, 130.9, 129.0, 128.8, 128.5, 127.7, 126.9, 120.9, 52.4, 43.3, 9.1; LRMS (EI) m/z 438.9 (M^+); HRMS (EI) m/z 439.0396 (M^+), calc. for $C_{22}H_{18}NO_4Br$ 439.0414. The *ee* was determined by HPLC analysis. CHIRALPAK IA (4.6 mm

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i.d. × 250 mm); hexane/2-propanol = 90/10; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time = 14.6 min (minor) and 18.7 min (major).

3ca, (*S*)-(+)-Methyl 2-((1-(3-bromophenyl)-4-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)(phenyl)methyl)acrylate. Yellow oil: 43.8 mg (0.1 mmol), 99% yield; 90% *ee*; $[\alpha]_D^{26}$ +40.5 (*c* 0.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.59 (s, 1H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 3H), 7.31 (t, *J* = 6.7 Hz, 2H), 7.27−7.23 (m, 2H), 6.52 (s, 1H), 5.46 (s, 1H), 5.32 (s, 1H), 3.77 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 169.5, 166.6, 140.0, 139.8, 138.6, 137.5, 133.1, 130.4, 130.1, 129.0, 128.9, 128.5, 128.4, 127.7, 123.9, 122.2, 52.3, 43.4, 9.1; LRMS (ESI) *m*/*z* 437.9 (M−H$^+$); HRMS (ESI) *m*/*z* 438.0344 (M−H$^+$), calc. for $C_{22}H_{17}BrNO_4$ 438.0346. The *ee* was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 80/20; flow rate 1.0 mL/min; 25 °C; 230 nm; retention time = 7.3 min (major) and 10.1 min (major).

3da, (*S*)-(+)-Methyl 2-((1-(3,5-difluorophenyl)-4-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)(phenyl)methyl)acrylate. Yellow oil: 38.2 mg (0.1 mmol), 96% yield; 87% *ee*; $[\alpha]_D^{26}$ +39.1 (*c* 0.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.37 (t, *J* = 7.3 Hz, 2H), 7.31 (dd, *J* = 8.6, 5.9 Hz, 1H), 7.23 (d, *J* = 7.1 Hz, 2H), 7.13−7.07 (m, 2H), 6.78−6.73 (m, 1H), 6.52 (s, 1H), 5.45 (s, 1H), 5.31 (s, 1H), 3.77 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 169.9, 169.1, 166.6, 164.0, 163.9, 161.6, 161.4, 140.2, 139.7, 138.7, 137.3, 129.1, 128.8, 128.6, 127.8, 108.3, 108.0, 102.8, 102.6, 102.3, 52.4, 43.4, 9.1; LRMS (ESI) *m*/*z* 420.1 (M + Na$^+$); HRMS (ESI) *m*/*z* 420.1019 (M + Na$^+$), calc. for $C_{22}H_{17}F_2NNaO_4$ 420.1018. The *ee* was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90/10; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time = 5.4 min (major) and 6.1 min (minor).

3ea, (*S*)-(+)-Methyl 2-((1-(4-*tert*-butylphenyl)-4-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)(phenyl)methyl)acrylate. Yellow oil: 35.8 mg (0.1 mmol), 86% yield; 91% *ee*; $[\alpha]_D^{26}$ +22.0 (*c* 0.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.44−7.24 (m, 9H), 6.51 (s, 1H), 5.47 (s, 1H), 5.34 (s, 1H), 3.76 (s, 3H), 1.93 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.9, 170.1, 166.6, 150.5, 139.9, 139.7, 138.5, 137.8, 129.1, 129.0, 128.9, 128.4, 127.6, 125.9, 125.2, 52.3, 43.3, 34.6, 31.3, 9.1; LRMS (ESI) *m*/*z* 440.1 (M + Na$^+$); HRMS (ESI) *m*/*z* 440.1841 (M + Na$^+$), calc. for $C_{26}H_{27}NNaO_4$ 440.1832. The *ee* was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90/10; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time = 10.0 min (major) and 12.6 min (minor).

3fa, (*S*)-(+)-Methyl 2-((4-methyl-1-(naphthalen-2-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)(phenyl)methyl)acrylate. Yellow oil: 29.7 mg (0.1 mmol), 72% yield; 88% *ee*; $[\alpha]_D^{26}$ +117.1 (*c* 0.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.90 (dd, *J* = 8.8, 3.3 Hz, 1H), 7.86−7.82 (m, 3H), 7.52−7.47 (m, 3H), 7.43−7.37 (m, 3H), 7.34−7.31 (m, 1H), 7.29 (d, *J* = 1.5 Hz, 1H), 6.54 (d, *J* = 1.6 Hz, 1H), 5.49 (d, *J* = 1.6 Hz, 1H), 5.38 (s, 1H), 3.79 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.9, 170.1, 166.6, 139.8 (two peaks), 138.6, 137.6, 133.2, 132.2, 129.2, 129.0, 128.9, 128.7, 128.5, 128.0, 127.6 (two peaks), 126.4 (two peaks), 124.2, 123.5, 52.4, 43.3, 9.2; LRMS (ESI) *m*/*z* 434.1 (M + Na$^+$); HRMS (ESI) *m*/*z* 434.1361 (M + Na$^+$), calc. for $C_{26}H_{21}NNaO_4$ 434.1363. The *ee* was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90/10; flow rate 1.0 mL/min; 25 °C; 210 nm; retention time = 20.7 min (minor), 25.9 min (major).

3ga, (*S*)-(+)-Methyl 2-((1-(4-methoxyphenyl)-4-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)(phenyl)methyl)acrylate. Yellow oil: 38.1 mg (0.1 mmol), 97% yield; 90% *ee*; $[\alpha]_D^{26}$ +236 (*c* 0.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.41−7.28 (m, 4H), 7.25−7.23 (m, 3H), 6.95−6.93 (m, 2H), 6.51 (s, 1H), 5.46 (d, *J* = 1.4 Hz, 1H), 5.33 (s, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.0, 170.2, 166.6, 158.7, 139.8, 139.5, 138.4, 137.6, 128.9, 128.8, 128.4, 127.6, 127.1, 124.4, 114.2, 55.4, 52.3, 43.2, 9.1; LRMS (ESI) *m*/*z* 414.0 (M + Na$^+$); HRMS (ESI) *m*/*z* 414.1302 (M + Na$^+$), calc. for $C_{23}H_{21}NNaO_5$ 414.1312. The *ee* was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 80/20; flow rate 1.0 mL/min; 25 °C; 210 nm; retention time = 16.1 min (major) and 20.6 min (minor).

3ha, (*S*)-(+)-Methyl 2-((1-butyl-4-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)(phenyl)methyl)acrylate. Yellow oil: 21.3 mg (0.1 mmol), 62% yield; 83% *ee*; $[\alpha]_D^{26}$ +16.4 (*c* 0.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 77.33 (t, *J* = 6.9 Hz, 2H), 7.29−7.25 (m, 1H), 7.18 (d, *J* = 7.2 Hz, 2H), 6.47 (s, 1H), 5.38 (s, 1H), 5.25 (s, 1H), 3.73 (s, 3H), 3.47 (t, *J* = 7.2 Hz, 2H), 1.81 (s, 3H), 1.58−1.50 (m, 2H), 1.32−1.23 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 172.1, 171.3, 166.6, 140.0, 139.3, 138.2, 137.8, 128.9, 128.7, 128.0, 127.4, 52.2, 43.0, 37.9, 30.6, 19.9, 13.5, 8.8; LRMS (ESI) *m*/*z* 364.1 (M + Na$^+$); HRMS (ESI) *m*/*z* 364.1529 (M + Na$^+$), calc. for $C_{20}H_{23}NNaO_4$ 364.1519. The *ee* was determined by HPLC analysis. CHIRALCEL OD-H (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90/10; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time = 6.6 min (minor), 7.3 min (major).

3eb, (*S*)-(+)-Methyl 2-((1-(4-*tert*-butylphenyl)-4-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)(4-nitrophenyl)methyl)-acrylate. Yellow oil: 39.4 mg (0.1 mmol), 85% yield; 79% *ee*; $[\alpha]_D^{26}$ +10.0 (*c* 0.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.23 (d, *J* = 8.6 Hz, 2H), 7.45 (dd, *J* = 8.6, 3.8 Hz, 4H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.60 (s, 1H), 5.54 (d, *J* = 0.9 Hz, 1H), 5.47 (s, 1H), 3.78 (s, 3H), 1.98 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.3, 169.7, 166.1, 150.8, 147.3, 145.4, 139.6, 138.4, 138.0, 129.7, 129.1, 128.7, 126.0, 125.2, 124.1, 52.6, 42.9, 34.6, 31.2, 9.3; LRMS (ESI) *m*/*z* 461.1 (M−H$^+$); HRMS (ESI) *m*/*z* 461.1710 (M−H$^+$), calc. for $C_{26}H_{26}N_2O_6$ 461.1718. The *ee* was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 80/20; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time = 18.8 min (major) and 37.5 (minor).

3ec, (*S*)-(+)-Methyl 2-((1-(4-*tert*-butylphenyl)-4-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)(4-(trifluoromethyl)phenyl)-methyl)acrylate. Yellow oil: 36.3 mg (0.1 mmol), 75% yield; 90% *ee*; $[\alpha]_D^{26}$ +65.9 (*c* 0.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.63 (d, *J* = 8.2 Hz, 2H), 7.46−7.43 (m, 2H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.26 (s, 1H), 7.24 (t, *J* = 2.1 Hz, 1H), 6.56 (s, 1H), 5.50 (d, *J* = 1.5 Hz, 1H), 5.42 (s, 1H), 3.78 (s, 3H), 1.96 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.5, 169.8, 166.3, 150.6, 141.9 (two peaks), 139.1, 139.0, 138.6, 129.2, 128.8, 126.1, 126.0, 125.9 (two peaks), 125.5, 125.2, 52.4, 43.0, 34.6, 31.2, 9.2; LRMS (ESI) *m*/*z* 485.2 (M$^+$); HRMS (ESI) *m*/*z* 485.1803 (M$^+$), calc. for $C_{27}H_{26}F_3NO_4$ 485.1814. The *ee* was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 80/20; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time = 8.6 min (major) and 14.0 (minor).

3ed, (*S*)-(+)-Methyl 2-((1-(4-*tert*-butylphenyl)-4-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)(4-fluorophenyl)methyl)-acrylate. Yellow oil: 29.4 mg (0.1 mmol), 67% yield; 85% *ee*; $[\alpha]_D^{26}$ +7.8 (*c* 0.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 77.46−7.42 (m, 2H), 7.27 (s, 1H), 7.25−7.20 (m, 3H), 7.06 (t, *J* = 8.6 Hz, 2H), 6.52 (s, 1H), 5.47 (d, *J* = 1.5 Hz, 1H), 5.32 (s, 1H), 3.77 (s, 3H), 1.94 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.8, 167.0, 166.5, 163.3, 160.9, 150.5, 139.7, 139.4, 138.5, 133.4, 130.5, 130.4, 128.9, 128.4, 126.0, 125.2, 116.0, 115.8, 52.4, 42.6, 34.6, 31.2, 9.1; LRMS (ESI) *m*/*z* 434.2 (M−H$^+$); HRMS (ESI) *m*/*z* 434.1756 (M−H$^+$), calc. for $C_{26}H_{25}FNO_4$ 434.1773. The *ee* was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90/10; flow rate 1.0 mL/min; 25 °C; 230 nm; retention time = 11.0 min (major) and 14.8 min (minor).

3ee, (*S*)-(+)-Methyl 2-((1-(4-*tert*-butylphenyl)-4-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)(4-chlorophenyl)methyl)-acrylate. Yellow oil: 38.3 mg (0.1 mmol), 85% yield; 91% *ee*; $[\alpha]_D^{26}$ +59.7 (*c* 0.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ ^{1} H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.6, 2H), 7.34 (d, *J* = 8.4, 2H), 7.27−7.24 (m, 2H), 7.20 (d, *J* = 8.5, 2H), 6.52 (s, 1H), 5.49 (d, *J* = 1.5, 1H), 5.32 (s, 1H), 3.76 (s, 3H), 1.94 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.6, 169.9, 166.4, 150.5, 139.4, 139.0, 138.7, 136.3, 133.5, 130.2, 129.1, 128.9, 128.4, 125.9, 125.2, 52.3, 42.7, 34.6, 31.2, 9.1; LRMS (ESI) *m*/*z* 474.0 (M + Na$^+$); HRMS (ESI) *m*/*z* 474.1461 (M + Na$^+$), calc. for $C_{26}H_{26}ClNO_4Na$ 474.1443. The *ee* was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250

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mm); hexane/2-propanol = 90/10; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time = 10.0 min (major) and 12.6 min (minor).

3ef, (*S*)-(+)-Methyl 2-((1-(4-*tert*-butylphenyl)-4-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)(4-bromophenyl)methyl)-acrylate. Yellow oil: 40.1 mg (0.1 mmol), 81% yield; 91% *ee*; $[\alpha]_D^{26}$ +48.1 (*c* 0.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.46 (dd, *J* = 19.6, 8.6 Hz, 5H), 7.24 (s, 1H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.53 (d, *J* = 1,5 Hz, 1H), 5.49 (d, *J* = 1.5, 1H), 5.29 (s, 1H), 3.76 (s, 3H), 1.94 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.6, 169.9, 166.4, 150.5, 139.2, 139.0, 138.7, 136.8, 132.1, 130.5, 128.9, 128.5, 125.9, 125.1, 121.6, 52.4, 42.7, 34.6, 31.2, 9.2; LRMS (EI) *m*/*z* 495.1 (M^+); HRMS (ESI) *m*/*z* 496.1124 (M + H^+), calc. for $C_{26}H_{27}O_4NBr$ 496.1123. The *ee* was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 80/20; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time = 9.6 min (major) and 14.4 min (minor).

3eg, (*S*)-(+)-Methyl 2-((1-(4-*tert*-butylphenyl)-4-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)(3-(trifluoromethyl)phenyl)-methyl)acrylate. Yellow oil: 41.9 mg (0.1 mmol), 86% yield; 85% *ee*; $[\alpha]_D^{26}$ +31.6 (*c* 0.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.46 (t, *J* = 9.0 Hz, 6H), 7.28 (s, 1H), 7.24 (s, 1H), 6.47 (d, *J* = 1.6 Hz, 1H), 5.49 (s, 1H), 5.43 (s, 1H), 3.77 (s, 3H), 1.95 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.7, 170.5, 166.2, 150.7, 150.6, 145.7, 139.1, 139.0, 138.8, 138.6, 129.4, 128.8 (two peaks), 127.4, 126.1, 126.0, 125.4, 125.1, 52.4, 42.9, 34.6, 31.2, 9.2; LRMS (ESI) *m*/*z* 484.1 (M−H^+); HRMS (ESI) *m*/*z* 484.1749 (M−H^+), calc. for $C_{27}H_{25}F_3NO_4$ 484.1741. The *ee* was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90/10; flow rate 1.0 mL/min; 25 °C; 210 nm; retention time = 11.0 min (major) and 14.8 min (minor).

3eh, (*S*)-(+)-Methyl 2-((1-(4-*tert*-butylphenyl)-4-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)(3-chlorophenyl)methyl)-acrylate. Yellow oil: 28.2 mg (0.1 mmol), 62% yield; 89% *ee*; $[\alpha]_D^{26}$ +7.0 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.45 (d, *J* = 8.6 Hz, 2H), 7.30−7.24 (m, 5H), 7.15 (d, *J* = 6.2 Hz, 1H), 6.55 (s, 1H), 5.50 (s, 1H), 5.33 (s, 1H), 3.77 (s, 3H), 1.95 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.6, 169.9, 166.3, 150.5, 139.8, 139.1, 138.9, 138.8, 134.8, 130.2, 128.9, 128.7, 127.8, 127.0, 125.9, 125.2, 52.4, 42.8, 34.6, 31.2, 9.2; LRMS (ESI) *m*/*z* 451.2 (M^+); HRMS (ESI) *m*/*z* 451.1541 (M^+), calc. for $C_{26}H_{26}ClNO_4$ 451.1550. The *ee* was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 80/20; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time = 5.8 min (minor major) and 9.1 min (minor).

3ei, (*S*)-(+)-Methyl 2-((1-(4-*tert*-butylphenyl)-4-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)(2-fluorophenyl)methyl)-acrylate. Yellow oil: 27.7 mg (0.1 mmol), 64% yield; 91% *ee*; $[\alpha]_D^{26}$ +18.1 (*c* 0.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.47−7.45 (m, 2H), 7.35−7.25 (m, 4H), 7.18−7.09 (m, 2H), 6.55 (d, *J* = 1.5 Hz, 1H), 5.61 (s, 1H), 5.53 (d, *J* = 1.5 Hz, 1H), 3.78 (s, 3H), 1.95 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.6, 169.8, 166.3, 161.7, 159.2, 150.4, 139.1, 138.3, 138.0, 129.9, 129.9, 129.5, 129.4, 128.9, 128.1, 125.9, 125.1, 124.4 (two peaks), 115.9, 115.7, 52.4, 36.6, 36.6, 34.6, 31.2, 8.9; LRMS (ESI) *m*/*z* 435.2 (M^+); HRMS (ESI) *m*/*z* 435.1835 (M^+), calc. for $C_{26}H_{26}FNO_4$ 435.1846. The *ee* was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90/10; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time = 8.5 min (major) and 10.5 min (minor).

3ej, (*S*)-(+)-Methyl 2-((1-(4-*tert*-butylphenyl)-4-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)(2-chlorophenyl)methyl)-acrylate. Yellow oil: 32.8 mg (0.1 mmol), 72% yield; 91% *ee*; $[\alpha]_D^{26}$ −17.2 (*c* 0.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.47−7.41 (m, 4H), 7.29−7.27 (m, 3H), 7.26−7.23 (m, 1H), 6.55 (d, *J* = 1.5 Hz, 1H), 5.72 (s, 1H), 5.47 (d, *J* = 1.5 Hz, 1H), 3.76 (s, 3H), 1.86 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.6, 169.8, 166.2, 150.4, 139.6, 138.4, 138.1, 135.7, 134.2, 130.1, 129.7, 129.0, 128.2, 127.0, 125.9, 125.1, 52.4, 40.4, 34.6, 31.2, 9.0; LRMS (ESI) *m*/*z* 451.2 (M^+); HRMS (ESI) *m*/*z* 451.1558 (M^+), calc. for $C_{26}H_{26}ClNO_4$ 451.1550. The *ee* was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 98/2; flow rate 1.0 mL/min; 25 °C; 210 nm; retention time = 14.2 min (major) and 17.5 min (minor).

3ek, (*S*)-(+)-Methyl 2-((1-(4-*tert*-butylphenyl)-4-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)(*p*-tolyl)methyl)acrylate. Yellow oil: 24.6 mg (0.1 mmol), 57% yield; 89% *ee*; $[\alpha]_D^{26}$ +43.7 (*c* 0.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.45 (dd, *J* = 15.4 Hz, 8.7, 2H), 7.26 (d, *J* = 8.7 Hz, 2H), 7.15 (q, *J* = 8.3 Hz, 4H), 6.50 (s, 1H), 5.48 (d, *J* = 1.2 Hz, 1H), 5.29 (s, 1H), 3.76 (s, 3H), 2.35 (s, 3H), 1.94 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.0, 170.1, 166.7, 150.4, 139.9, 139.8, 138.2, 137.3, 134.6, 129.6, 129.0, 128.7, 128.2, 125.9, 125.2, 52.3, 42.9, 34.6, 31.2, 21.0, 9.1; LRMS (ESI) *m*/*z* 454.2 (M + Na^+); HRMS (ESI) *m*/*z* 454.1993 (M + Na^+), calc. for $C_{27}H_{29}NO_4Na$ 454.1989. The *ee* was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90/10; flow rate 1.0 mL/min; 25 °C; 230 nm; retention time = 9.2 min (major) and 15.6 min (minor).

3el, (*S*)-(+)-Methyl 2-((1-(4-*tert*-butylphenyl)-4-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)(4-isopropylphenyl)methyl)-acrylate. Yellow oil: 18.4 mg (0.1 mmol), 40% yield; 90% *ee*; $[\alpha]_D^{26}$ −7.0 (*c* 0.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.46−7.41 (m, 2H), 7.27−7.24 (m, 2H), 7.22−7.15 (m, 4H), 6.50 (s, 1H), 5.48 (d, *J* = 1.2 Hz, 1H), 5.30 (s, 1H), 3.76 (s, 3H), 2.93−2.86 (m, 1H), 1.95 (s, 3H), 1.31 (s, 9H), 1.24 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.0, 170.1, 166.7, 150.4, 148.2, 140.0, 139.8, 138.2, 134.8, 129.1, 128.8, 128.3, 127.0, 125.9, 125.2, 52.3, 42.9, 34.6, 33.7, 31.3, 23.9, 23.9, 9.1; LRMS (ESI) *m*/*z* 459.2 (M^+); HRMS (ESI) *m*/*z* 459.2401 (M^+), calc. for $C_{29}H_{33}NO_4$ 459.2410. The *ee* was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 80/20; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time = 5.4 min (major) and 8.0 min (minor).

3em, (*S*)-(+)-Methyl 2-((1-(4-*tert*-butylphenyl)-4-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)(4-methoxyphenyl)methyl)-acrylate. Yellow oil: 28.1 mg (0.1 mmol), 63% yield; 90% *ee*; $[\alpha]_D^{26}$ +24.0 (*c* 0.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.43 (d, *J* = 8.6 Hz, 2H), 7.27 (s, 1H), 7.24 (s, 1H), 7.17 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.49 (s, 1H), 5.47 (s, 1H), 5.27 (s, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 1.94 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.0, 170.1, 166.7, 158.9, 150.4, 140.1, 139.9, 138.0, 130.0, 129.5, 129.0, 128.2, 125.9, 125.2, 114.3, 55.3, 52.3, 42.6, 34.6, 31.3, 9.1; LRMS (ESI) *m*/*z* 447.2 (M^+); HRMS (ESI) *m*/*z* 447.2034 (M^+), calc. for $C_{27}H_{29}NO_5$ 447.2046. The *ee* was determined by HPLC analysis. CHIRALCEL AD-H (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90/10; flow rate 1.0 mL/min; 25 °C; 210 nm; retention time = 13.5 min (major) and 20.6 min (minor).

3en, (*S*)-(+)-Methyl 2-((1-(4-*tert*-butylphenyl)-4-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)(3-methoxyphenyl)methyl)-acrylate. Yellow oil: 30.0 mg (0.1 mmol), 67% yield; 90% *ee*; $[\alpha]_D^{26}$ −16.3 (*c* 0.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.46−7.42 (m, 2H), 7.30−7.26 (m, 2H), 7.25 (d, *J* = 2.9 Hz, 1H), 6.86−6.78 (m, 3H), 6.51 (s, 1H), 5.50 (d, *J* = 1.3 Hz, 1H), 5.31 (s, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 1.94 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 174.2, 174.1, 164.2, 156.6, 152.1, 149.6, 133.1, 130.6, 129.70, 129.2, 129.0, 128.6, 128.4, 123.2, 120.2, 85.0, 54.6, 34.0, 30.0, 24.9, 23.6, 23.6; LRMS (ESI) *m*/*z* 447.2 (M^+); HRMS (ESI) *m*/*z* 447.2040 (M^+), calc. for $C_{27}H_{29}NO_5$ 447.2046. The *ee* was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90/10; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time = 7.2 min (major) and 11.9 min (minor).

5a, (*R*)-(−)-Methyl 3-(4-chlorophenyl)-5-((*R*)-(4-methyl-2,5-dioxo-1-phenyl-2,5-dihydro-1*H*-pyrrol-3-yl)(phenyl)methyl)-4,5-dihydroisoxazole-5-carboxylate. White solid: mp 73.2−74.9 °C; 36.7 mg (0.1 mmol), 71% yield; 90% *ee*; 9:1 *dr*; $[\alpha]_D^{26}$ −15.2 (*c* 0.2, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$, ppm) δ = 7.45 (t, *J* = 8.1 Hz, 6H), 7.39−7.27 (m, 6H), 7.24 (d, *J* = 7.4 Hz, 2H), 5.00 (s, 1H), 3.93 (d, *J* = 18.0 Hz, 1H), 3.72 (s, 3H), 3.68 (d, *J* = 18.0 Hz, 1H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ = 171.0, 170.7, 170.0, 156.1, 142.4, 137.4, 136.5, 135.6, 131.4, 129.5, 129.0 (two peaks), 128.7, 127.9, 127.8, 126.7, 125.8, 91.1, 53.2, 46.7, 42.6, 9.6; LRMS (ESI) *m*/*z* 537.1 (M + Na^+); HRMS (ESI) *m*/*z* 537.1183 (M + Na^+), calc. for $C_{29}H_{23}ClN_2NaO_5$ 537.1188. The *ee* was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-

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propanol = 80/20; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time = 11.7 min (major) and 16.2 min (minor).

5b, (*R*)-(−)-Methyl 3-(4-bromophenyl)-5-((*R*)-(1-(4-bromophenyl)-4-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)(phenyl)methyl)-4,5-dihydroisoxazole-5-carboxylate. White solid: mp 92.5−94.3 °C; 48.4 mg (0.1 mmol), 76% yield; 89% *ee*; 7:1 *dr*; $[\alpha]_D^{26}$ −17.8 (*c* 0.1, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 7.56 (d, *J* = 8.7 Hz, 2H), 7.46 (t, *J* = 9.5 Hz, 4H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.33−7.24 (m, 3H), 7.16 (d, *J* = 8.7 Hz, 2H), 4.98 (s, 1H), 3.92 (d, *J* = 17.9 Hz, 1H), 3.71 (s, 3H), 3.65 (d, *J* = 17.9 Hz, 1H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ = ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.7, 170.6, 169.6, 156.1, 142.5, 137.7, 135.4, 132.2, 132.0, 130.4, 129.5, 128.7, 128.1, 128.0, 127.1, 124.9, 121.4, 91.1, 77.3, 77.0, 76.7, 53.2, 46.7, 42.6, 9.6.; LRMS (ESI) *m*/*z* 659.0 (M + Na^+); HRMS (ESI) *m*/*z* 658.9786 (M + Na^+), calc. for $C_{29}H_{22}O_5N_2Br_2Na$ 658.9788. The *ee* was determined by HPLC analysis. CHIRALPAK IC (4.6 mm i.d. × 250 mm); hexane/2-propanol = 80/20; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time = 9.7 min (minor) and 17.1 min (major).

■ ASSOCIATED CONTENT

Supporting Information

General information, HPLC spectra of chiral products, crystallographic data of **5b**, details of DFT calculations, and NMR spectra of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(18) CCDC-874217 (**5b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.