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Note

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N-TFA-Gly-Bt Based Stereoselective Synthesis of Substituted 3-Amino Tetrahydro-2*H*-pyran-2-ones *via* an Organocatalyzed Cascade Process

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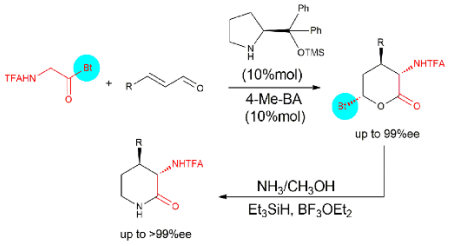
Supporting Information



ABSTRACT: Chiral substituted 3-amino tetrahydro-2*H*-pyran-2-ones were prepared in excellent ees (up to 99% ee) *via* an organocatalyzed cascade procedure with *N*-TFA-Gly-Bt and α,β-unsaturated aldehydes as the substrates. The corresponding tetrahydro-2*H*-pyran-2-ones can be used for further synthetic transformations that furnish chiral substituted 3-amino piperidin-2-ones with high levels of stereoselectivity.

Chiral α-amino acids and their derivatives are among the most important building blocks for natural products, bioactive entities and pharmaceuticals. Many drugs contain both natural and more importantly, unnatural α-amino acid fragments, meaning new methodologies for accessing α-amino acids are of utmost importance to both academic and pharmaceutical chemists.[1-2] A wide variety of asymmetric transformations have been developed for the synthesis of chiral α-amino acids with readily available pro-chiral or chiral precursors,[3-5] among which glycine and its derivatives, especially glycine imino esters, have been extensively studied and used for the preparation of many non-natural amino acid derivatives as drug intermediates in multi- to several hundred kilogram quantities (Fig. 1).[6,7,8] It was assumed that the unique properties of the imino group should be responsible for the α-activation of glycine derivatives, which could react with diverse electrophiles in enantioselective manners.[9-11] Fantastic improvements with the imino activa-

tion strategies using chiral aldehydes as the organocatalysts were achieved recently by Guo's, Ouyang's, Zhao's and Yuan's groups, respectively: glycine esters without *N*-protection reacted with α,β-unsaturated ketones or aryl *N*-diphenylphosphinyl imines in excellent yields, drs and ees; similar glycine Schiff base intermediates, formed *in situ* during the reactions, were proposed to be the active species. [12-13] Asymmetric reactions with other glycine derivatives as glycinate Schiff bases Ni(II) complexes,[14] triketopiperazines[15] and *N*,*N*-disubstituted glycinates [16] were also reported. However, except for some intramolecular procedures, [17-18] other glycine derivatives with general nitrogen protections (amides, carbamates and sulfonamides) have not been extensively studied due to poor reactivity. Hence, auxiliary strategies, and even chiral resolution methods are still needed for the preparation of some important intermediates. [19-23]

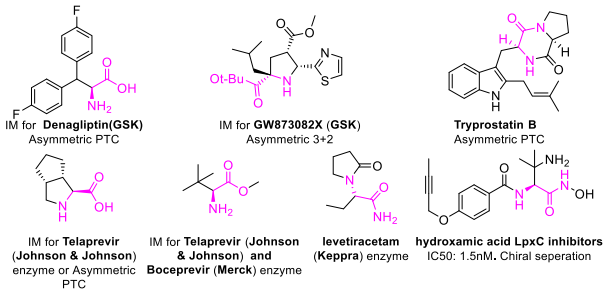
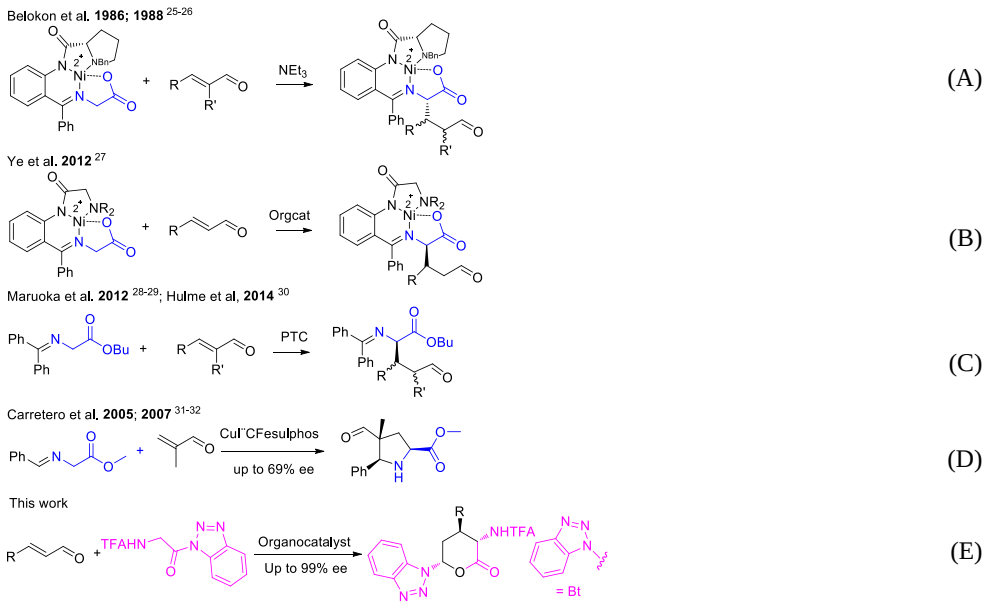


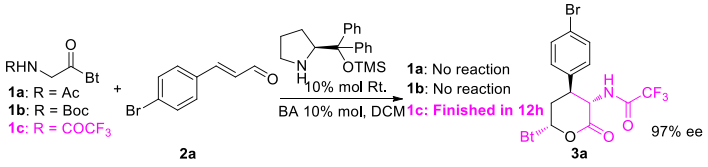
Fig 1 Representative unnatural amino acids and their derivatives.

As part of our continuous efforts to develop new methodologies for the asymmetric functionalization of α-amino carbonyl compounds, we found that amino protections played decisive roles for the formation of enol intermediates, which reacted with α,β-unsaturated aldehydes and afforded polysubstituted pyrrolidines with controlled stereochemistry in excellent ees.[24] We envisioned that efficient activations and good chiral inductions with non-imino glycine derivatives could be achieved through the regulation of amino protections and carboxyl derivations. Asymmetric reactions between imino-glycine derivatives and α,β-unsaturated aldehydes were first developed by Belokon et al., wherein a chiral glycinate Schiff base Ni(II) complex reacted with substituted acroleins under basic conditions to yield Michael addition products in excellent chiral induction (Scheme 1 A).[25-26] An organocatalyzed asymmetric version of this transformation with non-chiral Ni(II) complexes afforded Michael adducts in up to 95% ee (Scheme 1 B). [27] Other than the nickel complexes, free glycine ester Schiff bases are also good partners for Michael additions under chiral PTC conditions and an optically pure bicyclic amino acid, which is the key intermediate for Telaprevir production was prepared in up to 93% ee. (Scheme 1 C).[28-30] Asymmetric 1,3-dipolar cycloaddition of imino glycinates with methacrolein was discovered by Carretero et al. and chiral pyrrolidines were prepared in good enantioselectivity (69% ee) (Scheme 1 D).[31-32]



Scheme 1 Asymmetric reactions between glycine derivatives and α,β-unsaturated aldehydes

N-Acyl derivatives of benzotriazole (COBt) are known as powerful acylating agents and have found widespread application in organic synthesis.[33] Albeit the strong electron withdrawing properties of Bt group can significantly increase the acidity of hydrogen atom in α-position, only a few researches focused on the α-functionalization of COBts.[34-35] Katritzky et al. reported a fascinating formation of polysubstituted 3,4-dihydropyran-2-ones or 1,3-dienes by intramolecular cyclization of lithium enolates of *N*-acylbenzotriazoles to α,β-unsaturated carbonyl compounds in good yields and up to 20:1 drs.[36] Barbas III et al. found the first organocatalyzed asymmetric α-functionalization of 4-nitro-benzyl COBt to yield the product with low chiral induction (20% ee). We reported herein an efficient organocatalyzed asymmetric cascade reaction with *N*-TFA glycine Bt and α,β-unsaturated aldehydes as the substrates affording chiral 3,4,6-trisubstituted tetrahydro-2*H*-pyran- 2-ones in up to 65% overall yield and 99% ee (Scheme 1 E).

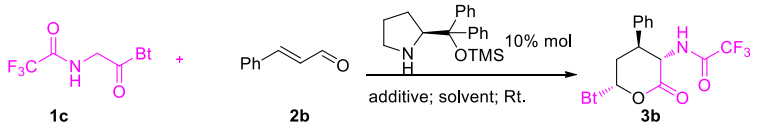


Scheme 2 Amino protection screen

Our initial investigation started by using acylbenzotriazole **1** and 4-Br-cinnamaldehyde (**2a**) as the substrates with a traditional (*S*)-diphenyl prolinol silyl ether (10% mol)/benzoic acid (10% mol)/CH_2Cl_2 system (Scheme 2). No reaction was observed with **1a** and **1b**, which was attributed to the poor electron withdrawing properties of the protective groups. Replacing the protective group with TFA (**1c**), to our delight, the reaction finished in 12 hours and a novel 3,4,6-trisubstituted-tetrahydro-2*H*-pyran-2-one (**3a**) was obtained in excellent enantioselectivity (97% ee). Characteristic LCMS signals of Bromo containing components of the reaction mixture indicated that there was predominately one product produced (dr>10:1, by LC normalization), though decomposed BtH

was observed. The promising results promoted further optimization of the reaction with cinnamaldehyde (**2b**) as the standard substrate (Table 1**)**. Without any additive, the reaction afforded product in 23% yield and 80% ee (Table 1, entry 1). Remarkable improvements in both yields and ees were achieved with most of the acidic additives (Table 1, entries 2-7). Compared with HOAc, $MeSO_3H$, $ArSO_3H$, TfOH and CF_3CO_2H, reaction with benzoic acid (BA) afforded the product in the highest yield and ee (36% yield and 97% ee; Table 1, entry 7). Para-substitution of BA were further optimized and elevation of the yields was reached with Br, I, $-NMe_2$ and methyl substitutions (Table 1, entries 8-11); up to 59% yield and 97% ee were obtained with 4-Me-BA as the co-catalyst (Table 1, entry 11). Additionally, other common solvents were also examined, and acetone was the best choice of solvent in terms of yield and enantioselectivity (Table 1, entries 12-16).

Table 1. Optimization of Reaction Conditions[a]

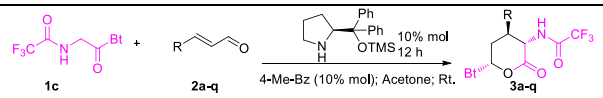


Entry	Additive	Solvent	Yield (%)[b]	Ee (%)[c]
1	None	CH_2Cl_2	23	80
2	HOAc	CH_2Cl_2	36	93
3	BA	CH_2Cl_2	36	97
4	TFA	CH_2Cl_2	24	83
5	LABSA	CH_2Cl_2	23	93
6	TsOH	CH_2Cl_2	30	91
7	TfOH	CH_2Cl_2	18	95
8	4-Br-BA	CH_2Cl_2	55	96
9	4-I-BA	CH_2Cl_2	45	89
10	4-$N(CH_3)_2$-BA	CH_2Cl_2	55	93
11	4-CH_3-BA	CH_2Cl_2	59	97
12	4-CH_3-BA	THF	49	92
13	4-CH_3-BA	CH_3CN	53	92
14	4-CH_3-BA	EtOAc	55	96
15	**4-CH_3-BA**	**Me_2CO**	**61**	**97**
16	4-CH_3-BA	MIBK	42	97

[a] Reactions performed with **1c** (0.5 mmol) and **2b** (0.55 mmol) in 1 mL of solvent for 12h. [b] Isolated yield. [c] Determined by HPLC on chiral stationary phase.

After establishment of the optimal catalytic system, the substrate scope of the reaction were then examined. Various substituted α,β-unsaturated aldehydes were well tolerated in this reaction, giving the products in low to moderate isolated yields (27-65%) and good to excellent enantioselectivities (80-99% ee) (Table 2). As shown in Table 2, halogen-substituted cinnamaldehydes (**2a, 2c, 2d, 2e**) reacted with **1c** to give the corresponding products with similar yields and enantioselectivities (58-65% yield and > 95% ee) (Table 2, Entries 1,3-5). But unexpectedly, with 2-chloro cinnamaldehyde (**2c**) as the substrate, a 1:1 diastereomer mixture (at C-6 position) was obtained in a total 62% yield and 97/99% ees (Table 2, Entry 3). With 3-cyano substitution (**2f**), **3f** was obtained in the lowest ee (80%) (Table 2, Entry 6). Considering the result, that a slight ee decrease was also observed for 3-Cl substituted product **3d,** the enantioselectivity of the reaction seems more sensitive in comparison with the electron properties of para substitution. Thus, we propose that the steric repulsion between substituted phenyl and bulky nucleophile might be responsible for the ees' erosion of both meta substituted substrates (A slightly deviation of the phenyl ring from the iminium plane was observed in reported single crystal X-ray structures [37]). Further evidence stems from the fact that para substituted cinnamaldehydes with both electron-withdrawing groups (-CN and -NO_2) and electron-donating groups (-Ph, -OMe, -O-2-naphthyl) gave chiral tetrahydro-2*H*-pyran-2-ones (**3g-k**) in 45-62% yields and 93-98% ees (Table 2, Entries7-11). (2*E*,4*E*)-5-(3,4dichlorophenyl)penta-2,4-dienal (**2l**) reacted selectively following the same process with **1c** to afford a chiral tetrahydro-2*H*-pyran-2-one (**3l**) in 51% yield and 86% ee (Table 2, Entry 12). Disubstituted substrate 3,4-dichloro cinnaldehyde **2m** gave the product **3m** in the same ee (95%) as that of 3-chloro cinnaldehyde **2d**. Unlike meta mono substituted **2d** and **2f**, meta disubstituted substrates **2n** and **2o** produced the products **3n** and **3o** in excellent ees (97 and 98% ee respectively), we envisioned that the ee erosion caused by one substituent oriented to the si-face was neutralized by the other one, which further blocked re-face of the iminium intermediate (because of the rotatable single bond between phenyl ring and the double bond). (Table 2, Entries 13-15). Varying phenyl group to furanyl, 54% yield and 95% ee were achieved (Table 2, Entry 16). With 3-Ferrocenyl acrolein, 90% ee was achieved, but, however, only 27% yield was obtained because of the poor stability of Fc fragment during column purification (Table 2, Entry 17). With crotonaldehyde as the substrate, a complex mixture was obtained following current procedure (Table 2, Entry 18).

Table 2. Substrate Scope of α,β-Unsaturated aldehydes[a]

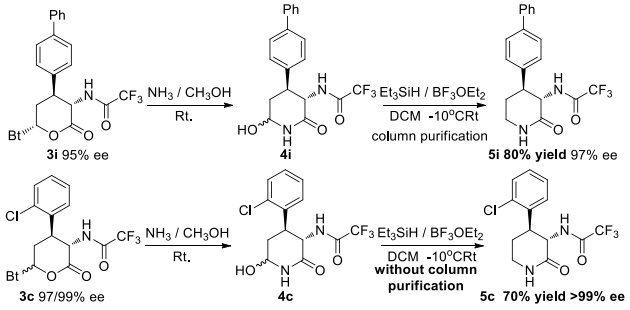


entry	**2** (R=)	**3**	Yield (%)[b]	Ee (%)[c]
1	**2a** (4-Br-C_6H_4-)	**3a**	58	97
2	**2b** (C_6H_5-)	**3b**	61	97
3	**2c** (2-Cl-C_6H_4-)	**3c**[d]	62	97/99
4	**2d** (3-Cl-C_6H_4-)	**3d**	60	95

5	**2e** (4-Cl-C_6H_4-)	**3e**	65	97
6	**2f** (3-CN-C_6H_4-)	**3f**	62	80
7	**2g** (4-CN-C_6H_4-)	**3g**	62	94
8	**2h** (4-NO_2-C_6H_4-)	**3h**	53	95
9	**2i** (4-Ph-C_6H_4-)	**3i**	45	93
10	**2j** (4-CH_3O-C_6H_4-)	**3j**	56	95
11	**2k**(4-(2-naphthyl)O-C_6H_4-)	**3k**	51	98
12	**2l**((*E*)-(3,4)$Cl_2C_6H_3$-CH=CH-)	**3l**	51	86
13	**2m** (3,4-$Cl_2C_6H_3$-)	**3m**	44	95
14	**2n** (3,5-$Cl_2C_6H_3$-)	**3n**	49	97
15	**2o**(3,5-$(CF_3)_2C_6H_3$-)	**3o**	55	98
16	**2p** (2-Furanyl-)	**3p**	54	95
17	**2q** (Ferrocenyl-)	**3q**	27	90
18	**2r** (CH_3-)[e]	**3r**	--	--

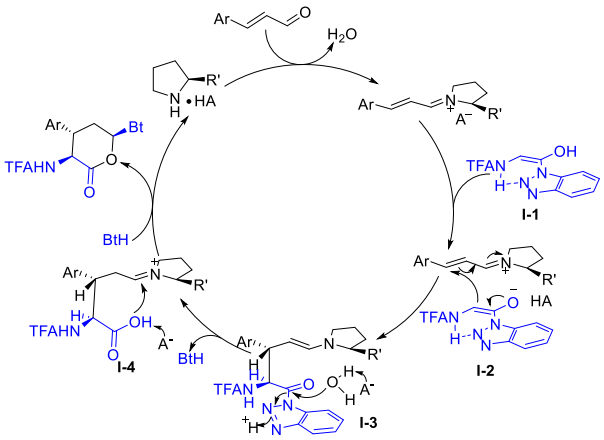
[a] Reactions were performed with **1c** (0.5 mmol) and **2a–q** (0.55 mmol) in 1 mL acetone. [b] Isolated yield. [c] Determined by HPLC on chiral stationary phase. [d] The two diasteromers (1:1) that configurationally differed at the 6 position were not separated since both isomers could be converted into one single product after removing the Bt group *via* reduction. [e] The reaction mixture contains less desired diastereomers and more unknown byproducts.

The presence of the Bt–C–OCO fragment within the products allowed for further derivatization of **3** into a stereo-defined 3-amino-piperidin-2-ones (Scheme 3). Facile aminolysis of **3i** in NH_3/MeOH at room temperature generated 6-hydroxyl-piperidin- 2-one **4i**, which undergoes a dehydroxyl/reduction process in a BF_3OEt_2/$HSiEt_3$/CH_2Cl_2 system to afford 4-([1,1'-biphenyl]-4-yl)-3-(2,2,2-trifluoroacetamido)-piperidin-2-one **5i** in 80% yield and 97% ee. To verify the stereochemistry of **3c** (diastereomer mixture at C-6 position), following the same procedure, pure **5c** was prepared with **3c** in 70% yield and >99% ee without column purification. Chiral 3-amino-4-aryl-2-piperidone derivatives, which were prepared by multi-step procedures with chiral auxiliaries,[38-39] had been used as phenylalanine isosteres in Renin inhibitors design.[40]



Scheme 3 Synthesis of chiral substituted 3-amino piperidin-2-ones

The absolute configuration of **3q** was confirmed by X-ray single crystal diffraction analysis (Supporting Information), namely, with *(S)*-diphenyl prolinol silyl ether as the catalyst, trisubstituted chiral tetrahydro-2*H*-pyran-2-one obtained adopts a (3*S*,4*S*,6*S*) configuration, and all bulky groups are in equatorial orientations. According to the above results, a proposed catalytic cycle was shown in Scheme 4. As shown in the scheme, the TFA protection, together with a strong electron-withdrawing COBt group facilitates the formation of the active enol intermediate, which adopts a configuration constrained intermediate **I-1** because of a possible intramolecular hydrogen bond formed between Bt and N-H. Secondly, deprotonation of **I-1** by $\mathbf{A}^-$ formed during iminium active intermediate formation, generates enolate anion, which forms a compact ion pair **I-2** with iminium cation. The reaction occurs from the si face of the enolate to the si face of the iminium ion that builds the absolute configurations of C-3 and C-4 simultaneously. [37, 41] Finally, following an active amide hydrolyzation (**I-3**), lactonization and Bt substitution (**I-4**) procedure, the chiral 3,4,6-trisubstituted tetrahydro-2*H*-pyran-2-one is formed and the labile hemi-amino acetal structure in favor of the Bt group opt for a thermodynamic stable configuration.



Scheme 4 Proposed mechanism

In conclusion, an atom economical enantioselective organocatalysis has been developed for the synthesis of substituted 3-amino tetrahydro-2*H*-pyran-2-ones from readily available *N*-TFA-Gly-Bt and α,β-unsaturated aldehydes. The reaction presumably proceeded via a Michael addition/amide hydrolyzation/lactonization/Bt substitution process. The high level of diastereoselectivity and enantioselectivity might be determined by the compact ion pair **I-2** formed during the reaction. Enantioenriched 3-amino-piperidin-2-ones can be obtained following a one pot procedure without column purification. Extremely mild deprotection conditions for trifluoroacetamide endows the current method excellent compatibility with sensitive substrates. Developing more practical, catalytic, and enantioselective processes for the α-functionalization of inactive carbonyl compounds are in progress.

EXPERIMENTAL SECTION

General Information. All solvents and reagents were used as received without further purification. α,β-Unsaturated aldehydes were prepared according to reported procedures. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded at 400 MHz for ^{1}H and at 101

MHz for ^{13}C. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvents (DMSO-d_6 at 2.50 ppm ^{1}H NMR, 39.5 ppm $^{13}C\{^{1}H\}$ NMR, Acetone-d_6 at 2.05 ppm ^{1}HNMR, 29.92 ppm, 206.68 ppm $^{13}C\{^{1}H\}$ NMR). Coupling constants are given in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel plates. The products were purified by flash chromatography on silica gel (200-300 mesh). Organic solutions were concentrated under reduced pressure using a rotary evaporator. HPLC analyses on chiral stationary phase were performed on a DAICEL CHIRALPAK AD-H column with n-hexane/i-PrOH (7/3) as the eluent. Optical rotations were reported as follows: $[\alpha]_D^T$(c g/100 mL, solvent). HRMS (ESI or EI) was obtained with a HRMS instrument (LTQ Orbitrap XL TM).

Synthesis of TFANHCH$_2$COBt (1c) To a stirring solution of glycine (10 g, 130 mmol) and CH_3OH (100 mL) in a 250 mL round bottom flask, was added Et_3N (130 mmol, 18 mL) and ethyl trifluoroacetate (160 mmol, 19 mL) in sequence at room temperature. After stirring vigorously for three days, the solvent was removed under reduced pressure, and the resulting residue was dissolved in water (50 mL), acidified with concentrated aqueous hydrochloric acid until a pH of 2 was obtained. The mixture was then extracted with ethyl acetate (30 mL × 2), and the organic layers were combined. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to provide **TFANHCH$_2$COOH** as a white solid (18.71 g, 84% yield). Thionyl chloride (4.8 g, 41 mmol) was added to the 1*H*-benzotriazole (10.4 g, 85 mmol) dissolved in anhydrous dichloromethane (100 mL), and the solution was stirred at room temperature for 30 min. After cooling to -10 ℃, **TFANHCH$_2$COOH** (5.0 g, 29 mmol) was added, and the mixture was stirred at 20 ℃ for 2 h. The solvent was removed under reduced pressure, and the residue was dissolved in ethyl acetate (50 mL) followed by washing with saturated sodium carbonate (50 mL × 5) and brine (20 mL × 2) and drying with anhydrous Na_2SO_4. Evaporation of the solvent gave product **1c** as a white solid (5.7 g, 72% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.26 (t, *J* = 5.3 Hz, 1H), 8.23 (d, *J* = 8.3 Hz, 1H), 8.17 (d, *J* = 8.2 Hz, 1H), 7.77 (t, *J* = 7.6 Hz, 1H), 7.61 (t, *J* = 7.7 Hz, 1H), 5.16 (d, *J* = 5.6 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 167.4, 157.8 (q, *J* = 36.4 Hz), 145.7, 131.4, 130.9, 127.1, 120.6, 116.3 (q, *J* = 288.9 Hz), 114.0, 43.2. HRMS (ESI) m/z: [M-H$^+$] Calcd for $C_{10}H_6F_3N_4O_2$ 271.0448; Found 271.0454..

General Procedure for the synthesis of 3: To a solution of (*S*)-Jorgensen-Hayashi catalyst (0.05 mmol, 10% mol) in dry acetone (1 mL), was added *p*-methylbenzoic acid (0.05 mmol, 10% mol). The reaction mixture was stirred at room temperature for 30 min. Then **2a-q** (0.5 mmol) and **1c** (0.55 mmol, 1.1 eq) were added and the reaction mixture was stirred overnight. The crude residue was purified by column chromatography to afford the chiral product **3a-q**.

(3*S*,4*S*,6*S*)-3-*N*-TFA-6-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-4-(4-bromophenyl)-tetrahydro-2*H*-pyran-2-one (3a). Following the general procedure, **3a** was prepared from **2a** as white solid (140.4 mg, 58%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (d, *J* = 8.5 Hz, 1H), 8.17 (d, *J* = 8.3 Hz, 1H), 8.10 (d, *J* = 8.3 Hz, 1H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.58 (d, *J* = 7.4 Hz, 3H), 7.52 (t, *J* = 7.6 Hz, 1H),

7.42 (d, *J* = 8.1 Hz, 2H), 5.45–5.34 (m, 1H), 4.07 (m, 1H), 3.33–3.23 (m, 1H), 3.15–3.02 (m, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 167.3, 156.4 (q, *J* = 37.37 Hz), 145.1, 139.8, 132.7, 131.5, 130.0, 128.5, 125.0, 120.6, 119.5, 115.6 (q, *J* = 289.87 Hz), 111.2, 82.2, 53.3, 38.2, 32.1. Mp 145.2-146.0°C. $[\alpha]_D^{13}$ 60 (c 0.10, acetone). HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{15}BrF_3N_4O_3$ 483.0274; Found 483.0277.

(3*S*,4*S*,6*S*)-3-*N*-TFA-6-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-4-phenyltetrahydro-2*H*-pyran-2-one (3b). Following the general procedure, **3b** was prepared from **2b** as white amorphous solid (123 mg, 61%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (d, *J* = 8.5 Hz, 1H), 8.15 (d, *J* = 8.3 Hz, 1H), 8.10 (d, *J* = 8.3 Hz, 1H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.56– 7.47 (m, 2H), 7.45 (d, *J* = 7.4 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 2H), 7.27 (t, *J* = 6.9 Hz, 1H), 5.39 (dd, *J* = 11.6, 9.0 Hz, 1H), 4.07 (m,1H), 3.33–3.22 (m, 1H), 3.15–3.01 (m, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 167.5, 156.4 (q, *J* = 37.37 Hz), 145.2, 140.4, 132.8, 128.5, 128.4, 127.6, 127.4, 124.9, 119.4, 115.6 (q, *J* = 289.87 Hz), 111.2, 82.3, 53.5, 38.5, 32.4. $[\alpha]_D^{14}$ -2.8 (c 0.32, acetone). HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{16}F_3N_4O_3$ 405.1169; Found 405.1169.

(3*S*,4*S*,6*(R,S)*)-3-*N*-TFA-6-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-4-(2-chlorophenyl)-tetrahydro-2*H*-pyran-2-one (3c). Following the general procedure, **3c** was prepared from **2c** as white solid (135 mg, 62%, diastereomer mixture). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (d, *J* = 7.3 Hz, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 8.17 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.89 (d, *J* = 7.4 Hz, 1H), 7.70 (dd, *J* = 15.1, 7.1 Hz, 1H), 7.58–7.39 (m, 4H), 7.3–7.29 (m, 1H), 5.59 (dd, *J* = 11.5, 8.5 Hz, 1H), 4.68 (m, 1H), 3.67 (m, 1H), 2.98 (m, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 167.2, 156.5 (q, *J* = 37.37 Hz), 145.6, 137.6, 133.4, 132.0, 129.4, 129.0, 128.5, 127.8, 125.0, 119.6, 115.6 (q, *J* = 289.87 Hz), 111.2, 84.8, 54.5, 36.6, 32.0.

^{1}H NMR (400 MHz, DMSO-d_6) δ10.06 (d, *J* = 8.3 Hz, 1H), 8.17 (dd, *J* = 8.3, 2.1 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.70 (dd, *J* = 15.1, 7.1 Hz, 2H), 7.58–7.39 (m, 4H), 7.37 –7.29 (m, 1H), 5.15–5.01 (m, 1H), 4.49–4.33 (m, 1H), 3.33–3.21 (m, 1H), 2.69 (m, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 166.4, 156.5 (q, *J* = 37.37 Hz), 145.2, 137.4, 132.7, 129.6, 129.1, 128.8, 128.4, 127.6, 124.9, 119.4, 115.6 (q, *J* = 289.87 Hz), 111.1, 82.2, 52.2, 35.2, 31.9.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{15}ClF_3N_4O_3$ 439.0779; Found 439.0770.

(3*S*,4*S*,6*S*)-3-*N*-TFA-6-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-4-(3-chlorophenyl)-tetrahydro-2*H*-pyran-2-one (3d). Following the general procedure, **3d** was prepared from **2d** as white solid (131.4 mg, 60%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (d, *J* = 7.9 Hz, 1H), 8.17 (d, *J* = 8.2 Hz, 1H), 8.11 (d, *J* = 8.2 Hz, 1H), 7.70 (t, *J* = 7.1 Hz, 1H), 7.59 (s, 2H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.38 (d, *J* = 10.4 Hz, 3H), 5.63–5.25 (m, 1H), 4.07 (m, 1H), 3.31 (m, 1H), 3.11 (m, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 167.3, 156.4 (q, *J* = 37.37 Hz), 145.2, 142.8, 133.2, 132.8, 130.3, 128.4, 127.5, 127.5, 126.7, 124.9, 119.5, 115.6 (q, *J* = 288.86 Hz), 111.2, 82.2, 53.2, 38.4, 31.9. Mp 175.8-176.4°C. $[\alpha]_D^{13}$ 22.0 (c 0.30, acetone). HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{15}ClF_3N_4O_3$ 439.0779; Found 439.0783.

(3*S*,4*S*,6*S*)-3-*N*-TFA-6-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-4-(4-chlorophenyl)- tetrahydro-2*H*-pyran-2-one (3e). Following the general procedure, **3e** was prepared from **2e** as white solid (142 mg, 65%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (d, *J* = 8.6 Hz, 1H), 8.17 (d, *J* = 8.3 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.57 (t, *J* = 5.1 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.51–7.43 (m, 4H), 5.39 (dd, *J* = 12.0, 8.8 Hz, 1H), 4.08 (m, 1H), 3.27 (m, 1H), 3.09 (m, 1H). ^{13}C{^{1}H} NNMR (101 MHz, DMSO-d_6) δ 167.3, 156.4 (q, *J* = 37.37 Hz), 145.2, 139.3, 132.7, 132.1, 129.6, 128.5, 128.4, 124.9, 119.5, 115.6 (q, *J* = 288.86 Hz), 111.2, 82.2, 53.3, 38.1, 32.1. Mp 234.4-234.5^{o}C. $[\alpha]_D^{13}$ -4.4 (c 0.25, acetone). HRMS (ESI) m/z: $[M+H]^+$: Calcd for $C_{19}H_{15}ClF_3N_4O_3$ 439.0779; Found 439.0780.

(3*S*,4*S*,6*S*)-3-*N*-TFA-6-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-4-(3-cyanopheny)-tetrahydro-2*H*-pyran-2-one (3f). Following the general procedure, **3f** was prepared from **2f** as white amorphous solid (134 mg, 62%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (d, *J* = 7.9 Hz, 1H), 8.17 (d, *J* = 8.3 Hz, 1H), 8.12 (d, *J* = 8.3 Hz, 1H), 8.01 (s, 1H), 7.77 (t, *J* = 7.9 Hz, 2H), 7.74–7.68 (m, 1H), 7.65 (m, 1H), 7.59 (t, *J* = 7.7 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 5.53–5.40 (m, 1H), 4.11 (m, 1H), 3.38 (m, 1H), 3.13 (m, 1H). ^{13}C{^{1}H} NNMR (101 MHz, DMSO-d_6) δ 167.2, 156.4 (q, *J* = 36.36 Hz), 145.2, 141.9, 133.2, 132.8, 131.4, 131.3, 129.8, 128.4, 124.7, 119.5, 118.7, 115.6 (q, *J* = 289.87 Hz), 111.6, 111.1, 82.1, 53.1, 38.4, 31.8. $[\alpha]_D^{14}$ 11.3 (c 0.31, acetone). HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{15}F_3N_5O_3$ 430.1122; Found 430.1117.

(3*S*,4*S*,6*S*)-3-*N*-TFA-6-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-4-(4-cyanopheny)-tetrahydro-2*H*-pyran-2-one (3g). Following the general procedure, **3g** was prepared from **2g** as white amorphous solid (133 mg, 62%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (d, *J* = 8.6 Hz, 1H), 8.17 (d, *J* = 8.3 Hz, 1H), 8.11 (d, *J* = 8.3 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 2H), 7.70 (dd, *J* = 17.0, 7.9 Hz, 3H), 7.61 (t, *J* = 5.1 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 1H), 5.48 (dd, *J* = 12.1, 8.8 Hz, 1H), 4.20 (m, 1H), 3.38–3.34 (m, 1H), 3.14 (m, 1H). ^{13}C{^{1}H} NNMR (101 MHz, DMSO-d_6) δ 167.1, 156.4 (q, *J* = 36.36 Hz), 145.9, 145.1, 132.7, 132.5, 128.9, 128.4, 124.9, 119.4, 118.6, 115.5 (q, *J* = 289.87 Hz), 111.1, 110.4, 82.1, 52.9, 38.8, 31.8. $[\alpha]_D^{14}$ 36.7 (c 0.27, acetone). HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{15}F_3N_5O_3$ 430.1122; Found 430.1113.

(3*S*,4*S*,6*S*)-3-*N*-TFA-6-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-4-(4-nitrophenyl)-tetrahydro-2*H*-pyran-2-one (3h). Following the general procedure, **3h** was prepared from **2h** as white solid (120 mg, 53%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02 (d, *J* = 8.2 Hz, 1H), 8.27 (d, *J* = 8.5 Hz, 2H), 8.19 (d, *J* = 12.4 Hz, 1H), 8.11 (d, *J* = 8.3 Hz, 1H), 7.81–7.72 (m, 3H), 7.62 (t, *J* = 5.0 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 5.52 (dd, *J* = 11.6, 8.3 Hz, 1H), 4.27 (m 1H), 3.33–3.26 (m, 1H), 3.16 (m, 1H). ^{13}C{^{1}H} NNMR (101 MHz, DMSO-d_6) δ 167.0, 156.4 (q, *J* = 37.37 Hz), 148.0, 146.9, 145.1, 132.7, 129.2, 128.5, 124.9, 123.7, 119.5, 115.5 (q, *J* = 288.86 Hz), 111.1, 82.2, 52.9, 38.6, 31.8. Mp 117.7-119.4^{o}C. $[\alpha]_D^{14}$ 27.3 (c 0.22, acetone). HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{15}F_3N_5O_5$ 450.1020; Found 450.1018.

(3*S*,4*S*,6*S*)-3-*N*-TFA-6-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-4-([1,1'-biphenyl]-4-yl)tetrahydro-2*H*-pyran-2-one (3i). Following the general procedure, **3i** was prepared from **2i** as white solid (107 mg, 45%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (d, *J* = 8.5 Hz,

1H), 8.16 (d, *J* = 8.3 Hz, 1H), 8.11 (d, *J* = 8.3 Hz, 1H), 7.68 (m, 5H), 7.59 (t, *J* = 4.9 Hz, 1H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.2 Hz, 1H), 5.44 (dd, *J* = 11.6, 9.0 Hz, 1H), 4.15 (m, 1H), 3.31 (m, 1H), 3.13 (m, 1H). $^{13}C\{^{1}H\}$ NNMR (101 MHz, DMSO-d_6) δ 167.5, 156.5 (q, *J* = 36.36 Hz), 145.2, 139.7, 139.6, 139.2, 132.8, 128.9, 128.4, 128.3, 127.5, 126.8, 126.6, 124.9, 119.5, 115.7 (q, *J* = 289.87 Hz), 111.2, 82.3, 53.5, 38.2, 32.4. Mp 211.0-212.9°C. $[\alpha]_D^{14}$ 5.9 (c 0.29, acetone). HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{25}H_{20}F_3N_4O_3^+$ 481.1482; Found 481.1489.

(3*S*,4*S*,6*S*)-3-*N*-TFA-6-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-2-one (3j). Following the general procedure **3j** was prepared from **2j** as white solid (121 mg, 56%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (d, *J* = 8.6 Hz, 1H), 8.17 (d, *J* = 8.3 Hz, 1H), 8.11 (d, *J* = 8.3 Hz, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.54 (m, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 6.93 (d, *J* = 8.5 Hz, 2H), 5.34 (dd, *J* = 11.6, 8.9 Hz, 1H), 4.03 (m, 1H), 3.74 (s, 3H), 3.30–3.21 (m, 1H), 3.07 (m, 1H). $^{13}C\{^{1}H\}$ NNMR (101 MHz, DMSO-d_6) δ 167.6, 158.5, 156.4 (q, *J* = 37.37 Hz), 145.2, 132.8, 132.3, 128.7, 128.4, 124.9, 119.4, 115.6 (q, *J* = 288.86 Hz), 113.9, 111.2, 82.3, 55.1, 53.7, 37.8, 32.6. Mp 168.2-170.3°C. $[\alpha]_D^{13}$ 6.6 (c 0.35, acetone). HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{18}F_3N_4O_4$ 435.1275; Found 435.1272.

(3*S*,4*S*,6*S*)-3-*N*-TFA-6-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-4-(4-(naphthalen-2-yloxy)phenyl)tetrahydro-2*H*-pyran-2-one (3k). Following the general procedure **3k** was prepared from **2k** as white solid (140 mg, 51%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (d, J = 8.7 Hz, 1H), 8.16 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 8.6 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.74–7.65 (m, 2H), 7.58 (s, 1H), 7.53–7.39 (m, 5H), 7.28 – 7.26 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.6 Hz, 2H), 5.40 (dd, J = 12.0, 8.8 Hz, 1H), 4.14–4.00 (m, 1H), 3.32 (m, 1H), 3.14 (m 1H). $^{13}C\{^{1}H\}$ NNMR (101 MHz, DMSO-d_6) δ 167.5, 156.4 (q, J = 37.37 Hz), 155.6, 154.9, 145.2, 135.8, 133.9, 132.8, 130.1, 129.7, 129.5, 128.4, 127.7, 126.9, 126.7, 124.9, 124.8, 119.5, 119.3, 115.7 (q, J = 288.86 Hz), 113.1, 111.2, 82.3, 53.7, 38.1, 32.1. Mp 112.6-113.4°C. $[\alpha]_D^{14}$ 49.6 (c 0.25, acetone). HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{29}H_{22}F_3N_4O_4$ 547.1588; Found 547.1587.

(3*S*,4*S*,6*S*)-3-*N*-TFA-6-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-4-(3,4-dichlorostyryl)-tetrahydro-2*H*-pyran-2-one (3l). Following the general procedure **3l** was prepared from **2l** as white solid (127 mg, 51%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.03 (d, *J* = 8.1 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 8.07 (d, *J* = 8.2 Hz, 1H), 7.74–7.66 (m, 2H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.39 (d, *J* = 8.1 Hz, 1H), 6.55 (d, *J* = 15.8 Hz, 1H), 6.44 (dd, *J* = 15.9, 8.4 Hz, 1H), 5.19–4.92 (m, 1H), 3.54 (m,1H), 3.21 (m, 1H), 2.85 (m, 1H). $^{13}C\{^{1}H\}$ NNMR (126 MHz, DMSO-d_6) δ 166.9, 156.4 (q, *J* = 37.37 Hz), 145.1, 137.3, 132.6, 131.7, 131.4, 130.8, 129.9, 129.3, 128.5, 127.8, 126.3, 124.9, 119.5, 115.7 (q, *J* = 288.86 Hz), 111.0, 81.9, 52.0, 37.1, 30.7. Mp 177.7-179.1°C. $[\alpha]_D^{13}$ 4.3 (c 0.30, acetone). HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{16}Cl_2F_3N_4O_3$ 499.0546; Found 499.0541.

(3*S*,4*S*,6*S*)-3-*N*-TFA-6-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-4-(3,4-dichlorophenyl)-tetrahydro-2*H*-pyran-2-one (3m). Following the general procedure **3m** was prepared from **2m** as white solid (105 mg, 44%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (d, *J* = 8.6 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.81 (s, 1H), 7.76–7.61 (m, 3H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.46 (dd, *J* =

8.4, 1.9 Hz, 1H), 5.46 (dd, *J* = 12.1, 8.7 Hz, 1H), 4.18–4.06 (m, 1H), 3.34 (m, 1H), 3.14 (m, 1H). $^{13}C\{^{1}H\}$ NNMR (101 MHz, DMSO-d_6) δ 167.1, 156.5 (q, *J* = 36.36 Hz), 145.2, 141.4, 132.8, 131.2, 130.6, 130.1, 129.8, 128.4, 128.4, 124.9, 119.4, 115.6 (q, *J* = 288.86 Hz), 111.1, 82.1, 53.1, 38.0, 31.8. Mp 226.2-228.4°C. $[\alpha]_D^{14}$ 43.3 (c 0.30, acetone). HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{14}Cl_2F_3N_4O_3$ 473.0390; Found 473.0384.

(3*S*,4*S*,6*S*)-3-*N*-TFA-6-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-4-(3,5-dichlorophenyl)-tetrahydro-2*H*-pyran-2-one (3n). Following the general procedure **3n** was prepared from **2n** as white solid (115 mg, 49%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (d, *J* = 8.2 Hz, 1H), 8.12 (dd, *J* = 19.0, 8.2 Hz, 2H), 7.68-7.62 (m, 2H), 7.51 (dd, *J* = 15.2, 7.9 Hz, 4H), 5.51–5.39 (dd, *J* = 12.1, 8.7 Hz, 1H), 4.05 (m, 1H), 3.38 (m, 1H), 3.10 (m, 1H). $^{13}C\{^{1}H\}$ NNMR (101 MHz, DMSO-d_6) δ 167.6, 156.9 (q, *J* = 37.37 Hz), 145.6, 144.9, 134.6, 133.2, 128.9, 127.7, 127.3, 125.4, 119.9, 115.6 (q, *J* = 288.86 Hz), 111.6, 82.5, 53.5, 38.8, 32.0. Mp 235.0-236.6°C. $[\alpha]_D^{14}$ 30.0 (c 0.30, acetone). HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{14}Cl_2F_3N_4O_3$ 473.0390; Found 473.0394.

(3*S*,4*S*,6*S*)-3-*N*-TFA-6-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-4-(3,5-bis(trifluoromethyl)-henyl)tetrahydro-2*H*-pyran-2-one (3o). Following the general procedure **3o** was prepared from **2o** as white solid (148 mg, 55%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.03 (d, *J* = 8.6 Hz, 1H), 8.18 (s, 3H), 8.14 (d, *J* = 8.4 Hz, 1H), 8.06 (s, 1H), 7.71 (dd, *J* = 14.6, 6.7 Hz, 2H), 7.54 (t, *J* = 7.6 Hz, 1H), 5.56 (dd, *J* = 11.8, 9.0 Hz, 1H), 4.27 (dd, *J* = 19.8, 8.5 Hz, 1H), 3.47 (m, 1H), 3.30–3.20 (m, 1H). $^{13}C\{^{1}H\}$ NNMR (101 MHz, DMSO-d_6) δ167.0, 156.4 (q, *J* = 37.37 Hz), 145.2, 143.4, 132.7, 130.4 (q, *J* = 33.33 Hz), 129.08, 128.5, 124.8 (q, *J* = 37.37 Hz), 121.9, 121.4, 119.5, 115.5 (q, *J* = 288.86 Hz), 111.1, 82.0, 52.9, 38.6, 31.1. Mp 221.6-223.0°C. $[\alpha]_D^{14}$ 42.4 (c 0.34, acetone). HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{14}F_9N_4O_3$ 541.0917; Found 541.0911.

(3*S*,4*R*,6*S*)-3-*N*-TFA-6-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-4-(furan-2-yl)tetrahydro-2*H*-pyran-2-one (3p). Following the general procedure **3p** was prepared from **2p** as white solid (106.4 mg, 54%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.04 (d, *J* = 8.5 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.69 (t, *J* = 7.7 Hz, 1H), 7.63 (d, *J* = 1.2 Hz, 1H), 7.54–7.43 (m, 2H), 6.43 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.35 (d, *J* = 3.2 Hz, 1H), 5.29 (dd, *J* = 11.6, 8.5 Hz, 1H), 4.20 (m, 1H), 3.30 (m, 1H), 3.05 (m, 1H). $^{13}C\{^{1}H\}$ NNMR (101 MHz, DMSO-d_6) δ 166.8, 156.4 (q, *J* = 37.37 Hz), 153.1, 145.2, 142.8, 132.7, 128.5, 125.0, 119.5, 115.7 (q, *J* = 288.86 Hz), 111.1, 110.5, 106.7, 81.9, 51.9, 32.8, 30.1. Mp 191.9-193.1°C. $[\alpha]_D^{13}$ -1.3 (c 0.23, acetone). HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{14}F_3N_4O_4$ 395.0962; Found 395.0963.

(3*S*,4*S*,6*S*)-3-*N*-TFA-6-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-4-(ferrocenyl)tetrahydro-2*H*-pyran-2-one (3q). Following the general procedure **3q** was prepared from **2q** as white solid (69 mg, 27%). ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.95 (d, *J* = 8.5 Hz, 0.5H), 8.13 (d, *J* = 8.3 Hz, 1H), 8.04 (d, *J* = 8.3 Hz, 1H), 7.68 (t, *J* = 7.7 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.46 (t, *J* = 4.9 Hz, 1H), 4.89–4.76 (m, 1H), 4.37 (d, *J* = 30.6 Hz, 2H), 4.25 (s, 5H), 4.19 (d, *J* = 12.6 Hz, 2H), 3.90–3.77 (m, 2H), 3.33 (m, 1H). $^{13}C\{^{1}H\}$ NNMR (101 MHz, Acetone-d_6) δ 166.7, 157.0 (q, *J* = 36.36 Hz), 146.2, 133.4, 128.6, 125.0 119.9, 116.3 (q, *J* = 287.85 Hz), 111.1, 88.3,

83.2, 69.1, 68.8, 68.3, 68.0, 65.4, 55.6, 34.2, 32.0. Mp 150.0-151.1°C. $[\alpha]_D^{13}$ -1.3 (c 0.23, acetone). HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{23}H_{20}F_3FeN_4O_3$ 513.0831; Found 513.0834.

Synthesis of chiral substituted 3-amino piperidin-2-ones (5i): Into a 25 mL round bottom flask were placed **3i** (66 mg, 0.14 mmol) and a solution of NH_3/CH_3OH (2 M, 5 mL). The mixture was stirred at room temperature for 2h, then the solvent was removed under reduced pressure to provide crude **4i**, which was re-dissolved in 5 mL CH_2Cl_2. The solution was cooled to −10 ℃, Et_3SiH (9.3 mmol, 1.5 mL) and BF_3OEt_2 (8 mmol, 1 mL) were added dropwise in sequence. After the consumption of the starting material (monitored by TLC), the reaction was quenched with saturated aqueous Na_2CO_3 (20 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (10 mL × 3). The combined organic extracts were dried over Na_2SO_4. After removal of solvent the residue was chromatographed on silica gel (CH_2Cl_2/CH_3OH=50/1) to give **5i** (40 mg, 0.11 mmol) as a white solid in 80% yield and 97% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.50 (d, *J* = 8.8 Hz, 1H), 7.90 (s, 1H), 7.65 (d, *J* = 7.3 Hz, 2H), 7.60 (d, *J* = 8.2 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.38–7.32 (m, 3H), 4.43 (dd, *J* = 11.4, 9.0 Hz, 1H), 3.32–3.16 (m, 3H), 2.27 (qd, *J* = 12.8, 5.8 Hz, 1H), 1.95 (t, *J* = 12.5 Hz, 1H). ^{13}C{^{1}H} NNMR (101 MHz, DMSO-d_6) δ167.8, 156.1 (q, *J* = 36.36 Hz), 141.2, 139.7, 138.4, 128.9, 127.9, 127.3, 126.5, 126.4, 115.8 (q, *J* = 289.87 Hz), 54.9, 42.7, 40.6, 29.1. Mp 202.5-204.5°C. $[\alpha]_D^{13}$ -71.2 (c 0.38, CH_3OH). HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{18}F_3N_2O_2$ 363.1315; Found 363.1310.

Synthesis of chiral substituted 3-amino piperidin-2-ones (5c): Into a 25 mL round bottom flask were placed **3c** (80 mg, 0.18 mmol) and a solution of NH_3/CH_3OH (2 M, 5 mL). The mixture was stirred at room temperature for 2h, then the solvent was removed under reduced pressure to provide crude **4c**, which was re-dissolved in 5 mL CH_2Cl_2. The solution was cooled to −10 ℃, Et_3SiH (9.3 mmol, 1.5 mL) and BF_3OEt_2 (8 mmol, 1 mL) were added dropwise in sequence. After the consumption of the starting material (monitored by TLC), the reaction was quenched with saturated aqueous Na_2CO_3 (20 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (10 mL × 3). The combined organic extracts were dried over Na_2SO_4. After removal of solvent the residue was washed with minimum amount of dichloromethane to afford pure **5c** as a white powder (40 mg) in 70% yield and > 99% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.0 Hz, 1H), 7.31 (dt, *J* = 15.1, 6.8 Hz, 2H), 7.24–7.19 (m, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 6.42 (s, 1H), 4.72–4.57 (m, 1H), 3.86 (m, 1H), 3.63–3.51 (m, 1H), 3.51–3.42 (m, 1H), 2.21 (m, 2H). ^{13}C{^{1}H} NNMR (101 MHz, $CDCl_3$) δ 169.3, 157.6 (q, *J* = 38.38 Hz), 137.3, 133.9, 129.9, 128.8, 127.6, 127.5, 115.6 (q, *J* = 289.87 Hz), 55.0, 41.3, 40.0, 28.9. Mp 189.4-190.4°C. $[\alpha]_D^{13}$ -71.2 (c 0.38, CH_3OH). HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{13}H_{13}ClF_3N_2O_2$ 321.0612; Found 321.0607..

Deprotection procedure: method A: To a 25 mL round bottom flask, was added **5i** (80 mg, 0.22 mmol, 96% ee), K_2CO_3 (3 equiv.), methanol (3 mL) and H_2O (0.5 mL). The resulting solution was stirred at 70℃ for 12 hours. After cooling to room temperature and removing solvent, the reaction was diluted with dichloromethane (80 mL), washed with brine (10 mL × 2) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave (3*S*,4*S*)-4-([1,1'-biphenyl]-4-yl)-3-aminopiperidin-2-one as a white solid (40

mg, 67% yield, 83% ee). **Method B: 5i** (10 mg, 0.028 mmol) was dissolved in CH_3OH (0.6 mL) and concentrated HCl (0.5 mL).The resulting solutions were then stirred at 70℃ for 5 hours. After cooling to room temperature and removing solvent, the mixture was extracted with dichloromethane (3 mL × 3) and saturated sodium bicarbonate (4 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and the solvent was removed under reduced pressure to provide (3*S*,4*S*)-4-([1,1'-biphenyl]-4-yl)-3-aminopiperidin-2-one (>99% ee).

^{1}HNMR (400 MHz, MeOD) δ 7.66-7.60 (m, 4H), 7.43 (dd, *J* = 15.4, 7.7 Hz, 4H), 7.38–7.30 (m, 1H), 3.66 (d, *J* = 10.6 Hz, 1H), 3.51-3.36 (m, 2H), 2.96 (t, *J* = 10.3Hz, 1H), 2.21 (m 1H), 2.01 (d, *J* = 13.5Hz, 1H). ^{13}C{^{1}H} NNMR (101 MHz, MeOD) δ 173.4, 141.2, 140.5, 139.9, 128.4, 127.4, 127.0, 126.9, 126.4, 55.7, 45.9, 40.9, 29.1. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{17}H_{18}N_2O$ 266.1419; Found 266.1422.

SUPPORTING INFORMATION

^{1}HNMR and ^{13}CNMR spectra; HPLC for all new compounds and X-ray Crystallographic Data of 3q.

ACCESSION CODES

CCDC 1912111 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from http://www.ccdc.cam.ac.uk/data_request/cif, by contacting data_ request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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