

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

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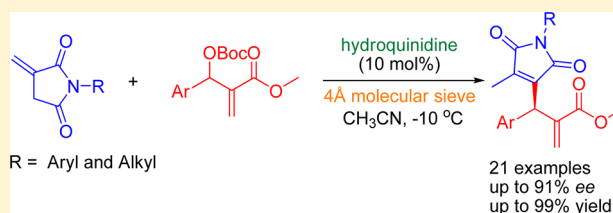
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Supporting Information

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 MBH⁵ 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 spirocyclic¹¹ 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.

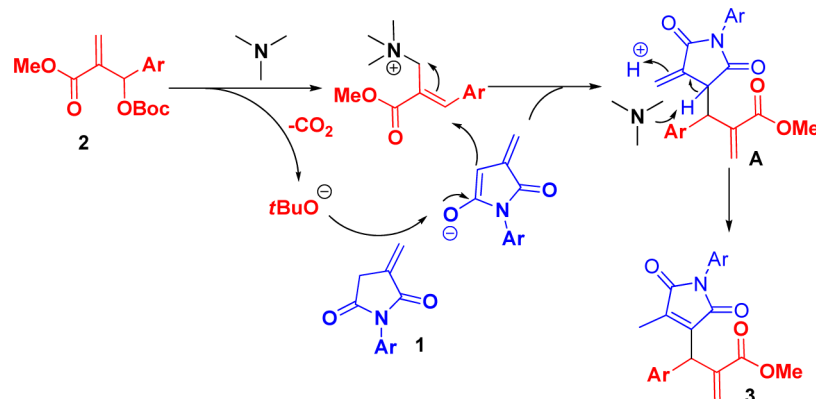
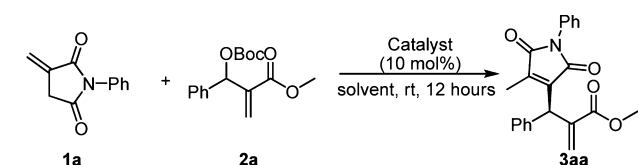
Inspired by this progress and furthering our research interest, we herein report the first example of enantioselective allylic alkenylation^{6p} of *N*-itaconimides with *O*-Boc-protected MBH carbonates to produce α -methylene- β -maleimide esters in high yields and good to excellent *ee* values. As 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 organocatalysts¹² 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 BaseTable 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) ₂ PHAL	DCE	rt	12	trace	27
8	(DHQD) ₂ AQN	DCE	rt	12	52	17
9	(DHQD) ₂ PYR	DCE	rt	12	47	10
10	(DHQ) ₂ AQN	DCE	rt	12	62	10
11	(DHQD) ₂ PHAL	DCE	rt	12	55	47
12	HQD	CH ₂ Cl ₂	rt	12	90	66
13	HQD	CH ₃ CN	rt	12	94	65
14	HQD	Toluene	rt	12	89	80
15	HQD	THF	rt	12	66	62
16	HQD	Et ₂ O	rt	12	88	70
17	HQD	Toluene	0	24	91	79
18	HQD	Et ₂ O	0	24	68	72
19	HQD	CH ₃ CN	0	24	72	85
20	HQD	CH ₃ CN	-10	30	88	86
21	HQD	CH ₃ CN	-20	48	67	87
22 ^d	HQD	CH ₃ CN	-10	68	97	89 ^{e,f}
23 ^d	HQD	CH ₃ CN	-20	80	84	87 ^e

^aUnless 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.

^bIsolated yield after silica gel column chromatography. ^cDetermined by HPLC analysis. ^d4 Å molecular sieve (1:1, m/m) was added. ^e0.1 mmol scale in 1.0 mL of CH₃CN. ^f0.5 mmol scale in 5.0 mL of CH₃CN, 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

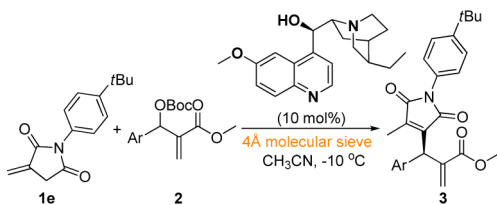
entry	1, R	3	t (h)	yield (%) ^b	ee (%) ^c
1	1b , 4-BrC ₆ H ₄	3ba	58	83	90
2	1c , 3-BrC ₆ H ₄	3ca	54	99	90
3	1d , 3,5-F ₂ C ₆ H ₃	3da	48	96	87
4	1e , 4- <i>t</i> BuC ₆ H ₄	3ea	62	86	91
5	1f , 2-naphthyl	3fa	96	72	88
6	1g , 4-MeOC ₆ H ₄	3ga	96	97	90
7	1h , <i>n</i> Bu	3ha	96	62	83

^aUnless otherwise noted, the reaction was carried out with 0.2 mmol of **1a**, 0.1 mmol of **2a**, and 0.01 mol of hydroquinidine in 1.0 mL of solvent. ^bIsolated yield after silica gel column chromatography. ^cDetermined 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**).

With *N*-itaconimide **1e** as the nucleophile, we investigated the scope of MBH carbonates in the presence of 10 mol % hydroquinidine in acetonitrile at $-10\text{ }^{\circ}\text{C}$ using 4 Å molecular sieve as additive (Table 3). All reactions proceeded smoothly

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 ₂ C ₆ H ₄	3eb	48	85	79
2	2c, 4-CF ₃ C ₆ H ₄	3ec	64	75	90
3	2d, 4-FC ₆ H ₄	3ed	96	67	85
4	2e, 4-ClC ₆ H ₄	3ee	32	85	91
5	2f, 4-BrC ₆ H ₄	3ef	83	81	91
6	2g, 3-CF ₃ C ₆ H ₄	3eg	74	86	85
7	2h, 3-ClC ₆ H ₄	3eh	96	62	89
8	2i, 2-FC ₆ H ₄	3ei	60	64	91
9	2j, 2-ClC ₆ H ₄	3ej	70	72	91
10	2k, 4-MeC ₆ H ₄	3ek	96	57	89
11	2l, 4- <i>i</i> PrC ₆ H ₄	3el	96	40	90
12	2m, 4-MeOC ₆ H ₄	3em	68	63	90
13	2n, 3-MeOC ₆ H ₄	3en	60	67	90

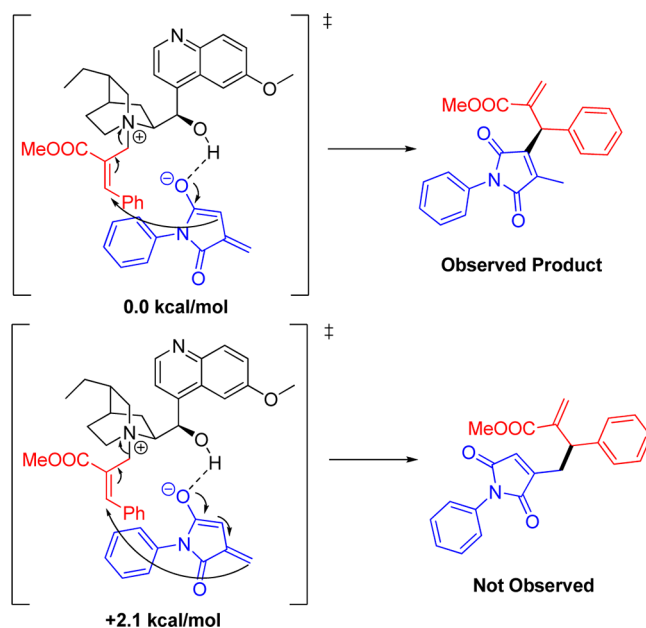
^aUnless otherwise noted, the reaction was carried out with 0.2 mmol of **1e**, 0.1 mmol of **2**, and 0.01 mol of hydroquinidine in 1.0 mL of solvent. ^bIsolated yield after silica gel column chromatography. ^cDetermined by HPLC analysis.

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 substituents 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

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 program¹⁵ and modeling experiments at the B3LYP/6-31G** level of theory¹⁶ 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 CO₂ 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

Scheme 2. Regioselectivity for the Formation of Different Alkenylation Products



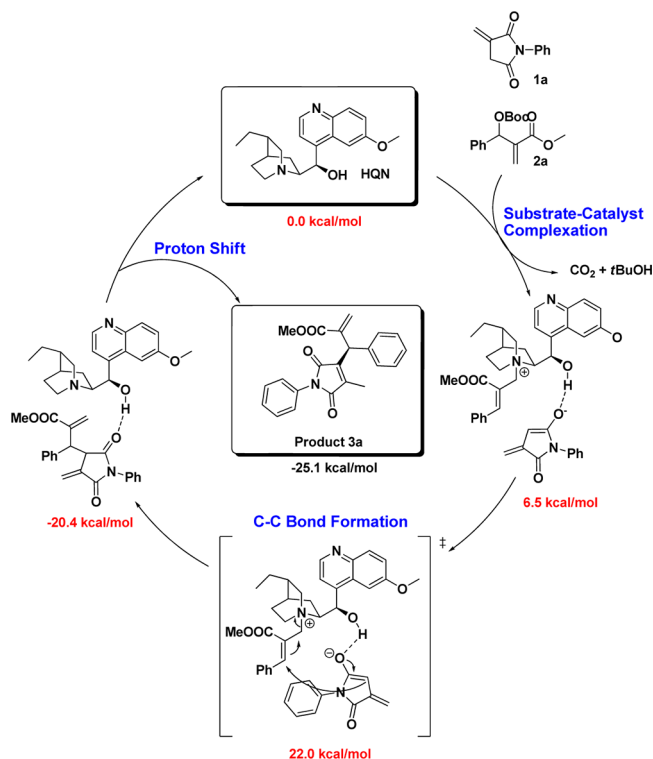
product was not observed experimentally, and DFT calculations revealed that the activation barrier for the *S*-enantiomer of this product was much higher, by +3.4 kcal/mol. With these information in mind, we were able to formulate a possible catalytic cycle for this reaction (Scheme 3).

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

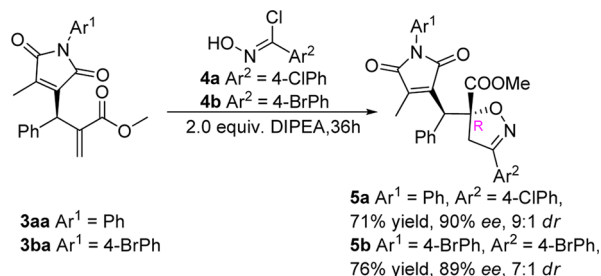
CONCLUSION

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

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 \sim 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 F₂₅₄. After elution, plate was visualized under UV illumination at 254 nm for UV active material. Further visualization was achieved by

staining KMnO₄, 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 (¹H NMR) and carbon NMR (¹³C NMR) spectra were recorded in CDCl₃ unless otherwise stated. ¹H (400 MHz) and ¹³C (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: CDCl₃ (¹H NMR: δ 7.26, singlet; ¹³C 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 CH₃CN (HPLC grade) unless otherwise stated. Optical rotations were recorded with a sodium lamp of wavelength 589 nm and reported as follows; [α]_D²⁰ (*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 CaH₂ and stored under N₂ atmosphere. 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-1H-pyrrol-3-yl)(phenyl)methyl)acrylate. Yellow oil: 163.2 mg (0.5 mmol), 90% yield; 90% ee; [α]_D²⁶ +27.4 (*c* 0.19, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₂H₁₉NNaO₄ 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-1H-pyrrol-3-yl)(phenyl)methyl)acrylate. Colorless oil: 36.7 mg (0.1 mmol), 83% yield; 90% ee; [α]_D²⁶ +16.4 (*c* 0.25, CHCl₃); ¹H NMR (400 MHz, CDCl₃, 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); ¹³C NMR (100 MHz, CDCl₃, 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 C₂₂H₁₈NO₄Br 439.0414. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm

i.d. \times 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-1H-pyrrol-3-yl)(phenyl)methyl)acrylate. Yellow oil: 43.8 mg (0.1 mmol), 99% yield; 90% ee; $[\alpha]_{\text{D}}^{25} +40.5$ (c 0.2, CHCl₃); ¹H NMR (400 MHz, CDCl₃, 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); ¹³C NMR (100 MHz, CDCl₃, 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 C₂₂H₁₇BrNO₄ 438.0346. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. \times 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 (minor).

3da, (S)-(+)-Methyl 2-((1-(3,5-difluorophenyl)-4-methyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)(phenyl)methyl)acrylate. Yellow oil: 38.2 mg (0.1 mmol), 96% yield; 87% ee; $[\alpha]_{\text{D}}^{25} +39.1$ (c 0.2, CHCl₃); ¹H NMR (400 MHz, CDCl₃, 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); ¹³C NMR (100 MHz, CDCl₃, 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 C₂₂H₁₇F₂NNaO₄ 420.1018. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. \times 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-1H-pyrrol-3-yl)(phenyl)methyl)acrylate. Yellow oil: 35.8 mg (0.1 mmol), 86% yield; 91% ee; $[\alpha]_{\text{D}}^{25} +22.0$ (c 0.4, CHCl₃); ¹H NMR (400 MHz, CDCl₃, 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); ¹³C NMR (100 MHz, CDCl₃, 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 C₂₆H₂₇NNaO₄ 440.1832. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. \times 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-((1-(4-methyl-1-(naphthalen-2-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)(phenyl)methyl)acrylate. Yellow oil: 29.7 mg (0.1 mmol), 72% yield; 88% ee; $[\alpha]_{\text{D}}^{25} +117.1$ (c 0.2, CHCl₃); ¹H NMR (400 MHz, CDCl₃, 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); ¹³C NMR (100 MHz, CDCl₃, 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 C₂₆H₂₁NNaO₄ 434.1363. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. \times 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-1H-pyrrol-3-yl)(phenyl)methyl)acrylate. Yellow oil: 38.1 mg (0.1 mmol), 97% yield; 90% ee; $[\alpha]_{\text{D}}^{25} +236$ (c 0.1, CHCl₃); ¹H NMR (400 MHz, CDCl₃, 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); ¹³C NMR (100 MHz, CDCl₃, 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 C₂₃H₂₁NNaO₅ 414.1312. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. \times

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-1H-pyrrol-3-yl)(phenyl)methyl)acrylate. Yellow oil: 21.3 mg (0.1 mmol), 62% yield; 83% ee; $[\alpha]_{\text{D}}^{25} +16.4$ (c 0.3, CHCl₃); ¹H NMR (400 MHz, CDCl₃, ppm) δ 7.733 (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); ¹³C NMR (100 MHz, CDCl₃, 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 C₂₀H₂₃NNaO₄ 364.1519. The ee was determined by HPLC analysis. CHIRALCEL OD-H (4.6 mm i.d. \times 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-1H-pyrrol-3-yl)(4-nitrophenyl)methyl)acrylate. Yellow oil: 39.4 mg (0.1 mmol), 85% yield; 79% ee; $[\alpha]_{\text{D}}^{25} +10.0$ (c 0.3, CHCl₃); ¹H NMR (400 MHz, CDCl₃, 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); ¹³C NMR (100 MHz, CDCl₃, 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 C₂₆H₂₆N₂O₆ 461.1718. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. \times 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 min (minor).

3ec, (S)-(+)-Methyl 2-((1-(4-tert-butylphenyl)-4-methyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)(4-(trifluoromethyl)phenyl)methyl)acrylate. Yellow oil: 36.3 mg (0.1 mmol), 75% yield; 90% ee; $[\alpha]_{\text{D}}^{25} +65.9$ (c 0.4, CHCl₃); ¹H NMR (400 MHz, CDCl₃, 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); ¹³C NMR (100 MHz, CDCl₃, 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 C₂₇H₂₆F₃NO₄ 485.1814. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. \times 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 min (minor).

3ed, (S)-(+)-Methyl 2-((1-(4-tert-butylphenyl)-4-methyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)(4-fluorophenyl)methyl)acrylate. Yellow oil: 29.4 mg (0.1 mmol), 67% yield; 85% ee; $[\alpha]_{\text{D}}^{25} +7.8$ (c 0.4, CHCl₃); ¹H NMR (400 MHz, CDCl₃, ppm) δ 7.746–7.42 (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); ¹³C NMR (100 MHz, CDCl₃, 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 C₂₆H₂₃FNO₄ 434.1773. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. \times 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-1H-pyrrol-3-yl)(4-chlorophenyl)methyl)acrylate. Yellow oil: 38.3 mg (0.1 mmol), 85% yield; 91% ee; $[\alpha]_{\text{D}}^{25} +59.7$ (c 0.4, CHCl₃); ¹H NMR (400 MHz, CDCl₃, ppm) 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); ¹³C NMR (100 MHz, CDCl₃, 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 C₂₆H₂₆ClNO₄Na 474.1443. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. \times 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).

3ef, (S)-(+)-Methyl 2-((1-(4-*tert*-butylphenyl)-4-methyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)(4-bromophenyl)methyl)acrylate. Yellow oil: 40.1 mg (0.1 mmol), 81% yield; 91% ee; $[\alpha]_{\text{D}}^{26} +48.1$ (c 0.3, CHCl₃); ¹H NMR (400 MHz, CDCl₃, 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 Hz, 1H), 5.29 (s, 1H), 3.76 (s, 3H), 1.94 (s, 3H), 1.31 (s, 9H); ¹³C NMR (100 MHz, CDCl₃, 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 C₂₆H₂₇O₄NBr 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-1H-pyrrol-3-yl)(3-(trifluoromethyl)phenyl)methyl)acrylate. Yellow oil: 41.9 mg (0.1 mmol), 86% yield; 85% ee; $[\alpha]_{\text{D}}^{26} +31.6$ (c 0.7, CHCl₃); ¹H NMR (400 MHz, CDCl₃, 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); ¹³C NMR (100 MHz, CDCl₃, 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 C₂₇H₂₅F₃NO₄ 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-1H-pyrrol-3-yl)(3-chlorophenyl)methyl)acrylate. Yellow oil: 28.2 mg (0.1 mmol), 62% yield; 89% ee; $[\alpha]_{\text{D}}^{26} +7.0$ (c 0.5, CHCl₃); ¹H NMR (400 MHz, CDCl₃, 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); ¹³C NMR (100 MHz, CDCl₃, 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 C₂₆H₂₆ClNO₄ 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-1H-pyrrol-3-yl)(2-fluorophenyl)methyl)acrylate. Yellow oil: 27.7 mg (0.1 mmol), 64% yield; 91% ee; $[\alpha]_{\text{D}}^{26} +18.1$ (c 0.3, CHCl₃); ¹H NMR (400 MHz, CDCl₃, 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); ¹³C NMR (100 MHz, CDCl₃, 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, 34.6, 31.2, 8.9; LRMS (ESI) *m/z* 435.2 (M⁺); HRMS (ESI) *m/z* 435.1835 (M⁺), calc. for C₂₆H₂₆FNO₄ 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-1H-pyrrol-3-yl)(2-chlorophenyl)methyl)acrylate. Yellow oil: 32.8 mg (0.1 mmol), 72% yield; 91% ee; $[\alpha]_{\text{D}}^{26} -17.2$ (c 0.3, CHCl₃); ¹H NMR (400 MHz, CDCl₃, 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); ¹³C NMR (100 MHz, CDCl₃, 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 C₂₆H₂₆ClNO₄ 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-1H-pyrrol-3-yl)(*p*-tolyl)methyl)acrylate. Yellow oil: 24.6 mg (0.1 mmol), 57% yield; 89% ee; $[\alpha]_{\text{D}}^{26} +43.7$ (c 0.4, CHCl₃); ¹H NMR (400 MHz, CDCl₃, 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); ¹³C NMR (100 MHz, CDCl₃, 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 C₂₇H₂₉NO₄Na 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-1H-pyrrol-3-yl)(4-isopropylphenyl)methyl)acrylate. Yellow oil: 18.4 mg (0.1 mmol), 40% yield; 90% ee; $[\alpha]_{\text{D}}^{26} -7.0$ (c 0.2, CHCl₃); ¹H NMR (400 MHz, CDCl₃, 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); ¹³C NMR (100 MHz, CDCl₃, 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 C₂₉H₃₃NO₄ 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-1H-pyrrol-3-yl)(4-methoxyphenyl)methyl)acrylate. Yellow oil: 28.1 mg (0.1 mmol), 63% yield; 90% ee; $[\alpha]_{\text{D}}^{26} +24.0$ (c 0.7, CHCl₃); ¹H NMR (400 MHz, CDCl₃, 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); ¹³C NMR (100 MHz, CDCl₃, 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 C₂₇H₂₉NO₅ 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-1H-pyrrol-3-yl)(3-methoxyphenyl)methyl)acrylate. Yellow oil: 30.0 mg (0.1 mmol), 67% yield; 90% ee; $[\alpha]_{\text{D}}^{26} -16.3$ (c 0.3, CHCl₃); ¹H NMR (400 MHz, CDCl₃, 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); ¹³C NMR (100 MHz, CDCl₃, 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 C₂₇H₂₉NO₅ 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-1H-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*; $[\alpha]_{\text{D}}^{26} -15.2$ (c 0.2, CHCl₃); ¹H NMR (400 MHz, CDCl₃, 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); ¹³C NMR (100 MHz, CDCl₃, 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 C₂₉H₂₃ClN₂NaO₅ 537.1188. 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 = 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-1H-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; $[\alpha]_D^{25}$ –17.8 (c 0.1, CHCl₃) ¹H NMR (400 MHz, CDCl₃, 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); ¹³C NMR (100 MHz, CDCl₃, ppm) δ = ¹³C NMR (101 MHz, CDCl₃) 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 C₂₉H₂₂O₅N₂Br₂Na 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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■ REFERENCES

- (1) (a) Ahmed, S. *Drug Des. Discovery* **1996**, *14*, 77. (b) Katritzky, A. R.; Yao, J.; Qi, M.; Chou, Y.; Sikora, D. J.; Davis, S. *Heterocycles* **1998**, *48*, 2677. (c) Ballini, R.; Bosica, G.; Cioci, G.; Fiorini, D.; Petrini, M. *Tetrahedron* **2003**, *59*, 3603.
- (2) For selected examples of *N*-maleimides in asymmetric synthesis, see: (a) Bartoli, G.; Bosco, M.; Carlone, A.; Cavalli, A.; Locatelli, M.; Mazzanti, A.; Ricci, P.; Sambri, L.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 4966. (b) Zu, L.; Xie, H.; Li, H.; Wang, J.; Jiang, W.; Wang, W. *Adv. Synth. Catal.* **2007**, *349*, 1882. (c) Li, X.; Hu, S.; Xi, Z.; Zhang, L.; Luo, S.; Cheng, J.-P. *J. Org. Chem.* **2010**, *75*, 8697. (d) Liao, Y.-H.; Liu, X.-L.; Wu, Z.-J.; Du, X.-L.; Zhang, X.-M.; Yuan, W.-C. *Adv. Synth. Catal.* **2011**, *353*, 1720. For our recent examples, see: (e) Shen, J.; Nguyen, T. T.; Goh, Y.-P.; Ye, W.; Fu, X.; Xu, J.; Tan, C.-H. *J. Am. Chem. Soc.* **2006**, *128*, 13692. (f) Ye, W.; Jiang, Z.; Zhao, Y.; Goh, L. M. S.; Leow, D.; Soh, Y.-T.; Tan, C.-H. *Adv. Synth. Catal.* **2007**, *349*, 2454. (g) Jiang, Z.; Pan, Y.; Zhao, Y.; Ma, T.; Lee, R.; Yang, Y.; Huang, K.-W.; Wong, M. W.; Tan, C.-H. *Angew. Chem., Int. Ed.* **2009**, *48*, 3627. (h) Soh, J. Y.-T.; Tan, C.-H. *J. Am. Chem. Soc.* **2009**, *131*, 6904.
- (3) Karthikeyan, K.; Sivakumar, P.-M.; Doble, M.; Perumal, P.-T. *Eur. J. Med. Chem.* **2010**, *45*, 3446.

(4) (a) Leow, D.; Lin, S.; Chittimalla, S. K.; Fu, X.; Tan, C.-H. *Angew. Chem., Int. Ed.* **2008**, *47*, 5641. (b) Lin, S.; Leow, D.; Huang, K.-W.; Tan, C.-H. *Chem.—Asian J.* **2009**, *4*, 1741. (c) Wang, J.; Liu, H.; Fan, Y.; Yang, Y.; Jiang, Z.; Tan, C.-H. *Chem.—Eur. J.* **2010**, *16*, 12534.

(5) For reviews on Morita–Baylis–Hillman reaction, see: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. (b) Basavaiah, D.; Rao, K. V.; Reddy, R. J. *Chem. Soc. Rev.* **2007**, *36*, 1581. (c) Singh, V.; Batra, S. *Tetrahedron* **2008**, *64*, 4511. (d) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.* **2010**, *110*, 5447. For review on organocatalytic asymmetric transformations of Morita–Baylis–Hillman adducts, see: (e) Rios, R. *Catal. Sci. Technol.* **2012**, *2*, 267. (f) Liu, T.-Y.; Xie, M.; Chen, Y.-C. *Chem. Soc. Rev.* **2012**, *41*, 4101.

(6) For selected examples, see: (a) van Steenis, D. J. V. C.; Marcelli, T.; Lutz, M.; Spek, A. L.; van Maarseveen, J. H.; Hiemstra, H. *Adv. Synth. Catal.* **2007**, *349*, 281. (b) Jiang, Y.-Q.; Shi, Y.-L.; Shi, M. *J. Am. Chem. Soc.* **2008**, *130*, 7202. (c) Cui, H.-L.; Peng, J.; Feng, X.; Du, W.; Jiang, K.; Chen, Y.-C. *Chem.—Eur. J.* **2009**, *15*, 1574. (d) Jiang, K.; Peng, J.; Cui, H.-L.; Chen, Y.-C. *Chem. Commun.* **2009**, *45*, 3955. (e) Cui, H.-L.; Huang, J.-R.; Lei, J.; Wang, Z.-F.; Chen, S.; Wu, L.; Chen, Y.-C. *Org. Lett.* **2010**, *12*, 720. (f) Peng, J.; Huang, X.; Cui, H.-L.; Chen, Y.-C. *Org. Lett.* **2010**, *12*, 4260. (g) Peng, J.; Cui, H.-L.; Chen, Y.-C. *Sci. China, Ser. B: Chem.* **2011**, *54*, 81. (h) Yang, Y.-L.; Pei, C.-K.; Shi, M. *Org. Biomol. Chem.* **2011**, *9*, 3349. (i) Liu, C.; Tan, B.-X.; Jin, J.-L.; Dong, N.; Li, X.; Chen, J.-P. *J. Org. Chem.* **2011**, *76*, 5838. (j) Furukawa, T.; Nishimine, T.; Tokunaga, E.; Hasegawa, K.; Shiro, M.; Shibata, N. *Org. Lett.* **2011**, *13*, 3972. (k) Jiang, L.; Lei, Q.; Huang, X.; Cui, H.-L.; Zhou, X.; Chen, Y.-C. *Chem.—Eur. J.* **2011**, *34*, 9489. (l) Peng, J.; Huang, X.; Jiang, L.; Cui, H.-L.; Chen, Y.-C. *Org. Lett.* **2011**, *13*, 4584. (m) Yang, W.; Wei, X.; Pan, Y.; Lee, R.; Zhu, B.; Liu, H.; Yan, L.; Huang, K.-W.; Jiang, Z.; Tan, C.-H. *Chem.—Eur. J.* **2011**, *17*, 8066. (n) Furukawa, T.; Kawazoe, J.; Zhang, W.; Nishimine, T.; Tojunaga, E.; Matsumoto, T.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 9684. (o) Companyó, X.; Valero, G.; Ceban, V.; Calvet, T.; Font-Bardía, M.; Moyano, A.; Rios, R. *Org. Biomol. Chem.* **2011**, *9*, 7986. (p) Cui, H.-L.; Sun, X.-H.; Jiang, L.; Dong, L.; Chen, Y.-C. *Eur. J. Org. Chem.* **2011**, *2011*, 7366.

(7) For selected examples, see: (a) Ma, G.-N.; Cao, S.-H.; Shi, M. *Tetrahedron: Asymmetry* **2009**, *20*, 1086. (b) Cui, H.-L.; Feng, X.; Peng, J.; Lei, J.; Jiang, K.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5737. (c) Peng, J.; Cui, H.-L.; Chen, Y.-C. *Sci. China, Ser. B: Chem.* **2011**, *54*, 81. (d) Huang, J.-R.; Cui, H.-L.; Lei, J.; Sun, X.-H.; Chen, Y.-C. *Chem. Commun.* **2011**, *47*, 4784. (e) Deng, H.-P.; Wei, Y.; Shi, M. *Eur. J. Org. Chem.* **2011**, *2011*, 1956. (f) Lin, A.; Mao, H.; Zhu, X.; Ge, H.; Tan, R.; Zhu, C.; Cheng, Y. *Chem.—Eur. J.* **2011**, *17*, 13676.

(8) For selected examples, see: (a) Trost, B. M.; Tsui, H.-C.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 3534. (b) Kim, J. N.; Lee, H. J.; Gong, J. H. *Tetrahedron Lett.* **2002**, *43*, 9141. (c) Trost, B. M.; Brennan, M. K. *Org. Lett.* **2007**, *9*, 3961. (d) Feng, X.; Yuan, Y.-Q.; Jiang, K.; Chen, Y.-C. *Org. Biomol. Chem.* **2009**, *7*, 3660. (e) Hu, Z.-K.; Cui, H.-L.; Jiang, K.; Chen, Y.-C. *Sci. China, Ser. B: Chem.* **2009**, *52*, 1309. (f) Zhu, B.; Yan, L.; Pan, Y.; Lee, R.; Liu, H.; Han, Z.; Huang, K.-W.; Tan, C.-H.; Jiang, Z. *J. Org. Chem.* **2011**, *76*, 6894.

(9) For selected examples, see: (a) Hong, L.; Sun, W.; Liu, C.; Zhao, D.; Wang, R. *Chem. Commun.* **2010**, *46*, 2856. (b) Sun, W.; Hong, L.; Liu, C.; Wang, R. *Org. Lett.* **2010**, *12*, 3914. (c) Deng, H.-P.; Shi, M. *Eur. J. Org. Chem.* **2012**, *2012*, 183.

(10) Lin, A.; Mao, H.; Zhu, X.; Ge, H.; Tan, R.; Zhu, C.; Cheng, Y. *Adv. Synth. Catal.* **2011**, *353*, 3301.

(11) (a) Tan, B.; Candeias, N. R.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2011**, *133*, 4672. (b) Zhong, F.; Han, X.; Wang, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 7837. (c) Peng, J.; Huang, X.; Jiang, L.; Cui, H.-L.; Chen, Y.-C. *Org. Lett.* **2011**, *13*, 4584.

(12) For review on *Cinchona* alkaloids as Lewis base catalysts, see: (a) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560. (b) Tian, S.-K.; Chen, Y.; Huang, J.; Tang, L.; Mcdaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621. For selected examples, see: (c) Chen, Y.; Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2000**, *122*, 9542. (d) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195. (e) Tian,

S.-K.; Hong, R.; Deng, L. *J. Am. Chem. Soc.* **2003**, *125*, 9900. (f) Shi, M.; Chen, L.-H.; Li, C.-Q. *J. Am. Chem. Soc.* **2005**, *127*, 3790. (g) Wang, J.; Li, H.; Yu, X.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4293. (h) Li, H.; Liu, X.; Wu, F.; Tang, L.; Deng, L. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20625.

(13) For a selected example on the application of 4 Å molecular, see: Tian, X.; Jiang, K.; Peng, J.; Du, W.; Chen, Y.-C. *Org. Lett.* **2008**, *10*, 3583.

(14) Li, Y.; Liang, F.; Li, Q.; Xu, Y.-C.; Wang, Q.-R.; Jiang, L. *Org. Lett.* **2011**, *13*, 6082.

(15) (a) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A.; Peralta, Jr., J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, J.; Foresman, B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, Revision A.1; Gaussian, Inc., Wallingford CT, 2004. (b) Full details of the computational studies can be found in the Supporting Information.

(16) (a) Becke, D. J. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. (c) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724. (d) W. Hehre, J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257. (e) Hariharan, P. C.; Pople, J. A. *Theor. Chem. Acc.* **1973**, *28*, 213.

(17) For selected examples, see: (a) Balachandra, S.; Gadekar, P. K.; Parkale, S.; Yadav, V. N.; Kamath, D.; Ramaswamy, S.; Sharma, S.; Vishwakarma, R. A.; Dagia, N. M. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1508. (b) Rousseau, A. L.; Buddoo, S. R.; Gordon, G. E. R.; Beemadu, S.; Kupi, B. G.; Lepuru, M. J.; Maumela, M. C.; Parsoo, A.; Sibiyi, D. M.; Brady, D. *Org. Process Res. Dev.* **2011**, *15*, 249.

(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.