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Catalytic Asymmetric Access to Noncanonical Chiral α-Amino Acids from Cyclic Iminoglyoxylates and Enamides

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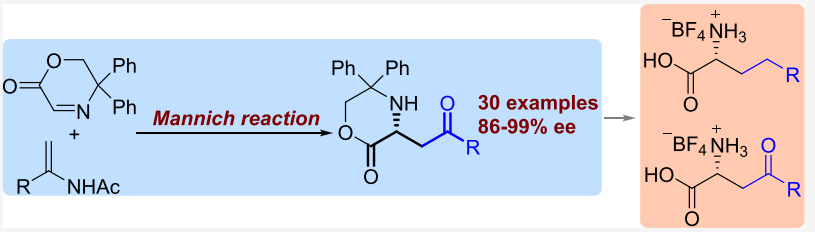
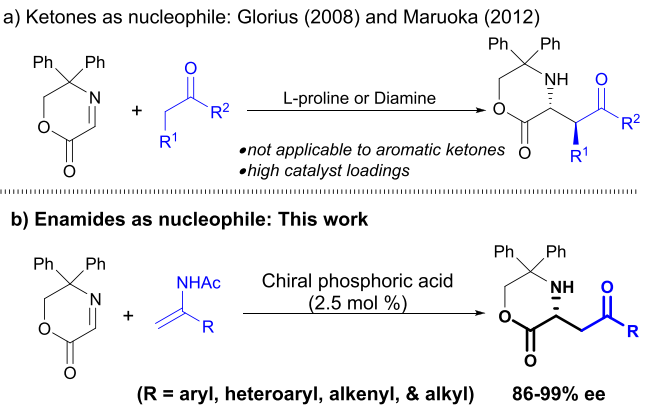


ABSTRACT: Here we describe an enantioselective Mannich reaction of cyclic iminoglyoxylates with enamides by virtue of chiral phosphoric acid catalysis in a one-pot manner. The wide substrate scope, mild reaction conditions, and constantly excellent enantioselectivities (>95% ee in most cases) render this protocol highly practical for the rapid construction of valuable noncanonical chiral α-amino-acid building blocks.

INTRODUCTION

Chiral unnatural α-amino acids (UAAs) play significant roles in peptide modification, protein drug discovery, and functional biomolecular development.[1] As a consequence, the asymmetric construction of optically active UAAs has drawn increasingly enormous attention among the organic community.[2] In this context, direct enantioselective transformation of prochiral iminoglyoxylates represents one of the most convergent and efficient routes to construct optically active UAAs, and numerous Mannich reaction systems with various nucleophilic partners have been developed to give the desired UAAs.[3] However, nearly all previous studies have focused on the utilization of unstable acyclic iminoglyoxylates.[4] In stark contrast, rare progress has been achieved in developing cyclic iminoglyoxylates as the Mannich substrates, and only two reports by Glorius[5] and Maruoka[6] have addressed 5,5-disubstituted 5,6-dihydro-1,4-oxazin-2-ones as electrophilic species with aliphatic acyclic and cyclic ketones, independently (Scheme 1a). Encouraged by this seminal investigation, we surmised that enamides,[7] which possess the acetamido moiety as a transient activating and directing group, could function as an alternative type of feasible ketone equivalent to engage in the Mannich reaction with cyclic iminoglyoxylates. Thus, herein we present the implementation of this proof of concept by means of an interesting water-promoted, chiral phosphoric acid catalyzed one-pot Mannich reaction under simple conditions. This transformation is highly enantioselective, and a broad range of aryl, heteroaryl, alkenyl, and alkyl enamides could be conveniently converted into nonracemic UAAs with excellent enantiocontrol and good to high yields (Scheme 1b).

Scheme 1. . Catalytic Asymmetric Mannich Reactions of Cyclic Iminoglyoxylates



RESULTS AND DISCUSSION

At the outset, we were pleased to find that the terminal β-keto α-amino ester **3a** was afforded as the major product from cyclic iminoglyoxylate **1** and phenyl enamide **2a** by employing three typical chiral phosphoric acids (**CPA-1**−**3**) (Table 1, entries 2−4).[8] Subsequently, a series of **CPA**s bearing different

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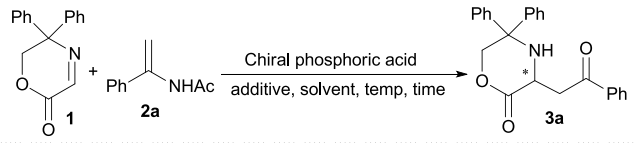
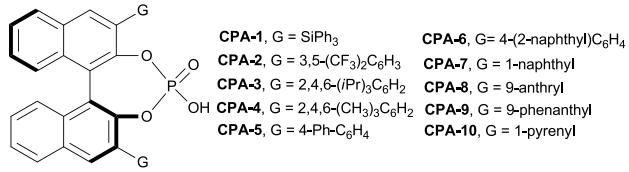
Table 1. Reaction Development[a]





Entry	Catalyst	Solvent	Temp (°C)/ time (h)	Yield[b] (%)	ee[c] (%)
1	–	toluene	25/24	NR	–
2	**CPA-1**	toluene	0/12	26	5
3	**CPA-2**	toluene	0/12	42	39
4	**CPA-3**	toluene	0/12	65	41
5	**CPA-4**	toluene	0/12	92	97
6	**CPA-5**	toluene	0/12	90	77
7	**CPA-6**	toluene	0/12	93	95
8	**CPA-7**	toluene	0/12	91	97
9	**CPA-8**	toluene	0/12	94	95
10	**CPA-9**	toluene	0/12	92	95
11	**CPA-10**	toluene	0/12	91	98
12	**CPA-4**	CH_2Cl_2	0/12	92	96
13	**CPA-4**	THF	0/12	86	98
14	**CPA-4**	Et_2O	0/12	92	96
15	**CPA-4**	1,4-dioxane	0/12	95	96
16	**CPA-4**	toluene	−20/12	92	98
17	**CPA-4**	toluene	25/5	93	96
18[d]	**CPA-4**	toluene	0/12	94	97
19[e]	**CPA-4**	toluene	0/12	94	97
20[f]	**CPA-4**	toluene	0/12	86	97
21[e,g]	**CPA-4**	toluene	0/5	95	98
22[e,h]	**CPA-4**	toluene	0/5	93	98
23[e,i]	**CPA-4**	toluene	0/5	93	98
24[e,j]	**CPA-4**	H_2O	0/5	66	98

[a]General reaction conditions: iminoglyoxylate **1** (0.1 mmol), enamide **2a** (0.15 mmol), and **CPA** (10 mol %) in 1 mL of solvent was reacted at the indicated temperature under air for 5−12 h unless specifically annotated. [b]Yield of isolated adduct. [c]Enantiomeric excess (ee) was measured by chiral HPLC. [d]5 mol % of **CPA**. [e]2.5 mol % of **CPA**. [f]1 mol % of **CPA**. [g]5 equiv of water. [h]20 equiv of water. [i]50 equiv of water. [j]0.8 mL of water and 0.2 mL of toluene were used as mixed solvent.

aromatic motifs at the 3,3′-positions of the BINOL backbone were probed (entries 5−11). Encouragingly, 2,4,6-$Me_3C_6H_2$-substituted **CPA-4** and several polycyclic aromatic hydrocarbons-substituted **CPAs** (**CPA-6−10**) all proudced **3a** in high yields with a constantly excellent level of enantiodiscrimination. It is notable that switching solvent or reaction temperature resulted in no significant change on both yields and enantioselectivities when employing **CPA-4** as the catalyst of choice (entries 12−17). Further optimizations show that lowering the catalyst loadings to 2.5 mol % could still retain comparable results (entries 18−20), thus delivering **3a** in 94% yield with 97% ee (entry 19). It should be pointed out that all the above experiments were performed under air without excluding moisture (*vide infra*). As the addition of water in organocatalysis may accelerate imine hydrolysis,[9] the model reaction was further improved by adding varied amounts of water, with 5 equiv giving the best performance (entries 21−24).

The applicability of this one-pot asymmetric Mannich reaction was assessed by exploring a variety of enamides **2** to react with cyclic iminoglyoxylate **1** (Scheme 2). Aromatic enamides bearing electron-donating groups at various positions on the benzene core all participated in the desired reaction uneventfully and generated corresponding products **3b−3h** in good to almost quantitative yields with remarkably maintained ee greater than 97%. Halogen-substituted phenyl enamides are also well compatible with this asymmetric process (products **3i−3o**), thus offering potential amino acid handles for further derivations. Notably, the absolute configuration of *β*-keto *α*-amino ester **3l** was established to be *R* based on X-ray results, and the other Mannich adducts are assigned by analogy. This one-pot enantioselective Mannich reaction is also tolerant of stong electron-withdrawing moieties, such as the trifluoromethyl group and the nitro group (products **3p−3r**). Furthermore, an array of naphthyl-, thienyl-, and furyl-derived enamides could react with iminoglyoxylate **1** uneventfully with exceptional enantiocontrol (products **3s−3w**). In addition, alkyl enamides proved to be feasible nucleophiles in this reaction and furnished corresponding adducts **3x−3b′** in practical to high yields at a constant high level of enantiopurity. Finally, benzalacetone and mesityl oxide derived enamides, which proved to be challenging substrates in Glorius's study (for example, 30% yield, 80% ee for **3d′**),[5] could engage in the reaction smoothly to give the *δ*,*ε*-unsaturated *β*-keto *α*-amino esters **3c′** and **3d′** with maintained high ee values in 60% and 93% yield, respectively. These remote functionalized chiral *α*-amino acid derivatives can serve as potentially useful synthetic building blocks to access valuable cyclic peptides.[10] Overall, the direct generation of terminal *β*-keto *α*-amino esters with such broad substrate scope clearly validate the excellent promise of developing enamides as powerful ketone equivalents in asymmetric synthesis.[11] Unfortunately, trisubstituted enamides are currently not tolerated in this reaction, and only a trace amount of desired product **3e′** was observed.

Subsequently, further transformations with obtained chiral *α*-amino esters were performed to showcase the synthetic value of this method. A gram-scale experiment was found to proceed efficiently in 5 h to give compound **3a** with outcomes similar to that of the model version, illustrating this method's robust characteristic (Scheme 3a). Subsequently, treating adducts **3** with $Pd(OH)_2/C$ under a hydrogen atmosphere produced two types of optically active unnatural *α*-amino acids (Scheme 3b). For instance, deprotection of alkyl-derived compounds **3z** and **3b′** gave rise to the free *α*-amino acids **8a** and **8b** in a yield of 95% and 75%, respectively. Intriguingly, unnatural *γ*-aryl amino acids,[12] such as homophenylalanine **8c** and homotyrosine derivative **8d**, were afforded in practical yields attributed to the concomitant cleavage of the carbonyl moiety during hydrogenolysis. Moreover, the aromatic *β*-keto *α*-amino acid **8e** could also be obtained in comparable yield by reducing the hydrogen pressure and reaction temperature.

We then operated a set of mechanistic control experiments to probe the reaction mechanism and stereochemical results. First, two other surrogates of the acetophenone including silyl enol ether **5** and *β*-keto acid **6**, together with simple acetophenone **9**, were treated with iminoglyoxylate **1** under otherwise identical conditions, whereas both nucleophiles gave **3a** in severely inferior results compared with enamide **2a** (Scheme 4a). Particularly, no reaction was observed when *N*-

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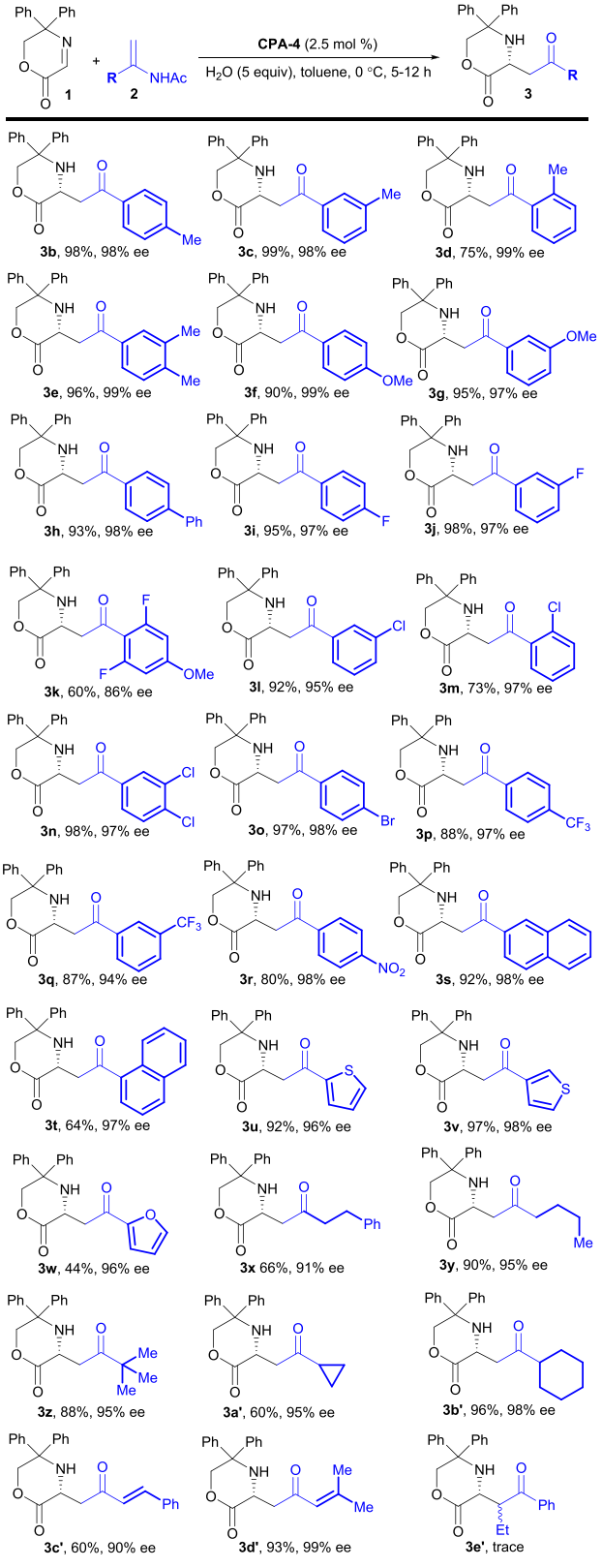
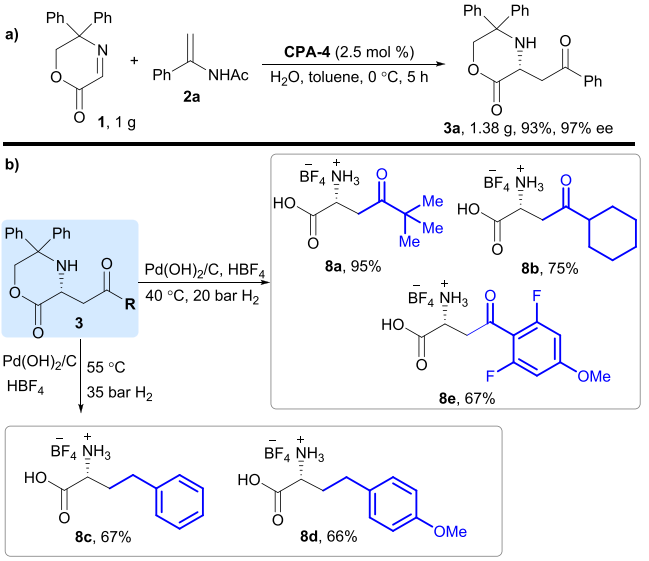
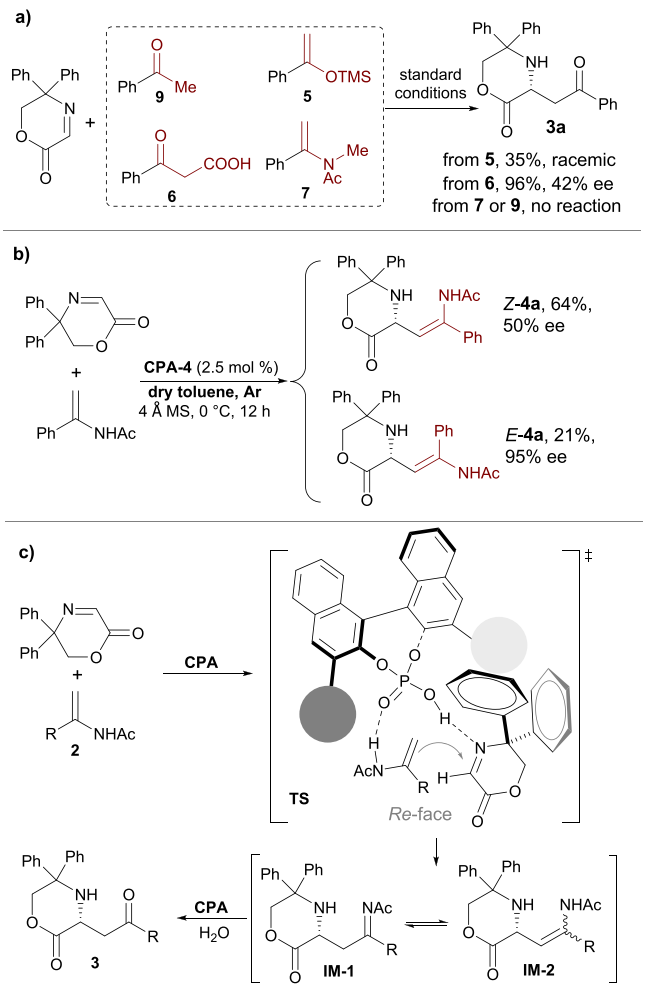
Scheme 2. . Scope of β-Keto α-Amino Esters 3 via the Catalytic Asymmetric Mannich Reaction



Scheme 3. . Gram-Scale Experiment and Preparation of Optically Active Unnatural α-Amino Acids



Scheme 4. Control Experiments and Proposed Mechanism



methylated enamide **7** was employed instead of **2a**, indicating a crucial role of N−H moiety in the reaction process (Scheme 4a). Remarkably, both geometric isomers of enamide **4a** were obtained when the Mannich reaction was conducted under argon in extra-dry solvent, among which only the minor *E*-isomer was observed with comparable ee values (Scheme 4b). Moreover, converting either isomer of **4a** with **CPA-4** in the presence of water to the targeted final product **3a** encountered

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with significantly decreased efficiency.[13] These preliminary results clearly highlight the superiority of performing a water-promoted version of this enantioselective Mannich reaction between cyclic iminoglyoxylates and enamides. Based on these results and the observed stereochemistry, a potential mechanistic pathway together with an asymmetry-inducing model was tendered.[14] As depicted in Scheme 4c, the Brønsted acid **CPA-4** could simultaneously interact with cyclic iminoglyoxylate **1** and enamide **2** via hydrogen bonding, thereby generating the chiral circumstances wherein the enamide attacks the *Re* face of the C═N group selectively.[15] Once imine intermediate **IM-1** was formed, it would undergo hydrolysis rapidly to produce β-keto α-amino ester **3** as the terminal Mannich adduct in the presence of water and **CPA**. On the other hand, enamide **IM-2** could be generated reversibly as concomitant intermediates, especially when water is excluded from the reaction.

CONCLUSIONS

In summary, a mild and highly enantioselective access to chiral unnatural α-amino acids from cyclic iminoglyoxylates and readily accessible enamides is developed. This protocol entails water as an effective promoter in cooperation with chiral phosphoric acid to realize the key one-pot asymmetric Mannich reaction, and substantially expands the substrate scope compared with previous reports. Futher application of this method to obtain versatile functionalized α-amino-acid building blocks is ongoing in our laboratory.

EXPERIMENTAL SECTION

General Information. All experiments were monitored by analytical thin layer chromatography (TLC). TLC was performed on precoated plates. After elution, the plate was visualized under UV illumination at 254 nm for UV active material. Further visualization was achieved by staining $KMnO_4$ solution. Columns for flash chromatography (FC) contained silica gel 200−300 mesh. Columns were packed as a slurry of silica gel in petroleum ether and equilibrated solution using the appropriate solvent system. The elution was assisted by applying pressure of about 2 atm with an air pump. ^{1}H, ^{19}F, and ^{13}C NMR were recorded at 400 MHz (^{1}H NMR), 376 MHz (^{19}F NMR), and 100 MHz (^{13}C NMR), respectively. Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (d_4-methanol: δ_H = 4.87, 3.31 ppm, δ_C = 49.15 ppm; $CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.20 ppm; CD_2Cl_2: δH = 5.32 ppm, δ_C = 53.84 ppm; D_2O: δH = 4.79 ppm). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), dt (doublet of (triplets). Coupling constants (J) were reported in hertz (Hz). High resolution mass spectrometry (HRMS) spectra were obtained on a microTOF-QII or Waters Micromass GCT Premier Instrument. Melting points were measured on a WRS-1A digital melting point apparatus and are uncorrected. Optical rotations were recorded on a polarimeter with a sodium lamp of wavelength 589 nm and reported as follows: $[\alpha]_\lambda^T$ (c = g/100 mL, solvent). Enantiomeric excesses were determined by chiral High Performance Liquid Chromatography (HPLC) analysis. HPLC samples were dissolved in HPLC grade isopropanol (IPA) unless otherwise stated. X-ray structural analysis was conducted on the Bruker APEX-II CCD instrument. All commercially available reagents were used without further purification. Cyclic iminoglyoxylate **1**[5] and enamides **2**[16] were synthesized according to the literature procedures. All the chiral phosphoric acids were purchased from commerical sources such as DAICEL CHIRAL Co. The optimal catalyst **CPA-4** was first reported by Akiyama et al. in 2004.[17]

General Procedure for Asymmetric Mannich Reaction with Enamides. To a 25 mL Schlenk flask equipped with a stirring bar were added 5,5-diphenyl-5,6-dihydro-2*H*-1,4-oxazin-2-one **1** (50.2 mg, 0.2 mmol, 1.0 equiv), enamides **2** (0.3 mmol, 1.5 equiv), and chiral phosphoric acid **CPA-4** (2.9 mg, 2.5 mol %). Then toluene (3 mL) and H_2O (18 μL, 5.0 equiv) were added successively at 0 °C, and the resulting mixture was stirred at the same temperature for 5−12 h until the disappearance of the starting material as monitored by thin layer chromatography (TLC). Afterward, the reaction mixture was concentrated under vacuum to yield the crude expected product which was subjected to column chromatography on silica gel (PE/EA = 15:1 to 6:1 as the eluent) to give the pure product **3**.

General Procedure for the Preparation of the Racemic Products. To a 25 mL Schlenk flask equipped with a stirring bar were added 5,5-diphenyl-5,6-dihydro-2*H*-1,4-oxazin-2-one **1** (25.1 mg, 0.1 mmol, 1.0 equiv), enamides **2** (0.15 mmol, 1.5 equiv), and racemic 1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (7.0 mg, 20 mol %). Then toluene (1.5 mL) and H_2O (9 μL, 5.0 equiv) were added successively at room temperature, and the resulting mixture was stirred for 10−12 h until the disappearance of the starting material as monitored by thin layer chromatography (TLC). Afterward, the reaction mixture was concentrated under vacuum to yield the crude expected product which was subjected to column chromatography on silica gel (PE/EA = 15:1 to 6:1 as the eluent) to give the racemic product **3**. For racemic **3b′**, 3-cyclohexyl-3-oxopropanoic acid (25.5 mg, 0.15 mmol, 1.5 equiv) was used to react with iminoglyoxylate **1** (25.1 mg, 0.1 mmol, 1.0 equiv) in the absence of catalyst at room temperature.

*(R)-3-(2-Oxo-2-phenylethyl)-5,5-diphenylmorpholin-2-one (**3a**).* White solid, 70.5 mg, 95%, 98% ee, mp 138.5−139.5 °C, HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 70:30, 0.8 mL/min, 245 nm): t_R(major) = 10.85 min, t_R(minor) = 13.96 min, $[\alpha]_D^{20}$ +74 (c 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12−7.80 (m, 2H), 7.60−7.49 (m, 3H), 7.46−7.38 (m, 4H), 7.34−7.17 (m, 6H), 5.05 (d, J = 11.6 Hz, 1H), 4.71 (d, J = 11.6 Hz, 1H), 3.82 (dd, J = 7.6, 2.9 Hz, 1H), 3.71 (dd, J = 18.4, 2.9 Hz, 1H), 3.62 (dd, J = 18.4, 7.6 Hz, 1H), 3.14 (s, 1H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 198.2, 170.3, 143.2, 140.9, 136.2, 133.9, 129.2, 128.9, 128.6, 128.2, 127.9, 127.8, 127.6, 126.5, 75.2, 61.2, 51.3, 41.8. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{22}NO_3$ 372.1594; found 372.1599.

*(R)-3-(2-Oxo-2-(p-tolyl)ethyl)-5,5-diphenylmorpholin-2-one (**3b**).* White solid, 75.1 mg, 98%, 98% ee, mp 139.5−140.5 °C, HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 70:30, 0.8 mL/min, 245 nm): t_R(major) = 12.11 min, t_R(minor) = 14.18 min, $[\alpha]_D^{20}$ +68 (c 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.2 Hz, 2H), 7.51−7.42 (m, 2H), 7.35 (t, J = 7.7 Hz, 2H), 7.28−7.13 (m, 8H), 5.01 (d, J = 11.6 Hz, 1H), 4.65 (d, J = 11.6 Hz, 1H), 3.75 (dd, J = 7.7, 2.8 Hz, 1H), 3.64 (dd, J = 18.3, 2.8 Hz, 1H), 3.55 (dd, J = 18.3, 7.8 Hz, 1H), 3.16 (s, 1H), 2.35 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 197.9, 170.5, 144.9, 143.3, 141.0, 133.9, 129.6, 129.2, 128.7, 128.5, 128.0, 127.9, 127.8, 126.6, 75.3, 61.2, 51.4, 41.8, 21.9. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{24}NO_3$ 386.1751; found 386.1754.

*(R)-3-(2-Oxo-2-(m-tolyl)ethyl)-5,5-diphenylmorpholin-2-one (**3c**).* White solid, 76.0 mg, 99%, 98% ee, mp 111.5−112.5 °C, HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 70:30, 0.8 mL/min, 245 nm): t_R(major) = 9.33 min, t_R(minor) = 11.67 min, $[\alpha]_D^{20}$ +72 (c 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 11.9 Hz, 2H), 7.57−7.55 (m, 2H), 7.48−7.38 (m, 4H), 7.38−7.27 (m, 6H), 5.09 (d, J = 11.6 Hz, 1H), 4.74 (d, J = 11.6 Hz, 1H), 3.86 (dd, J = 7.9, 2.8 Hz, 1H), 3.76 (dd, J = 18.4, 2.8 Hz, 1H), 3.65 (dd, J = 18.4, 7.9 Hz, 1H), 3.24 (s, 1H), 2.44 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 198.5, 170.5, 143.3, 141.0, 138.8, 136.3, 134.7, 129.2, 128.9, 128.8, 128.7, 128.0, 127.9, 127.7, 126.7, 125.6, 75.3, 61.3, 51.4, 41.9 21.5. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{24}NO_3$ 386.1751; found 386.1756.

*(R)-3-(2-Oxo-2-(o-tolyl)ethyl)-5,5-diphenylmorpholin-2-one (**3d**).* White solid, 57.4 mg, 75%, 99% ee, mp 131.5−132.5 °C, HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 70:30, 0.8 mL/min, 245 nm): t_R(major) = 9.11 min, t_R(minor) = 11.68 min, $[\alpha]_D^{20}$ +78 (c 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 7.8 Hz, 1H), 7.47−7.43 (m, 2H), 7.36−7.31 (m, 3H), 7.27−7.14 (m, 8H), 5.00 (d,

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J = 11.7 Hz, 1H), 4.68 (d, J = 11.7 Hz, 1H), 3.74 (dd, J = 6.9, 3.5 Hz, 1H), 3.56 (dd, J = 18.2, 3.6 Hz, 1H), 3.50 (dd, J = 18.2, 7.0 Hz, 1H), 3.10 (s, 1H), 2.46 (s, 3H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 201.8, 170.5, 143.4, 141.0, 139.0, 136.7, 132.4, 132.2, 129.2, 129.2, 128.8, 128.0, 127.9, 127.7, 126.5, 126.0, 75.2, 61.2, 51.6, 44.3, 21.8. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{24}NO_3$ 386.1751; found 386.1753.

*(R)-3-(2-(3,4-Dimethylphenyl)-2-oxoethyl)-5,5-diphenylmorpholin-2-one (**3e**).* White solid, 77.0 mg, 96%, 99% ee, mp 151.5−152.5 °C, HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 90:10, 1.0 mL/min, 245 nm): t_R(major) = 16.34 min, t_R(minor) = 19.08 min, $[\alpha]_D^{20}$ +56 (c 0.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.64 (dd, J = 7.9, 1.6 Hz, 1H), 7.48−7.46 (m, 2H), 7.37−7.33 (m, 2H), 7.27−7.15 (m, 7H), 5.00 (d, J = 11.6 Hz, 1H), 4.64 (d, J = 11.6 Hz, 1H), 3.75 (dd, J = 7.9, 2.8 Hz, 1H), 3.65 (dd, J = 18.3, 2.8 Hz, 1H), 3.54 (dd, J = 18.3, 7.9 Hz, 1H), 3.17 (s, 1H), 2.25 (s, 3H), 2.24 (s, 3H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.2, 170.5, 143.6, 143.3, 141.0, 137.3, 134.3, 130.2, 129.5, 129.2, 128.7, 128.0, 127.9, 127.8, 126.6, 126.1, 75.3, 61.2, 51.5, 41.8, 20.3, 19.9. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{26}H_{26}NO_3$ 400.1907; found 400.1905.

*(R)-3-(2-(4-Methoxyphenyl)-2-oxoethyl)-5,5-diphenylmorpholin-2-one (**3f**).* White solid, 72.4 mg, 90%, 99% ee, mp 59.5−60.5 °C, HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 70:30, 0.8 mL/min, 245 nm): t_R(major) = 16.06 min, t_R(minor) = 18.94 min, $[\alpha]_D^{20}$ +48 (c 0.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.9 Hz, 2H), 7.51 (d, J = 7.4 Hz, 2H), 7.39 (t, J = 7.7 Hz, 2H), 7.33−7.14 (m, 6H), 6.91 (d, J = 8.9 Hz, 2H), 5.05 (d, J = 11.6 Hz, 1H), 4.68 (d, J = 11.6 Hz, 1H), 3.84 (s, 3H), 3.77 (dd, J = 7.5, 2.7 Hz, 1H), 3.65 (dd, J = 18.2, 2.9 Hz, 1H), 3.57 (dd, J = 18.2, 7.6 Hz, 1H), 3.21 (s, 1H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.7, 170.6, 164.2, 143.3, 141.0, 130.7, 129.4, 129.2, 128.7, 127.9, 127.9, 127.8, 126.6, 114.1, 75.3, 61.2, 55.7, 51.5, 41.5. HRMS (ESI^+): HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{24}NO_4$ 402.1700; found 402.1705.

*(R)-3-(2-(3-Methoxyphenyl)-2-oxoethyl)-5,5-diphenylmorpholin-2-one (**3g**).* White solid, 76.3 mg, 95%, 97% ee, mp 113.5−114.5 °C, HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 70:30, 0.8 mL/min, 245 nm): t_R(major) = 11.92 min, t_R(minor) = 14.31 min, $[\alpha]_D^{20}$ +76 (c 0.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.60−7.56 (m, 3H), 7.54−7.51 (m, 1H), 7.48−7.39 (m, 3H), 7.38−7.25 (m, 6H), 7.20−7.14 (m, 1H), 5.10 (d, J = 11.6 Hz, 1H), 4.75 (d, J = 11.6 Hz, 1H), 3.88 (s, 3H), 3.87−3.83 (m, 1H), 3.76 (dd, J = 18.4, 2.9 Hz, 1H), 3.66 (dd, J = 18.4, 7.7 Hz, 1H), 3.21 (s, 1H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.2, 170.4, 160.1, 143.3, 141.0, 137.6, 130.0, 129.2, 128.7, 128.0, 127.9, 127.7, 126.6, 121.1, 120.7, 112.3, 75.3, 61.2, 55.7, 51.4, 42.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{24}NO_4$ 402.1700; found 402.1696.

*(R)-3-(2-([1,1′-Biphenyl]-4-yl)-2-oxoethyl)-5,5-diphenylmorpholin-2-one (**3h**).* White solid, 83.2 mg, 93%, 98% ee, mp 162.5−163.5 °C, HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 90:10, 1.0 mL/min, 245 nm): t_R(major) = 38.96 min, t_R(minor) = 44.45 min, $[\alpha]_D^{20}$ +32 (c 0.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.64−7.58 (m, 2H), 7.54−7.49 (m, 2H), 7.46−7.35 (m, 5H), 7.32−7.17 (m, 6H), 5.05 (d, J = 11.6 Hz, 1H), 4.70 (d, J = 11.6 Hz, 1H), 3.83 (dd, J = 7.7, 2.7 Hz, 1H), 3.74 (dd, J = 18.3, 2.8 Hz, 1H), 3.64 (dd, J = 18.3, 7.8 Hz, 1H), 3.20 (s, 1H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.9, 170.5, 146.6, 143.3, 141.0, 139.8, 135.0, 129.4, 129.2, 128.9, 128.7, 128.6, 128.0, 127.9, 127.7, 127.5, 127.5, 126.6, 75.3, 61.3, 51.4, 41.9. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{30}H_{26}NO_3$ 448.1907; found 448.1906.

*(R)-3-(2-(4-Fluorophenyl)-2-oxoethyl)-5,5-diphenylmorpholin-2-one (**3i**).* White solid, 74.1 mg, 95%, 97% ee, mp 150.0−151.0 °C, HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 70:30, 0.8 mL/min, 245 nm): t_R(major) = 13.73 min, t_R(minor) = 16.75 min, $[\alpha]_D^{20}$ +74 (c 0.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, J = 8.7, 5.4 Hz, 2H), 7.57 (d, J = 7.5 Hz, 2H), 7.46 (t, J = 7.6 Hz, 2H), 7.38−7.25 (m, 6H), 7.18 (t, J = 8.5 Hz, 2H), 5.10 (d, J = 11.6 Hz, 1H), 4.75 (d, J = 11.6 Hz, 1H), 3.86 (d, J = 5.5 Hz, 1H), 3.74 (dd, J = 18.3, 2.8 Hz, 1H), 3.64 (dd, J = 18.3, 7.7 Hz, 1H), 3.22 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −103.75 to −103.82 (m). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.7, 170.3, 166.3 (d, J = 256.0 Hz), 143.2, 140.9, 132.8 (d, J = 3.0 Hz), 131.02 (d, J = 9.5 Hz), 129.2, 128.7, 128.0, 127.9, 127.7, 126.6, 116.1 (d, J = 22.0 Hz), 75.3, 61.2, 51.4, 41.8. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{21}FNO_3$ 390.1500; found 390.1503.

*(R)-3-(2-(3-Fluorophenyl)-2-oxoethyl)-5,5-diphenylmorpholin-2-one (**3j**).* White solid, 76.2 mg, 98%, 97% ee, mp 121.3−122.3 °C, HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 70:30, 0.8 mL/min, 245 nm): t_R(major) = 10.27 min, t_R(minor) = 12.53 min, $[\alpha]_D^{20}$ +76 (c 0.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 7.8 Hz, 1H), 7.72−7.65 (m, 1H), 7.59−7.54 (m, 2H), 7.53−7.42 (m, 3H), 7.39−7.24 (m, 7H), 5.09 (d, J = 11.6 Hz, 1H), 4.75 (d, J = 11.6 Hz, 1H), 3.87 (dd, J = 7.7, 2.8 Hz, 1H), 3.74 (dd, J = 18.5, 2.9 Hz, 1H), 3.64 (dd, J = 18.5, 7.7 Hz, 1H), 3.18 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −111.28 to −111.34 (m). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.1 (d, J = 2.1 Hz), 170.2, 163.0 (d, J = 248.5 Hz), 143.2, 140.9, 138.3 (d, J = 6.2 Hz), 130.7 (d, J = 7.6 Hz), 129.3, 128.7, 128.0, 128.0, 127.7, 126.6, 124.1 (d, J = 3.0 Hz), 121.0 (d, J = 21.5 Hz), 115.0 (d, J = 22.5 Hz), 75.3, 61.3, 51.3, 42.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{21}FNO_3$ 390.1500; found 390.1504.

*(R)-3-(2-(2,6-Difluoro-4-methoxyphenyl)-2-oxoethyl)-5,5-diphenylmorpholin-2-one (**3k**).* Reaction performed on a 0.2 mmol scale utilizing **CPA-10** (3.7 mg, 2.5 mol %), **3k** was isolated as a white solid, 52.0 mg, 60%, 86% ee, mp 61.5−62.5 °C, HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 80:20, 1.0 mL/min, 245 nm): t_R(major) = 15.98 min, t_R(minor) = 18.30 min, $[\alpha]_D^{20}$ +74 (c 0.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.56−7.51 (m, 2H), 7.44−7.41 (m, 2H), 7.36−7.24 (m, 6H), 6.54−6.53 (m, 1H), 6.50−6.49 (m, 1H), 5.06 (d, J = 11.6 Hz, 1H), 4.75 (d, J = 11.6 Hz, 1H), 3.86 (s, 3H), 3.82 (dd, J = 7.0, 3.4 Hz, 1H), 3.64−3.59 (m, 1H), 3.58−3.51 (m, 1H), 3.09 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −107.51 (s), −107.54 (s). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 194.14 (t, J = 2.4 Hz), 170.15, 164.04 (t, J = 15.0 Hz), 162.72 (dd, J = 256.1, 9.9 Hz), 143.29, 140.99, 129.19, 128.70, 127.95, 127.84, 127.66, 126.60, 109.67 (t, J = 16.2 Hz), 99.01 (dd, J = 27.8, 2.5 Hz), 75.15, 61.21, 56.29, 51.50, 47.52 (t, J = 4.3 Hz). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{22}F_2NO_4$ 438.1511; found 438.1513.

*(R)-3-(2-(3-Chlorophenyl)-2-oxoethyl)-5,5-diphenylmorpholin-2-one (**3l**).* White solid, 74.7 mg, 92%, 95% ee, mp 89.0−90.0 °C, HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 70:30, 0.8 mL/min, 245 nm): t_R(major) = 10.55 min, t_R(minor) = 13.19 min, $[\alpha]_D^{20}$ +60 (c 0.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (t, J = 1.7 Hz, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.62−7.57 (m, 1H), 7.56−7.52 (m, 2H), 7.45 (t, J = 7.7 Hz, 3H), 7.38−7.23 (m, 6H), 5.07 (d, J = 11.6 Hz, 1H), 4.74 (d, J = 11.6 Hz, 1H), 3.86 (dd, J = 7.5, 2.3 Hz, 1H), 3.72 (dd, J = 18.5, 2.9 Hz, 1H), 3.61 (dd, J = 18.5, 7.8 Hz, 1H), 3.16 (s, 1H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.1, 170.2, 143.2, 140.9, 137.8, 135.3, 133.8, 130.3, 129.3, 128.7, 128.5, 128.0, 128.0, 127.7, 126.7, 126.4, 75.3, 61.3, 51.3, 42.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{21}ClNO_3$ 406.1204; found 406.1207.

*(R)-3-(2-(2-Chlorophenyl)-2-oxoethyl)-5,5-diphenylmorpholin-2-one (**3m**).* White solid, 59.8 mg, 73%, 97% ee, mp 129.5−130.5 °C, HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 70:30, 0.8 mL/min, 245 nm): t_R(major) = 10.81 min, t_R(minor) = 16.32 min, $[\alpha]_D^{20}$ +80 (c 0.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 7.0 Hz, 1H), 7.55 (d, J = 6.8 Hz, 2H), 7.46−7.44 (m, 4H), 7.39−7.25 (m, 7H), 5.06 (d, J = 11.5 Hz, 1H), 4.78 (d, J = 11.5 Hz, 1H), 3.89 (s, 1H), 3.73 (d, J = 17.8 Hz, 1H), 3.63 (dd, J = 18.3, 6.8 Hz, 1H), 3.10 (s, 1H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 200.7, 170.1, 143.2, 140.9, 137.8, 132.5, 131.4, 130.9, 129.6, 129.1, 128.6, 127.9, 127.8, 127.5, 127.1, 126.5, 75.0, 61.1, 51.5, 45.7. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{21}ClNO_3$ 406.1204; found 406.1206.

*(R)-3-(2-(3,4-Dichlorophenyl)-2-oxoethyl)-5,5-diphenylmorpholin-2-one (**3n**).* White solid, 86.0 mg, 98%, 97% ee, mp 143.4−144.4 °C, HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 70:30, 0.8 mL/min, 245 nm): t_R(major) = 16.12 min, t_R(minor) = 18.27 min, $[\alpha]_D^{20}$ +54 (c 0.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 1.9 Hz, 1H), 7.80 (dd, J = 8.4, 2.0 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 7.5 Hz, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.37−7.24 (m, 6H), 5.06 (d, J = 11.6 Hz, 1H), 4.73 (d, J = 11.6 Hz, 1H), 3.86 (d, J = 5.8 Hz, 1H), 3.70 (dd, J = 18.4, 2.8 Hz, 1H), 3.58 (dd, J = 18.4, 7.8 Hz, 1H),

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3.14 (s, 1H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.1, 170.1, 143.2, 140.9, 138.6, 135.8, 133.7, 131.1, 130.3, 129.3, 128.8, 128.1, 128.0, 127.6, 127.3, 126.7, 75.3, 61.3, 51.3, 41.9. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{20}Cl_2NO_3$ 440.0815; found 440.0816.

*(R)-3-(2-(4-Bromophenyl)-2-oxoethyl)-5,5-diphenylmorpholin-2-one (**3o**)*. White solid, 87.4 mg, 97%, 98% ee, mp 167.0−168.0 °C, HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 70:30, 0.8 mL/min, 245 nm): t_R(major) = 18.00 min, t_R(minor) = 22.59 min, $[\alpha]_D^{20}$ +50 (*c* 0.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.5 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 7.4 Hz, 2H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.38−7.24 (m, 6H), 5.08 (d, *J* = 11.6 Hz, 1H), 4.74 (d, *J* = 11.6 Hz, 1H), 3.85 (dd, *J* = 7.7, 2.7 Hz, 1H), 3.71 (dd, *J* = 18.4, 2.8 Hz, 1H), 3.61 (dd, *J* = 18.4, 7.8 Hz, 1H), 3.17 (s, 1H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.3, 170.3, 143.2, 140.9, 135.0, 132.3, 129.8, 129.2, 128.7, 128.0, 127.9, 127.7, 126.6, 75.3, 61.3, 51.3, 41.8. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{21}BrNO_3$ 450.0699; found 450.0701.

*(R)-3-(2-Oxo-2-(4-(trifluoromethyl)phenyl)ethyl)-5,5-diphenylmorpholin-2-one (**3p**)*. White solid, 77.5 mg, 88%, 97% ee, mp 150.5−151.5 °C, HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 70:30, 0.8 mL/min, 245 nm): t_R(major) = 16.07 min, t_R(minor) = 21.21 min, $[\alpha]_D^{20}$ +70 (*c* 0.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.1 Hz, 2H), 7.79 (d, *J* = 8.3 Hz, 2H), 7.57−7.55 (m, 2H), 7.48−7.44 (m, 2H), 7.40−7.24 (m, 6H), 5.09 (d, *J* = 11.6 Hz, 1H), 4.76 (d, *J* = 11.7 Hz, 1H), 3.90 (dd, *J* = 7.8, 2.8 Hz, 1H), 3.79 (dd, *J* = 18.5, 2.9 Hz, 1H), 3.67 (dd, *J* = 18.5, 7.8 Hz, 1H), 3.18 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.18 (s). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.4, 170.2, 143.2, 140.9, 138.9, 135.2 (q, *J* = 32.8 Hz), 129.3, 128.8, 128.7, 128.1, 128.0, 127.7, 126.7, 126.0 (q, *J* = 3.7 Hz), 123.7 (q, *J* = 272.8 Hz), 75.3, 61.4, 51.3, 42.2. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{21}F_3NO_3$ 440.1468; found 440.1471.

*(R)-3-(2-Oxo-2-(3-(trifluoromethyl)phenyl)ethyl)-5,5-diphenylmorpholin-2-one (**3q**)*. White solid, 76.5 mg, 87%, 94% ee, mp 91.0−92.0 °C, HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 70:30, 0.8 mL/min, 245 nm): t_R(major) = 8.45 min, t_R(minor) = 10.79 min, $[\alpha]_D^{20}$ +60 (*c* 0.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.39−7.26 (m, 6H), 5.08 (d, *J* = 11.6 Hz, 1H), 4.75 (d, *J* = 11.6 Hz, 1H), 3.90 (d, *J* = 5.6 Hz, 1H), 3.78 (dd, *J* = 18.5, 2.7 Hz, 1H), 3.68 (dd, *J* = 18.5, 7.8 Hz, 1H), 3.17 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.85 (s). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.0, 170.2, 143.2, 140.9, 136.7, 131.7 (q, *J* = 33.0 Hz), 131.5, 130.3 (q, *J* = 3.5 Hz), 129.7, 129.3, 128.8, 128.1, 128.0, 127.7, 126.7, 125.2 (q, *J* = 3.8 Hz),123.7 (q, *J* = 272.8 Hz), 75.3, 61.3, 51.3, 42.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{21}F_3NO_3$ 440.1468; found 440.1469.

*(R)-3-(2-(4-Nitrophenyl)-2-oxoethyl)-5,5-diphenylmorpholin-2-one (**3r**)*. White solid, 65.7 mg, 80%, 98% ee, mp 168.0−169.0 °C, HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 50:50, 1.0 mL/min, 245 nm): t_R(major) = 19.25 min, t_R(minor) = 27.06 min, $[\alpha]_D^{20}$ +60 (*c* 0.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.7 Hz, 2H), 8.13 (d, *J* = 8.7 Hz, 2H), 7.52 (d, *J* = 7.5 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.38−7.21 (m, 6H), 5.05 (d, *J* = 11.7 Hz, 1H), 4.73 (d, *J* = 11.7 Hz, 1H), 3.92−3.86 (m, 1H), 3.76 (dd, *J* = 18.5, 2.7 Hz, 1H), 3.65 (dd, *J* = 18.5, 7.6 Hz, 1H), 3.10 (s, 1H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.8, 170.1, 150.8, 143.1, 140.9, 140.5, 129.4, 129.2, 128.7, 128.1, 128.0, 127.6, 126.6, 124.1, 75.2, 61.3, 51.2, 42.3. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{21}N_2O_5$ 417.1445; found 417.1446.

*(R)-3-(2-(Naphthalen-2-yl)-2-oxoethyl)-5,5-diphenylmorpholin-2-one (**3s**)*. White solid, 77.6 mg, 92%, 98% ee, mp 119.0−120.0 °C, HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 80:20, 0.8 mL/min, 245 nm): t_R(major) = 22.63 min, t_R(minor) = 25.75 min, $[\alpha]_D^{20}$ +42 (*c* 0.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.06 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.96−7.89 (m, 2H), 7.69−7.57 (m, 4H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.40−7.25 (m, 6H), 5.12 (d, *J* = 11.6 Hz, 1H), 4.79 (d, *J* = 11.6 Hz, 1H), 3.98−3.89 (m, 2H), 3.81 (dd, *J* = 18.4, 8.2 Hz, 1H), 3.31 (s, 1H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.2, 170.5, 143.3, 141.0, 136.0, 133.6, 132.6, 130.4, 129.8, 129.2, 129.0, 128.8, 128.7, 128.0, 127.9, 127.7, 127.1, 126.7, 123.6, 75.3, 61.3, 51.5, 41.9. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{24}NO_3$ 422.1751; found 422.1741.

*(R)-3-(2-(Naphthalen-1-yl)-2-oxoethyl)-5,5-diphenylmorpholin-2-one (**3t**)*. White solid, 53.6 mg, 64%, 97% ee, mp 171.5−172.5 °C, HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 70:30, 0.8 mL/min, 245 nm): t_R(major) = 12.19 min, t_R(minor) = 17.62 min, $[\alpha]_D^{20}$ +54 (*c* 0.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 8.5 Hz, 1H), 7.97−7.85 (m, 2H), 7.79 (d, *J* = 7.9 Hz, 1H), 7.54−7.50 (m, 1H), 7.47−7.39 (m, 4H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.26−7.14 (m, 6H), 4.99 (d, *J* = 11.7 Hz, 1H), 4.70 (d, *J* = 11.7 Hz, 1H), 3.81 (dd, *J* = 7.2, 3.2 Hz, 1H), 3.71 (dd, *J* = 18.1, 3.2 Hz, 1H), 3.64 (dd, *J* = 18.1, 7.2 Hz, 1H), 3.13 (s, 1H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 202.0, 170.5, 143.3, 141.0, 134.5, 134.1, 133.8, 130.3, 129.2, 128.7, 128.7, 128.5, 128.0, 127.9, 127.7, 126.8, 126.6, 125.9, 124.5, 75.2, 61.3, 51.8, 44.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{24}NO_3$ 422.1751; found 422.1747.

*(R)-3-(2-oxo-2-(thiophen-2-yl)ethyl)-5,5-diphenylmorpholin-2-one (**3u**)*. White solid, 69.7 mg, 92%, 96% ee, mp 113.0−114.0 °C, HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 70:30, 0.8 mL/min, 245 nm): t_R(major) = 11.59 min, t_R(minor) = 17.51 min, $[\alpha]_D^{20}$ +66 (*c* 0.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.81−7.76 (m, 1H), 7.72−7.66 (m, 1H), 7.53 (d, *J* = 7.5 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.37−7.23 (m, 6H), 7.16 (dd, *J* = 4.7, 4.0 Hz, 1H), 5.06 (d, *J* = 11.6 Hz, 1H), 4.72 (d, *J* = 11.6 Hz, 1H), 3.85 (dd, *J* = 7.8, 2.8 Hz, 1H), 3.71 (dd, *J* = 18.1, 2.8 Hz, 1H), 3.61 (dd, *J* = 18.1, 7.9 Hz, 1H), 3.17 (s, 1H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 191.1, 170.1, 143.3, 143.2, 140.9, 134.6, 132.9, 129.2, 128.7, 128.5, 128.0, 127.9, 127.7, 126.6, 75.3, 61.3, 51.4, 42.1. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{20}NO_3S$ 378.1158; found 378.1166.

*(R)-3-(2-Oxo-2-(thiophen-3-yl)ethyl)-5,5-diphenylmorpholin-2-one (**3v**)*. White solid, 73.2 mg, 97%, 98% ee, mp 127.5−128.5 °C, HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 70:30, 0.8 mL/min, 245 nm): t_R(major) = 13.15 min, t_R(minor) = 21.87 min, $[\alpha]_D^{20}$ +66 (*c* 0.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 2.8, 1.1 Hz, 1H), 7.58−7.49 (m, 3H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.37−7.22 (m, 7H), 5.07 (d, *J* = 11.6 Hz, 1H), 4.72 (d, *J* = 11.6 Hz, 1H), 3.83 (d, *J* = 5.5 Hz, 1H), 3.66 (dd, *J* = 18.2, 2.9 Hz, 1H), 3.57 (dd, *J* = 18.3, 7.8 Hz, 1H), 3.22 (s, 1H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 192.5, 170.3, 143.2, 141.5, 140.9, 133.0, 129.2, 128.7, 128.0, 127.9, 127.7, 126.9, 126.8, 126.6, 75.3, 61.2, 51.3, 42.8. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{20}NO_3S$ 378.1158; found 378.1161.

*(R)-3-(2-(Furan-2-yl)-2-oxoethyl)-5,5-diphenylmorpholin-2-one (**3w**)*. Reaction performed on a 0.2 mmol scale utilizing 10 mol % of **CPA−4**, **3v** was isolated as a white solid, 38.6 mg, 44%, 96% ee, mp 56.0−57.0 °C, HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 70:30, 0.8 mL/min, 245 nm): t_R(major) = 11.21 min, t_R(minor) = 14.44 min, $[\alpha]_D^{20}$ +52 (*c* 0.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.51 (d, *J* = 7.5 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.35−7.22 (m, 7H), 6.57 (dd, *J* = 3.5, 1.6 Hz, 1H), 5.03 (d, *J* = 11.6 Hz, 1H), 4.71 (d, *J* = 11.6 Hz, 1H), 3.83 (dd, *J* = 7.8, 3.0 Hz, 1H), 3.60 (dd, *J* = 18.3, 3.0 Hz, 1H), 3.50 (dd, *J* = 18.3, 7.9 Hz, 1H), 3.17 (s, 1H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 187.2, 170.2, 152.3, 147.1, 143.3, 141.0, 129.2, 128.7, 128.0, 127.9, 127.7, 126.7, 118.1, 112.7, 75.3, 61.3, 51.1, 41.3. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{20}NO_4$ 362.1387; found 362.1389.

*(R)-3-(2-Oxo-4-phenylbutyl)-5,5-diphenylmorpholin-2-one (**3x**)*. Light yellow solid, 52.9 mg, 66%, 91% ee, mp 151.5−152.5 °C, HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 70:30, 0.8 mL/min, 245 nm): t_R(major) = 11.00 min, t_R(minor) = 13.72 min, $[\alpha]_D^{20}$ +56 (*c* 0.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.4 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.34−7.23 (m, 8H), 7.22−7.17 (m, 3H), 5.00 (d, *J* = 11.7 Hz, 1H), 4.66 (d, *J* = 11.7 Hz, 1H), 3.67−3.61 (m, 1H), 3.14−3.00 (m, 2H), 2.97 (s, 1H), 2.92 (t, *J* = 7.5 Hz, 2H), 2.80 (t, *J* = 7.4 Hz, 2H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 208.6, 170.3, 143.2, 140.9, 140.6, 129.2, 128.7, 128.7, 128.4, 128.0, 127.9, 127.6, 126.6, 126.4, 75.1, 61.1, 51.1, 45.4, 44.5, 29.7. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{26}H_{26}NO_3$ 400.1907; found 400.1905.

*(R)-3-(2-Oxohexyl)-5,5-diphenylmorpholin-2-one (**3y**)*. White solid, 63.4 mg, 90%, 95% ee, mp 93.5−94.5 °C, HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 80:20, 0.8 mL/min, 245 nm):

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t_R(major) = 8.78 min, t_R(minor) = 10.87 min, $[\alpha]_D^{20}$ +120 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.4 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.32−7.22 (m, 6H), 5.01 (d, *J* = 11.6 Hz, 1H), 4.67 (d, *J* = 11.6 Hz, 1H), 3.64 (s, 1H), 3.15−3.07 (m, 2H), 3.05 (s, 1H), 2.47 (t, *J* = 7.4 Hz, 2H), 1.67−1.49 (m, 2H), 1.41−1.19 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 209.8, 170.3, 143.3, 141.0, 129.2, 128.7, 127.9, 127.8, 127.6, 126.5, 75.2, 61.1, 51.2, 45.2, 42.8, 25.9, 22.4, 14.0. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{22}H_{26}NO_3$ 352.1907; found 352.1906.

*(R)-3-(3,3-Dimethyl-2-oxobutyl)-5,5-diphenylmorpholin-2-one (**3z**).* White solid, 61.8 mg, 88%, 95% ee, mp 183.0−184.0 °C, HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 95:5, 1.0 mL/min, 245 nm): t_R(major) = 13.13 min, t_R(minor) = 21.49 min, $[\alpha]_D^{20}$ +124 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.43 (m, 2H), 7.39−7.35 (m, 2H), 7.31−7.18 (m, 6H), 5.00 (d, *J* = 11.6 Hz, 1H), 4.64 (d, *J* = 11.6 Hz, 1H), 3.59 (s, 1H), 3.22−3.10 (m, 2H), 3.01 (s, 1H), 1.16 (s, 9H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 215.2, 170.5, 143.3, 140.9, 129.2, 128.7, 127.9, 127.8, 127.7, 126.5, 75.2, 61.1, 51.3, 44.3, 40.2, 26.6. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{22}H_{26}NO_3$ 352.1907; found 352.1903.

*(R)-3-(2-Cyclopropyl-2-oxoethyl)-5,5-diphenylmorpholin-2-one (**3a′**).* Reaction performed on a 0.2 mmol scale utilizing *N*-(1-cyclopropylvinyl)acetamide **2z** (75.1 mg, 3.0 equiv); **3z** was isolated as a white solid, 40.3 mg, 60%, 95% ee, mp 95.5−96.5 °C, HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 85:15, 1.0 mL/min, 245 nm): t_R(major) = 9.59 min, t_R(minor) = 10.91 min, $[\alpha]_D^{20}$ +116 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.4 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.36−7.23 (m, 6H), 5.05 (d, *J* = 11.6 Hz, 1H), 4.67 (d, *J* = 11.6 Hz, 1H), 3.65 (dd, *J* = 6.7, 3.6 Hz, 1H), 3.33 (dd, *J* = 18.3, 3.5 Hz, 1H), 3.27 (dd, *J* = 18.4, 6.8 Hz, 1H), 3.10 (s, 1H), 2.00−1.97 (m, 1H), 1.15−1.04 (m, 2H), 1.01−0.95 (m, 2H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 209.3, 170.3, 143.3, 140.9, 129.2, 128.7, 128.0, 127.8, 127.7, 126.5, 75.3, 61.1, 51.2, 45.8, 21.0, 11.5, 11.5. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{22}NO_3$ 336.1594; found 336.1596.

*(R)-3-(2-Cyclohexyl-2-oxoethyl)-5,5-diphenylmorpholin-2-one (**3b′**).* White solid, 72.6 mg, 96%, 98% ee, mp 152.2−153.2 °C, HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 90:10, 1.0 mL/min, 245 nm): t_R(major) = 12.24 min, t_R(minor) = 15.76 min, $[\alpha]_D^{20}$ +110 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51−7.46 (m, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.33−7.21 (m, 6H), 5.02 (d, *J* = 11.6 Hz, 1H), 4.66 (d, *J* = 11.6 Hz, 1H), 3.62 (s, 1H), 3.20−3.07 (m, 2H), 3.06 (s, 1H), 2.44−2.33 (m, 1H), 1.89 (t, *J* = 9.2 Hz, 2H), 1.81−1.78 (m, 2H), 1.68 (d, *J* = 11.4 Hz, 1H), 1.42−1.18 (m, 5H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 212.9, 170.4, 143.3, 141.0, 129.2, 128.7, 128.0, 127.8, 127.7, 126.6, 75.2, 61.1, 51.2, 50.9, 43.3, 28.6, 28.5, 25.9, 25.7, 25.7. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{24}H_{28}NO_3$ 378.2064; found 378.2071.

*(R,E)-3-(2-Oxo-4-phenylbut-3-en-1-yl)-5,5-diphenylmorpholin-2-one (**3c′**).* Reaction mixture stirred at 0 °C for 12 h and then heated at 40 °C for 1 h; **3b′** was isolated as a white solid, 47.7 mg, 60%, 90% ee, mp 146.2−147.2 °C, HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 70:30, 0.8 mL/min, 245 nm): t_R(major) = 14.43 min, t_R(minor) = 16.74 min, $[\alpha]_D^{20}$ +44 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 16.3 Hz, 1H), 7.58−7.51 (m, 4H), 7.43−7.41 (m, 5H), 7.35−7.22 (m, 6H), 6.75 (d, *J* = 16.2 Hz, 1H), 5.04 (d, *J* = 11.6 Hz, 1H), 4.70 (d, *J* = 11.6 Hz, 1H), 3.76 (s, 1H), 3.44 (dd, *J* = 18.1, 2.7 Hz, 1H), 3.35 (dd, *J* = 18.2, 7.6 Hz, 1H), 3.19 (s, 1H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 198.1, 170.4, 144.2, 143.3, 141.0, 134.2, 131.1, 129.2, 128.7, 128.6, 128.0, 127.9, 127.7, 126.6, 125.7, 75.2, 61.2, 51.4, 43.4. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{26}H_{24}NO_3$ 398.1751; found 398.1749.

*(R)-3-(4-Methyl-2-oxopent-3-en-1-yl)-5,5-diphenylmorpholin-2-one (**3d′**).* White solid, 64.7 mg, 93%, 99% ee, mp 88.7−89.7 °C, HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 80:20, 0.8 mL/min, 245 nm): t_R(major) = 8.79 min, t_R(minor) = 10.61 min, $[\alpha]_D^{20}$ +90 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.5 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.32−7.23 (m, 6H), 6.09 (s, 1H), 5.07 (d, *J* = 11.6 Hz, 1H), 4.71 (d, *J* = 11.6 Hz, 1H), 3.64 (d, *J* = 4.0 Hz, 1H), 3.21−3.05 (m, 3H), 2.17 (s, 3H), 1.92 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 198.3, 170.6, 157.6, 143.4, 140.9, 129.2, 128.7, 127.9, 127.8, 127.7, 126.5, 123.3, 75.3, 61.0, 51.4, 46.5, 28.0, 21.2. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{22}H_{24}NO_3$ 350.1751; found 350.1750.

*4-Acetyl-5,5-dimethyl-3-(2-oxo-2-phenylethyl)morpholin-2-one (**3′**).* Reaction performed on a 0.2 mmol scale utilizing the starting material 5,5-dimethyl-5,6-dihydro-2*H*-1,4-oxazin-2-one **1′**. White solid, 24.2 mg, 42%, 96% ee, mp 54.6−55.6 °C, HPLC (DAICEL Chiralpak OD-H, hexane/IPA = 70:30, 1.0 mL/min, 245 nm): t_R(major) = 19.79 min, t_R(minor) = 16.95 min, $[\alpha]_D^{20}$ −40 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99−7.88 (m, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 5.31 (dd, *J* = 7.9, 4.4 Hz, 1H), 4.47 (d, *J* = 12.4 Hz, 1H), 4.00 (d, *J* = 12.4 Hz, 1H), 3.64 (dd, *J* = 16.6, 7.9 Hz, 1H), 3.33 (dd, *J* = 16.6, 4.3 Hz, 1H), 2.15 (s, 3H), 1.58 (s, 3H), 1.54 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4, 170.8, 168.5, 135.9, 134.2, 129.1, 128.4, 74.8, 54.8, 53.4, 43.7, 24.3, 24.1, 22.8. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{19}NNaO_4$ 312.1206; found 312.1210.

Control Experiment for the Model Reaction without Water. To a 25 mL Schlenk flask equipped with a stirring bar were added 5,5-diphenyl-5,6-dihydro-2*H*-1,4-oxazin-2-one **1** (50.2 mg, 0.2 mmol, 1.0 equiv), *N*-(1-phenylvinyl)acetamide **2a** (48.4 mg, 0.3 mmol, 1.5 equiv), 4 Å MS (100 mg), and chiral phosphoric acid **CPA-4** (2.9 mg, 2.5 mol %). The flask was vacuumed and backfilled with Ar three times. Then dry toluene (3 mL) was added at 0 °C, and the resulting mixture was stirred at the same temperature for 12 h until completion indicated by thin layer chromatography (TLC). Afterward, the reaction mixture was concentrated under vacuum to yield the crude expected product which was subjected to column chromatography on silica gel (PE/EA = 3:1 to 1:1 as the eluent) to give the product **4a**.

Procedure for the preparation of the racemic products **4a**. To a 25 mL Schlenk flask equipped with a stirring bar were added 5,5-diphenyl-5,6-dihydro-2*H*-1,4-oxazin-2-one **1** (50.2 mg, 0.2 mmol, 1.0 equiv), *N*-(1-phenylvinyl)acetamide **2a** (48.4 mg, 0.3 mmol, 1.5 equiv), 4 Å MS (100 mg), and racmic 1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (14.0 mg, 20 mol %). The flask was vacuumed and backfilled with Ar for three times. Then dry toluene (3 mL) was added at 0 °C, and the resulting mixture was stirred at the same temperature for 24 h until completion indicated by thin layer chromatography (TLC). Afterward, the reaction mixture was concentrated under vacuum to yield the crude expected product which was subjected to column chromatography on silica gel (PE/EA = 3:1 to 1:1 as the eluent) to give the racemic product *Z*-**4a** and *E*-**4a**.

*(R,Z)-N-(2-(2-Oxo-5,5-diphenylmorpholin-3-yl)-1-phenylvinyl)-acetamide (**Z-4a**).* White solid, 52.6 mg, 64%, 50% ee, mp 125.0−126.0 °C, R_f = 0.3 (petroleum ether/EtOAc 3:1), HPLC (DAICEL Chiralpak IC, hexane/IPA = 90:10, 1.0 mL/min, 245 nm): t_R(major) = 18.65 min, t_R(minor) = 23.86 min, $[\alpha]_D^{20}$ +10 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.56 (d, *J* = 17.7 Hz, 1H), 7.45 (t, *J* = 6.6 Hz, 4H), 7.42−7.26 (m, 11H), 5.94 (d, *J* = 8.1 Hz, 1H), 4.99 (d, *J* = 11.5 Hz, 1H), 4.59 (d, *J* = 11.5 Hz, 1H), 4.15 (dt, *J* = 13.7, 6.9 Hz, 1H), 3.33 (d, *J* = 11.1 Hz, 1H), 1.96 (d, *J* = 6.0 Hz, 3H). ^{13}C{1H} NMR (100 MHz, CD_2Cl_2) δ 169.7, 169.6, 143.4, 141.5, 138.4, 137.3, 129.3, 129.1, 128.9, 128.8, 128.2, 128.1, 128.1, 127.1, 126.5, 120.9, 75.9, 61.3, 54.2, 23.6. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{26}H_{25}N_2O_3$ 413.1860; found 413.1865.

*(R,E)-N-(2-(2-Oxo-5,5-diphenylmorpholin-3-yl)-1-phenylvinyl)-acetamide (**E-4a**).* White solid, 17.5 mg, 21%, 95% ee, mp 85.0−86.0 °C, R_f = 0.1 (petroleum ether/EtOAc 3:1), HPLC (DAICEL Chiralpak AD-H, hexane/IPA = 70:30, 0.8 mL/min, 245 nm): t_R(major) = 5.61 min, t_R(minor) = 6.88 min, $[\alpha]_D^{20}$ +26 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.38−7.23 (m, 10H), 7.21−7.15 (m, 5H), 6.75 (s, 1H), 6.71 (d, *J* = 9.4 Hz, 1H), 4.87 (d, *J* = 11.7 Hz, 1H), 4.60 (d, *J* = 11.7 Hz, 1H), 3.82 (d, *J* = 9.5 Hz, 1H), 2.28 (s, 1H), 2.03 (s, 3H). ^{13}C{1H} NMR (100 MHz, CD_2Cl_2) δ 169.9, 169.5, 143.7, 141.6, 140.4, 135.9, 129.4, 129.1, 129.0, 128.9, 128.2, 127.7, 127.3, 126.9, 111.3, 75.3, 61.5, 54.5, 24.9. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{26}H_{25}N_2O_3$ 413.1860; found 413.1864.

Gram-Scale Experiment. To a 250 mL Schlenk flask equipped with a stirring bar were added 5,5-diphenyl-5,6-dihydro-2*H*-1,4-

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oxazin-2-one **1** (1.0 g, 4.0 mmol, 1.0 equiv), *N*-(1-phenylvinyl)-acetamide **2a** (0.97 g, 6.0 mmol, 1.5 equiv), and chiral phosphoric acid **CPA-4** (58.5 mg, 2.5 mol %). Then toluene (60 mL) and H_2O (0.36 mL, 5.0 equiv) were added successively at 0 °C, and the resulting mixture was stirred at the same temperature for 5 h until the disappearance of the starting material as monitored by thin layer chromatography (TLC). Afterward, the mixture was extracted with ethyl acetate three times, and the combined organic phase was dried over Na_2SO_4. After filtration, the filtrate was concentrated under vacuum to yield the crude expected product which was subjected to column chromatography on silica gel (PE/EA = 10:1 as the eluent) to give the pure product **3a** (1.38 g, 93%, 97% ee).

Preparation of Optically Active Unnatural α-Amino Acids. **3** (0.2 mmol, 1.0 equiv) and 8 mg of 20% $Pd(OH)_2/C$ were weighed into a screw-cap vial, and then $EtOH/H_2O$ (5 mL, v/v = 2:1) was added, followed by 50% HBF_4 (25 μL, 0.21 mmol, 1.05 equiv). The vial was placed in an autoclave, and the mixture was stirred at 40 °C under 20 bar of H_2 for 20 h. In the case of **8c–d**, it was stirred at 55 °C under 35 bar of H_2 for 24 h. After cooling to room temperature, the crude reaction mixture was filtrated through kieselguhr and diluted with 20 mL of water. The aqueous layer was washed with CH_2Cl_2 (2 × 20 mL) and hexane (2 × 10 mL) and then concentrated under vacuum to obtain the desired amino α-amino acids **8a–b** and **8e**.

*(R)-2-Amino-5,5-dimethyl-4-oxohexanoic acid HBF4-salt (**8a**).* Yellow solid, 49.6 mg, 95%, $[\alpha]_D^{20}$ −10 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, D_2O) δ 4.34 (s, 1H), 3.49 (d, *J* = 18.2 Hz, 1H), 3.39 (d, *J* = 19.2 Hz, 1H), 1.17 (s, 9H). ^{19}F NMR (376 MHz, D_2O) δ −150.31 (s), −150.37 (s). ^{13}C{1H} NMR (100 MHz, D_2O) δ 217.4, 171.5, 48.8, 43.8, 36.7, 25.3. HRMS (ESI) *m/z*: $[M - BF_4^-]^+$ calcd for $C_8H_{16}NO_3$ 174.1125; found 174.1128.

*(R)-2-Amino-4-cyclohexyl-4-oxobutanoic acid HBF4-salt (**8b**).* Pale yellow solid, 43.1 mg, 75%, $[\alpha]_D^{20}$ −12 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, D_2O) δ 4.33 (t, *J* = 4.6 Hz, 1H), 3.47–3.30 (m, 2H), 2.57 (s, 1H), 1.90–1.88 (m, 2H), 1.76 (s, 2H), 1.67 (d, *J* = 11.9 Hz, 1H), 1.37–1.22 (m, 5H). ^{19}F NMR (376 MHz, D_2O) δ −150.30 (s), −150.36 (s). ^{13}C{1H} NMR (100 MHz, D_2O) δ 215.2, 171.6, 50.1, 48.7, 39.5, 28.0, 27.8, 25.3, 25.0, 25.0. HRMS (ESI) *m/z*: $[M - BF_4^-]^+$ calcd for $C_{10}H_{18}NO_3$ 200.1281; found 200.1283.

*(R)-2-Amino-4-phenylbutanoic acid HBF4-salt (**8c**).* Yellow solid, 37.7 mg, 67%, $[\alpha]_D^{20}$ −22 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, D_2O) δ 7.35 (d, *J* = 6.4 Hz, 2H), 7.28 (d, *J* = 6.5 Hz, 3H), 4.06 (s, 1H), 2.77–2.76 (m, 2H), 2.26–2.18 (m, 2H). ^{19}F NMR (376 MHz, D_2O) δ −150.34 (s), −150.40 (s). ^{13}C{1H} NMR (100 MHz, D_2O) δ 171.8, 140.1, 128.8, 128.5, 126.7, 52.4, 31.5, 30.3. HRMS (ESI) *m/z*: $[M - BF_4^-]^+$ calcd for $C_{10}H_{14}NO_2$ 180.1019; found 180.1026.

*(R)-2-Amino-4-(4-methoxyphenyl)butanoic acid HBF4-salt (**8d**).* Pale yellow solid, 41.3 mg, 66%, $[\alpha]_D^{20}$ −16 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, D_2O) δ 7.18 (d, *J* = 8.2 Hz, 2H), 6.89 (d, *J* = 8.3 Hz, 2H), 4.04 (t, *J* = 6.1 Hz, 1H), 3.74 (s, 3H), 2.72–2.62 (m, 2H), 2.28–1.98 (m, 2H). ^{19}F NMR (376 MHz, D_2O) δ −150.35 (s), −150.40 (s). ^{13}C{1H} NMR (100 MHz, D_2O) δ 171.9, 157.4, 132.6, 129.6, 114.2, 55.4, 52.4, 31.7, 29.4. HRMS (ESI) *m/z*: $[M - BF_4^-]^+$ calcd for $C_{11}H_{16}NO_3$ 210.1125; found 210.1126.

*(R)-2-Amino-4-(4-methoxyphenyl)butanoic acid HBF4-salt (**8e**).* Pale yellow solid, 35.1 mg, 67%, $[\alpha]_D^{20}$ −18 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, D_2O) δ 6.70 (s, 1H), 6.67 (s, 1H), 4.49 (t, *J* = 5.0 Hz, 1H), 3.88 (s, 3H), 3.81–3.70 (m, 2H). ^{19}F NMR (377 MHz, D_2O) δ −107.81 (s), −107.85 (s), −150.39 (s), −150.43 to −150.45 (m). ^{13}C{1H} NMR (100 MHz, D_2O) δ 194.29, 171.46, 164.91 (t, *J* = 15.9 Hz), 162.74 (dd, *J* = 255.6, 9.6 Hz), 107.69 (t, *J* = 14.8 Hz), 99.18 (dd, *J* = 27.6, 2.4 Hz), 56.42, 48.96, 43.26 (t, *J* = 5.4 Hz). HRMS (ESI) *m/z*: $[M - BF_4^-]^+$ calcd for $C_{11}H_{12}F_2NO_4$ 260.0729; found 260.0730.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c00436.

Additional experimental information, HPLC traces, and NMR spectrum (PDF)
Crystallographic data for **3l** (CIF)
Crystallographic data for *Z*-**4a** (CIF)
Crystallographic data for *E*-**4a** (CIF)

Accession Codes

CCDC 1914728 (**3l**), 1914731 (*Z*-**4a**), and 1914733 (*E*-**4a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

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Notes

The authors declare no competing financial interest.

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accounting for the observed low ee of compound *Z*-**4a**. In addition, preliminary computational studies show that *Z*-**4a** is calculated to be energetically more stable by 4.5 kcal mol^{-1} relative to *E*-**4a**, which is consistent with the experimental result. However, further combined experimental and computational studies are still needed to fully elucidate the mechanistic picture. See the SI for details.

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