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Direct Catalytic Asymmetric Synthesis of trifluoromethylated γ -Amino Esters/Lactones via Umpolung Strategy

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Abstract

Enabled by the discovery of new cinchonium salts and co-additives, a direct and efficient asymmetric access to trifluoromethylated γ -amino esters/lactones has been realized through the enantioselective and diastereoselective umpolung reaction of trifluoromethyl imines with acrylates or α,β -unsaturated lactones as carbon electrophiles. At 0.5 to 5.0 mol % catalyst loadings, the newly-developed catalytic system activates a variety of imine substrates as unconventional nucleophiles to mediate highly chemo-, regio-, diastereo- and enantioselective C-C bond forming reactions. The developed synthetic protocol represents an excellent strategy to target a series of versatile and enantiomerically enriched γ -amino esters/lactones in good to excellent yields from the readily available starting materials. Additionally, we found that the *epi*-vinyl catalysts based on cinchonidine and quinine promote a similarly high enantioselective reaction generating the opposite configuration of chiral products in highly efficient manner, which allows the convenient access to either *R* or *S*-enantiomer of the chiral amine products in high yields and excellent enantioselectivities.

Graphical Abstract

INTRODUCTION

Chiral γ -amino esters as a privileged structural scaffold are presented in a variety of natural products and biologically active molecules. Due to their important applications in the

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Supporting Information

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pharmaceutical industry and peptide chemistry, significant efforts have been devoted to the asymmetric synthesis of γ -amino acid derivatives.^{1–3} Meanwhile, the uniquely beneficial impact resulting from the presence of fluorine on organic molecules has led to a rapidly increasing demand for developing novel methodology to efficiently synthesize organofluorine compounds.⁴ Recently, γ -trifluoromethylated γ -amino acid motifs began to appear in many pharmaceutically appealing structures.⁵ A direct and general enantioselective method towards these chiral building blocks however is still less explored. Herein, we wish to disclose the discovery and development of new cinchona phase-transfer catalysts to promote the direct asymmetric generation of γ -trifluoromethylated γ -amino esters through the umpolung addition of various trifluoromethyl imines with readily available carbon electrophiles such as acrylates or α,β -unsaturated lactones.

RESULTS AND DISCUSSION

We⁶ and others^{7–9} demonstrated that the imine umpolung reactions through the catalytic activation of imines as nucleophiles could be performed as a powerful alternative strategy for the efficient synthesis of chiral amino compounds. Inspired by these pioneering studies, our group recently discovered that the quinidium salts could efficiently activate trifluoromethyl imines **1** as nucleophiles to promote highly regio-, chemo-, diastereo-, and enantioselective umpolung reactions of imines **1** with α,β -unsaturated *N*-acyl pyrroles **13**, and accordingly realized the enantioselective construction of γ,γ -disubstituted and β,γ -disubstituted γ -amino acid derivatives **15** in an efficient fashion (Scheme 1a).¹⁰ Following these interesting results, it would be highly desirable if we can extend this imine umpolung reactions to the readily available but significantly less reactive carbon electrophiles such as α,β -unsaturated esters **4** or α,β -unsaturated lactones **8**, which would allow the straightforward access to chiral γ -amino esters/lactones in an efficient manner (Scheme 1b).

Compared with the reactive and unstable *N*-acyl pyrrole electrophiles, acrylates **4** were readily available but significantly less reactive. We started the investigation with the model reaction of trifluoromethyl imine **1A** and methyl acrylate (**4a**) by utilizing our previously developed cinchona phase-transfer catalyst **C-1**. However, the substantially decreased electrophilicity of **4a** posed considerable challenges.¹¹ Specifically, we observed that the activated 2-azaallyl anion intermediate **2A** preferably underwent isomerization pathway to side product **6A** and only a tiny amount of desired adduct **5Aa** was obtained with poor enantioselectivity (**5Aa/6A** = 10/90, 15% ee of **5Aa**, entry 1, Table 1). Moreover, a significant amount of [3+2] side product **7Aa** was inevitably formed through the conjugate addition-Mannich reaction pathway (**5Aa/7Aa** = 79/21, entry 1, Table 1). Interestingly, we found that the quinidium catalyst QD-2 bearing the *N*-(9-methylanthracene) substituent demonstrated significantly superior control for the chemo-, and stereoselectivity, mediating efficient generation of the desired umpolung addition product **5Aa** with good enantioselectivity, although a considerable amount of side products **6A** and **7Aa** were still observed (**5Aa/6A** = 58/42, **5Aa/7Aa** = 80/20, 80% ee of **5Aa**, entry 2). These initial results indicated that further catalyst development was required to achieve the desired umpolung adduct **5Aa** with excellent enantioselectivity and high yield.

The 6'-methoxy group in catalyst QD-2 was an important structural modification position. The steric and electronic turning of 6'-OMe moiety represented an attractive route for the further catalyst optimizations.¹² Following these considerations, we next prepared catalyst QD-3, in which the methoxy motif was replaced by a sterically more bulky and electronically more donating 6'-OⁱPr group. To our delight, QD-3 was found to be a more effective catalyst that promoted almost complete reaction in 4 h with excellent enantioselectivity and significantly improved chemoselectivity (**5Aa/6A** = 66/34, 90 % ee of **5Aa**, entry 3). When the temperature was lowered to -30 °C, this reaction still progressed to high conversion with excellent steric control and slightly enhanced chemoselectivity (**5Aa/6A** = 71/29, 91 % ee of **5Aa**, entry 4). Following our previous observations that the presence of phenol-type additives efficiently suppress the formation of side products **6A** and **7Aa**,^{6c,10} we found that the addition of 2 mol % phenol additive **A-1** significantly accelerated the reaction rate, thereby promoting fully completed reaction with obviously improved chemoselectivity (**5Aa/6A** = 83/17, **5Aa/7Aa** = 90/10, entry 5). Interestingly, we observed that the model reaction proceeded with the predominant formation of desired product **5Aa** when a small amount of ethanol (2.5 μ L) was also utilized (**5Aa/6A** = 93/7, **5Aa/7Aa** = 90/10, entry 6). Further decreasing the reaction temperature to -40 °C, the desired adduct **5Aa** was obtained in excellent chemo- and enantioselectivity (**5Aa/6A** = 95/5, **5Aa/7Aa** = 90/10, 91% ee, entry 7).

We next examined catalyst Q-3, the pseudoenantiomer of QD-3. Unfortunately, we found that Q-3 failed to mediate the generation of opposite enantiomer of **5Aa** with satisfactory results (-33% ee of **5Aa**, 32% conv., entry 8). Building on our recent discovery that the *epi-vinyl*quinine- or *epi-vinyl*cinchonidine-derived derivatives could provide more efficient catalysis than that by the corresponding quinine- or cinchonidine-derived catalysts,¹³ we next prepared the *epi-vinyl* cinchona catalyst epiQ-3 and pleasantly found that it was a considerably improved catalyst, delivering the opposite enantiomer of product **5Aa** with excellent enantioselectivity and high chemoselectivity in full conversion (91% ee, **5Aa/6A** = 97/3, **5Aa/7Aa** = 91/9, entry 9).

With the optimal catalysts in hand, we next explored the reaction scope for both trifluoromethyl imines **1** and acrylates **4**. As shown in Table 2, the reactions of **1A** with a series of acrylate derivatives **4a-e** bearing simple and functionalized substituents consistently proceeded with good yields and high enantioselectivities (entries 1–5). We next examined various trifluoromethyl imines and found that a variety of simple and functionalized aliphatic imines of varying length **1B-E** reacted efficiently with methyl acrylate (**4a**) in highly enantioselective fashion to form the desired products **5B-E** in useful yield and ee (entries 6–9). Interestingly, the aldimine **1F** was also well tolerated by the catalysts (entry 10). The reaction of branched imines such as **1G** with methyl acrylate (**4a**) failed to deliver the desired addition products **5Ga** due to the reduced reactivity (entry 11). Nevertheless, these sterically more hindered α or β -branched imines **1G-J** were found to react with propargyl acrylate (**4b**) to furnish the products **5Gb-Jb** in good yield with high enantioselectivity (entries 12–15).

Chiral γ - and δ -lactones not only are commonly presented structural motifs in natural products but also serve as versatile synthetic intermediates to chiral tetrahydrofuran, tetrahydropyran, and hydroxycarboxylic acid derivatives.¹⁴ We therefore began to explore the imine umpolung reactions with α,β -unsaturated lactones. Our investigation commenced with the C-1 mediated reaction of trifluoromethyl imine **1L** with γ -crotonolactone (**8a**) and found that the isomerized imine **6L** was generated predominantly (**9La/6L** = 9/91, **9La/10La** = 25/75, entry 1, Table 3). Interestingly, with the addition of phenol additive A-1, the reaction formed an increased amount of the desired product **9La** with excellent enantioselectivity (**9La/6L** = 30/70, **9La/10La** = 87/13, 98% ee, entry 2). Further screening of different phenol additives revealed that the addition of **A-2** improved the reaction chemoselectivity considerably (**9La/6L** = 58/42, **9La/10La** = 89/11, entry 3). Catalysts screening also revealed that the quinidium analogue QD-1 was a more powerful catalyst which promoted complete reaction with better chemoselectivity and excellent enantioselectivity (**9La/6L** = 79/21, >99% ee of **9La**, entry 4). Notably, the reaction proceeded with obviously enhanced chemoselectivity when the amount of **A-2** was changed to 50 mol % (**9La/6L** = 90/10, entry 5). The reaction still progressed to full conversion without any deterioration of chemo- and enantioselectivity (**9La/6L** = 90/10, >99% ee of **9La**, entry 6) at a reduced 0.5 mol % catalyst loading. Once again, *epi*-Q-1 proved to be better than Q-1 as a catalyst (entries 7 vs 8), affording the opposite enantiomer of **9La** with good chemoselectivity and excellent optical purity (**9La/6L** = 90/10, **9La/10La** = 84/16, >99% ee of **9La**, entry 8).

We investigated the substrate scope with the optimized conditions. As summarized in Table 4, excellent diastereoselectivity and enantioselectivity for both enantiomers were readily accomplished for the aliphatic imines of varying length (**1A**, **1C**, entries 1–2). For the sterically hindered cyclohexyl trifluoromethyl imine **1G**, 2.0 mol % catalyst loading was sufficient for achieving highly enantioselective formation of **9Ga** in good yields (entry 3). Such highly efficient catalytic control could also be extended to the reaction with the α,β -unsaturated alkenyl imine **1K** (entry 4). The aryl substituted trifluoromethyl imines turned out to be more challenging substrates, as the addition of an increased amount of **A-2** from 10 mol % to 50 mol % was necessary for suppressing the formations of side products **6** and **10**. Under optimized conditions, the reactions of aryl substituted trifluoromethyl imines bearing either electron-donating or withdrawing groups proceeded efficiently in synthetically useful yields and high optical purities (entries 5–7). Notably, reaction of imine **1A** with the six-membered δ -lactone **8b** also delivered the chiral δ -lactone product **9Ab** in high yield and excellent enantioselectivity (entry 8).

As illustrated in Scheme 2, the reactions proceeded at gram-scale without any deterioration in efficiency and enantioselectivity. To further demonstrate the synthetic versatility of these new transformations, we converted products **5Aa** and **9Aa** into chiral γ -amino esters **11Aa** and **12Aa**, respectively in excellent yields. The absolute configuration of product **9Aa** was established by X-ray crystallography.¹⁵

CONCLUSION

We have identified new catalytic systems combining cinchona phase-transfer catalysts and phenol additives to realize highly diastereo- and enantioselective C-C bond-forming umpolung reaction of trifluoromethyl imines with less reactive but readily available carbon electrophiles such as acrylates or α,β -unsaturated lactones. Notably, these newly developed catalysts and co-catalysts resolve the issue of inadequate chemo-, regio-, and enantioselectivity mediated by existing catalysts, affording new access to either enantiomers of the highly versatile chiral γ -trifluoromethylated γ -amino esters directly in good yields and excellent enantioselectivities from the readily available prochiral starting materials.

EXPERIMENTAL SECTION

General Information.

^1H and ^{13}C $\{^1\text{H}\}$ NMR spectra were recorded on a Varian instrument (400 MHz and 100 MHz, respectively) and internally referenced to tetramethylsilane signal or residual protio solvent signals. Data for ^1H NMR are recorded as follows: chemical shift (δ , ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), integration, coupling constant (J , Hz). Data for ^{13}C $\{^1\text{H}\}$ NMR are reported in terms of chemical shift (δ , ppm). Infrared spectra were recorded on a Perkin Elmer FT-IR Spectrometer and are reported in frequency of absorption. High resolution mass spectra were recorded on either a Micromass 70-VSE-B instrument (EI, CI) or a Micromass Q-TOF instrument (ESI). Specific optical rotations were measured on a Jasco Digital Polarimeter. All simple chemicals were purchased and used as received. High performance liquid chromatography (HPLC) analyses were performed on a Hewlett-Packard 1100 Series instrument equipped with a quaternary pump, using Daicel Chiralpak AD-H (250 $\times$ 4.6 mm), Daicel Chiralcel OJ-H Columns (250 $\times$ 4.6 mm). UV absorption was monitored at 210, 220 or 254 nm.

Preparation of Trifluoromethyl Imine Substrates (1A-1N).

Trifluoromethyl imines **1A-1N** were obtained according to our previously reported procedures.^{6a,10}

Preparation of 6'-Isopropoxy Cinchona Alkaloids Intermediates (S1-S3).

6'-isopropoxy quinidine (**S1**) and 6'-iso-propoxy quinine (**S2**) were synthesized according to the exactly same literature procedures.^{12b-d} Epi-vinyl 6'-isopropoxy quinine (**S3**). The epi-vinyl 6'-isopropoxy quinine **S3** was prepared according to the same method starting from epi-vinyl 6'-OH quinine¹³ as white foam (2.5 mmol scale reaction, 0.79 g, 90% yield); $[\alpha]_{\text{D}}^{20} = -142.5$ ($c = 1.0$, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.54 (d, $J = 4.5$ Hz, 1H), 7.83 (d, $J = 9.0$ Hz, 1H), 7.53 (d, $J = 4.5$ Hz, 1H), 7.21–7.09 (m, 2H), 5.88 (brs, 1H), 5.86–5.74 (m, 1H), 5.05 (d, $J = 10.4$ Hz, 1H), 4.99 (d, $J = 17.3$ Hz, 1H), 4.71–4.58 (m, 1H), 3.83 (brs, 1H), 3.24–3.06 (m, 2H), 2.79 (t, $J = 12.6$ Hz, 1H), 2.65 (dd, $J_1 = 13.0$ Hz, $J_2 = 7.6$ Hz, 1H), 2.28 (q, $J = 8.6$ Hz, 1H), 2.02 (t, $J = 10.8$ Hz, 1H), 1.82 (s, 1H), 1.78–1.67 (m, 1H), 1.66–1.51 (m, 1H), 1.28 (d, $J = 5.8$ Hz, 6H), 1.27–1.23 (m, 1H); ^{13}C $\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 155.9, 147.1, 146.8, 143.6, 139.2, 131.3, 126.2, 122.8, 118.6, 118.5, 115.5, 102.8, 69.9, 59.6, 55.7, 44.1, 38.4, 27.9, 25.6, 22.1, 21.4, 20.4; IR (CHCl_3) ν 1618, 1240, 1215,

1111, 966, 744, 664, 639 cm^{-1} ; HRMS (ESI/[M+H]⁺) Calcd. for $\text{C}_{22}\text{H}_{29}\text{N}_2\text{O}_2$ m/z 353.2229, found m/z 353.2227.

General Procedure for the Preparation of Tertiary Amine Precursors (S5–S9).

(1S,2R,4S,5R)-2-((S)-((6-chloro-2,5-diphenylpyrimidin-4-yl)oxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (**S5**) and (1S,2S,4S,5R)-2-((R)-((6-chloro-2,5-diphenylpyrimidin-4-yl)oxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (**S6**) were prepared according to our previously reported procedures.^{10,13} Tertiary amine precursors **S7–S9** were prepared according to the following general procedure. Under N_2 atmosphere, to a solution of corresponding cinchona intermediates (**S1–S3**) (5.0 mmol, 1.0 equiv.) and 4,6-dichloro-2,5-diphenylpyrimidine (1.2 equiv.) in PhMe (0.1 M) was added grounded KOH powder (15.0 equiv.). The suspension was then refluxed for 30 mins. The resulting mixture was cooled to room temperature and diluted with water. The organic phase was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were successively washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified through flash chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 100/1$ to $10/1$) to afford desired cinchona tertiary amine precursors **S7–S9** as white solid.

(1S,2R,4S,5R)-2-((S)-((6-chloro-2,5-diphenylpyrimidin-4-yl)oxy)(6-isopropoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (**S7**). Cinchona tertiary amine precursor **S7** was obtained according to the general procedure as white solid (5.0 mmol scale reaction, 2.53 g, 82% yield). $[\alpha]_{\text{D}}^{20} = -101.7$ ($c = 0.5$, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.70 (d, $J = 4.5$ Hz, 1H), 8.07–7.96 (m, 3H), 7.59–7.47 (m, 4H), 7.46–7.33 (m, 4H), 7.30 (d, $J = 4.5$ Hz, 1H), 7.24 (t, $J = 7.6$ Hz, 2H), 5.45–5.23 (m, 1H), 4.94 (d, $J = 17.0$ Hz, 1H), 4.88 (dd, $J_1 = 10.0$ Hz, $J_2 = 1.4$ Hz, 1H), 4.72–4.59 (m, 1H), 3.26–3.14 (m, 1H), 2.88 (s, 1H), 2.85 (s, 1H), 2.83–2.76 (m, 1H), 2.73–2.63 (m, 1H), 2.15 (q, $J = 8.6$ Hz, 1H), 1.83 (t, $J = 11.0$ Hz, 1H), 1.68 (s, 1H), 1.50–1.44 (m, 1H), 1.41 (d, $J = 6.0$ Hz, 3H), 1.38 (d, $J = 6.0$ Hz, 3H), 1.14 (dd, $J_1 = 7.5$ Hz, $J_2 = 4.5$ Hz, 1H); ^{13}C { ^1H } NMR (100 MHz, CDCl_3) δ 166.4, 162.4, 160.1, 156.2, 147.3, 144.5, 135.6, 132.1, 132.0, 131.2, 129.9, 128.6, 128.5, 128.3, 128.2, 103.3, 70.1, 59.5, 50.0, 49.8, 40.2, 28.3, 26.1, 22.7, 22.0, 21.8, 18.0, 12.8; IR (CHCl_3) ν 2940, 1570, 1517, 1407, 1215, 999, 744, 701 cm^{-1} ; HRMS (ESI/[M+H]⁺) Calcd. for $\text{C}_{38}\text{H}_{38}\text{N}_4\text{O}_2\text{Cl}$ m/z 617.2683, found m/z 617.2677.

(1S,2S,4S,5R)-2-((R)-((6-chloro-2,5-diphenylpyrimidin-4-yl)oxy)(6-isopropoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (**S8**). Cinchona tertiary amine precursor **S8** was obtained according to the general procedure as white solid (3.0 mmol scale reaction, 1.44 g, 78% yield); $[\alpha]_{\text{D}}^{20} = +212.0$ ($c = 1.0$, CHQ3); ^1H NMR (400 MHz, CDCl_3) δ 8.68 (d, $J = 4.6$ Hz, 1H), 8.05 (d, $J = 9.2$ Hz, 1H), 7.97 (s, 1H), 7.95 (s, 1H), 7.60–7.31 (m, 8H), 7.28–7.18 (m, 3H), 6.96 (brs, 1H), 5.72–5.59 (m, 1H), 4.92 (d, $J = 15.5$ Hz, 1H), 4.88 (d, $J = 7.5$ Hz, 1H), 4.69 (brs, 1H), 3.27–3.14 (m, 1H), 3.14–2.99 (m, 2H), 2.72–2.54 (m, 2H), 2.22 (s, 1H), 1.69 (s, 1H), 1.63–1.50 (m, 2H), 1.42 (d, $J = 6.2$ Hz, 3H), 1.39 (d, $J = 6.2$ Hz, 3H), 1.34–1.24 (m, 1H), 1.09–0.97 (m, 1H); ^{13}C { ^1H } NMR (100 MHz, CDCl_3) δ 166.2, 162.5, 159.8, 156.3, 147.2, 144.4, 135.5, 132.1, 131.9, 131.2, 129.9, 128.6, 128.5, 128.2, 128.2, 126.4, 118.7, 103.2, 70.1, 59.3, 57.2, 43.2, 39.6, 27.5, 27.0, 22.4, 21.9, 21.7; IR (CHCl_3) ν

1569, 1516, 1407, 1215, 1001, 969, 745, 699, 665 cm^{-1} ; HRMS (ESI/[M+H]⁺) Calcd. for $\text{C}_{38}\text{H}_{38}\text{N}_4\text{O}_2\text{Cl}$ m/z 617.2683, found m/z 617.2680.

(1*S*,2*S*,4*S*)-2-((*R*)-((6-chloro-2,5-diphenylpyrimidin-4-yl)oxy)(6-isopropoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (**S9**). The epi-vinyl cinchona tertiary amine precursor **S9** was obtained according to the general procedure as white solid (2.0 mmol scale reaction, 1.05 g, 85% yield); $[\alpha]_{\text{D}}^{20} = +180.3$ ($c = 0.5$, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.68 (d, $J = 4.6$ Hz, 1H), 8.04 (d, $J = 9.2$ Hz, 1H), 7.97 (s, 1H), 7.95 (s, 1H), 7.63–7.31 (m, 8H), 7.28–7.18 (m, 3H), 6.91 (s, 1H), 5.87–5.72 (m, 1H), 4.97 (d, $J = 9.2$ Hz, 1H), 4.94 (d, $J = 16.8$ Hz, 1H), 4.69 (s, 1H), 3.28–3.15 (m, 1H), 3.12–2.92 (m, 2H), 2.62 (t, $J = 11.0$ Hz, 1H), 2.47 (dd, $J_1 = 12.8$ Hz, $J_2 = 7.6$ Hz, 1H), 2.24–2.11 (m, 1H), 1.77–1.59 (m, 2H), 1.58–1.47 (m, 2H), 1.42 (d, $J = 6.2$ Hz, 3H), 1.40 (d, $J = 6.2$ Hz, 3H), 0.98–0.86 (s, 1H); ^{13}C { ^1H } NMR (100 MHz, CDCl_3) δ 166.3, 162.5, 159.7, 156.3, 147.3, 144.4, 135.6, 132.1, 132.0, 131.2, 129.9, 128.6, 128.5, 128.3, 126.6, 122.9, 118.7, 103.4, 70.2, 59.2, 56.7, 44.0, 39.2, 28.0, 21.9, 21.8, 21.1; IR (CHCl_3) ν 2932, 1569, 1515, 1405, 1218, 1110, 1000, 747, 699 cm^{-1} ; HRMS (ESI/[M+H]⁺) Calcd. for $\text{C}_{38}\text{H}_{38}\text{N}_4\text{O}_2\text{Cl}$ m/z 617.2683, found m/z 617.2678.

Procedure for the Synthesis of Arylmethyl Bromides (**S10-S11**).

9-(bromomethyl)anthracene (**S10**). **S10** was prepared according to the same literature procedures.¹⁶ 5'-(bromomethyl)-2'-(tert-butoxy)-1,1'.3',1''-terphenyl (**S11**). **S11** was prepared according to our previously reported method.^{6a}

General Procedure for Preparation of Cinchona Phase-Transfer Catalysts.

Cinchona catalysts C-1 and QD-2 were synthesized according to our previously reported procedure.^{6a,10} Catalysts QD-1, epiQ-1, QD-3, Q-3, and epiQ-3 were synthesized by the following general procedures. To a solution of corresponding cinchona tertiary amine precursors (**S5-S9**) (1.0 equiv.) in CH_3CN (0.1 M) was added the corresponding arylmethyl bromide (**S10-S11**) (1.0 equiv.) at room temperature. The reaction mixture was stirred overnight and then concentrated under vacuum. The residue was applied to flash chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 50/1$ to $10/1$) on silica gel to afford desired cinchona phase-transfer catalysts.

(1*S*,2*R*,4*S*,5*R*)-1-(anthracen-9-ylmethyl)-2-((*S*)-((6-chloro-2,5-diphenylpyrimidin-4-yl)oxy)(6-isopropoxyquinolin-4-yl)methyl)-5-vinylquinuclidine bromide (**QD-3**). Catalyst QD-3 was obtained according to the general procedure as light yellow solid (0.96 g, 72% yield). $[\alpha]_{\text{D}}^{20} = +244.8$ ($c = 1.0$, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 9.64 (d, $J = 9.1$ Hz, 1H), 8.90 (d, $J = 4.5$ Hz, 1H), 8.62 (s, 1H), 8.25 (s, 1H), 8.15–7.84 (m, 7H), 7.79–7.60 (m, 5H), 7.58–7.40 (m, 4H), 7.39–7.18 (m, 4H), 6.47 (d, $J = 13.2$ Hz, 1H), 6.09 (t, $J = 9.8$ Hz, 1H), 5.70 (t, $J = 10.6$ Hz, 1H), 5.54 (d, $J = 13.2$ Hz, 1H), 5.48–5.37 (m, 1H), 4.86 (d, $J = 10.2$ Hz, 1H), 4.76 (d, $J = 16.4$ Hz, 1H), 4.71–4.59 (m, 1H), 3.39 (t, $J = 10.4$ Hz, 1H), 2.95 (t, $J = 11.2$ Hz, 1H), 2.55–2.36 (m, 2H), 2.16 (q, $J = 10.6$ Hz, 1H), 1.95 (q, $J = 8.6$ Hz, 1H), 1.79 (s, 1H), 1.73–1.62 (m, 1H), 1.55 (d, $J = 6.0$ Hz, 3H), 1.55–1.50 (m, 1H), 1.47 (d, $J = 6.0$ Hz, 3H); ^{13}C { ^1H } NMR (100 MHz, CDCl_3) δ 164.9, 163.4, 161.9, 157.0, 147.1, 144.7, 137.6, 134.8, 134.6, 132.8, 132.7, 132.1, 132.0, 131.6, 131.5, 130.9, 130.6, 129.7, 129.6, 129.5, 129.1, 128.6, 128.4, 127.7, 126.8, 126.2, 124.9, 119.0, 116.8, 106.5, 74.2, 71.1, 66.4,

56.9, 56.1, 54.5, 39.0, 26.7, 24.0, 23.0, 22.9, 21.8; IR (CHCl₃) ν 2932, 1571, 1514, 1363, 1240, 1215, 1107, 998, 970, 844, 742, 701, 659 cm⁻¹; HRMS (ESI/[M-Br]⁺) Calcd. for C₅₃H₄₈N₄O₂Cl m/z 807.3466, found m/z 807.3461.

(1S,2S,4S,5R)-1-(anthracen-9-ylmethyl)-2-((R)-((6-chloro-2,5-diphenylpyrimidin-4-yl)oxy)(6-isopropoxyquinolin-4-yl)methyl)-5-vinylquinuclidin-1-ium bromide (Q-3). Catalyst Q-3 was obtained according to the general procedure as light yellow solid (1.5 mmol scale reaction, 1.0 g, 75% yield). $[\alpha]_D^{20} = -105.8$ (c = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 9.46 (d, *J* = 9.2 Hz, 1H), 8.87 (d, *J* = 4.6 Hz, 1H), 8.54 (s, 1H), 8.17 (s, 1H), 8.09–7.92 (m, 5H), 7.90 (d, *J* = 4.6 Hz, 1H), 7.78 (t, *J* = 7.6 Hz, 1H), 7.68 (d, *J* = 9.2 Hz, 1H), 7.62–7.40 (m, 7H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 7.5 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 13.6 Hz, 1H), 6.08 (t, *J* = 8.7 Hz, 1H), 5.96–5.84 (m, 1H), 5.79 (d, *J* = 13.6 Hz, 1H), 5.27 (septet, *J* = 6.0 Hz, 1H), 5.21–5.13 (m, 1H), 5.13 (d, *J* = 17.1 Hz, 1H), 5.0 (d, *J* = 10.4 Hz, 1H), 3.57 (t, *J* = 11.5 Hz, 1H), 3.21 (t, *J* = 11.8 Hz, 1H), 2.38–2.17 (m, 3H), 2.02 (t, *J* = 12.7 Hz, 1H), 1.73 (s, 1H), 1.45 (d, *J* = 6.0 Hz, 3H), 1.39 (d, *J* = 6.0 Hz, 3H), 1.17–1.03 (m, 1H), 0.92–0.77 (m, 1H); ¹³C (¹H) NMR (100 MHz, CDCl₃) δ 165.2, 163.4, 161.3, 157.1, 147.1, 144.6, 137.9, 136.1, 134.7, 133.7, 132.6, 132.6, 132.2, 132.1, 131.4, 131.3, 130.9, 129.6, 129.4, 129.2, 128.6, 128.4, 126.6, 118.9, 117.2, 105.9, 73.4, 70.9, 66.5, 61.3, 55.1, 52.1, 38.4, 26.3, 24.5, 22.8, 22.7, 21.6; IR (CHCl₃) ν 1517, 1409, 1214, 743, 704, 665 cm⁻¹; HRMS (ESI/[M-Br]⁺) Calcd. for C₅₃H₄₈N₄O₂Cl m/z 807.3466, found m/z 807.3458.

(1S,2S,4S)-1-(anthracen-9-ylmethyl)-2-((R)-((6-chloro-2,5-diphenylpyrimidin-4-yl)oxy)(6-isopropoxyquinolin-4-yl)methyl)-5-vinylquinuclidin-1-ium bromide (epiQ-3). Catalyst epiQ-3 was obtained according to the general procedure as light yellow solid (1.0 mmol scale reaction, 0.64 g, 72% yield). $[\alpha]_D^{20} = -178.5$ (c = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 9.52 (d, *J* = 9.2 Hz, 1H), 8.86 (d, *J* = 4.6 Hz, 1H), 8.64 (s, 1H), 8.18 (s, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 8.07 (d, *J* = 9.3 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 8.00–7.92 (m, 3H), 7.72–7.78 (m, 2H), 7.74–7.45 (m, 8H), 7.40–7.29 (m, 2H), 7.22 (t, *J* = 7.7 Hz, 2H), 6.59 (d, *J* = 13.3 Hz, 1H), 6.24 (t, *J* = 9.1 Hz, 1H), 5.72 (t, *J* = 10.5 Hz, 1H), 5.65 (d, *J* = 13.3 Hz, 1H), 5.51–5.39 (m, 1H), 5.26–5.12 (m, 1H), 4.78 (d, *J* = 10.4 Hz, 1H), 4.58 (d, *J* = 17.2 Hz, 1H), 3.62–3.42 (m, 1H), 3.00–2.83 (m, 1H), 2.47–2.27 (m, 3H), 2.04–1.88 (m, 1H), 1.80 (s, 1H), 1.54 (d, *J* = 6.2 Hz, 3H), 1.43 (d, *J* = 6.2 Hz, 3H), 1.30–1.16 (m, 1H), 0.87–0.67 (m, 1H); ¹³C (¹H) NMR (100 MHz, CDCl₃) δ 165.0, 163.4, 161.1, 157.1, 146.9, 144.6, 137.6, 135.7, 134.5, 133.6, 132.8, 132.6, 132.1, 131.4, 131.3, 130.9, 129.6, 129.4, 129.2, 129.2, 129.1, 128.6, 128.4, 128.2, 127.6, 127.6, 126.6, 126.3, 126.2, 124.9, 122.7, 122.0, 120.4, 118.8, 117.4, 116.8, 105.4, 72.9, 70.9, 65.8, 61.2, 54.7, 52.2, 36.5, 27.8, 25.4, 22.9, 21.5, 19.7; IR (CHCl₃) ν 1573, 1516, 1408, 1215, 1000, 743, 701, 663 cm⁻¹; HRMS (ESI/[M-Br]⁺) Calcd. for C₅₃H₄₈N₄O₂Cl m/z 807.3466, found m/z 807.3455.

(1S,2R,4S,5R)-1-((2'-(tert-butoxy)-[1,1':3',1''-terphenyl]-5'-yl)methyl)-2-((S)-((6-chloro-2,5-diphenylpyrimidin-4-yl)oxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidin-1-ium bromide (QD-1). Catalyst QD-1 was obtained according to the general procedure as white solid (1.0 mmol scale reaction, 0.81 g, 82% yield). $[\alpha]_D^{20} = -28.5$ (c = 0.5, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.75 (d, *J* = 4.6 Hz, 1H), 8.07 (d, *J* = 2.2 Hz, 1H), 8.07 (d, *J* = 9.3 Hz, 1H), 7.84 (d, *J* = 7.4 Hz, 2H), 7.80–7.55 (m, 7H),

7.58–7.30 (m, 13H), 7.20 (t, J = 8.0 Hz, 2H), 6.62 (d, J = 11.8 Hz, 1H), 5.80 (t, J = 10.8 Hz, 1H), 5.20 (t, J = 8.4 Hz, 1H), 5.15–5.01 (m, 2H), 4.97–4.86 (m, 1H), 4.45 (s, 3H), 4.17 (d, J = 11.8 Hz, 1H), 3.27 (t, J = 11.6 Hz, 1H), 3.00–2.84 (m, 2H), 2.41–2.21 (m, 2H), 2.00–1.85 (m, 2H), 1.78–1.67 (m, 1H), 1.44–1.31 (m, 1H), 0.57 (s, 9H); ^{13}C { ^1H } NMR (100 MHz, CDCl_3) δ 164.7, 163.2, 161.4, 159.6, 153.4, 146.3, 145.0, 140.3, 139.5, 138.2, 135.1, 135.0, 134.5, 132.0, 131.9, 131.8, 130.1, 129.6, 129.3, 128.5, 128.4, 128.3, 127.6, 126.6, 123.5, 122.1, 119.7, 118.6, 102.2, 84.0, 72.4, 64.4, 60.7, 57.8, 55.9, 54.7, 38.2, 29.0, 27.4, 23.6, 23.3; IR (CHCl_3) ν 1574, 1515, 1410, 1214, 1152, 1004, 743, 699, 665 cm^{-1} ; HRMS (ESI/[M-Br] $^+$) Calcd. for $\text{C}_{59}\text{H}_{56}\text{N}_4\text{O}_3\text{Cl}$ m/z 903.4041, found m/z 903.4031.

(1S,2S,4S,5R)-1-((2'-(tert-butoxy)-[1,1':3',1''-terphenyl]-5'-yl)methyl)-2-((R)-((6-chloro-2,5-diphenylpyrimidin-4-yl)oxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidin-1-ium bromide (Q-1). Catalyst Q-1 was obtained according to the general procedure as white solid (0.5 mmol scale reaction, 0.41 g, 82% yield). $[\alpha]_{\text{D}}^{20}$ = +32.0 (c = 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.73 (d, J = 4.6 Hz, 1H), 8.05 (d, J = 9.3 Hz, 1H), 7.92 (d, J = 2.1 Hz, 1H), 7.75–7.28 (m, 19H), 7.17 (t, J = 7.8 Hz, 2H), 5.88–5.74 (m, 1H), 5.37 (d, J = 13.0 Hz, 1H), 5.26 (d, J = 17.2 Hz, 1H), 5.09 (t, J = 9.4 Hz, 1H), 5.01 (d, J = 10.5 Hz, 1H), 4.37 (s, 3H), 4.27 (d, J = 11.7 Hz, 1H), 3.30 (dd, J_1 = 12.6 Hz, J_2 = 11.0 Hz, 1H), 3.10–2.90 (m, 1H), 2.55 (s, 1H), 2.25–2.13 (m, 1H), 1.99 (s, 1H), 1.81–1.69 (m, 1H), 1.60–1.47 (m, 1H), 1.43–1.30 (m, 1H), 0.56 (s, 9H); ^{13}C { ^1H } NMR (100 MHz, CDCl_3) δ 164.7, 163.1, 160.7, 159.6, 153.3, 146.2, 144.9, 140.2, 139.5, 138.1, 136.1, 135.1, 134.5, 132.0, 131.9, 131.6, 130.1, 129.6, 129.3, 129.2, 128.4, 128.4, 128.3, 127.5, 126.4, 123.4, 122.1, 119.7, 118.7, 118.5, 101.8, 84.0, 71.9, 64.7, 61.6, 60.0, 57.6, 50.8, 37.7, 29.0, 27.1, 25.2, 24.0; IR (CHCl_3) ν 2932, 1573, 1514, 1408, 1365, 1216, 1152, 1027, 991, 743, 699, 661 cm^{-1} ; HRMS (ESI/[M-Br] $^+$) Calcd. for $\text{C}_{59}\text{H}_{56}\text{N}_4\text{O}_3\text{Cl}$ m/z 903.4041, found m/z 903.4036.

(1S,2S,4S)-1-((2'-(tert-butoxy)-[1,1':3',1''-terphenyl]-5'-yl)methyl)-2-((R)-((6-chloro-2,5-diphenylpyrimidin-4-yl)oxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidin-1-ium bromide (epiQ-1). Catalyst epiQ-1 was obtained according to the general procedure as white solid (1.0 mmol scale reaction, 0.79 g, 80% yield). $[\alpha]_{\text{D}}^{20}$ = +2.8 (c = 0.5, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.74 (d, J = 4.6 Hz, 1H), 8.05 (d, J = 9.4 Hz, 1H), 8.03 (d, J = 2.4 Hz, 1H), 7.67–7.29 (m, 19H), 7.15 (t, J = 7.8 Hz, 2H), 6.65 (d, J = 11.8 Hz, 1H), 5.76 (t, J = 11.0 Hz, 1H), 5.53–5.42 (m, 1H), 5.30 (t, J = 9.4 Hz, 1H), 5.02 (d, J = 10.4 Hz, 1H), 4.92 (d, J = 17.0 Hz, 1H), 4.42 (s, 3H), 4.09 (d, J = 11.8 Hz, 1H), 2.93 (t, J = 7.8 Hz, 1H), 2.76 (q, J = 8.0 Hz, 1H), 2.59 (dd, J_1 = 12.0 Hz, J_2 = 8.8 Hz, 1H), 2.30 (t, J = 11.8 Hz, 1H), 1.94 (s, 1H), 1.72–1.57 (m, 2H), 1.24–1.17 (m, 1H), 0.56 (s, 9H); ^{13}C { ^1H } NMR (100 MHz, CDCl_3) δ 164.6, 163.2, 160.5, 159.6, 153.4, 146.2, 145.0, 140.3, 139.5, 138.1, 134.9, 134.9, 132.0, 130.1, 129.7, 129.1, 128.4, 128.4, 128.3, 127.6, 123.5, 122.0, 119.7, 118.4, 118.3, 102.1, 83.9, 72.2, 64.3, 61.2, 60.2, 57.7, 50.7, 36.3, 29.0, 28.6, 26.9, 20.3; IR (CHCl_3) ν 1515, 1409, 1214, 1153, 992, 743, 700, 665 cm^{-1} ; HRMS (ESI/[M-Br] $^+$) Calcd. for $\text{C}_{59}\text{H}_{56}\text{N}_4\text{O}_3\text{Cl}$ m/z 903.4041, found m/z 903.4063.

Synthesis of Racemic Products (5 & 9).

Racemic samples of compounds **5** and **9** were obtained either from the reactions catalyzed by achiral phase-transfer catalyst tetra-*n*-butylammonium bromide (TBAB) following the same procedures as the ones catalyzed by chiral cinchona alkaloid-based phase-transfer catalysts or they were simply obtained from the mixture of two opposite enantiomers.

Monitoring of Reaction Crude Mixture.

The reaction was monitored by taking an aliquot of the reaction mixture (100 μ L) which was filtered through a pipet pack with silica gel (0.5 cm), washed with ether, concentrated and subject to ^1H and ^{19}F NMR analysis. The conversion, chemo- and regio-selectivity were determined by ^{19}F NMR analysis of the crude reaction mixture.

Preparation of deactivated silica.

The dry silica gel was packed in a column and washed with EtOH/MeOH/Et₃N = 5/1/1 solution [2 column volume (CV)], followed by Et₂O (5 CV) wash. The silica gel was then blown dry with compressed air and ready for use.

General Procedure for the Asymmetric Synthesis of Compound 5.

At indicated temperature, to a solution of trifluoromethyl imines **1** (0.2 mmol), acrylates **4** (0.4 mmol, 2.0 equiv.), phenol-additive **A-1** (0.004 mmol, 2.0 mol%), ethanol (20.0 μ L) and catalyst QD-**3** or *epi*Q-**3** (5.0 mol%) in PhMe (totally 2.0 mL) was added aqueous KOH solution (2.2 μ L, 50 wt%, 0.02 mmol). The mixture was then vigorously stirred and turned purple immediately. After the reaction was completed or reached the maximum conversion (checked by ^{19}F NMR), the reaction mixture was then passed through a small pad of deactivated silica (5 cm thick) and washed with Et₂O (1.0 mL $\times$ 3). The filtrates were combined, concentrated, purified through flash chromatography with deactivated silica gel (Hexanes/Et₂O) to afford the desired products.

Methyl (S)-5,5,5-trifluoro-4-methyl-4-((4-nitrobenzylidene)amino) pentanoate (5Aa). The product **5Aa** was obtained as oil in 80% yield after flash chromatography with deactivated silica gel (Hexanes/Et₂O = 100/1 to 10/1) from a reaction catalyzed by QD-**3** (5.0 mol%), **A-1** (2.0 mol%) and ethanol (20 μ L) in PhMe (2.0 mL) at -40°C for 8 h. 92% ee was determined by HPLC analysis [Daicel Chiralpak AD-H, Hexanes/IPA = 97/3, 1.0 mL/min, λ 254 nm, t (minor) = 12.78 min, t (major) = 17.88 min]. $[\alpha]_{\text{D}}^{20} = -85.7$ (c = 1.0, CHCl₃); ^1H NMR (400 MHz, CDCl₃) δ 8.42 (s, 1H), 8.29 (d, J = 8.7 Hz, 2H), 7.97 (d, J = 8.7 Hz, 2H), 3.63 (s, 3H), 2.48–2.30 (m, 3H), 2.23–2.11 (m, 1H), 1.48 (s, 3H); ^{13}C { ^1H } NMR (100 MHz, CDCl₃) δ 173.1, 159.0, 149.6, 140.9, 129.3 (2C), 126.4 (q, $J_{\text{C-F}}$ = 283 Hz), 123.9 (2C), 65.8 (q, $J_{\text{C-F}}$ = 26 Hz), 51.8, 30.9, 28.3, 17.4; ^{19}F NMR (376 MHz, CDCl₃) δ -78.0 ; IR (CHCl₃) ν 1734, 1650, 1603, 1523, 1345, 1273, 1145, 1098, 988, 838, 746, 688 cm⁻¹; HRMS (ESI/[M+H]⁺) Calcd. for C₁₄H₁₆N₂O₄F₃ m/z 333.1062, found m/z 333.1065. The product of opposite absolute configuration was obtained in 85% yield from a reaction catalyzed by *epi*Q-**3** (5.0 mol%), **A-1** (2.0 mol%) and ethanol (20 μ L) in PhMe (2.0 mL) at -40°C for 8 h. 92% ee was determined by HPLC analysis [t (major) = 12.86 min, t (minor) = 18.02 min]. $[\alpha]_{\text{D}}^{20} = +62.0$ (c = 0.5, CHCl₃).

Prop-2-yn-1-yl (S)-5,5,5-trifluoro-4-methyl-4-((4-nitrobenzylidene)amino)pentanoate (5Ab).

The product **5Ab** was obtained as oil in 89% yield after flash chromatography with deactivated silica gel (Hexanes/Et₂O = 100/1 to 4/1) from a reaction catalyzed by QD-3 (1.0 mol%), **A-1** (2.0 mol%) and ethanol (20 μ L) in PhMe (2.0 mL) at -30°C for 3 h. 91% ee was determined by HPLC analysis [Daicel Chiralpak AD-H, Hexanes/IPA = 95/5, 1.0 mL/min, λ 254 nm, t (minor) = 14.88 min, t (major) = 19.86 min]. $[\alpha]_{\text{D}}^{20} = -48.9$ ($c = 1.0$, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 8.42 (s, 1H), 8.29 (d, $J = 8.7$ Hz, 2H), 7.97 (d, $J = 8.7$ Hz, 2H), 4.62 (d, $J = 2.4$ Hz, 2H), 2.55–2.32 (m, 4H), 2.22–2.11 (m, 1H), 1.49 (s, 3H); ¹³C {¹H} NMR (100 MHz, CDCl₃) δ 171.9, 159.1, 149.6, 140.9, 129.4 (2C), 126.4 (q, $J_{\text{C-F}} = 283$ Hz), 123.9 (2C), 75.1, 65.7 (q, $J_{\text{C-F}} = 25$ Hz), 52.2, 30.8, 28.3, 17.4; ¹⁹F NMR (376 MHz, CDCl₃) δ -78.0 ; IR (CHCl₃) ν 1740, 1523, 1346, 1147, 1098, 990, 838, 747, 687, 637 cm^{-1} ; HRMS (ESI/[M+H]⁺) Calcd. for C₁₆H₁₆N₂O₄F₃ m/z 357.1062, found m/z 357.1064. The product of opposite absolute configuration was obtained in 92% yield from a reaction catalyzed by *epi*Q-3 (1.0 mol%), **A-1** (2.0 mol%) and ethanol (20 μ L) in PhMe (2.0 mL) at -30°C for 3 h. 93% ee was determined by HPLC analysis [t (major) = 14.93 min, t (minor) = 20.01 min]. $[\alpha]_{\text{D}}^{20} = +105.0$ ($c = 1.0$, CHCl₃).

Allyl (S)-5,5,5-trifluoro-4-methyl-4-((4-nitrobenzylidene)amino)pentanoate (5Ac).

The product **5Ac** was obtained as oil in 70% yield after flash chromatography with deactivated silica gel (Hexanes/Et₂O = 100/1 to 10/1) from a reaction catalyzed by QD-3 (5.0 mol%), **A-1** (2.0 mol%) and ethanol (20 μ L) in PhMe (2.0 mL) at -40°C for 20 h. 85% ee was determined by HPLC analysis [Daicel Chiralpak AD-H, Hexanes/IPA = 97/3, 1.0 mL/min, λ 254 nm, t (minor) = 11.90 min, t (major) = 17.69 min]. $[\alpha]_{\text{D}}^{20} = -72.0$ ($c = 1.0$, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 8.42 (s, 1H), 8.29 (d, $J = 8.8$ Hz, 2H), 7.97 (d, $J = 8.8$ Hz, 2H), 5.93–5.80 (m, 1H), 5.33–5.19 (m, 2H), 4.52 (dt, $J_1 = 5.8$ Hz, $J_2 = 1.2$ Hz, 2H), 2.52–2.33 (m, 3H), 2.23–2.11 (m, 1H), 1.48 (s, 3H); ¹³C {¹H} NMR (100 MHz, CDCl₃) δ 172.4, 159.0, 149.6, 140.9, 131.9, 129.3 (2C), 126.4 (q, $J_{\text{C-F}} = 283$ Hz), 123.9 (2C), 118.6, 65.8 (q, $J_{\text{C-F}} = 26$ Hz), 65.4, 30.9, 28.5, 17.4; ¹⁹F NMR (376 MHz, CDCl₃) δ -78.0 ; IR (CHCl₃) ν 1732, 1650, 1603, 1523, 1345, 1273, 1145, 1098, 985, 837, 748, 689 cm^{-1} ; HRMS (ESI/[M+H]⁺) Calcd. for C₁₆H₁₈F₃N₂O₄ m/z 359.1219, found m/z 359.1214. The product of opposite absolute configuration was obtained in 75% yield from a reaction catalyzed by *epi*Q-3 (5.0 mol%), **A-1** (2.0 mol%) and ethanol (20 μ L) in PhMe (2.0 mL) at -40°C for 20 h. 90% ee was determined by HPLC analysis [t (major) = 11.90 min, t (minor) = 17.70 min]. $[\alpha]_{\text{D}}^{20} = +33.8$ ($c = 0.5$, CHCl₃).

Ethyl (S)-5,5,5-trifluoro-4-methyl-4-((4-nitrobenzylidene)amino)pentanoate (5Ad).

The product **5Ad** was obtained as oil in 50% yield after flash chromatography with deactivated silica gel (Hexanes/Et₂O = 100/1 to 10/1) from a reaction catalyzed by QD-3 (5.0 mol%), **A-1** (2.0 mol%) and ethanol (20 μ L) in PhMe (2.0 mL) at -40°C for 20 h. 81% ee was determined by HPLC analysis [Daicel Chiralpak AD-H, Hexanes/IPA = 97/3, 1.0 mL/min, λ 254 nm, t (minor) = 11.07 min, t (major) = 16.73 min]. $[\alpha]_{\text{D}}^{20} = -68.1$ ($c = 1.0$, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.42 (s, 1H), 8.29 (d, $J = 8.7$ Hz, 2H), 7.97 (d, $J = 8.7$ Hz, 2H), 4.08 (q, $J = 7.1$ Hz, 1H), 2.46–2.27 (m, 3H), 2.23–2.10 (m, 1H), 1.48 (s, 3H), 1.22 (t, $J = 7.1$ Hz, 1H); ¹³C {¹H} NMR (100 MHz, CDCl₃) δ 172.7, 158.9, 149.5, 140.9, 129.3 (2C), 126.4 (q, $J_{\text{C-F}} = 283$ Hz), 123.9 (2C), 65.8 (q, $J_{\text{C-F}} = 25$ Hz), 60.7, 30.9, 28.6, 17.4, 14.2; ¹⁹F

NMR (376 MHz, CDCl₃) δ -78.1; IR (CHCl₃) ν 1729, 1650, 1524, 1345, 1273, U46, 1097, 838, 747, 688 cm⁻¹; HRMS (ESI/[M+H]⁺) Calcd. for C₁₅H₁₈N₂O₄F₃ m/z 347.1219, found m/z 347.1211. The product of opposite absolute configuration was obtained in 63% yield from a reaction catalyzed by *epi*Q-3 (5.0 mol%), **A-1** (2.0 mol%) and ethanol (20 μ L) in PhMe (2.0 mL) at -40 °C for 20 h. 86% ee was determined by HPLC analysis [t (major) = 11.09 min, t (minor) = 16.72 min]. [α]_D²⁰ = +59.2 (c = 1.0, CHCl₃).

Vinyl (S,E)-5,5,5-trifluoro-4-methyl-4-((4-nitrobenzylidene)amino)pentanoate (5Ae). The product **5Ae** was obtained as oil in 91% yield after flash chromatography with deactivated silica gel (Hexanes/Et₂O = 100/1 to 15/1) from a reaction catalyzed by QD-3 (1.0 mol%) and **A-1** (2.0 mol%) and ethanol (20 μ L) in PhMe (2.0 mL) at -30 °C for 8 h. 94% ee was determined by HPLC analysis [Daicel Chiralpak AD-H, Hexanes/IPA = 99/1, 1.0 mL/min, λ 254 nm, t (minor) = 17.73 min, t (major) = 24.73 min]. [α]_D²⁰ = -76.3 (c = 1.0, CHCl₃); ¹³H NMR (400 MHz, CDCl₃) δ 8.43 (s, 1H), 8.29 (d, J = 8.8 Hz, 2H), 7.96 (d, J = 8.8 Hz, 2H), 7.20 (dd, J_1 = 13.9 Hz, J_2 = 6.3 Hz, 1H), 4.86 (dd, J_1 = 13.9 Hz, J_2 = 1.7 Hz, 1H), 4.55 (dd, J_1 = 6.3 Hz, J_2 = 1.7 Hz, 1H), 2.61–2.37 (m, 3H), 2.24–2.13 (m, 1H), 1.50 (s, 3H); ¹³C {¹H} NMR (100 MHz, CDCl₃) δ 169.9, 159.2, 149.6, 141.0, 140.8, 129.4 (2C), 126.4 (q, J_{C-F} = 283 Hz), 123.9 (2C), 97.9, 65.7 (q, J_{C-F} = 25 Hz), 30.8, 28.4, 17.5; ¹⁹F NMR (376 MHz, CDCl₃) δ -77.8; IR (CHCl₃) ν 1752, 1648, 1523, 1344, 1146, 1096, 947, 837, 747, 688 cm⁻¹; HRMS (ESI/[M+H]⁺) Calcd. for C₁₅H₁₆N₂O₄F₃ m/z 345.1062, found m/z 345.1057. The product of opposite absolute configuration was obtained in 93% yield from a reaction catalyzed by *epi*Q-3 (1.0 mol%) and **A-1** (2.0 mol%) and ethanol (20 μ L) in PhMe (2.0 mL) at -30 °C for 8 h. 94% ee was determined by HPLC analysis [t (major) = 17.85 min, t (minor) = 24.80 min]. [α]_D²⁰ = +65.7 (c = 1.0, CHCl₃).

Methyl (S)-4-((4-nitrobenzylidene)amino)-4-(trifluoromethyl)hexanoate (5Ba). The product **5Ba** was obtained as oil in 71% yield after flash chromatography with deactivated silica gel (Hexanes/Et₂O = 100/1 to 10/1) from a reaction catalyzed by QD-3 (5.0 mol%), **A-1** (2.0 mol%) and ethanol (20 μ L) in PhMe (2.0 mL) at -40 °C for 5 h. 87% ee was determined by HPLC analysis [Daicel Chiralpak AD-H, Hexanes/IPA = 98/2, 1.0 mL/min, λ 254 nm, t (minor) = 14.17 min, t (major) = 16.99 min]. [α]_D²⁰ = -10.5 (c = 0.3, CHCl₃); ¹³H NMR (400 MHz, CDCl₃) δ 8.44 (s, 1H), 8.29 (d, J = 8.7 Hz, 2H), 7.96 (d, J = 8.7 Hz, 2H), 3.66 (s, 3H), 2.50–2.42 (m, 2H), 2.30–2.22 (m, 2H), 1.94 (q, J = 7.6 Hz, 2H), 0.97 (t, J = 7.6 Hz, 3H); ¹³C {¹H} NMR (100 MHz, CDCl₃) δ 173.4, 158.8, 149.5, 141.1, 129.2 (2C), 126.8 (q, J_{C-F} = 286 Hz), 123.9 (2C), 67.8 (q, J_{C-F} = 24 Hz), 51.8, 28.4, 27.9, 26.4, 7.7; ¹⁹F NMR (376 MHz, CDCl₃) δ -73.3; IR (CHCl₃) ν 1734, 1649, 1603, 1523, 1344, 1256, 1164, 1113, 1092, 839, 748, 722, 689 cm⁻¹; HRMS (ESI/[M+H]⁺) Calcd. for C₁₅H₁₈N₂O₄F₃ m/z 347.1219, found m/z 347.1216. The product of opposite absolute configuration was obtained in 73% yield from a reaction catalyzed by *epi*Q-3 (5.0 mol%), **A-1** (2.0 mol%) and ethanol (20 μ L) in PhMe (2.0 mL) at -40 °C for 5 h. 90% ee was determined by HPLC analysis [t (major) = 13.79 min, t (minor) = 16.47 min]. [α]_D²⁰ = +77.0 (c = 0.5, CHCl₃).

Methyl (S)-4-((4-nitrobenzylidene)amino)-4-(trifluoromethyl)octanoate (5Ca). The product **5Ca** was obtained as oil in 63% yield after flash chromatography with deactivated silica gel (Hexanes/Et₂O = 100/1 to 10/1) from a reaction catalyzed by QD-3 (5.0 mol%), **A-1** (2.0 mol%) and ethanol (20 μ L) in PhMe (2.0 mL) at -30 °C for 8 h. [α]_D²⁰ = +1.0 (c = 0.5,

CHCl₃). 91% ee was determined by HPLC analysis [Daicel Chiralpak AD-H, Hexanes/IPA = 98/2, 1.0 mL/min, λ 254 nm, t (minor) = 10.42 min, t (major) = 14.36 min]; ¹H NMR (400 MHz, CDCl₃) δ 8.44 (s, 1H), 8.29 (d, J = 8.7 Hz, 2H), 7.97 (d, J = 8.7 Hz, 2H), 3.66 (s, 3H), 2.50–2.42 (m, 2H), 2.31–2.23 (m, 2H), 1.86 (t, J = 7.9 Hz, 2H), 1.42–1.26 (m, 4H), 0.92 (t, J = 6.9 Hz, 3H); ¹³C {¹H} NMR (100 MHz, CDCl₃) δ 173.4, 158.6, 149.5, 141.1, 129.2 (2C), 126.7 (q, J_{C-F} = 285 Hz), 123.9 (2C), 67.6 (q, J_{C-F} = 23 Hz), 51.8, 28.4, 28.3, 25.1, 23.2, 13.9; ¹⁹F NMR (376 MHz, CDCl₃) δ –73.3; IR (CHCl₃) ν 1735, 1649, 1603, 1523, 1344, 1161, 1107, 854, 839, 748, 689 cm^{–1}; HRMS (ESI/[M+H]⁺) Calcd. for C₁₇H₂₂N₂O₄F₃ m/z 375.1532, found m/z 375.1530. The product of opposite absolute configuration was obtained in 68% yield from a reaction catalyzed by *epi*Q-3 (5.0 mol%), **A-1** (2.0 mol%) and ethanol (20 μ L) in PhMe (2.0 mL) at –30 °C for 8 h. 91% ee was determined by HPLC analysis [t (major) = 9.93 min, t (minor) = 13.65 min]. [α]_D²⁰ = +3.1 (c = 0.5, CHCl₃).

Methyl (S)-4-((4-nitrobenzylidene)amino)-4-(trifluoromethyl)non-8-enoate (5Da). The product **5Da** was obtained as oil in 64% yield after flash chromatography with deactivated silica gel (Hexanes/Et₂O = 100/1 to 10/1) from a reaction catalyzed by QD-3 (5.0 mol%), **A-1** (2.0 mol%) and ethanol (20 μ L) in PhMe (2.0 mL) at –30 °C for 8 h. 90% ee was determined by HPLC analysis [Daicel Chiralpak AD-H, Hexanes/IPA = 98/2, 1.0 mL/min, λ 254 nm, t (minor) = 11.03 min, t (major) = 17.79 min]; [α]_D²⁰ = –3.3 (c = 0.5, CHCl₃); ¹³H NMR (400 MHz, CDCl₃) δ 8.43 (s, 1H), 8.29 (d, J = 8.7 Hz, 2H), 7.96 (d, J = 8.7 Hz, 2H), 5.83–5.67 (m, 1H), 5.08–4.95 (m, 2H), 3.66 (s, 3H), 2.49–2.41 (m, 2H), 2.32–2.22 (m, 2H), 2.08 (q, J = 7.0 Hz, 2H), 1.87 (t, J = 8.5 Hz, 2H), 1.54–1.38 (m, 2H); ¹³C {¹H} NMR (100 MHz, CDCl₃) δ 173.3, 158.8, 149.5, 141.0, 137.6, 129.2 (2C), 126.6 (q, J_{C-F} = 285 Hz), 123.9 (2C), 115.6, 67.6 (q, J_{C-F} = 23 Hz), 51.9, 33.8, 33.0, 28.3, 22.2; ¹⁹F NMR (376 MHz, CDCl₃) δ –73.2; IR (CHCl₃) ν 1735, 1648, 1603, 1523, 1344, 1158, 915, 839, 748, 689 cm^{–1}; HRMS (ESI/[M+H]⁺) Calcd. for C₁₈H₂₂N₂O₄F₃ m/z 387.1532, found m/z 387.1527. The product of opposite absolute configuration was obtained in 68% yield from a reaction catalyzed by *epi*Q-3 (5.0 mol%), **A-1** (2.0 mol%) and ethanol (20 μ L) in PhMe (2.0 mL) at –30 °C for 8 h. 92% ee was determined by HPLC analysis [t (major) = 10.87 min, t (minor) = 15.56 min]. [α]_D²⁰ = +1.8 (c = 0.5, CHCl₃).

Methyl (S)-4-((4-nitrobenzylidene)amino)-6-phenyl-4-(trifluoromethyl)hexanoate (5Ea). The product **5Ea** was obtained as oil in 53% yield after flash chromatography with deactivated silica gel (Hexanes/Et₂O = 100/1 to 5/1) from a reaction catalyzed by QD-3 (5.0 mol%), **A-1** (2.0 mol%) and ethanol (20 μ L) in PhMe (2.0 mL) at –30 °C for 8 h. 90% ee was determined by HPLC analysis [Daicel Chiralpak AD-H, Hexanes/IPA = 97/3, 1.0 mL/min, λ 254 nm, t (minor) = 13.96 min, t (major) = 19.38 min]; [α]_D²⁰ = +1.0 (c = 1.0, CHCl₃); ¹³H NMR (400 MHz, CDCl₃) δ 8.49 (s, 1H), 8.29 (d, J = 8.7 Hz, 2H), 7.96 (d, J = 8.7 Hz, 2H), 7.33–7.13 (m, 5H), 3.66 (s, 3H), 2.78–2.16 (m, 2H), 2.54–2.46 (m, 2H), 2.40–2.32 (m, 2H), 2.17 (t, J = 8.7 Hz, 2H); ¹³C {¹H} NMR (100 MHz, CDCl₃) δ 173.2, 159.1, 149.6, 141.0, 129.3 (2C), 128.7 (2C), 128.2 (2C), 128.1 (2C), 126.6 (q, J_{C-F} = 285 Hz), 126.4, 123.9 (2C), 67.6 (q, J_{C-F} = 24 Hz), 51.9, 36.0, 29.6, 28.6, 28.4; ¹⁹F NMR (376 MHz, CDCl₃) δ –72.9; IR (CHCl₃) ν 1735, 1649, 1603, 1523, 1345, 1254, 1154, 841, 748, 701 cm^{–1}; HRMS (ESI/[M+H]⁺) Calcd. for C₂₁H₂₂N₂O₄F₃ m/z 423.1532, found m/z 423.1534.

The product of opposite absolute configuration was obtained in 55% yield from a reaction catalyzed by *epiQ-3* (5.0 mol%), **A-1** (2.0 mol%) and ethanol (20 μ L) in PhMe (2.0 mL) at $-30\text{ }^{\circ}\text{C}$ for 8 h. 88% ee was determined by HPLC analysis [t (major) = 13.88 min, t (minor) = 19.25 min]. $[\alpha]_{\text{D}}^{20} = -3.8$ (c = 1.0, CHCl_3).

Methyl (S)-5,5,5-trifluoro-4-((4-nitrobenzylidene)amino)pentanoate (5Fa). The product **5Fa** was obtained as oil in 62% yield after flash chromatography with deactivated silica gel (Hexanes/ Et_2O = 100/1 to 6/1) from a reaction catalyzed by **QD-3** (5.0 mol%), **A-1** (2.0 mol%) and ethanol (20 μ L) in PhMe (2.0 mL) at $-50\text{ }^{\circ}\text{C}$ for 4 h. 90% ee was determined by HPLC analysis [Daicel Chiralpak AD-H, Hexanes/IPA = 94/6, 1.0 mL/min, λ 254 nm, t (minor) = 11.72 min, t (major) = 18.47 min]. $[\alpha]_{\text{D}}^{20} = -77.0$ (c = 0.5, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.41 (s, 1H), 8.30 (d, J = 8.8 Hz, 2H), 7.97 (d, J = 8.8 Hz, 2H), 3.93–3.80 (m, 1H), 3.66 (s, 3H), 2.48–2.13 (m, 4H); ^{13}C { ^1H } NMR (100 MHz, CDCl_3) δ 172.7, 164.0, 149.7, 140.2, 129.5 (2C), 124.9 (q, $J_{\text{C-F}}$ = 280 Hz), 124.0 (2C), 70.4 (q, $J_{\text{C-F}}$ = 28 Hz), 51.8, 29.4, 24.5; ^{19}F NMR (376 MHz, CDCl_3) δ -74.5 (d, $J_{\text{C-F}}$ = 8.0 Hz); IR (CHCl_3) ν 1733, 1649, 1603, 1522, 1345, 1264, 1161, 1127, 1080, 1014, 853, 748, 688 cm^{-1} ; HRMS (ESI/[M+H] $^{+}$) Calcd. for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_4\text{F}_3$ m/z 319.0906, found m/z 319.0904. The product of opposite absolute configuration was obtained in 70% yield from a reaction catalyzed by *epiQ-3* (5.0 mol%), **A-1** (2.0 mol%) and ethanol (20 μ L) in PhMe (2.0 mL) at $-50\text{ }^{\circ}\text{C}$ for 4 h. 91% ee was determined by HPLC analysis [t (major) = 11.76 min, t (minor) = 18.51 min]. $[\alpha]_{\text{D}}^{20} = +80.2$ (c = 1.0, CHCl_3).

Prop-2-yn-1-yl (R)-4-cyclohexyl-5,5,5-trifluoro-4-((4-nitrobenzylidene)amino)pentanoate (5Gb). The product **5Gb** was obtained as oil in 65% yield after flash chromatography with deactivated silica gel (Hexanes/ Et_2O = 100/1 to 15/1) from a reaction catalyzed by **QD-3** (5.0 mol%), **A-1** (2.0 mol%) and ethanol (20 μ L) in PhMe (2.0 mL) at $-30\text{ }^{\circ}\text{C}$ for 8 h. 91% ee was determined by HPLC analysis [Daicel Chiralpak AD-H, Hexanes/IPA = 98/2, 1.0 mL/min, λ 254 nm, t (minor) = 13.89 min, t (major) = 17.55 min]. $[\alpha]_{\text{D}}^{20} = +18.7$ (c = 0.5, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.41 (s, 1H), 8.29 (d, J = 8.7 Hz, 2H), 7.96 (d, J = 8.7 Hz, 2H), 4.70–4.66 (m, 2H), 2.56–2.19 (m, 5H), 1.94–1.75 (m, 4H), 1.70 (t, J = 11.3 Hz, 2H), 1.34–1.09 (m, 5H); ^{13}C { ^1H } NMR (100 MHz, CDCl_3) δ 172.3, 158.2, 149.5, 141.2, 129.2 (2C), 126.8 (q, $J_{\text{C-F}}$ = 289 Hz), 123.9 (2C), 75.1, 70.5 (q, $J_{\text{C-F}}$ = 22 Hz), 52.2, 44.2, 28.4, 27.5, 27.1, 26.9, 26.9, 26.2, 25.7; ^{19}F NMR (376 MHz, CDCl_3) δ -67.0; IR (CHCl_3) ν 1740, 1524, 1345, 1216, 1155, 1108, 839, 746, 667, 633 cm^{-1} ; HRMS (ESI/[M+H] $^{+}$) Calcd. for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_4\text{F}_3$ m/z 425.1688, found m/z 425.1684. The product of opposite absolute configuration was obtained in 63% yield from a reaction catalyzed by *epiQ-3* (5.0 mol%), **A-1** (2.0 mol%) and ethanol (20 μ L) in PhMe (2.0 mL) at $-30\text{ }^{\circ}\text{C}$ for 8 h. 93% ee was determined by HPLC analysis [t (major) = 13.58 min, t (minor) = 17.18 min]. $[\alpha]_{\text{D}}^{20} = -44.8$ (c = 0.5, CHCl_3).

Prop-2-yn-1-yl (R)-4-(cyclohexylmethyl)-5,5,5-trifluoro-4-((4-nitrobenzylidene)amino)pentanoate (5Hb). The product **5Hb** was obtained as oil in 71% yield after flash chromatography with deactivated silica gel (Hexanes/ Et_2O = 100/1 to 15/1) from a reaction catalyzed by **QD-3** (5.0 mol%), **A-1** (2.0 mol%) and ethanol (20 μ L) in PhMe (2.0 mL) at $-30\text{ }^{\circ}\text{C}$ for 8 h. 90% ee was determined by HPLC analysis [Daicel Chiralpak AD-H, Hexanes/IPA = 98/2, 1.0 mL/min, λ 254 nm, t (minor) = 13.53 min, t

(major) = 16.02 min]. $[\alpha]_D^{20} = +2.0$ ($c = 1.0$, CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ 8.47 (s, 1H), 8.30 (d, $J = 8.7$ Hz, 2H), 7.95 (d, $J = 8.7$ Hz, 2H), 4.66 (d, $J = 2.4$ Hz, 2H), 2.58–2.51 (m, 2H), 2.47 (t, $J = 2.4$ Hz, 1H), 2.38–2.20 (m, 2H), 1.87–1.45 (m, 8H), 1.26–0.85 (m, 5H); ^{13}C { ^1H } NMR (100 MHz, CDCl_3) δ 172.2, 158.6, 149.5, 141.1, 129.2 (2C), 126.7 (q, $J_{\text{C-F}} = 286$ Hz), 124.0 (2C), 75.1, 68.0 (q, $J_{\text{C-F}} = 23$ Hz), 52.2, 41.9, 35.3, 35.2, 33.0, 29.3, 28.7, 26.3, 26.3, 26.0; ^{19}F NMR (376 MHz, CDCl_3) δ –72.8; IR (CHCl_3) ν 2925, 1741, 1523, 1344, 1160, 853, 748, 688, 667 cm^{-1} ; HRMS (ESI/[$\text{M}+\text{H}$] $^+$) Calcd. for $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_4\text{F}_3$ m/z 439.1845, found m/z 439.1827. The product of opposite absolute configuration was obtained in 72% yield from a reaction catalyzed by *epi*Q-3 (5.0 mol%), A-1 (2.0 mol%) and ethanol (20 μL) in PhMe (2.0 mL) at -30°C for 8 h. 93% ee was determined by HPLC data [t (major) = 13.45 min, t (minor) = 16.00 min]. $[\alpha]_D^{20} = -9.9$ ($c = 1.0$, CHCl_3).

Prop-2-yn-1-yl (R)-4-benzyl-5,5,5-trifluoro-4-((4-nitrobenzylidene)amino)pentanoate (5Ib).

The product **5Ib** was obtained as oil in 63% yield after flash chromatography with deactivated silica gel (Hexanes/ $\text{Et}_2\text{O} = 100/1$ to 12/1) from a reaction catalyzed by QD-3 (5.0 mol%), A-1 (2.0 mol%) and ethanol (20 μL) in PhMe (2.0 mL) at -30°C for 8 h. 90% ee was determined by HPLC analysis [Daicel Chiralpak AD-H, Hexanes/IPA = 93/7, 1.0 mL/min, λ 254 nm, t (major) = 10.14 min, t (minor) = 10.93 min]; $[\alpha]_D^{20} = +62.8$ ($c = 0.5$, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.28 (d, $J = 8.7$ Hz, 2H), 7.86 (d, $J = 8.7$ Hz, 2H), 7.76 (s, 1H), 7.29–7.19 (m, 3H), 7.06–7.00 (m, 2H), 4.65 (d, $J = 2.4$ Hz, 2H), 3.18 (d, $J = 13.6$ Hz, 1H), 3.10 (d, $J = 13.6$ Hz, 1H), 2.65–2.52 (m, 1H), 2.47 (t, $J = 2.4$ Hz, 1H), 2.44–2.18 (m, 3H); ^{13}C { ^1H } NMR (100 MHz, CDCl_3) δ 172.0, 159.6, 149.5, 140.8, 133.5, 131.6 (2C), 129.1 (2C), 128.1 (2C), 127.5, 126.7 (q, $J_{\text{C-F}} = 285$ Hz), 124.0 (2C), 75.1, 68.5 (q, $J_{\text{C-F}} = 23$ Hz), 52.2, 39.8, 28.2, 26.3; ^{19}F NMR (376 MHz, CDCl_3) δ –73.8; IR (CHCl_3) ν 1741, 1524, 1345, 1215, 1161, 1087, 745, 703, 667 cm^{-1} ; HRMS (ESI/[$\text{M}+\text{H}$] $^+$) Calcd. for $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_4\text{F}_3$ m/z 433.1375, found m/z 433.1369. The product of opposite absolute configuration was obtained in 72% yield from a reaction catalyzed by *epi*Q-3 (5.0 mol%), A-1 (2.0 mol%) and ethanol (20 μL) in PhMe (2.0 mL) at -30°C for 8 h. 92% ee was determined by HPLC analysis [t (minor) = 10.13 min, t (major) = 10.89 min]. $[\alpha]_D^{20} = -66.0$ ($c = 0.5$, CHCl_3).

Prop-2-yn-1-yl (R)-4-(4-bromobenzyl)-5,5,5-trifluoro-4-((4-

nitrobenzylidene)amino)pentanoate (5Jb). The product **5Jb** was obtained as oil in 68% yield after flash/ $\text{Et}_2\text{O} = 100/1$ to 10/1) from a reaction catalyzed by QD-3 (5.0 mol%), A-1 (2.0 mol%) and ethanol (20 μL) in PhMe (2.0 mL) at -30°C for 8 h. 88% ee was determined by HPLC analysis [Daicel Chiralpak AD-H, Hexanes/IPA = 93/7, 1.0 mL/min, λ 254 nm, t (minor) = 12.55 min, t (major) = 13.56 min]. $[\alpha]_D^{20} = +80.2$ ($c = 1.0$, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.30 (d, $J = 8.7$ Hz, 2H), 7.92 (s, 1H), 7.89 (d, $J = 8.7$ Hz, 2H), 7.36 (d, $J = 8.4$ Hz, 2H), 6.93 (d, $J = 8.4$ Hz, 2H), 4.65 (d, $J = 2.4$ Hz, 2H), 3.15 (d, $J = 13.8$ Hz, 1H), 3.08 (d, $J = 13.8$ Hz, 1H), 2.63–2.52 (m, 1H), 2.47 (t, $J = 2.4$ Hz, 1H), 2.44–2.35 (m, 1H), 2.29–2.16 (m, 2H); ^{13}C { ^1H } NMR (100 MHz, CDCl_3) δ 171.8, 159.6, 149.7, 140.6, 133.0 (2C), 132.7, 131.3 (2C), 129.2 (2C), 126.5 (q, $J_{\text{C-F}} = 285$ Hz), 124.0 (2C), 121.7, 75.2, 68.4 (q, $J_{\text{C-F}} = 24$ Hz), 52.3, 39.5, 28.2, 26.6; ^{19}F NMR (376 MHz, CDCl_3) δ –73.2; IR (CHCl_3) ν 1525, 1346, 1163, 746, 667, 634 cm^{-1} ; HRMS (ESI/[$\text{M}+\text{H}$] $^+$) Calcd. for $\text{C}_{22}\text{H}_{19}\text{N}_2\text{O}_4\text{F}_3\text{Br}$ m/z 511.0480, found m/z 511.0477. The product of opposite absolute

configuration was obtained in 66% yield from a reaction catalyzed by *epi*Q-3 (5.0 mol%), A-1 (2.0 mol%) and ethanol (20 μ L) in PhMe (2.0 mL) at $-30\text{ }^{\circ}\text{C}$ for 8 h. 91% ee was determined HPLC analysis [t (major) = 12.53 min, t (minor) = 13.63 min]. $[\alpha]_{\text{D}}^{20} = -114.9$ (c = 1.0, CHCl_3).

General Procedure for the Asymmetric Synthesis of Compound 9.

At indicated temperature, to a solution of trifluoromethyl imines **1** (0.2 mmol), α,β -unsaturated lactones **8** (0.4 mmol, 2.0 equiv.), phenol-additive A-2 (10–50 mol%) and catalyst QD-1 or *epi*Q-1 (0.5 mol%) in PhMe (totally 2.0 mL) was added aqueous KOH solution (2.2 μ L, 50 wt%, 0.02 mmol). The mixture was then vigorously stirred and turned purple immediately. After the reaction was completed or reached the maximum conversion (checked by ^{19}F NMR), the reaction mixture was then passed through a small pad of deactivated silica (5 cm thick) and washed with Et_2O (1.0 mL $\times$ 3). The filtrates were combined, concentrated, purified through flash chromatography with deactivated silica gel (Hexanes/ Et_2O) to afford the desired products **9**.

(*R*)-4-((*S*)-1,1,1-trifluoro-2-((4-nitrobenzylidene)amino)propan-2-yl)dihydrofuran-2(3*H*)-one (**9Aa**). The product **9Aa** was obtained as oil in 93% yield after flash chromatography with deactivated silica gel (Hexanes/ Et_2O = 5/1 to 1/2) from a reaction catalyzed by QD-1 (1.0 mol%) and A-2 (10 mol%) in PhMe (2.0 mL) at $-30\text{ }^{\circ}\text{C}$ for 1 h. 99% ee was determined by HPLC analysis [Daicel Chiralpak AD-H, Hexanes/IPA = 90/10, 1.2 mL/min, λ 254 nm, $40\text{ }^{\circ}\text{C}$, t (minor) = 13.95 min, t (major) = 16.41 min]. $[\alpha]_{\text{D}}^{20} = -84.1$ (c = 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.56 (s, 1H), 8.32 (d, $J = 8.8$ Hz, 2H), 7.99 (d, $J = 8.8$ Hz, 2H), 4.58 (t, $J = 9.3$ Hz, 1H), 4.49 (t, $J = 8.6$ Hz, 1H), 3.34–3.21 (m, 1H), 2.57 (dd, $J_1 = 17.2$ Hz, $J_2 = 8.8$ Hz, 1H), 2.41 (dd, $J_1 = 17.2$ Hz, $J_2 = 10.9$ Hz, 1H), 1.53 (s, 3H); ^{13}C (^1H) NMR (100 MHz, CDCl_3) δ 175.1, 161.8, 149.9, 140.2, 129.6 (2C), 125.8 (q, $J_{\text{C-F}} = 285$ Hz), 124.1 (2C), 68.5 (q, $J_{\text{C-F}} = 3.6$ Hz), 65.7 (q, $J_{\text{C-F}} = 25$ Hz), 41.5, 29.5, 17.4; ^{19}F NMR (376 MHz, CDCl_3) δ -75.6 ; IR (CHCl_3) ν 1778, 1650, 1523, 1346, 1157, 1102, 1046, 1019, 837, 745, 668, 630 cm^{-1} HRMS (ESI/[$\text{M}+\text{H}$] $^{+}$) Calcd. for $\text{C}_{14}\text{N}_4\text{O}_4\text{F}_3$ m/z 331.0906, found m/z 331.0909. The product of opposite absolute configuration was obtained in 94% yield from a reaction catalyzed by *epi*Q-1 (1.0 mol%) and A-2 (10 mol%) in PhMe (2.0 mL) at $-30\text{ }^{\circ}\text{C}$ for 1 h. 98% ee was determined by HPLC analysis [t (major) = 14.10 min, t (minor) = 17.01 min]. $[\alpha]_{\text{D}}^{20} = +99.4$ (c = 1.0, CHCl_3).

(*R*)-4-((*S*)-*i*, *i*, *i*-trifluoro-2-((4-nitrobenzylidene)amino)hexan-2-yl)dihydrofuran-2(3*H*)-one (**9Ca**). The product **9Ca** was obtained as oil in 89% yield after flash chromatography with deactivated silica gel (Hexanes/ Et_2O = 10/1 to 3/1) from a reaction catalyzed by QD-1 (1.0 mol%) and A-2 (10 mol%) in PhMe (2.0 mL) at $-30\text{ }^{\circ}\text{C}$ for 3 h. 99% ee was determined by HPLC analysis [Daicel Chiralpak AD-H, Hexanes/IPA = 90/10, 0.6 mL/min, λ 254 nm, $8\text{ }^{\circ}\text{C}$, t (major) = 24.05 min, t (minor) = 25.68 min]. $[\alpha]_{\text{D}}^{20} = -52.1$ (c = 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.58 (d, $J = 1.2$ Hz, 1H), 8.31 (d, $J = 8.8$ Hz, 2H), 7.96 (d, $J = 8.8$ Hz, 2H), 4.48–4.34 (m, 2H), 3.403.27 (m, 2H), 2.77 (dd, $J_1 = 17.1$ Hz, $J_2 = 11.0$ Hz, 1H), 2.56 (dd, $J_1 = 17.1$ Hz, $J_2 = 8.7$ Hz, 1H), 2.01–1.88 (m, 1H), 1.74–1.62 (m, 1H), 1.55–1.27 (m, 4H), 0.95 (t, $J = 7.1$ Hz, 3H); ^{13}C (^1H) NMR (100 MHz, CDCl_3) δ 175.5, 161.0, 149.9, 140.6, 129.3 (2C), 126.2 (q, $J_{\text{C-F}} = 288$ Hz), 124.0 (2C), 68.7 (q, $J_{\text{C-F}} = 3.2$ Hz), 67.2

(q, $J_{C-F} = 24$ Hz), 39.5, 34.4, 29.3, 25.8, 23.2, 13.7; ^{19}F NMR (376 MHz, CDCl_3) δ -69.1; IR (CHCl_3) ν 1779, 1648, 1524, 1346, 1216, 1163, 1106, 1022, 838, 746, 667 cm^{-1} ; HRMS (ESI/[M+H]⁺) Calcd. for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_4\text{F}_3$ m/z 373.1375, found m/z 373.1371. The product of opposite absolute configuration was obtained in 90% yield from a reaction catalyzed by *epi***Q-1** (1.0 mol%) and **A-2** (10 mol%) in PhMe (2.0 mL) at -30 °C for 3 h. 98% ee was determined by HPLC analysis [*t* (minor) = 21.65 min, *t* (major) = 23.42 min]. $[\alpha]_{\text{D}}^{20} = +45.0$ ($c = 1.0$, CHCl_3).

(*R*)-4-((*S*)-1-cyclohexyl-2,2,2-trifluoro-1-((4-nitrobenzylidene)amino)ethyl)dihydrofuran-2(*jH*)-one (**9Ga**). The product **9Ga** was obtained as oil in 84% yield after flash chromatography with deactivated silica gel (Hexanes/Et₂O = 10/1 to 3/1) from a reaction catalyzed by **QD-1** (2.0 mol%) and **A-2** (10 mol%) in PhMe (2.0 mL) at -30 °C for 5 h. 99% ee was determined by HPLC analysis [Daicel Chiralpak AD-H, Hexanes/IPA = 90/10, 1.0 mL/min, λ 254 nm, 25 °C, *t* (minor) = 9.13 min, *t* (major) = 10.38 min]. $[\alpha]_{\text{D}}^{20} = -42.8$ ($c = 0.5$, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.47 (q, $J = 2.1$ Hz, 1H), 8.32 (d, $J = 8.8$ Hz, 2H), 7.96 (d, $J = 8.8$ Hz, 2H), 4.40–4.31 (m, 1H), 3.99 (t, $J = 9.6$ Hz, 1H), 3.49–3.37 (m, 1H), 3.14 (dd, $J_1 = 16.9$ Hz, $J_2 = 11.6$ Hz, 1H), 2.63 (dd, $J_1 = 16.9$ Hz, $J_2 = 8.4$ Hz, 1H), 1.95–1.83 (m, 2H), 1.83–1.67 (m, 3H), 1.57 (s, 1H), 1.41–1.10 (m, 5H); ^{13}C (1H) NMR (100 MHz, CDCl_3) δ 175.6, 160.0, 149.8, 140.6, 129.2 (2C), 126.6 (q, $J_{C-F} = 292$ Hz), 124.1 (2C), 70.5 (q, $J_{C-F} = 21$ Hz), 69.1 (q, $J_{C-F} = 4.3$ Hz), 44.9, 39.4, 29.8, 28.0, 27.7, 27.5, 27.2, 26.3; ^{19}F NMR (376 MHz, CDCl_3) δ -63.4; IR (CHCl_3) ν 1779, 1524, 1345, 1218, 1171, 1155, 1140, 1100, 1028, 836, 745, 685, 665 cm^{-1} ; HRMS (ESI/[M+H]⁺) Calcd. for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_4\text{F}_3$ m/z 399.1532, found m/z 399.1544. The product of opposite absolute configuration was obtained in 82% yield from a reaction catalyzed by *epi***Q-1** (2.0 mol%) and **A-2** (10 mol%) in PhMe (2.0 mL) at -30 °C for 5 h. 98% ee was determined by HPLC analysis [*t* (major) = 9.12 min, *t* (minor) = 10.35 min]. $[\alpha]_{\text{D}}^{20} = +11.7$ ($c = 0.4$, CHCl_3).

(*R*)-4-((*S,E*)-1,1,1-trifluoro-2-((4-nitrobenzylidene)amino)-4-phenylbut-3-en-2-yl)dihydrofuran-2(*3H*)-one (**9Ka**). The product **9Ka** was obtained as oil in 75% yield after flash chromatography with deactivated silica gel (Hexanes/Et₂O = 10/1 to 3/1) from a reaction catalyzed by **QD-1** (0.5 mol%) and **A-2** (50 mol%) in PhMe (2.0 mL) at -30 °C for 2 h. >99% ee was determined by HPLC analysis [Daicel Chiralpak AD-H, Hexanes/IPA = 90/10, 1.0 mL/min, λ 254 nm, 25 °C, *t* (minor) = 19.03 min, *t* (major) = 25.91 min]. $[\alpha]_{\text{D}}^{20} = -63.1$ ($c = 1.0$, CHCl_3);

^1H NMR (400 MHz, CDCl_3) δ 8.67 (s, 1H), 8.33 (d, $J = 8.8$ Hz, 2H), 8.02 (d, $J = 8.8$ Hz, 2H), 7.45–7.30 (m, 5H), 6.65 (d, $J = 16.4$ Hz, 1H), 6.17 (d, $J = 16.4$ Hz, 1H), 4.56–4.41 (m, 2H), 3.49 (pentet, $J = 8.6$ Hz, 1H), 2.76 (dd, $J_1 = 17.7$ Hz, $J_2 = 9.1$ Hz, 1H), 2.67 (dd, $J_1 = 17.7$ Hz, $J_2 = 9.1$ Hz, 1H); ^{13}C { ^1H } NMR (100 MHz, CDCl_3) δ 175.4, 163.7, 150.0, 140.2, 136.7, 134.9, 129.6 (2C), 129.2, 128.9 (2C), 126.8 (2C), 125.3 (q, $J_{C-F} = 288$ Hz), 124.1 (2C), 122.1, 70.5 (q, $J_{C-F} = 24$ Hz), 68.5 (q, $J_{C-F} = 3.3$ Hz), 40.7, 30.1; ^{19}F NMR (376 MHz, CDCl_3) δ -70.9; IR (CHCl_3) ν 1778, 1645, 1603, 1524, 1345, 1215, 1167, 1131, 1025, 974, 746, 689, 666 cm^{-1} ; HRMS (ESI/[M+H]⁺) Calcd. for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_4\text{F}_3$ m/z 419.1219, found m/z 419.1229. The product of opposite absolute configuration was obtained in 71% yield from a reaction catalyzed by *epi***Q-1** (0.5 mol%) and **A-2** (50 mol%) in PhMe (2.0 mL) at

–30 °C for 2 h. 99% ee was determined by HPLC analysis [t (major) = 19.02 min, t (minor) = 26.29 min]. $[\alpha]_D^{20} = +65.7$ (c = 1.0, CHCl₃).

(R)-4-((*R*)-2,2,2-trifluoro-1-((4-nitrobenzylidene)amino)-1-phenylethyl)dihydrofuran-2(3*H*)-one (**9La**). The product **9La** was obtained as oil in 70% yield after flash chromatography with deactivated silica gel (Hexanes/Et₂O = 10/1 to 3/1) from a reaction catalyzed by QD-1 (0.5 mol%) and A-2 (50 mol%) in PhMe (2.0 mL) at –30 °C for 2 h. >99% ee was determined by HPLC analysis [Daicel Chiralpak AD-H, Hexanes/IPA = 92/8, 1.0 mL/min, λ 254 nm, 25 °C, t (minor) = 27.53 min, t (major) = 30.28 min]. $[\alpha]_D^{20} = -108.2$ (c = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.69 (q, *J* = 2.1 Hz, 1H), 8.32 (dt, *J*₁ = 8.8 Hz, *J*₂ = 2.1 Hz, 2H), 8.05 (dt, *J*₁ = 8.8 Hz, *J*₂ = 2.1 Hz, 2H), 7.45–7.38 (m, 3H), 7.32–7.27 (m, 2H), 4.53 (t, *J* = 9.0 Hz, 1H), 4.31 (dd, *J*₁ = 9.5 Hz, *J*₂ = 7.5 Hz, 1H), 3.80 (pentet, *J* = 8.3 Hz, 1H), 2.71 (dd, *J*₁ = 17.8 Hz, *J*₂ = 8.6 Hz, 1H), 2.63 (dd, *J*₁ = 17.8 Hz, *J*₂ = 9.0 Hz, 1H); ¹³C {¹H} NMR (100 MHz, CDCl₃) δ 175.5, 163.0, 150.1, 140.4, 135.0, 129.6 (2C), 129.2, 129.0 (2C), 127.3 (2C), 125.5 (q, *J*_{C-F} = 289 Hz), 124.1 (2C), 72.1 (q, *J*_{C-F} = 23 Hz), 68.6 (q, *J*_{C-F} = 3.8 Hz), 41.7, 30.7; ¹⁹F NMR (376 MHz, CDCl₃) δ –67.4; IR (CHCl₃) ν 1777, 1525, 1346, 1216, 1151, 1037, 837, 746, 701, 666 cm^{–1}; HRMS (ESI/[M+H]⁺) Calcd. for C₁₉H₁₆N₂O₄F₃ *m/z* 393.1062, found *m/z* 393.1064. The product of opposite absolute configuration was obtained in 69% yield from a reaction catalyzed by *epi*Q-1 (0.5 mol%) and A-2 (50 mol%) in PhMe (2.0 mL) at –30 °C for 2 h. >99% ee was determined by HPLC analysis [t (major) = 27.18 min, t (minor) = 29.98 min]. $[\alpha]_D^{20} = +52.3$ (c = 1.0, CHCl₃).

(R)-4-((*R*)-2,2,2-trifluoro-1-(3-methoxyphenyl)-1-((4-nitrobenzylidene)amino)ethyl)dihydrofuran-2(3*H*)-one (**9Ma**). The product **9Ma** was obtained as oil in 55% yield after flash chromatography with deactivated silica gel (Hexanes/Et₂O = 10/1 to 3/1) from a reaction catalyzed by QD-1 (0.5 mol%) and A-2 (50 mol%) in PhMe (2.0 mL) at –30 °C for 3 h. >99% ee was determined by HPLC analysis [Daicel Chiralpak AD-H, Hexanes/IPA = 80/20, 0.5 mL/min, λ 254 nm, 3 °C, t (minor) = 30.56 min, t (major) = 33.20 min]. $[\alpha]_D^{20} = -86.5$ (c = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.68 (q, *J* = 2.0 Hz, 1H), 8.36 (d, *J* = 8.7 Hz, 2H), 8.04 (d, *J* = 8.7 Hz, 2H), 7.34 (t, *J* = 8.2 Hz, 1H), 6.93 (dd, *J*₁ = 8.2 Hz, *J*₂ = 2.3 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 6.80 (s, 1H), 4.52 (t, *J* = 8.7 Hz, 1H), 4.30 (dd, *J*₁ = 9.2 Hz, *J*₂ = 7.6 Hz, 1H), 3.79 (s, 3H), 3.75 (pentet, *J* = 8.4 Hz, 1H), 2.73 (dd, *J*₁ = 17.8 Hz, *J*₂ = 8.6 Hz, 1H), 2.43 (dd, *J*₁ = 17.8 Hz, *J*₂ = 9.0 Hz, 1H); ¹³C {¹H} NMR (100 MHz, CDCl₃) δ 175.5, 163.1, 159.9, 150.1, 140.4, 136.6, 130.1, 129.6 (2C), 125.5 (q, *J* = 291 Hz), 124.2 (2C), 119.4, 114.6, 113.3, 72.0 (q, *J*_{C-F} = 24 Hz), 68.6 (q, *J*_{C-F} = 3.6 Hz), 55.4, 41.8, 30.7; ¹⁹F NMR (376 MHz, CDCl₃) δ –67.1; IR (CHCl₃) ν 1776, 1603, 1523, 1345, 1256, 1166, 1144, 1034, 854, 837, 746, 729, 710, 688, 667 cm^{–1}; HRMS (ESI/[M+H]⁺) Calcd. for C₂₀H₁₈N₂O₅F₃ *m/z* 423.1168, found *m/z* 423.1151. The product of opposite absolute configuration was obtained in 51% yield from a reaction catalyzed by *epi*Q-1 (0.5 mol%) and A-2 (50 mol%) in PhMe (2.0 mL) at –30 °C for 3 h. >99% ee was determined by HPLC analysis [t (major) = 30.37 min, t (minor) = 33.66 min]. $[\alpha]_D^{20} = +85.4$ (c = 1.0, CHCl₃).

(R)-4-((*R*)-1-(4-chlorophenyl)-2,2,2-trifluoro-1-((4-nitrobenzylidene)amino)ethyl)dihydrofuran-2(3*H*)-one (**9Na**). The product **9Na** was obtained as oil in 50% yield after flash chromatography with deactivated silica gel

(Hexanes/Et₂O = 10/1 to 3/1) from a reaction catalyzed by QD-1 (0.5 mol%) and A-2 (50 mol%) in PhMe (2.0 mL) at -30 °C for 2 h. >99% ee was determined by HPLC analysis [Daicel Chiralpak AD-H, Hexanes/IPA = 90/10, 1.0 mL/min, λ 254 nm, 25 °C, t (minor) = 24.22 min, t (major) = 29.91 min]. $[\alpha]_D^{20} = -35.9$ (c = 0.5, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.68 (q, $J = 2.0$ Hz, 1H), 8.37 (d, $J = 8.8$ Hz, 2H), 8.04 (d, $J = 8.8$ Hz, 2H), 7.40 (d, $J = 8.8$ Hz, 2H), 7.23 (d, $J = 8.8$ Hz, 2H), 4.52 (dd, $J_1 = 9.6$ Hz, $J_2 = 8.4$ Hz, 1H), 4.28 (dd, $J_1 = 9.6$ Hz, $J_2 = 7.3$ Hz, 1H), 3.76 (pentet, $J = 8.0$ Hz, 1H), 2.69 (dd, $J_1 = 17.7$ Hz, $J_2 = 8.4$ Hz, 1H), 2.43 (dd, $J_1 = 17.7$ Hz, $J_2 = 9.0$ Hz, 1H); ¹³C {¹H} NMR (100 MHz, CDCl₃) δ 175.1, 163.2, 150.2, 150.1, 140.1, 135.6, 133.6, 129.7 (2C), 129.3 (2C), 128.8 (2C), 125.3 (q, $J = 289$ Hz), 124.3 (2C), 71.83 (q, $J_{C-F} = 23$ Hz), 68.4 (q, $J_{C-F} = 3.6$ Hz), 41.6, 30.6; ¹⁹F NMR (376 MHz, CDCl₃) δ -67.4; IR (CHCl₃) ν 1774, 1743, 1525, 1346, 1154, 1093, 1036, 839, 809, 746, 689, 666 cm⁻¹; HRMS (ESI/[M+H]⁺) Calcd. for C₁₉H₁₅N₂O₄F₃Cl m/z 427.0672, found m/z 427.0655. The product of opposite absolute configuration was obtained in 48% yield from a reaction catalyzed by *epi*Q-1 (0.5 mol%) and A-2 (50 mol%) in PhMe (2.0 mL) at -30 °C for 2 h. >99% ee was determined by HPLC analysis [t (major) = 23.87 min, t (minor) = 31.01 min]. $[\alpha]_D^{20} = +40.6$ (c = 0.5, CHCl₃).

(*R*)-4-((*S*)-1,1,1-trifluoro-2-((4-nitrobenzylidene)amino)propan-2-yl)tetrahydro-2H-pyran-2-one (**9Ab**). The product **9Ab** was obtained as oil in 86% yield after flash chromatography with deactivated silica gel (Hexanes/Et₂O = 5/1 to 1/2) from a reaction catalyzed by QD-1 (2.0 mol%) and A-2 (10 mol%) in PhMe (2.0 mL) at -30 °C for 3 h. 94% ee was determined by HPLC analysis [Daicel Chiralpak AD-H, Hexanes/IPA = 90/10, 1.2 mL/min, λ 254 nm, 40 °C, t (minor) = 15.42 min, t (major) = 20.69 min]. $[\alpha]_D^{20} = -83.2$ (c = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.49 (s, 1H), 8.31 (d, $J = 8.8$ Hz, 2H), 7.97 (d, $J = 8.8$ Hz, 2H), 4.47–4.40 (m, 1H), 4.32–4.23 (m, 1H), 2.82–2.64 (m, 2H), 2.46 (dd, $J_1 = 16.6$ Hz, $J_2 = 9.6$ Hz, 1H), 2.08–1.94 (m, 2H), 1.49 (s, 1H); ¹³C {¹H} NMR (100 MHz, CDCl₃) δ 170.4, 160.6, 149.7, 140.5, 129.5 (2C), 126.1 (q, $J_{C-F} = 285$ Hz), 124.0 (2C), 67.9, 67.8 (q, $J_{C-F} = 24$ Hz), 37.5, 31.4, 24.3, 15.4; ¹⁹F NMR (376 MHz, CDCl₃) δ -73.4; IR (CHCl₃) ν 1732, 1649, 1603, 1522, 1345, 1299, 1267, 1173, 1124, 1076, 966, 837, 746, 684, 666 cm⁻¹; HRMS (ESI/[M+H]⁺) Calcd. for C₁₅H₁₁N₂O₄F₃ m/z 345.1062, found m/z 345.1058. The product of opposite absolute configuration was obtained in 91% yield from a reaction catalyzed by *epi*Q-1 (2.0 mol%) and A-2 (10 mol%) in PhMe (2.0 mL) at -30 °C for 3 h. 91% ee was determined by HPLC analysis [t (major) = 15.30 min, t (minor) = 20.62 min]. $[\alpha]_D^{20} = +79.5$ (c = 1.0, CHCl₃).

Procedure for Gram-Scale Reaction to Compound 5Aa.

Methyl (*S*)-5,5,5-trifluoro-4-methyl-4-((4-nitrobenzylidene)amino)pentanoate (**5Aa**). At -40 °C, to a solution of trifluoromethyl imine **1A** (1.5 g, 6.0 mmol), **4a** (1.1 mL, 12.0 mmol, 2.0 equiv.), **A-1** (19.0 mg, 0.12 mmol, 2.0 mol%), ethanol (0.6 mL) and catalyst QD-4 (266.0 mg, 0.3 mmol, 5.0 mol%) in PhMe (60.0 mL) was added aqueous KOH solution (100.0 μ L, 50 wt%, 1.2 mmol, 0.2 equiv.). The mixture was then vigorously stirred and turned purple in a few minutes (The reaction mixture was sticky, make sure the stirring is good). After 6 h, the reaction was fully completed (checked with crude NMR). The reaction mixture was then passed through a pad of Celite (5 cm thick) and washed with CH₂Cl₂ (60.0 mL). The filtrates were combined, concentrated under vacuum and purified through flash

chromatography (deactivated silica gel, Hexanes/Et₂O = 50/1 to Hexanes/Et₂O = 10/1) to afford the desired product **5Aa** as light-yellow oil in 81% yield. 90% ee was determined by HPLC analysis [Daicel Chiralpak AD-H, Hexanes/IPA = 97/3, 1.0 mL/min, λ 254 nm, t (minor) = 13.01 min, t (major) = 18.13 min].

Procedure for Gram-Scale Reaction to Compound **9Aa**.

(*R*)-4-((*S*)-1,1,1-trifluoro-2-((4-nitrobenzylidene)amino)propan-2-yl)dihydrofuran-2(3*H*)-one (**9Aa**). At -30 °C, to a solution of trifluoromethyl imine **1A** (1.5 g, 6.0 mmol), **8a** (0.85 mL, 12.0 mmol, 2.0 equiv.), **A-2** (82.0 mg, 0.6 mmol, 10.0 mol%), and catalyst **QD-4** (60.0 mg, 0.06 mmol, 1.0 mol%) in PhMe (60.0 mL) was added aqueous KOH solution (100.0 μ L, 50 wt%, 1.2 mmol, 0.2 equiv.). The mixture was then vigorously stirred and turned purple in a few minutes. After 3 h, the reaction was fully completed (checked with crude NMR). The reaction mixture was then passed through a pad of Celite (5 cm thick) and washed with CH₂Q₂ (60.0 mL). The filtrates were combined, concentrated under vacuum and purified through flash chromatography (deactivated silica gel, Hexanes/Et₂O = 10/1 to Hexanes/Et₂O = 1/1) to afford the desired product **9Aa** as clear oil in 91% yield (which could be solidified in ether solution at low temperature). 99% ee was determined by HPLC analysis [Daicel Chiralpak AD-H, Hexanes/IPA = 90/10, 1.2 mL/min, λ 254 nm, 40 °C, t (minor) = 14.34 min, t (major) = 16.87 min].

Synthetic Transformation to Compound (**11Aa**).

Methyl (*S*)-4-amino-5,5,5-trifluoro-4-methylpentanoate hydrochloride (**11Aa**). To a solution of **4Aa** (1.0 mmol) in Et₂O (10.0 mL) at room temperature was added 1N HCl aqueous solution (10.0 mL). The reaction mixture was then stirred at the same temperature for 3 h for the complete hydrolysis of imine **4Aa**. After that, the aqueous layer was separated, and concentrated under vacuum to afford the desired product **11Aa**. ¹H NMR (400 MHz, CD₃OD) δ 3.68 (s, 3H), 3.28–3.26 (m, 1H), 2.60–2.54 (m, 2H), 2.24–2.18 (m, 2H), 1.53 (s, 3H); ¹³C {¹H} NMR (100 MHz, CD₃OD) δ 173.6, 126.5 (q, J_{C-F} = 284 Hz), 59.6 (q, J_{C-F} = 29 Hz), 52.6, 29.2, 28.2, 17.7; ¹⁹F NMR (376 MHz, CD₃OD) δ -80.0.

Synthetic Transformation to Compound (**12Aa**).

(*R*)-4-((*S*)-2-amino-1,1,1-trifluoropropan-2-yl)dihydrofuran-2(3*H*)-one (**12Aa**). To a solution of **9Aa** (1.0 mmol) in Et₂O (10.0 mL) at room temperature was added 1N HCl aqueous solution (10.0 mL). The reaction mixture was then stirred at the same temperature for 3 h for the complete hydrolysis of imine **9Aa**. After that, the aqueous layer was separated, and concentrated under vacuum to afford the desired product **12Aa**. $[\alpha]_D^{20}$ = -0.9 (c = 1.0, CHCl₃). ¹H NMR (400 MHz, CD₃OD) δ 4.49 (t, J = 9.2 Hz, 1H), 4.34 (t, J = 9.2 Hz, 1H), 3.36 (quintet, J = 9.2 Hz, 1H), 2.83–2.66 (m, 2H), 1.61 (s, 3H); ¹³C {¹H} NMR (100 MHz, CD₃OD) δ 174.9, 124.8 (q, J_{C-F} = 283 Hz), 66.6, 58.8 (q, J_{C-F} = 29 Hz), 38.11, 28.91, 14.46; ¹⁹F NMR (376 MHz, CD₃OD) δ -78.9; IR (MeOH) ν 2811, 2577, 1781, 1539, 1179, 1021 cm⁻¹; HRMS (ESI/[MCl]⁺) Calcd. for C₇H₉NO₂F₃ m/z 198.0742, found m/z 198.0737.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(a) Catalytic umpolung addition of trifluoromethyl imines to α , β -unsaturated *N*-acyl pyrroles.

(b) **Present work**: catalytic umpolung addition of imines to acrylates or α , β -unsaturated lactones.

Scheme 1.

Imine Umpolung Reactions for Asymmetric Synthesis of γ -Trifluoromethylated γ -Amino Acids.

Scheme 2.
Gram-scale Reactions and Synthetic Applications.

Table 1.

Development of Phase-Transfer Catalysts^a

entry	catyst	T (°C)	conv. (%) ^b	5Aa/6A; 5Aa/7Aa ^b	ee of 5Aa (%) ^c
1 ^d	C-1	-20	100	10/90; 79/21	15 (S)
2 ^d	QD-2	-20	69	58/42; 80/20	80 (S)
3 ^d	QD-3	-20	95	66/34; 89/11	90 (S)
4	QD-3	-30	92	71/29; 90/10	91 (S)
5 ^e	QD-3	-30	100	83/17; 90/10	92 (S)
6 ^{e,f}	QD-3	-30	100	93/7; 90/10	88 (S)
7 ^{e,f}	QD-3	-40	100	95/5; 90/10	91 (S)
8 ^{e,f}	Q-3	-40	32	75/25; 61/39	33 (R)
9 ^{e,f}	epiQ-3	-40	100	97/3; 91/9	91 (R)

^a Unless noted, reactions were performed with **1A** (0.025 mmol), **4a** (0.05 mmol), aqueous KOH (0.22 μ L, 50 wt %, 10 mol %) in PhMe (0.25 mL) with catalyst (5.0 mol %) at the indicated temperature for 8 h.

^b Determined by ^{19}F NMR analysis.

^c Determined by HPLC analysis.

^d Reaction time was 4 h.

^e 2.0 mol % additive **A-1** was added.

^f EtOH (2.5 μ L) was added.

Table 2.

Substrate Scope of Trifluoromethyl Imines with Various Acrylates^a

entry	R ¹ ; 1	4	t (h)	yield of 5 (%) ^b	ee of 5 (%) ^c
1 ^d	Me; 1A	4a	8	80 (85); 5Aa	92(92)
2 ^e	Me; 1A	4b	3	89 (92); 5Ab	91 (93)
3 ^d	Me; 1A	4c	20	70 (75); 5Ac	85 (90)
4 ^d	Me; 1A	4d	20	50 (63); 5Ad	81 (86)
5 ^e	Me; 1A	4e	8	91 (93); 5Ae	94 (94)
6 ^d	Et; 1B	4a	5	71 (73); 5Ba	87 (90)
7	<i>n</i> -Bu; 1C	4a	8	63 (68); 5Ca	91 (91)
8	CH ₂ =CH(CH ₂) ₃ ; 1D	4a	8	64 (68); 5Da	90 (92)
9	Ph(CH ₂) ₂ ; 1E	4a	8	53 (55); 5Ea	90 (88)
10 ^f	H; 1F	4a	4	62 (70); 5Fa	90 (91)
11	Cy; 1G	4a	8	-- (--); 5Ga	-- (--)
12	Cy; 1G	4b	8	65 (63); 5Gb	91 (93)
13	CyCH ₂ ; 1H	4b	8	71 (72); 5Hb	90 (93)
14	Bn; 1I	4b	8	63 (72); 5Ib	90 (92)
15	4-BrBn; 1J	4b	8	68 (66); 5Jb	88 (91)

^aUnless noted, reactions were performed with **1** (0.2 mmol), acrylates **4** (0.4 mmol), **A-1** (2.0 mol %), ethanol (20 μ L) and aqueous KOH solution (2.2 μ L, 50 wt %, 10 mol %) in PhMe (2.0 mL) with catalyst QD-**3** (5.0 mol %) at the indicated temperature; results in parentheses were obtained from reactions catalyzed by *epi*Q-**3** (5.0 mol %) in same conditions.

^bIsolated yield of **5**.

^cDetermined by HPLC analysis.

^dReaction was performed at -40 °C.

^e1.0 mol % catalyst was used.

^fReaction was performed at -50 °C

Table 3.

Screening of Chiral Phase-Transfer Catalysts.

entry	catalyst	additive	conv. (%) ^b	9La/6L; 9La/10La ^b	ee of 9La (%) ^c
1	C-1	--	83	9/91; 25/75	--
2	C-1	A-1 (100)	100	30/70; 87/13	98 (<i>S</i> , <i>R</i>)
3	C-1	A-2 (100)	87	58/42; 89/11	>99 (<i>S</i> , <i>R</i>)
4	QD-1	A-2 (100)	100	79/21; 81/19	>99 (<i>S</i> , <i>R</i>)
5	QD-1	A-2 (50)	100	90/10; 82/18	>99 (<i>S</i> , <i>R</i>)
6 ^d	QD-1	A-2 (50)	100	90/10; 82/18	>99 (<i>S</i> , <i>R</i>)
7 ^d	Q-1	A-2 (50)	100	82/18; 78/22	99 (<i>R</i> , <i>S</i>)
8 ^d	epiQ-1	A-2 (50)	100	90/10; 84/16	>99 (<i>R</i> , <i>S</i>)

^a Unless noted, reactions were performed with **1L** (0.025 mmol), **8a** (0.05 mmol), additive (y mol %), aqueous KOH solution (0.22 μL , 50 wt %, 10 mol %) in PhMe (0.25 mL) with catalyst (x mol %) at $-30\text{ }^{\circ}\text{C}$.

^b Determined by ^{19}F NMR analysis.

^c Determined by HPLC analysis.

^d 0.5 mol % catalyst was used.

Table 4.

Substrate Scope of Trifluoromethyl Imines with α,β -Unsaturated Lactones^a

entry	R ¹ ; 1	8	t (h)	Yield of 9 (%) ^b	ee of 9 (%) ^c
1 ^d	Me; 1A	8a	1	93 (94); 9Aa	99 (98)
2 ^d	<i>n</i> -Bu; 1C	8a	3	89 (90); 9Ca	99 (98)
3 ^e	Cy; 1G	8a	5	84 (82); 9Ga	99 (98)
4	PhCH=CH; 1K	8a	2	75 (71); 9Ka	99 (98)
5	Ph; 1L	8a	2	70 (69); 9La	>99 (>99)
6	3-OMeC ₆ H ₄ ; 1M	8a	2	55 (51); 9Ma	>99 (>99)
7	4-ClC ₆ H ₄ ; 1N	8a	2	50 (48); 9Na	>99 (>99)
8 ^e	Me; 1A	8b	3	86 (91); 9Ab	94 (91)

^a Unless noted, reactions were performed with **1** (0.2 mmol), **8** (0.4 mmol), aqueous KOH solution (2.2 μ L, 50wt %, 10 mol %), **A-2** (10 mol % for entries 1–3 and 8, 50 mol % for entries 4–7) in PhMe (2.0 mL) with catalyst QD-1 (0.5 mmol %); results in parentheses were obtained from reactions catalyzed by *epi*Q-1 (0.5 mol %) in same conditions..

^b Isolated yield of **9**, dr of **9** >95/5.

^c Determined by HPLC analysis.

^d 1.0 mol % catalysts were employed.

^e 2.0 mol % catalysts were employed.