Enantioselective synthesis of 5-trifluoromethyl-2-oxazolines under dual silver/organocatalysis

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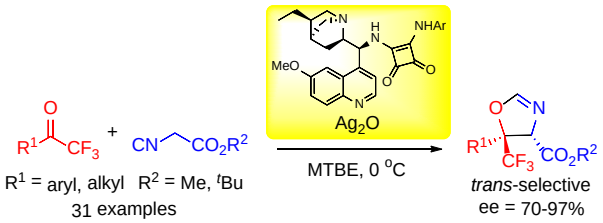


ABSTRACT: The first enantioselective formal [3+2] cycloaddition between α-isocyanoesters and trifluoromethylketones to give 5-trifluoromethyl-2-oxazolines bearing two contiguous stereogenic centers, one of them being a quaternary stereocenter substituted with a CF_3 group has been developed. The reaction is based upon a multicatalytic approach that combines a bifunctional Brønsted base-squaramide organocatalyst and Ag^+ as Lewis acid. The reaction could be achieved with a range of aryl and heteroaryl trifluoromethyl ketones and the resulting oxazolines were obtained with good to excellent diastereo- and enantioselectivity**.**

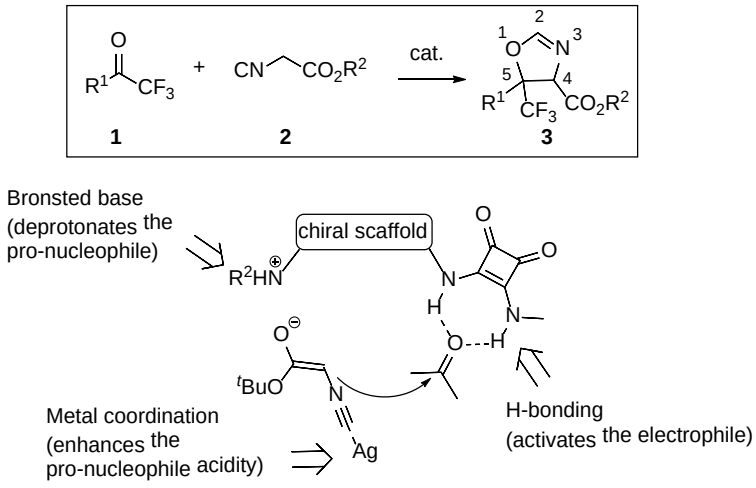
INTRODUCTION

The 2-oxazoline moiety is present in a large number of natural products, drugs and bioactive compounds.[1] Chiral oxazolines have also found important applications in organic synthesis as ligands in asymmetric catalysis,[2] as well as synthetic intermediates for 1,2-aminoalcohols and other relevant compounds.[3] In recent years, the enantioselective formal [3+2] cycloaddition of α-isocyanoesters with carbonyl compounds has emerged as an elegant and powerful strategy for the construction of chiral substituted 2-oxazolines bearing two adjacent stereocenters and considerable success on this reaction has been obtained with aldehydes[4] and, in less extent, with ketones.[5]

On the other hand, the introduction of trifluoromethyl substituents[6] into organic molecules has attracted great attention in the field of medicinal chemistry because of the significant impact of the trifluoromethyl group on the metabolic stability and bioavailability of drugs.[7] For these reasons, different strategies have been devised for the synthesis of trifluoromethylated heterocycles, involving either the trifluoromethylation of non-fluorinated heterocycles[8] or cycloaddition/cyclization reactions from trifluoromethylated building blocks.[9] In this context, the 5-trifluoromethyl-2-oxazoline moiety is especially appealing as it is a synthetic precursor for fluorinated non-proteinogenic amino acids and trifluoromethyl amino alcohols, which have important applications in medicinal chemistry[10] and biochemical studies,[11] and as conformational modifiers in physiologically active proteins and enzymes.[12]

Herein we report the enantioselective formal [3+2] cycloaddition between α-isocyanoesters and trifluoromethylketones to give 5-trifluoromethyl-2-oxazolines bearing two contiguous stereogenic centers, one of them being a quaternary stereocenter substituted with a CF_3 group (Scheme 1). Although such reaction has been diastereoselectively performed, a catalytic asymmetric version has not been developed so far, to the best of our knowledge.[13]

Scheme 1. Formal [3+2] cycloaddition between trifluoromethylketones and α-isocyanoesters, and plausible mode of action of the catalyst.

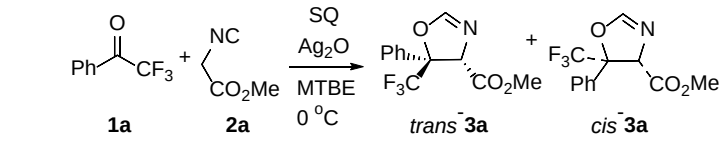


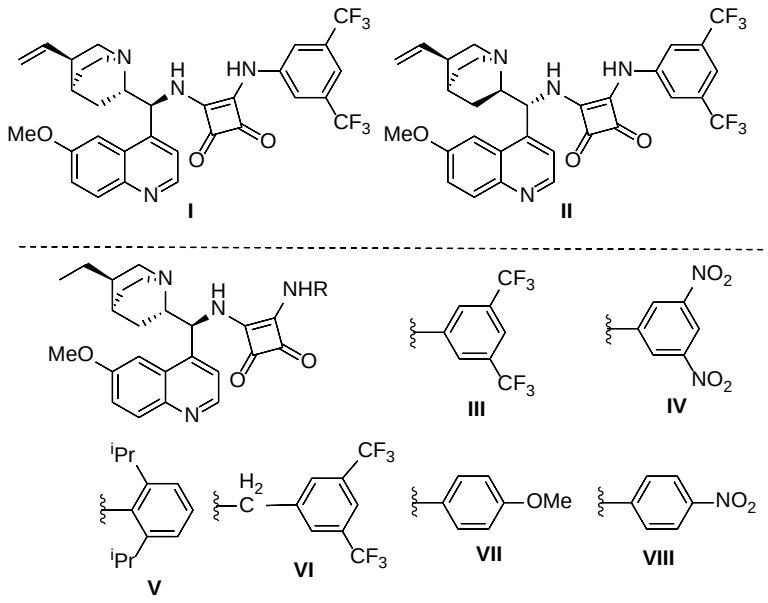
RESULTS AND DISCUSSION

Recently, based on a cooperative strategy previously reported by Escolano et al. for the asymmetric cycloaddition of isocyanoacetates with vinyl ketones,[14] our group developed a highly catalytic enantioselective cycloaddition reaction between ketones and α-

isocyanoesters using a multicatalytic approach that combined a bifunctional Brønsted base-squaramide organocatalyst and Ag^+ as Lewis acid (Scheme 1).[5d]

Table 1. Bifunctional squaramide screening[a]





Entry	**SQ**	*t* (h)	Yield (%)[b]	*trans:cis*[c]	$ee_{trans/cis}$ (%)[d]
1[e]	**I**	72	-	-	-
2	**I**	0.5	>95	99:1	77/57
3	**II**	0.5	85	99:1	-66/-28[f]
4	**III**	0.5	>95	95:5	83/61
5	**IV**	17	>95	95:5	81/56
6	**V**	0.5	50	100:--	67/--
7	**VI**	5	>95	50:50	29/70
8	**VII**	0.5	>95	85:15	58/33
9	**VIII**	0.5	>95	79:21	78/65

[a] **1a** (0.25 mmol), **2a** (0.33 mmol), **SQ** (0.026 mmol), Ag_2O (0.0125 mmol), MTBE (2 mL), 0 °C. [b] Yield of isolated product. [c] Determined by ^1H NMR. [d] Determined by HPLC over chiral chromatography phases. [e] Reaction carried out in absence of silver salt. No advance was observed after the indicated time. [f] The opposite enantiomer was obtained.

Following this approach,[14] we tested the reaction of trifluoroacetophenone (**1a**) and methyl isocyanoacetate (**2a**) in the presence of several bifunctional squaramides (**SQ**, 10 mol %) and Ag_2O (5 mol %) in methyl *tert*-butyl ether (MTBE) at 0 °C (Table 1, see also Tables S1-S3 in SI). The reaction did not proceed in the absence of Ag_2O (Table 1, entry 1). On the other hand, all the squaramides tested in combination with silver oxide provided oxazoline **3a** in good yields and in a short reaction time. The *trans* diastereomer was obtained diastereoselectively in all the cases except with squaramide **VI** (Table 1, entry 7). The best result in terms of enantioselectivity was obtained with squaramide **III**, derived from dihydroquinine and 3,5-bis(trifluoromethyl)aniline, that provided oxazoline **3a** in almost quantitative yield with 95:5 dr and 83% ee for the major diastereomer (Table 1, entry 4).

A strong concentration effect was also found, the diastereo- and enantioselectivity of the reaction increasing with the dilution of the reaction mixture (Table 2, entries 1-3). The use of 1:2 squaramide/Ag_2O ratio increased the diastereoselectivity but unfortunately lowered the enantioselectivity (Table 2, entry 4). Notably, the use of a 1:1 squaramide/Ag_2O mixture provided similar results to the initially tested 2:1 mixture, being possible to reduce the catalyst load to 2.5 mol % without noticeable effect on the stereoselectivity (Table 2, entries 3 and 5).

Table 2. Effect of concentration and squaramide/Ag_2O ratio[a]

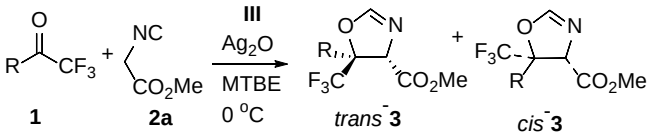
Entry	[**1a**][b]	**III**:Ag_2O	*t* (h)	Yield(%)[c]	*trans:cis*[d]	ee_{trans}(%)[e]
1	0.13	2:1	0.5	>95	95:5	83
2	0.26	2:1	0.5	>95	87:13	75
3	0.033	2:1	4	>95	96:4	90
4[f]	0.033	1:2	3	90	99:1	82
5[g]	0.033	1:1	18	>95	94:6	90

[a] **1a** (0.25 mmol), **2a** (0.33 mmol), **III** (0.026 mmol), Ag_2O (0.0125 mmol), MTBE, 0 °C. [b] Molar concentration. [c] Yield of isolated product. [d] Determined by ^{1}H NMR. [e] Determined by HPLC over chiral chromatography phases. [f] **III** (0.0065 mmol). [g] **III** (0.0033 mmol).

Under the optimized conditions, the scope of the reaction of methyl isocyanoacetate (**2a**) and several substituted trifluoroacetophenones **1** was studied (Table 3).[15] In general, the presence of substituents at the *ortho* or *para* positions of the aromatic ring brought about some decrease of enantioselectivity whilst the *meta*-substituted

trifluoroacetophenones gave similar or higher enantiomeric excesses than ketone **1a** (Table 3, entries 5-7). A negative effect of electron-withdrawing groups on the diastereoselectivity was also observed (Table 3, entries 4, 9 and 10). The heterocyclic trifluoroacetylthiophene (**1k**) proved to be a suitable substrate that reacted with good diastereo- and enantioselectivity (Table 2, entry 11). Alkyl-substituted trifluoromethylketones **1l** and **1m** were also tested, which provided oxazolines **3l** and **3m**, respectively, with moderate diastereo- and enantioselectivity (Table 2, entries 12 and 13). Finally, the reaction was scaled up to 1.25 mmol of compound **1a**, obtaining oxazoline **3a** without any noticeable loss of efficiency, indicating the robustness of the method (Table 3, entry 14).

Table 3. Enantioselective reaction of trifluoromethylketones and methyl isocyanoacetate. Substrate scope[a]

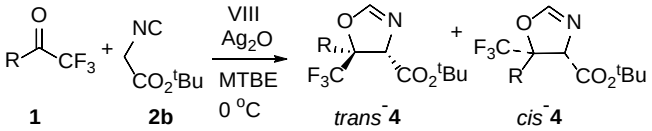


Entry	**1**	R	*t* (h)	**3**	yield (%)[b]	*trans:cis*[c]	ee$_{trans}$ (%)[d]
1	**1a**	Ph	4	**3a**	>95	96:4	90
2	**1b**	4-MeC_6H_4	5	**3b**	>95	94:6	87
3	**1c**	4-MeOC_6H_4	3.5	**3c**	88	96:4	85
4	**1d**	4-ClC_6H_4	4	**3d**	>95	80:20	84
5	**1e**	3-MeC_6H_4	5	**3e**	>95	94:6	90
6	**1f**	3-MeOC_6H_4	4	**3f**	94	92:8	88
7	**1g**	3-BrC_6H_4	3.5	**3g**	95	86:14	92
8	**1h**	2-MeOC_6H_4	16	**3h**	>95	99:1	85
9	**1i**	2-BrC_6H_4	14	**3i**	93	85:15	70
10	**1j**	3,4-$Cl_2C_6H_3$	16	**3j**	>95	77:23	85
11	**1k**	2-thienyl	5.5	**3k**	>95	92:8	90
12	**1l**	$PhCH_2CH_2$	15	**3l**	66	86:14	81
13	**1m**	CH_3	7	**3m**	80	92:8	82
14[e]	**1a**	Ph	2	**3a**	>95	92:8	90

[a] **1a** (0.25 mmol), **2a** (0.33 mmol), **III** (0.0063 mmol), Ag_2O (0.0063 mmol), MTBE (8 mL), 0 °C. [b] Yield of isolated product. [c] Determined by ^{1}H NMR. [d] Determined by HPLC over chiral chromatography phases. [e] Reaction scaled up to 1.25 mmol of **1a**.

The configuration of the stereogenic centers in compound *trans*-**3g** was determined as (4*S*,5*S*) after hydrolysis and X-ray analysis of the resulting amino alcohol **7g** (Scheme 2).[16] For the remaining compounds **3**, the stereochemistry was assigned under the assumption of a uniform mechanistic pathway.[17]

Table 4. Enantioselective reaction of trifluoromethylketones and *tert*-butyl isocyanoacetate. Substrate scope[a]



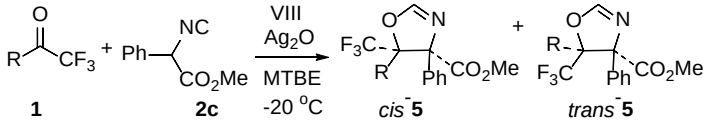
Entry	**1**	R	*t* (d)	**4**	Yield (%)[b]	*trans:cis*[c]	ee$_{trans/cis}$ (%)[d]
1	**1a**	Ph	1	**4a**	>95	70:30	96/90
2	**1b**	4-MeC_6H_4	7	**4b**	87	66:34	93/96
3	**1c**	4-MeOC_6H_4	7	**4c**	>95	63:37	84/77
4	**1d**	4-ClC_6H_4	1	**4d**	>95	53:47	96/90
5	**1e**	3-MeC_6H_4	6	**4e**	94	76:24	97/87
6	**1f**	3-MeOC_6H_4	4	**4f**	84	72:28	97/85
7	**1g**	3-BrC_6H_4	1	**4g**	>95	64:36	97/90
8	**1h**	2-MeOC_6H_4	12	**4h**	80	94:6	94/70
9	**1i**	2-BrC_6H_4	3	**4i**[e]	>95	99:1	91/nd
10	**1j**	3,4-$Cl_2C_6H_3$	1	**4j**	>95	53:47	94/85
11	**1k**	2-thienyl	1	**4k**	>95	62:38	97/91
12	**1l**	CH_2CH_2Ph	1	**4l**	83	72:28	84/87

[a] **1** (0.25 mmol), **2b** (0.33 mmol), **VIII** (0.0063 mmol), Ag_2O (0.0063 mmol), MTBE (8 mL), 0 °C. [b] Yield of isolated product. [c] Determined by ^{1}H NMR. [d] Determined by HPLC over chiral chromatography phases. [e] Structure determined by X-ray analysis (see ref. 16).

Next, we tested the performance of other isocyano esters having different alkoxy groups (see Table S4 in SI). *tert*-Butyl isocyanoacetate seemed to promote the highest enantioselectivity using squaramide **VIII** instead of **III**. The reaction of trifluoromethylketones **1** with *tert*-butyl isocyanoacetate (**2b**) showed a similar substrate scope as the reaction with the methyl ester. In general the reaction took place with moderate to good diastereoselectivity and high to excellent enantioselectivity for the major diastereomer (Table 4). X-Ray analysis of compound **4i**[16] allowed us to assign the

absolute sterochemistry of compounds **4** as (4*S*,5*S*), indicating a similar stereochemical pathway as the reaction with methyl isocyanoacetate.[17]

Table 5. Enantioselective reaction of trifluoromethylketones and methyl 2-isocyano-2-phenylacetate. Substrate scope[a]



Entry	**1**	R	*t* (d)	**5**	Yield (%)[b]	*trans:cis*[c]	ee$_{cis}$ (%)[d]
1	**1a**	Ph	1	**5a**	89	15:85	90
2	**1c**	4-MeOC$_6$H$_4$	3	**5c**	42	21:79	89
3	**1d**	4-ClC$_6$H$_4$	1	**5d**	>95	10:90	89
4	**1n**	4-BrC$_6$H$_5$	2	**5n**	82	13:87	89
5	**1e**	3-MeC$_6$H$_4$	1	**5e**	86	1:99	90
6	**1f**	3-MeOC$_6$H$_4$	3	**5f**	86	15:85	89
7	**1g**	3-BrC$_6$H$_4$	7	**5g**	81	2:98	88
8	**1h**	2-MeOC$_6$H$_4$	5	**5h**	-[e]	-	-

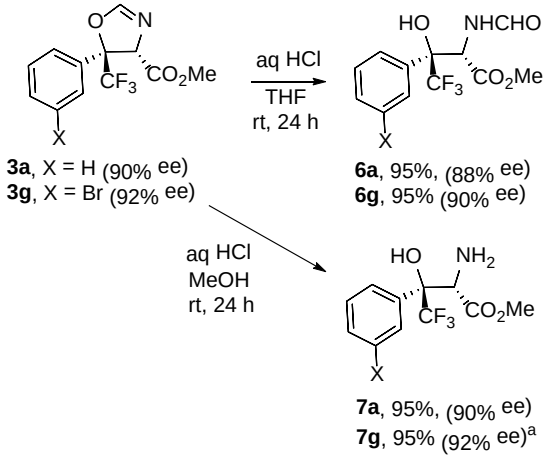
[a] **1** (0.25 mmol), **2c** (0.33 mmol), **VIII** (0.0125 mmol), Ag_2O (0.0063 mmol), MTBE (2 mL), –20 °C. [b] Yield of isolated product. [c] Determined by ^{1}H NMR. [d] Determined by HPLC over chiral chromatography phases. [e] No advance observed after 5 days.

Finally, the reaction of several trifluoromethylketones **1** with methyl 2-isocyano-2-phenylacetate (**2c**) to give oxazolines **5** bearing two contiguous quaternary stereocenters was achieved in the presence of squaramide **VIII** and Ag_2O (Table 5).[18] In this case, the reaction worked better under higher concentration and with a 2:1 ratio of squaramide/Ag_2O and yielded the *cis* diastereomer as the major one.[17] Fair to good diastereomeric ratios and high enantiomeric excesses were obtained for trifluoroacetophenone derivatives having electron-donating or slightly electron-withdrawing groups. However, the reaction did not proceed with *ortho*-substituted trifluoroacetophenones.

Tosylmethylisocyanide (TOSMIC) was also tested in the reaction with trifluoromethylketone **1a**, although, unfortunately, no reaction was observed under any of the optimized conditions.

The prepared oxazolines are synthetic precursors for trifluoromethylated amino alcohols. Thus, treatment of oxazolines **3a** or **3g** with aqueous HCl in THF gave almost quantitative yields of hydroxyformamides **6a** or **6g**, respectively, with a minor decrease of ee. On the other hand, treatment of **3a** or **3g** with aqueous hydrochloric acid in MeOH yielded amino alcohols **7a** and **7g** in high yields, without erosion of enantiomeric excesses (Scheme 2).

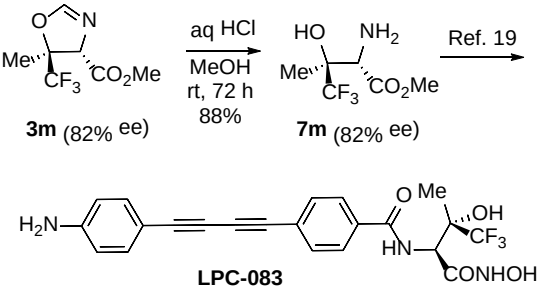
Scheme 2. Hydrolysis of oxazolines 3a and 3g.



[a] Structure determined by X-ray analysis (see ref. 16)

Furthermore, oxazoline **3m**, prepared in 82% ee from methyl isocyanoacetate and 1,1,1-trifluoroacetone (Table 1, entry13), upon treatment with aqueous HCl in methanol for 72 hours, could be transformed into amino alcohol **7m** (82% ee), a known intermediate in the synthesis of LPC-083, which is an inhibitor of LpxC, an essential enzyme of the lipid A biosynthetic pathway in Gram-negative bacteria and a validated antibiotic target (Scheme 3).[19]

Scheme 3. Formal enantioselective synthesis of LPC-083



CONCLUSIONS

In summary, we have developed the first catalytic enantioselective formal [3+2] cycloaddition of trifluoromethylketones and isocyanoacetates. Using a multicatalytic approach that combines a bifunctional Brønsted base-squaramide organocatalyst and Ag^+ as Lewis acid we were able to obtain chiral oxazolines bearing a quaternary stereocenter substituted with a trifluoromethyl group and a contiguous tertiary or quaternary stereocenter. The reaction was broad in scope and provided a straightforward access to chiral trifluoromethylated hydroxy amino esters.

EXPERIMENTAL SECTION

General Experimental Methods. Formal [3+2] cycloaddition reactions were carried out in round bottom flasks closed with a stopper. Starting materials, including trifluoromethylketones, methyl and *t*-butyl isocyanoacetate were obtained from commercial sources. Methyl *tert*-butyl ether (MTBE) was stored over 4 Å MS until it was used. Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin layer plates. Flash column chromatography was performed on Merck silica gel 60, 0.040-0.063 mm. Melting points were determined in capillary tubes. Unless otherwise stated, NMR spectra were run at 300 MHz for ^{1}H and at 75 MHz for ^{13}C NMR using residual nondeuterated solvent ($CHCl_3$) as internal standard (δ 7.26 and 77.0 ppm, respectively), and at 282 MHz for ^{19}F NMR using $CFCl_3$ as internal standard. Chemical shifts are given in ppm. The carbon type was determined by DEPT experiments. High resolution mass spectra (ESI) were recorded on a Q-TOF spectrometer equipped with an electrospray source with a capillary voltage of 3.3 kV (ESI). Specific optical rotations were measured using sodium light (D line 589 nm). Chiral HPLC analyses were performed in a chromatograph equipped with a UV diode-array detector using chiral stationary phase columns from Daicel or Phenomenex. Chiral GLC analyses were carried out in a chromatograph equipped with a flame ionization detector using nitrogen (1 mL/min) as carrier gas, $T_{injector}$ = 220 ◦C, $T_{detector}$ = 220 ◦C.

General procedure for the enantioselective formal [3+2] cycloaddition reaction with methyl isocyanoacetate.

Squaramide **III** (3.9 mg, 0.0063 mmol) and silver oxide (1.5 mg, 0.0063 mmol) were introduced in a 25 mL round bottom flask followed by MTBE (8 mL) and trifluoroacetophenone **1** (0.25 mmol). The flask was closed with a stopper and

introduced in an ice bath. After 5 min, methyl isocyanoacetate (**2a**, 30 μL, 0.33 mmol) was added and the mixture was stirred at 0 °C until consumption of the trifluoroacetophenone **1** (TLC). After this time, the reaction mixture was filtered through a short pad of silica gel and concentrated under reduced pressure. A small aliquot was analyzed by ^{1}H NMR to determine the diastereomer ratio and by HPLC to determine the enantiomeric excess of products **3**. The remaining crude was chromatographed on silica gel eluting with hexane:EtOAc mixtures (9:1 to 8:2) to obtain the oxazolines **3**.[20]

The racemic products were obtained by a similar procedure using *N*-[3,5-bis(trifluoromethyl)phenyl]-*N*'-(3-dimethylaminopropyl)squaramide as a substitutive for squaramide **III**.

*Methyl 5-phenyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3a**)*. Colorless oil (83.4 mg, >95% from 55.0 mg of **1a**). HPLC (Chiracel IC, hexane:*i*PrOH 95:5, 0.7 mL/min): ***trans*-(4*S*,5*S*)-3a** (major diastereomer, 90% ee): major enantiomer, t_r = 12.4 min, minor enantiomer 18.3 min; ***cis*-3a** (minor diastereomer): major enantiomer, t_r = 22.6 min, minor enantiomer t_r = 28.6 min; dr *trans:cis* = 96:4. ***trans*-(4*S*,5*S*)-3a (major diastereomer):** $[\alpha]_D^{25}$ +143.0 (*c* 0.30, $CHCl_3$, for the diastereomer mixture); ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.44-7.43 (2H, m, Ar), 7.39-7.37 (3H, m, Ar), 7.24 (1H, d, *J* = 1.8 Hz, N=CHO), 5.24 (1H, d, *J* = 1.8 Hz, CH), 3.27 (3H, s, CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 167.1 (C), 155.7 (CH), 130.7 (C), 129.6 (CH), 128.4 (CH), 125.9 (CH, q, $J_{C\text{-}F}$ = 1.6 Hz), 123.8 (C, q, $J_{C\text{-}F}$ = 283 Hz), 87.6 (C, q, $J_{C\text{-}F}$ = 30 Hz), 74.2 (CH), 52.2 (CH_3); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ –80.1 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{11}F_3NO_3^+$: 274.0686, found: 274.0689. ***cis*-3a (minor diastereomer)**: representative signals taken from the NMR spectra of the diastereomer mixture, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70-7.35 (5H, Ar), 7.16 (1H, d, *J* = 2.4 Hz, N=CHO), 5.14 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 3.91 (3H, s, CH_3); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ –76.0 (s, CF_3).

*Methyl 5-(p-tolyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3b**)*. Colorless oil (68.9 mg, >95% from 47.0 mg of **1b**). HPLC (Chiralpak AS-H, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-3b** (major diastereomer, 87% ee): major enantiomer, t_r = 6.0 min, minor enantiomer, t_r = 8.6 min; ***cis*-3b** (minor diastereomer): major enantiomer, t_r = 15.7 min, minor enantiomer, t_r = 17.0 min; dr *trans:cis* = 94:6. ***trans*-(4*S*,5*S*)-3b** (major

diastereomer): $[\alpha]_D^{25}$ +127.8 (*c* 0.58, $CHCl_3$, for the diastereomer mixture); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (2H, d, *J* = 8.1 Hz, Ar), 7.23 (1H, d, *J* = 1.8 Hz, N=CHO), 7.17 (2H, d, *J* = 8.1 Hz, Ar), 5.22 (1H, d, *J* = 2.1 Hz, CH), 3.30 (3H, s, CH_3), 2.34 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 167.1 (C), 155.7 (CH), 139.6 (C), 129.0 (CH), 127.6 (C), 125.7 (CH, q, J_{C-F} = 1.6 Hz), 123.8 (C, q, J_{C-F} = 283 Hz), 87.5 (C, q, J_{C-F} = 30 Hz), 74.0 (CH), 52.1 (CH_3), 21.0 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –80.2 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{12}F_3NO_3^+$: 288.0842, found: 288.0849. ***cis*-3b** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture, ^1H NMR (300 MHz, $CDCl_3$) δ 5.12 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 3.83 (3H, s, CH_3), 2.38 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –76.1 (s, CF_3).

*Methyl 5-(4-methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3c**).* Colorless oil (65.9 mg, 88% from 51.0 mg of **1c**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-3c** (major diastereomer, 85% ee): major enantiomer, t_r = 13.2 min, minor enantiomer, t_r = 29.0 min; ***cis*-3c** (minor diastereomer): major enantiomer, t_r = 27.9 min, minor enantiomer, t_r = 34.7 min; dr *trans:cis* = 96:4. ***trans*-(4*S*,5*S*)-3c** (major diastereomer): $[\alpha]_D^{25}$ +122.5 (*c* 0.25, $CHCl_3$, for the diastereomer mixture); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (2H, d, *J* = 8.6 Hz, Ar), 7.23 (1H, dd, *J* = 2.1, 0.6 Hz, N=CHO), 6.88 (2H, d, *J* = 9.0 Hz, Ar), 5.20 (1H, d, *J* = 2.1 Hz, CH), 3.80 (s, CH_3), 3.33 (s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 167.2 (C), 160.3 (C), 155.7 (CH), 127.3 (CH, q, J_{C-F} = 1.9 Hz), 123.8 (C, q, J_{C-F} = 283 Hz), 122.4 (C), 113.8 (CH), 87.5 (C, q, J_{C-F} = 30 Hz), 74.0 (CH), 55.2 (CH_3), 52.3 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –80.4 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{13}F_3NO_4^+$: 304.0791, found: 304.0795. ***cis*-3c** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture, ^1H NMR (300 MHz, $CDCl_3$) δ 7.13 (1H, d, *J* = 2.4 Hz, CH), 5.11 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 3.89 (3H, s, CH_3), 3.82 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –76.7 (s, CF_3).

*Methyl 5-(4-chlorophenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3d**).* Colorless oil (75.7 mg, >95% from 54.1 mg of **1d**). HPLC (Chiralpak IC, hexane:*i*PrOH 90:10, 1 mL/min): ***trans*-(4*S*,5*S*)-3d** (major diastereomer, 84% ee): major enantiomer, t_r = 5.9 min, minor enantiomer, t_r = 8.1 min; ***cis*-3d** (minor diastereomer, 64% ee): major enantiomer, t_r = 12.7 min, minor enantiomer, t_r = 13.1 min; dr *trans:cis* = 80:20. ***trans*-(4*S*,5*S*)-3d** (major diastereomer): $[\alpha]_D^{25}$ +120.8 (*c* 0.20, $CHCl_3$, 84% ee); ^1H NMR (300

MHz, $CDCl_3$), δ 7.37-7.35 (4H, m, Ar), 7.23 (1H, d, *J* = 2.1 Hz, N=CHO), 5.23 (1H, d, *J* = 2.1 Hz, CH), 3.33 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.9 (C), 155.6 (CH), 135.9 (C), 129.3 (C), 128.7 (CH), 127.4 (CH, q, $J_{C\text{-}F}$ = 1.6 Hz), 123.6 (C, q, $J_{C\text{-}F}$ = 283 Hz), 87.2 (C, q, $J_{C\text{-}F}$ = 30.8 Hz), 74.0 (CH), 52.4 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –80.2 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{10}ClF_3NO_3^+$: 308.0296, found: 308.0299. ***cis*-3d** (minor diastereomer): $[\alpha]_D^{25}$ +63.5 (*c* 0.14, $CHCl_3$, 64% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (2H, d, *J* = 8.5 Hz, Ar), 7.45 (2H, d, *J* = 8.5 Hz, Ar), 7.16 (1H, d, *J* = 2.1 Hz, CH), 5.08 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 3.92 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 167.3 (C), 154.5 (CH), 136.2 (C), 133.5 (C), 129.2 (CH), 127.9 (CH), 122.6 (C, q, $J_{C\text{-}F}$ = 283 Hz), 87.7 (C, q, $J_{C\text{-}F}$ = 31 Hz), 76.5 (CH), 53.3 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –76.0 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{10}ClF_3NO_3^+$: 308.0296, found: 308.0299.

*Methyl 5-(m-tolyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3e**)*: Colorless oil (68.8 mg, >95% from 47.0 mg of **1e**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-3e** (major diastereomer, 90% ee): major enantiomer, t_r = 8.3 min, minor enantiomer, t_r = 12.0 min; ***cis*-3e** (minor diastereomer): major enantiomer, t_r = 13.8 min, minor enantiomer, t_r = 18.2 min; dr *trans:cis* = 94:6. ***trans*-(4*S*,5*S*)-3e** (major diastereomer): $[\alpha]_D^{25}$ +132.4 (*c* 0.50, $CHCl_3$, for the diastereomer mixture); ^1H NMR (300 MHz, $CDCl_3$) δ 7.24-7.15 (5H, m, Ar, N=CHO), 5.22 (1H, d, *J* = 1.8 Hz, CH), 3.30 (3H, s, CH_3), 2.36 (3H, d, *J* = 0.6 Hz, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 167.1 (C), 155.7 (CH), 138.2 (C), 130.6 (C), 130.3 (CH), 128.3 (CH), 126.4 (CH, q, $J_{C\text{-}F}$ = 1.8 Hz), 123.8 (C, q, $J_{C\text{-}F}$ = 283 Hz), 122.9 (CH, q, $J_{C\text{-}F}$ = 1.9 Hz), 87.6 (C, q, $J_{C\text{-}F}$ = 30 Hz), 74.1 (CH), 52.2 (CH_3), 21.4 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –80.1 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{13}F_3NO_3^+$: 288.0842, found: 288.0845. ***cis*-3e** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture, ^1H NMR (300 MHz, $CDCl_3$) δ 5.13 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 3.83 (3H, s, CH_3), 2.41 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –75.8 (s, CF_3).

*Methyl 5-(3-methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3f**)*: Colorless oil (71.3 mg, 94% from 51.0 mg of **1f**). HPLC (Chiralpak AS-H, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-3f** (major diastereomer, 88% ee): major enantiomer, t_r = 7.3 min, minor enantiomer, t_r = 10.0 min; ***cis*-3f** (minor diastereomer): major enantiomer, t_r = 21.8 min, minor enantiomer, t_r = 19.9 min; dr *trans:cis* = 92:8.

***trans*-(4*S*,5*S*)-3f** (major diastereomer): $[\alpha]_D^{25}$ −26.7 (*c* 0.56, $CHCl_3$, for the diastereomer mixture); ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (1H, t, *J* = 8.4 Hz, Ar), 7.22 (1H, d, *J* = 2.1 Hz, N=CHO), 7.01-6.98 (2H, m, Ar), 6.92-6.90 (1H, m, Ar), 5.22 (1H, d, *J* = 1.8 Hz, CH), 3.80 (3H, s, CH_3), 3.33 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 167.1 (C), 159.5 (C), 155.7 (CH), 132.1 (C), 129.5 (CH), 123.7 (C, q, $J_{C\text{-}F}$ = 283 Hz), 118.1 (CH, q, $J_{C\text{-}F}$ = 2.2 Hz), 114.9 (CH), 111.9 (CH, q, $J_{C\text{-}F}$ = 1.7 Hz), 87.5 (C, q, $J_{C\text{-}F}$ = 30 Hz), 74.1 (CH), 55.3 (CH_3), 52.3 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –80.2 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{13}F_3NO_4^+$: 304.0791, found: 304.0794. ***cis*-3f** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture, ^1H NMR (300 MHz, $CDCl_3$) δ 7.14 (1H, d, *J* = 2.1 Hz, N=CHO), 5.13 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 3.91 (3H, s, CH_3), 3.84 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –75.9 (s, CF_3).

*Methyl 5-(3-bromophenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3g**):* Colorless oil (83.0 mg, 95% from 63.3 mg of **1g**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-3g** (major diastereomer, 92% ee): major enantiomer, t_r = 7.3 min, minor enantiomer, t_r = 9.8 min; ***cis*-3g** (minor diastereomer): major enantiomer, t_r = 14.5 min, minor enantiomer, t_r = 18.3 min; dr *trans:cis* = 86:14. ***trans*-(4*S*,5*S*)-3g** (major diastereomer): $[\alpha]_D^{25}$ +107.7 (*c* 0.66, $CHCl_3$, for the diastereomer mixture); ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (1H, s, Ar), 7.53 (1H, ddd, *J* = 8.0, 1.9, 1.1 Hz, Ar), 7.38 (1H, brd, *J* = 8.0 Hz, Ar), 7.25 (1H, t, *J* = 8.0 Hz, Ar), 7.23 (1H, d, *J* = 1.8 Hz, N=CHO), 5.23 (1H, d, *J* = 2.1 Hz, CH), 3.36 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.8 (C), 155.5 (CH), 132.9 (C), 132.8 (CH), 129.9 (CH), 129.1 (CH, q, $J_{C\text{-}F}$ = 1.7 Hz), 125.4 (C, q, $J_{C\text{-}F}$ = 283 Hz), 124.6 (CH, q, $J_{C\text{-}F}$ = 1.7 Hz), 122.6 (C), 86.9 (C, q, $J_{C\text{-}F}$ = 30 Hz), 74.1 (CH), 52.4 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –80.1 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{10}BrF_3NO_3^+$: 351.9791, found: 351.9791. ***cis*-3g** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture, ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (1H, d, *J* = 2.1 Hz, N=CHO), 5.08 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 3.90 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –75.8 (s, CF_3).

*Methyl 5-(2-methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3h**):* White solid (86.3 mg, >95% from 58.1 mg of **1h**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-3h** (major diastereomer, 85% ee): major enantiomer, t_r = 11.6 min, minor enantiomer, t_r = 15.9 min; ***cis*-3h** (minor diastereomer):

major enantiomer, t_r = 17.2 min, minor enantiomer, t_r = 26.9 min; dr *trans:cis* = 99:1. ***trans*-(4*S*,5*S*)-3h** (major diastereomer): mp 129-130 °C; $[\alpha]_D^{25}$ +228.1 (*c* 0.41, $CHCl_3$, for the diastereomer mixture, dr = 98:2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (1H, dd, *J* = 7.8, 1.8 Hz, Ar), 7.38 (1H, td, *J* = 7.5, 1.8 Hz, Ar), 7.13 (1H, d, *J* = 2.1 Hz, N=CHO), 7.05 (1H, td, *J* = 7.8, 1.2 Hz, Ar), 6.86 (1H, dd, *J* = 8.1, 0.9 Hz, Ar), 5.28 (1H, d, *J* = 2.1 Hz, CH), 3.75 (3H, s, CH_3), 3.54 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 167.7 (C), 155.3 (C), 155.2 (CH), 130.9 (CH), 128.8 (CH), 123.8 (C, q, $J_{C\text{-}F}$ = 283 Hz), 120.9 (CH), 119.8 (C), 110.3 (CH), 86.9 (C, q, $J_{C\text{-}F}$ = 30.8 Hz), 72.8 (CH), 54.7 (CH_3), 52.1 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –81.9 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{13}F_3NO_4^+$: 304.0791, found: 304.0791.

*Methyl 5-(2-bromophenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3i**):* Colorless oil (81.7 mg, 93% from 63.3 mg of **1i**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-3i** (major diastereomer, 70% ee): major enantiomer, t_r = 8.9 min, minor enantiomer, t_r = 12.6 min; ***cis*-3i** (minor diastereomer): major enantiomer, t_r = 17.8 min, minor enantiomer, t_r = 24.3 min; dr *trans:cis* = 85:15; major isomer:, minor isomer: 54% ee. ***trans*-(4*S*,5*S*)-3i** (major diastereomer): $[\alpha]_D^{25}$ +150.9 (*c* 0.43, $CHCl_3$, for the diastereomer mixture, dr = 85:15); ^1H NMR (500 MHz, $CDCl_3$, 50 ºC) δ 7.90 (1H, unresolved d, Ar), 7.73 (1H, dd, *J* = 8.0, 1.3 Hz, Ar), 7.52 (1H, td, *J* = 8.0, 1.0 Hz, Ar), 7.37 (1H, td, *J* = 8.0, 1.5 Hz, Ar), 7.27 (1H, d, *J* = 2.0 Hz, N=CHO), 5.62 (1H, s, CH), 3.72 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 50 ºC) δ 167.4 (C), 155.0 (CH), 136.3 (C), 134.6 (br CH), 130.8 (CH), 130.4 (CH), 127.6 (CH), 123.7 (C, q, $J_{C\text{-}F}$ = 283 Hz), 120.8 (C), 88.8 (C, q, $J_{C\text{-}F}$ = 29 Hz), 72.9 (CH), 52.6 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –79.4 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{10}BrF_3NO_3^+$:351.9791, found: 351.9798. ***cis*-3i** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture, ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (br d, J = 8.1 Hz, Ar), 7.83 (1H, dd, J = 8.1, 1.3 Hz, Ar), 7.52 (1H, td, *J* = 8.0, 1.0 Hz, Ar), 7.39 (1H, td, *J* = 8.0, 1.5 Hz, Ar), 7.26 (1H, d, *J* = 2.0 Hz, N=CHO), 5.62 (1H, s, CH), 3.98 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –72.2 (s, CF_3).

*Methyl 5-(3,4-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3j**):* Yellow oil (90.1 mg, >95% from 64.1 mg of **1j**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-3j** (major diastereomer, 85% ee): major enantiomer, t_r = 6.4 min, minor enantiomer, t_r = 8.7 min; ***cis*-3j** (minor diastereomer):

major enantiomer, t_r = 16.4 min, minor enantiomer, t_r = 19.6 min; dr *trans:cis* = 77:23. ***trans*-(4*S*,5*S*)-3j** (major diastereomer): $[\alpha]_D^{25}$ +105.0 (*c* 0.92, $CHCl_3$, for the diastereomer mixture); ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (1H, d, *J* = 2.3 Hz, Ar), 7.46 (1H, d, *J* = 8.7 Hz, Ar), 7.27 (1H, ddd, *J* = 8.4, 2.1, 0.9 Hz, Ar), 7.22 (1H, d, *J* = 1.8 Hz, N=CHO), 5.22 (1H, d, *J* = 1.8 Hz, CH), 3.40 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz) δ 166.7 (C), 155.4 (CH), 134.3 (C), 133.1 (C), 131.0 (C), 130.5 (CH), 128.2 (CH, q, J_{C-F} = 1.8 Hz), 125.4 (CH, q, J_{C-F} = 1.7 Hz), 125.2 (C, q, J_{C-F} = 283 Hz), 86.6 (C, q, J_{C-F} = 29 Hz), 74.0 (CH), 52.5 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –80.2 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_9Cl_2F_3NO_3^+$: 341.9906, found: 341.9909. ***cis*-3j** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture, ^1H NMR (300 MHz, $CDCl_3$) δ 7.14 (1H, d, *J* = 2.1 Hz, N=CHO), 5.05 (1H, dd, *J* = 2.1, 0.9 Hz, CH), 3.91 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –76.0 (s, CF_3).

*Methyl 5-(thiophen-2-yl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3k**)*: Yellow oil (80.1 mg, >95% from 52.3 mg of **3k**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-3k** (major diastereomer, 90% ee): major enantiomer, t_r = 10.0 min, minor enantiomer, t_r = 13.8; ***cis*-3k** (minor diastereomer): major enantiomer, t_r = 17.6 min, minor enantiomer, t_r = 22.1 min; dr *trans:cis* = 92:8. ***trans*-(4*S*,5*S*)-3k** (major diastereomer): $[\alpha]_D^{25}$ +48.0 (*c* 0.79, $CHCl_3$, for the diastereomer mixture); ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (1H, dd, *J* = 5.1, 1.5 Hz, Ar), 7.19 (1H, dd, *J* = 2.1, 0.6 Hz, N=CHO), 7.10-7.08 (1H, m, Ar), 7.03 (1H, dd, *J* = 5.1, 3.9 Hz, Ar), 5.22 (1H, d, *J* = 2.1 Hz, CH), 3.41 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.7 (C), 155.1 (CH), 132.7 (C), 127.5 (CH), 126.9 (CH), 126.8 (CH, q, J_{C-F} = 2.1 Hz), 123.2 (C, q, J_{C-F} = 283 Hz), 86.3 (C, q, J_{C-F} = 32 Hz), 74.6 (CH), 52.4 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –81.5 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{10}H_9F_3NO_3S^+$: 280.0250, found: 280.0253. ***cis*-3k** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture, ^1H NMR (300 MHz, $CDCl_3$) δ 7.12 (1H, d, *J* = 2.1 Hz, N=CHO), 5.19 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 3.89 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –76.4 (s, CF_3).

*Methyl 5-phenethyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3l**):* Yellow oil (50.1 mg, 66% from 51.0 mg of **1l**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-3l** (major diastereomer, 81% ee): major enantiomer, t_r = 7.9 min, minor enantiomer, t_r = 19.6 min; ***cis*-3l** (minor diastereomer): major enantiomer, t_r

= 39.5 min, minor enantiomer, t_r = 28.4 min; dr *trans:cis* = 86:14. ***trans*-(4*S*,5*S*)-3l** (major diastereomer): $[\alpha]_D^{25}$ +17.5 (*c* 0.81, $CHCl_3$, for the diastereomer mixture); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.26 (4H, m, Ar), 7.13-7.10 (1H, m, Ar), 7.03 (1H, d, *J* = 2.4 Hz, N=CHO), 4.98 (1H, d, *J* = 2.4 Hz, CH), 3.81 (3H, s, CH_3), 2.78-2.55 (2H, m, CH_2), 2.33-2.06 (2H, m, CH_2); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.1 (C), 155.2 (CH), 139.9 (C), 128.6 (CH), 128.1 (CH), 126.4 (CH), 124.2 (C, q, $J_{C\text{-}F}$ = 283 Hz), 85.7 (C, q, $J_{C\text{-}F}$ = 30.1 Hz), 71.3 (CH), 52.8 (CH_3), 31.4 (CH_2), 28.6 (CH_2); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –80.7 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{15}F_3NO_3^+$: 302.0999, found: 302.1004. ***cis*-3l** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture, ^1H NMR (300 MHz, $CDCl_3$) δ 4.82 (1H, d, *J* = 2.1 Hz, CH), 3.81 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –76.3 (s, CF_3).

*Methyl 5-methyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**3m**):* Volatile colorless oil (42.2 mg, 80% from 28.1 mg of **1m**). HPLC (Chiralpak IC, hexane:*i*PrOH 90:10, 1 mL/min): ***trans*-(4*S*,5*S*)-3m** (major diastereomer 82%): major enantiomer, t_r = 6.9 min, minor enantiomer, t_r = 8.5 min; ***cis*-3m** (minor diastereomer): major enantiomer, t_r = 12.7 min, minor enantiomer, t_r = 14.0 min; dr *trans:cis* = 92:8. ***trans*-(4*S*,5*S*)-3m** (major diastereomer): $[\alpha]_D^{25}$ +75.3 (*c* 0.33, $CHCl_3$, for the diastereomer mixture); ^1H NMR (300 MHz, $CDCl_3$) δ 6.97 (1H, d, *J* = 1.5 Hz, N=CHO), 4.88 (1H, d, *J* = 2.5 Hz, CH), 3.79 (3H, s, CH_3), 1.49 (3H, m, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.0 (C), 155.5 (CH), 124.0 (C, q, $J_{C\text{-}F}$ = 283 Hz), 83.9 (C, q, $J_{C\text{-}F}$ = 32 Hz), 71.3 (CH), 52.7 (CH_3), 15.3 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –83.3 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_7H_9F_3NO_3^+$: 212.0529, found: 212.0536. ***cis*-3m** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture, ^1H NMR (300 MHz, $CDCl_3$) δ 4.62 (1H, dd, *J* = 2.2, 0.6 Hz, CH), 3.79 (3H, s, CH_3), 1.74 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –77.7 (s, CF_3).

General procedure for the enantioselective formal [3+2] cycloaddition reaction with *tert*-butyl isocyanoacetate.

Squaramide **VIII** (6.8 mg, 0.0125 mmol) and silver oxide (1.5 mg, 0.0063 mmol) were introduced in a round bottom flask followed by MTBE (8 mL) and trifluoroacetophenone **1** (0.25 mmol). The flask was closed with a stopper and

introduced in an ice bath. After 5 min, *tert*-butyl isocyanoacetate (**2b,** 48 μL, 0.33 mmol) was added and the mixture was stirred at 0 ºC until consumption of the trifluoroacetophenone **1** (TLC). After this time, the reaction mixture was filtered through a short pad of silica gel and concentred under reduced pressure. A small aliquot was analyzed by ^{1}H NMR to determine the diastereomer ratio and by HPLC to determine the enantiomeric excess of products **4**. The remaining crude was chromatographed on silica gel eluting with hexane:EtOAc mixtures (9:1 to 8:2) to obtain compounds **4**.[20]

The racemic product was obtained using a similar procedure using the catalyst 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-((3-(dimethylamino)propyl)amino)cyclobut-3-ene-1,2-dione and silver oxide.

*tert-Butyl 5-phenyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**4a**):* Colorless oil (102.2 mg, >95% from 57.3 mg of **1a**). HPLC (Chiralpak IC, hexane:*i*PrOH 90:10, 0.7 mL/min): ***trans*-(4*S*,5*S*)-4a** (major diastereomer, 96% ee): major enantiomer, t_r = 7.2 min, minor enantiomer, t_r = 8.5 min; ***cis*-4a** (minor diastereomer, 90% ee**)**: major enantiomer, t_r = 11.1 min, minor enantiomer, t_r = 15.2 min; dr *trans:cis* = 70:30. ***trans*-(4*S*,5*S*)-4a** (major diastereomer): $[\alpha]_D^{25}$ +178.1 (*c* 1.15, $CHCl_3$, 96% *ee*); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50-7.46 (2H, m, Ar), 7.39-7.37 (3H, m, Ar), 7.20 (1H, d, *J* = 1.8 Hz, N=CHO), 5.08 (1H, d, *J* = 1.8 Hz, CH), 1.03 (9H, s, CH_3); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ 165.3 (C), 155.3 (CH), 131.0 (C), 129.4 (CH), 128.4 (CH), 126.4 (CH, q, $J_{C\text{-}F}$ = 2.0 Hz), 123.9 (C, q, $J_{C\text{-}F}$ = 284 Hz), 87.6 (C, q, $J_{C\text{-}F}$ = 30 Hz), 82.7 (C), 74.6 (CH), 27.1 (CH_3); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ –80.3 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{17}F_3NO_3^+$: 316.1155, found: 316.1154. ***cis*-4a (minor diastereomer)**: $[\alpha]_D^{25}$ +77.2 (*c* 0.23, $CHCl_3$, 90% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72-7.69 (2H, m, Ar), 7.46-7.44 (3H, m, Ar), 7.12 (1H, d, *J* = 2.4 Hz, N=CHO), 5.02 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 1.58 (9H, s, CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 165.7 (C), 154.0 (CH), 135.6 (C), 129.7 (CH), 128.7 (CH), 128.6 (C, q, $J_{C\text{-}F}$ = 283 Hz), 126.4 (CH), 123.0 (C, q, $J_{C\text{-}F}$ = 283 Hz), 87.9 (C, q, $J_{C\text{-}F}$ = 30.7 Hz), 83.6 (C), 77.4 (CH), 27.7 (CH_3); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ –75.0 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{17}F_3NO_3^+$: 316.1155, found: 316.1154.

*tert-Butyl 5-(p-tolyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**4b**)*: White solid (71.7 mg, 87% from 47.0 mg of **1b**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1

mL/min): ***trans*-(4*S*,5*S*)-4b** (major diastereomer, 93% ee): major enantiomer, t_r = 6.9 min, minor enantiomer, t_r = 9.4 min; ***cis*-4b** (minor diastereomer, 96% ee): major enantiomer, t_r = 12.2 min, minor enantiomer, t_r = 18.3 min; dr *trans:cis* = 66:34. ***trans*-(4*S*,5*S*)-4b** (major diastereomer): mp: 63-65 ºC; $[\alpha]_D^{25}$ +153.3 (*c* 0.96, $CHCl_3$, 93% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (2H, d, *J* = 8.1, Ar), 7.19 (1H, d, *J* = 2.1 Hz, N=CHO), 7.18 (2H, d, *J* = 8.1 Hz, Ar), 5.05 (1H, d, *J* = 2.1 Hz, CH), 2.33 (3H, d, *J* = 0.9 Hz, CH_3), 1.05 (9H, s, CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 165.4 (C), 155.3 (CH), 139.4 (C), 129.0 (CH), 128.0 (C), 126.3 (CH, q, $J_{C\text{-}F}$ = 1.7 Hz), 123.9 (C, q, $J_{C\text{-}F}$ = 283 Hz), 87.6 (C, q, $J_{C\text{-}F}$ = 30 Hz), 82.6 (C), 74.5 (CH), 27.1 (CH_3), 21.0 (CH_3); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ –80.4 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{19}F_3NO_3^+$: 330.1312, found: 330.1316. ***cis*-4b** (minor diastereomer): colorless oil; $[\alpha]_D^{25}$ +84.8 (*c* 1.09, $CHCl_3$, 96% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (2H, d, *J* = 8.1 Hz, Ar), 7.26 (2H, d, *J* = 8.1 Hz, Ar), 7.10 (1H, d, *J* = 2.1 Hz, N=CHO), 5.00 (1H, dd, *J* = 2.4, 0.9 Hz, CH), 2.38 (3H, s, CH_3), 1.57 (9H, s, CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 165.8 (C), 154.0 (CH), 139.7 (C), 132.6 (C), 129.4 (CH), 126.3 (CH), 123.0 (C, q, $J_{C\text{-}F}$ = 283 Hz), 87.9 (C, q, $J_{C\text{-}F}$ = 30.1 Hz), 83.5 (C), 27.7 (CH_3), 21.1 (CH_3); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ –75.1 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{19}F_3NO_3^+$: 330.1312, found: 330.1316.

*tert-Butyl (4S,5S)-5-(4-methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**4c**):* Colorless oil (84.0 mg, >95% from 51.2 mg of **1c**). HPLC (Chiralpak IC, hexane:*i*PrOH 90:10, 0.7 mL/min): ***trans*-(4*S*, 5*S*)-4c** (major diastereomer, 84%): major enantiomer, t_r = 8.7 min, minor enantiomer, t_r = 14.2 min; ***cis*-4c** (minor diastereomer, 77% ee): major enantiomer, t_r = 16.8 min, minor enantiomer, t_r = 20.9 min; dr *trans:cis* = 63:37. ***trans*-(4*S*, 5*S*)-4c** (major diastereomer): $[\alpha]_D^{25}$ +127.3 (*c* 0.82, $CHCl_3$, 84% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (2H, d, *J* = 9.0, Ar), 7.18 (1H, d, *J* = 1.8 Hz, N=CHO), 6.89 (2H, d, *J* = 9.0 Hz, Ar), 5.04 (1H, d, *J* = 1.8 Hz, CH), 3.79 (3H, s, CH_3), 1.08 (9H, s, CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 165.5 (C), 160.4 (C), 155.3 (CH), 127.9 (CH, q, $J_{C\text{-}F}$ = 1.8 Hz), 123.9 (C, q, $J_{C\text{-}F}$ = 284 Hz), 122.9 (C), 113.8 (CH), 87.5 (C, q, $J_{C\text{-}F}$ = 29 Hz), 82.7 (C), 74.5 (CH), 55.3 (CH_3), 27.3 (CH_3); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ –80.5 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{19}F_3NO_4^+$: 346.1261, found: 346.1251. ***cis*-4c** (minor diastereomer): $[\alpha]_D^{25}$ +47.1 (*c* 0.75, $CHCl_3$, 77% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (2H, d, *J* = 9.0 Hz, Ar), 7.10 (1H, d, *J* = 2.4 Hz, N=CHO), 6.96 (2H, d, *J* = 9.0 Hz, Ar), 5.00 (1H, dd, *J* = 2.1, 0.6 Hz,

CH), 3.83 (3H, s, CH_3), 1.57 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.8 (C), 160.5 (C), 154.0 (CH), 127.8 (CH), 127.4 (C), 123.0 (C, q, J_{C-F} = 283 Hz), 114.1 (CH), 87.8 (C, q, J_{C-F} = 30 Hz), 83.5 (C), 77.4 (CH), 55.3 (CH_3), 27.7 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –75.4 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{19}F_3NO_4^+$: 346.1261, found: 346.1251.

*tert-Butyl 5-(4-chlorophenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**4d**):* Colorless oil (103.4 mg, >95% from 62.0 mg of **1d**). HPLC (Chiralpak IC, hexano:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-4d** (major diastereomer, 96% ee): major enantiomer, t_r = 7.6 min, minor enantiomer, t_r = 9.0 min; ***cis*-4d** (minor diastereomer, 90% ee): major enantiomer, t_r = 16.7 min, minor enantiomer, t_r = 18.5 min; dr *trans:cis* = 53:47. ***trans*-(4*S*,5*S*)-4d** (major diastereomer): $[\alpha]_D^{25}$ +81.7 (*c* 0.30, $CHCl_3$, 96% *ee*); ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (2H, d, *J* = 9.0 Hz, Ar), 7.37 (2H, d, *J* = 9.0 Hz, Ar), 7.19 (1H, d, *J* = 2.0 Hz, N=CHO), 5.07 (1H, d, *J* = 2.0 Hz, CH), 1.08 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.2 (C), 155.2 (CH), 135.8 (C), 129.5 (C), 128.7 (CH), 128.0 (CH, q, J_{C-F} = 1.9 Hz), 123.7 (C, q, J_{C-F} = 283 Hz), 87.5 (C, q, J_{C-F} = 30 Hz), 83.1 (C), 74.6 (CH), 27.3 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –80.4 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{16}ClF_3NO_3^+$: 350.0765, found: 350.0757. ***cis*-4d** (minor diastereomer): $[\alpha]_D^{25}$ +48.6 (*c* 0.46, $CHCl_3$, 90% *ee*); ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (2H, d, *J* = 9.0 Hz, Ar), 7.42 (2H, d, *J* = 9.0 Hz, Ar), 7.10 (1H, d, *J* = 2.1 Hz, N=CHO), 4.96 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 1.57 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.4 (C), 153.9 (CH), 136.0 (C), 133.9 (C), 129.0 (CH), 127.9 (CH), 122.8 (C, q, J_{C-F} = 283 Hz), 87.5 (C, q, J_{C-F} = 31 Hz), 83.9 (C), 77.4 (CH), 27.7 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –75.2 (s, CF_3). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{16}ClF_3NO_3^+$: 350.0765, found: 350.0757.

*tert-Butyl 5-(m-tolyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**4e**):* Colorless oil (77.1 mg, 94% from 47.2 mg of **1e**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-4e** (major diastereomer, 97% ee): major enantiomer, t_r = 5.6 min, minor enantiomer, t_r = 6.7 min; ***cis*-4e** (minor diastereomer, 87% ee): major enantiomer: t_r = 10.0 min, minor enantiomer: t_r = 14.4 min; dr *trans:cis* = 76:24. ***trans*-(4*S*,5*S*)-4e** (major diastereomer): $[\alpha]_D^{25}$ +166.8 (*c* 0.55, $CHCl_3$, 97% *ee*); ^1H NMR (300 MHz, $CDCl_3$) δ 7.27-7.25 (3H, m, Ar), 7.21-7.18 (2H, m, Ar, NCHO), 5.06 (1H, d, *J* = 2.1 Hz, CH), 2.35 (3H, s, CH_3), 1.04 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.3 (C), 155.3 (CH), 138.0 (C), 130.9 (C), 130.1 (CH), 128.3 (CH), 126.9 (CH, q, J_{C-F}

= 2.0 Hz), 123.9 (C, q, $J_{C\text{-}F}$ = 283 Hz), 123.5 (CH, q, $J_{C\text{-}F}$ = 1.9 Hz), 87.6 (C, q, $J_{C\text{-}F}$ = 30 Hz), 82.5 (C), 74.6 (CH), 27.1 (CH_3), 21.4 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –80.3 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{19}F_3NO_3^+$: 330.1312, found: 330.1308. ***cis*-4e** (minor diastereomer): $[\alpha]_D^{25}$ +52.9 (*c* 0.98, $CHCl_3$, 87% *ee*); ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (1H, s, Ar), 7.49 (1H, d, *J* = 9.0 Hz, Ar), 7.33 (1H, td, *J* = 7.5, 0.6 Hz, Ar), 7.25 (1H, br d, *J* = 7.6 Hz, Ar), 7.11 (1H, d, *J* = 2.1 Hz, N=CHO), 5.01 (1H, dd, *J* = 2.4, 0.9 Hz, CH), 2.40 (3H, s, CH_3), 1.58 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.7 (C), 154.0 (CH), 138.5 (C), 135.5 (C), 130.4 (CH), 128.6 (CH), 126.9 (CH), 123.4 (CH), 123.0 (C, q, $J_{C\text{-}F}$ = 283 Hz), 87.9 (C, q, $J_{C\text{-}F}$ = 30 Hz), 83.5 (CH), 77.4 (CH), 27.7 (CH_3), 21.5 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –75.0 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{19}F_3NO_3^+$: 330.1312, found: 330.1308.

*tert-Butyl 5-(3-methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**4f**):* Colorless oil (72.7 mg, 84% from 51.1 mg of **1f**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-4f** (major diastereomer, 97% ee): major enantiomer, t_r = 6.8 min, minor enantiomer, t_r = 16.0 min, ***cis*-4f** (minor diastereomer, 85% ee): major enantiomer, t_r = 13.2 min, minor enantiomer, t_r = 20.9 min; dr *trans:cis* = 72:28. ***trans*-(4*S*,5*S*)-4f** (major diastereomer): $[\alpha]_D^{25}$ +164.7 (*c* 0.49, $CHCl_3$, 97% *ee*); ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (1H, td, *J* = 8.0, 0.6 Hz, Ar), 7.19 (1H, dd, *J* = 1.9, 0.5 Hz, N=CHO), 7.06 (1H, m, Ar), 7.00 (1H, m, Ar), 6.91 (1H, ddd, *J* = 8.2, 2.5, 0.9 Hz, Ar), 5.06 (1H, d, *J* = 1.9 Hz, CH), 3.80 (3H, s, CH_3), 1.07 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.3 (C), 159.5 (C), 155.3 (CH), 132.3 (C), 129.5 (CH), 123.8 (C, q, $J_{C\text{-}F}$ = 283 Hz), 118.6 (CH, q, $J_{C\text{-}F}$ = 2.0 Hz), 114.8 (CH), 112.5 (CH, q, $J_{C\text{-}F}$ = 1.8 Hz), 87.5 (C, q, $J_{C\text{-}F}$ = 30 Hz), 82.7 (C), 74.6 (CH), 55.3 (CH_3), 27.2 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –80.4 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{19}F_3NO_4^+$: 346.1261, found: 346.1260. ***cis*-4f** (minor diastereomer): $[\alpha]_D^{25}$ +56.9 (*c* 0.77, $CHCl_3$, 85% *ee*); ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (1H, t, *J* = 7.8, Ar), 7.30-7.24 (2H, m, Ar), 7.11 (1H, d, *J* = 2.1 Hz, N=CHO), 6.96 (1H, ddd, *J* = 8.1, 2.6, 1.2 Hz, Ar), 5.02 (1H, dd, *J* = 2.1, 0.6 Hz, CH), 3.84 (3H, s, CH_3), 1.57 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.7 (C), 159.7 (C), 154.0 (CH), 132.2 (C), 129.8 (CH), 122.9 (C, q, $J_{C\text{-}F}$ = 283 Hz), 118.5 (CH), 115.1 (CH), 112.2 (CH), 87.9 (C, q, $J_{C\text{-}F}$ = 30 Hz), 83.6 (C), 77.4 (CH), 55.4 (CH_3), 27.7 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –74.9 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calc for $C_{16}H_{19}F_3NO_4^+$: 346.1261, found: 346.1260.

*tert-Butyl 5-(3-bromophenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**4g**):* Colorless oil (95.7 mg, >95%, from 63.5 mg of **1g**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 0.5 mL/min): ***trans*-(4*S*,5*S*)-4g** (major diastereomer, 90% ee): major enantiomer, t_r = 10.8 min, minor enantiomer, t_r = 12.7 min, ***cis*-4g** (minor diastereomer, 97% ee): major enantiomer, t_r = 24.3 min, minor enantiomer, t_r = 35.5 min; dr *trans:cis* = 64:36. ***trans*-(4*S*,5*S*)-4g** (major diastereomer): $[\alpha]_D^{25}$ +143.5 (*c* 0.52, $CHCl_3$, 97% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (1H, bs, Ar), 7.52 (1H, ddd, *J* = 7.9, 1.9, 1.0 Hz, Ar), 7.42 (1H, m, Ar), 7.26 (1H, td, *J* = 8.1, 0.6 Hz, Ar), 7.19 (1H, dd, *J* = 2.1, 0.6, N=CHO), 5.06 (1H, d, *J* = 2.0 Hz, CH), 1.10 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.1 (C), 155.1 (CH), 133.2 (C), 132.6 (CH), 130.0 (CH), 129.5 (CH, q, $J_{C\text{-}F}$ = 1.8 Hz), 125.1 (CH, q, $J_{C\text{-}F}$ = 2.0 Hz), 123.6 (C, q, $J_{C\text{-}F}$ = 283 Hz), 122.6 (C), 86.9 (C, q, $J_{C\text{-}F}$ = 30 Hz), 83.1 (C), 74.6 (CH), 27.2 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –80.3 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{16}BrF_3NO_3^+$: 394.0260, found: 394.0251. ***cis*-4g** (minor diastereomer): $[\alpha]_D^{25}$ +42.7 (*c* 1.39, $CHCl_3$, 90% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (1H, bs, Ar), 7.64 (1H, br d, *J* = 8.0 Hz, Ar), 7.58 (1H, ddd, *J* = 8.0, 1.9, 1.0 Hz, Ar), 7.33 (1H, t, *J* = 7.9 Hz, Ar), 7.11 (1H, d, *J* = 2.3 Hz, N=CHO), 4.96 (1H, dd, *J* = 2.3, 0.9 Hz, CH), 1.58 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.2 (C), 153.9 (CH), 137.6 (C), 132.9 (CH), 130.3 (CH), 129.7 (CH), 125.1 (CH), 122.8 (C), 122.7 (C, q, $J_{C\text{-}F}$ = 283 Hz), 87.2 (C, q, $J_{C\text{-}F}$ = 30.1 Hz), 83.9 (C), 77.3 (CH), 27.7 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –75.1 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{16}BrF_3NO_3^+$: 394.0260, found: 394.0251.

*tert-Butyl 5-(2-methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**4h**):* White solid (69.0 mg, 80% from 51.0 mg of **1h**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-4h** (major diastereomer, 94% ee): major enantiomer, t_r = 7.0 min, minor enantiomer, t_r = 23.0 min; ***cis*-4h** (minor diastereomer, 70% ee): major enantiomer, t_r = 19.9 min, minor enantiomer, t_r = 30.2 min; dr *trans:cis* = 94:6. ***trans*-(4*S*,5*S*)-4h** (major diastereomer): Mp: 76-79 ºC; $[\alpha]_D^{25}$ +252.5 (*c* 0.78, $CHCl_3$, 94% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (1H, dd, *J* = 7.8, 1.8 Hz, Ar), 7.37 (1H, ddd, *J* = 8.4, 7.5, 1.8 Hz, Ar), 7.09 (1H, d, *J* = 2.0 Hz, N=CHO), 7.02 (1H, td, *J* = 7.5, 1.0 Hz, Ar), 6.85 (1H, dd, *J* = 8.4, 1.2 Hz, Ar), 5.12 (1H, d, *J* = 2.0 Hz, CH), 3.76 (3H, s, CH_3), 1.12 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.6 (C), 155.7 (C), 154.9 (CH), 130.6 (CH), 128.6 (CH), 123.9 (C, q, $J_{C\text{-}F}$ = 283 Hz), 120.6 (CH), 120.5 (C), 110.4 (CH), 87.0 (C, q, $J_{C\text{-}F}$ = 30 Hz), 81.5 (C), 74.2 (CH), 54.7 (CH_3), 27.3

(CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –81.7 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{19}F_3NO_4^+$: 346.1261, found: 346.1259. ***cis*-4h** (minor diastereomer): $[\alpha]_D^{25}$ +70.7 (*c* 0.17, $CHCl_3$, 70% *ee*); ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (1H, td, *J* = 7.8, 1.5 Hz, Ar), 7.40 (1H, ddd, *J* = 8.2, 7.4, 1.7 Hz, Ar), 7.09 (1H, dd, *J* = 2.1, 0.6 Hz, N=CHO), 7.00 (1H, td, *J* = 7.5, 1.2 Hz, Ar), 6.98 (1H, dd, *J* = 7.2, 2.4 Hz, Ar), 5.23 (1H, dd, *J* = 2.1, 0.9 Hz, CH), 3.89 (3H, s, CH_3), 1.54 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.2 (C), 156.6 (C), 153.6 (CH), 131.3 (CH), 128.2 (CH), 123.3 (C, q, J_{C-F} = 283), 123.0 (C), 120.6 (CH), 111.9 (CH), 87.6 (C, q, J_{C-F} = 32 Hz), 82.4 (C), 75.5 (CH), 55.2 (CH_3), 27.8 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –72.4 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{19}F_3NO_4^+$: 346.1261, found: 346.1259.

*tert-Butyl 5-(2-bromophenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**4i**):* White solid (122.8 mg, >95% from 79.0 mg of **1i**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-4i** (major diastereomer, 91% ee): major enantiomer, t_r = 5.8 min, minor enantiomer, t_r = 9.3 min; dr *trans:cis* > 99:1. ***trans*-(4*S*,5*S*)-4i** (major diastereomer): Mp: 96-99 ºC; $[\alpha]_D^{25}$ +190.2 (*c* 0.54, $CHCl_3$, 91% *ee*); (two possible rotamers are observed) ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (1H, unresolved d, *J* = 7.4 Hz, Ar), 7.60 (1H, dd, *J* = 7.8, 1.2 Hz, Ar), 7.38 (1H, ddd, *J* = 7.9, 7.3, 1.3 Hz, Ar), 7.24 (1H, ddd, *J* = 8.0, 7.4, 1.7 Hz, Ar), 7.13 (1H, d, *J* = 1.8 Hz, N=CHO), 5.35 (1H, bs, CH), 1.22 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.3 (C), 154.8 (CH), 136.1 (C), 134.5 (CH), 130.6 (CH), 130.3 (CH), 127.4 (CH), 123.7 (C, q, *J* = 286 Hz), 120.8 (C), 88.5 (C, q, J_{C-F} = 30 Hz), 82.6 (CH), 74.0 (CH), 27.2 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –79.0 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{16}BrF_3NO_3^+$: 394.0260, found: 394.0251. For the X-ray structure of **4i** see Figure S1 in the SI.

*tert-Butyl 5-(3,4-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**4j**):* Colorless oil (95.1 mg, >95% from 61.0 mg of **1j**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-4j** (major diastereomer, 94% ee): major enantiomer, t_r = 6.7 min, minor enantiomer, t_r = 7.5 min; ***cis*-4j** (minor diastereomer, 85% ee): major enantiomer, t_r = 14.9 min, minor enantiomer, t_r = 17.2 min; dr *trans:cis* = 53:47. ***trans*-(4*S*,5*S*)-4j** (major diastereomer): $[\alpha]_D^{25}$ +131.8 (*c* 0.48, $CHCl_3$, 94% *ee*); ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (1H, d, *J* = 1.8 Hz, Ar), 7.47 (1H, d, *J* = 8.4 Hz, Ar), 7.33 (1H, ddd, *J* = 8.4, 2.2, 0.8 Hz, Ar), 7.19 (1H, d, *J* = 2.1 Hz, N=CHO), 5.06 (1H, d, *J* = 2.1 Hz, CH), 1.13 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.0 (C), 155.0

(CH), 134.2 (C), 132.9 (C), 131.1 (C), 130.5 (CH), 128.7 (CH, q, J_{C-F} = 1.9 Hz), 125.8 (CH, q, J_{C-F} = 1.7 Hz), 123.5 (C, q, J_{C-F} = 283 Hz), 86.5 (C, q, J_{C-F} = 30 Hz), 83.4 (C), 74.6 (CH), 27.3 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –80.4 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{15}Cl_2F_3NO_3^+$: 384.0376, found: 384.0371. ***cis*-4j** (minor diastereomer): $[\alpha]_D^{25}$ +68.2 (*c* 0.45, $CHCl_3$, 85% *ee*); ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (1H, brs, Ar), 7.60-7.50 (2H, m, Ar), 7.11 (1H, d, *J* = 2.4 Hz, N=CHO), 4.94 (1H, dd, *J* = 2.4, 0.9 Hz, CH), 1.58 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) 165.1 (C), 153.8 (CH), 135.4 (C), 134.4 (C), 133.3 (C), 130.9 (CH), 128.7 (CH), 125.8 (CH), 122.6 (C, q, J_{C-F} = 283 Hz), 86.9 (C, q, J_{C-F} = 30.8 Hz), 84.1 (CH), 77.4 (CH), 27.7 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –75.2 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{15}Cl_2F_3NO_3^+$: 384.0376, found: 384.0371.

*tert-Butyl 5-(thiophen-2-yl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**4k**):* Yellow oil (87.1 mg, >95% from 48.9 mg of **1k**). HPLC (Lux Cellulose-4, hexane:*i*PrOH 98:2, 1 mL/min): ***trans*-(4*S*,5*S*)-4k** (major diastereomer, 97% ee): major enantiomer, t_r = 7.7 min, minor enantiomer, t_r = 9.3 min, ***cis*-4k** (minor diastereomer, 91% ee): major enantiomer, t_r = 15.3 min, minor enantiomer, t_r = 17.7 min; dr *trans:cis* = 62:38. ***trans*-(4*S*,5*S*)-4k** (major diastereomer): $[\alpha]_D^{25}$ +127.4 (*c* 0.49, $CHCl_3$, 97% *ee*); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (1H, dd, *J* = 5.1, 1.2 Hz, Ar), 7.16-7.11 (2H, m, Ar, N=CHO), 7.02 (1H, dd, *J* = 5.1, 3.6 Hz, Ar), 5.06 (1H, d, *J* = 2.1 Hz, CH), 1.14 (9H, s, CH_3). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.0 (C), 154.6 (CH), 132.8 (C), 127.5 (CH), 127.3 (CH, q, J_{C-F} = 2.0 Hz, Ar), 126.5 (CH), 123.3 (C, q, J_{C-F} = 283 Hz), 86.3 (C, q, J_{C-F} = 32 Hz), 82.9 (C), 75.0 (CH), 27.3 (CH_3). $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –81.8 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{15}F_3NO_3S^+$: 322.0719, found 322.0713. ***cis*-4k** (minor diastereomer): $[\alpha]_D^{25}$ +164.7 (*c* 0.49, $CHCl_3$, 91% *ee*); ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (1H, dd, *J* = 5.1, 1.3 Hz, Ar), 7.39-7.38 (1H, m, Ar), 7.09 (1H, d, *J* = 2.4 Hz, N=CHO), 7.08 (1H, t, *J* = 3.7 Hz, Ar), 5.08 (1H, dd, *J* = 2.4, 0.9 Hz, CH), 1.55 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.0 (C), 153.9 (CH), 137.7 (C), 127.4 (CH), 127.3 (CH), 127.2 (CH), 122.5 (C, q, J_{C-F} = 283 Hz), 86.4 (C, q, J_{C-F} = 32 Hz), 83.7 (C), 78.2 (CH), 27.7 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –75.5 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{15}F_3NO_3S^+$+ 322.0719, found 322.0713.

*tert-Butyl 5-phenethyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**4l**):* Yellow oil (71.2 mg, 83% from 50.0 mg of **1l**). HPLC (Chiralpak AY-H, hexane:*i*PrOH

95:5, 1 mL/min): ***trans*-(4*S*,5*S*)-4l** (major diastereomer, 84% ee): minor enantiomer, t_r = 5.2 min, major enantiomer, t_r = 7.0 min; ***cis*-4l** (minor diastereomer, 87% ee): minor enantiomer, t_r = 8.7 min, major enantiomer, t_r = 12.6 min; dr *trans:cis* = 72:28. ***trans*-(4*S*,5*S*)-4l** (major diastereomer): $[\alpha]_D^{25}$ +51.2 (*c* 0.86, $CHCl_3$, 84% *ee*); ^{1}H NMR (300MHz, $CDCl_3$) δ ^{1}H NMR (300MHz, $CDCl_3$) δ 7.30-7.26 (2H, m, Ar), 7.22-7.19 (1H, m, Ar), 7.17-7.13 (2H, m, Ar), 7.00 (1H, d, *J* = 2.2 Hz, N=CHO), 4.88 (1H, d, *J* = 2.3 Hz, CH), 2.75 (2H, t, *J* = 8.9 Hz, CH_2), 2.38-2.27 (1H, m, CH), 2.22-2.11 (1H, m, CH), 1.47 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.5 (C), 154.8 (CH), 140.1 (C), 128.5 (CH), 128.0 (CH), 126.4 (CH), 124.3 (C, q, $J_{C\text{-}F}$ = 282 Hz), 85.7 (C, q, $J_{C\text{-}F}$ = 30 Hz), 83.4 (C), 72.1 (CH), 31.3 (CH_2), 28.6 (CH_2), 27.9 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –79.9 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{21}F_3NO_3^+$: 344.1468, found: 344.1472. ***cis*-4l** (minor diastereomer): $[\alpha]_D^{25}$ +52.1 (*c* 0.59, $CHCl_3$, 87% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.29 (2H, m, Ar), 7.26-7.17 (3H, m, Ar), 7.01 (1H, d, *J* = 2.2 Hz, N=CHO), 4.71 (1H, d, *J* = 1.7 Hz, CH), 2.81-2.66 (2H, m, CH_2), 2.46-2.36 (1H, m, CH), 2.30-2.17 (1H, m, CH), 1.50 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.7 (C), 154.7 (CH), 139.7 (C), 128.7 (CH), 128.2 (CH), 126.6 (CH), 123.7 (C, q, $J_{C\text{-}F}$ = 284.3 Hz), 86.9 (C, q, $J_{C\text{-}F}$ = 29 Hz), 83.2 (CH), 73.2 (C), 35.7 (CH_2), 28.4 (CH_2), 27.7 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –74.6 (s, CF_3). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{21}F_3NO_3^+$: 344.1468, found: 344.1472.

General procedure for the enantioselective formal [3+2] cycloaddition reaction with methyl 2-isocyano-2-phenylacetate.

Squaramide **VIII** (6.8 mg, 0.0125 mmol) and silver oxide (1.5 mg, 0.0063 mmol) were introduced in a round bottom flask followed by MTBE (2 mL) and trifluoroacetophenone **1** (0.25 mmol). The flask was closed with a stopper and introduced in a bath at −20 ºC. After 5 min, methyl 2-isocyano-2-phenylacetate (**2c**, 40 μL, 0.33 mmol) was added and the mixture was stirred at −20 ºC until consumption of the trifluoroacetophenone **1** (TLC). After this time, the reaction mixture was filtered through a short pad of silica gel and concentred under reduced pressure. Compounds **5** were quickly hydrolyzed during slow column chromatography, so separation of both diastereomers by this procedure was not possible.

The racemic product was obtained using a similar procedure using the catalyst 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-((3-(dimethylamino)propyl)amino)cyclobut-3-ene-1,2-dione and silver oxide.

*Methyl 4,5-diphenyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**5a**):* Yellow oil (76.9 mg, 89% from 43.0 mg of **1a**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-5a** (minor diastereomer): major enantiomer, t_r = 8.4 min, minor enantiomer, t_r = 6.7 min; ***cis*-5a** (major diastereomer, 90% ee): major enantiomer, t_r = 18.3 min, minor enantiomer, t_r = 12.3 min; dr *trans:cis* = 15:85. ***cis*-5a** (major diastereomer): $[\alpha]_D^{25}$ –5.3 (*c* 1.0, $CHCl_3$, for the diastereomer mixture); ^1H NMR (300 MHz, $CDCl_3$) δ 7.46-7.41 (3H, m, Ar), 7.43 (1H, s, N=CHO), 7.15-7.08 (2H, s, Ar), 7.03 (5H, s, Ar), 3.98 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.6 (C), 153.2 (CH), 134.4 (C), 130.6 (C), 128.7 (CH), 128.3 (CH), 127.8 (CH), 127.6 (CH), 127.51 (CH), 127.46 (CH), 123.7 (C, q, $J_{C\text{-}F}$ = 283 Hz), 92.6 (C, q, $J_{C\text{-}F}$ = 29 Hz), 86.1 (C), 53.4 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ -72.9 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{15}F_3NO_3^+$: 350.0999, found: 350.0995. ***trans*-5a** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture, ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (2H, dd, *J* = 8.1, 3.0 Hz, Ar), 7.72 (2H, dd, J = 8.0, 3.0 Hz, Ar), 7.50-7.35 (7H, m, Ar, N=CHO), 3.14 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –72.3 (s, CF_3).

*Methyl 5-(4-methoxyphenyl)-4-phenyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**5c**):* Yellow oil (40.3 mg, 42% from 51.0 mg of **1c**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-5c** (minor diastereomer): major enantiomer, t_r = 8.6 min, minor enantiomer, t_r = 12.1 min; ***cis*-5c** (major diastereomer, 89% ee): major enantiomer, t_r = 25.6 min, minor enantiomer t_r = 18.5 min; dr *trans:cis* = 21:79. ***cis*-5c** (major diastereomer): $[\alpha]_D^{25}$ –12.3 (*c* 1.7, $CHCl_3$, for the diastereomer mixture); ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (1H, s, N=CHO), 7.34 (2H, d, *J* = 8.4 Hz, Ar), 7.05-7.03 (5H, s, Ar), 6.62 (2H, d, *J* = 9.0 Hz, Ar), 3.97 (3H, s, CH_3), 3.68 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.7 (C), 159.6 (C), 153.2 (CH), 134.6 (C), 129.7 (C), 129.0 (CH), 128.3 (C), 127.8 (CH), 127.5 (CH), 123.7 (C, q, $J_{C\text{-}F}$ = 283 Hz), 112.9 (CH), 92.6 (C, q, $J_{C\text{-}F}$ = 28.5 Hz), 86.1 (C), 55.0 (CH_3), 53.3 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –73.28 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{17}F_3NO_4^+$: 380.1104, found: 380.1106. ***trans*-5c** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture, ^1H NMR (300 MHz, $CDCl_3$) δ 7.93-

7.90 (2H, m, Ar), 7.62 (2H, d, *J* = 8.7 Hz, Ar), 7.44 (1H, s, N=CHO), 6.96 (2H, d, *J* = 9.0 Hz, Ar), 3.84 (3H, s, CH_3), 3.19 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –72.6 (s, CF_3).

*Methyl 5-(4-chlorophenyl)-4-phenyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**5d**):* Yellow oil (95.9 mg, >95% from 53.0 mg of **1d**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-5d** (minor diastereomer): major enantiomer, t_r = 8.0 min, minor enantiomer, t_r = 6.0 min; ***cis*-5d** (major diastereomer, 89% ee): major enantiomer, t_r = 15.7 min, minor enantiomer t_r = 12.0 min; dr *trans:cis* = 10:90. ***cis*-5d** (major diastereomer): $[\alpha]_D^{25}$ –8.0 (*c* 0.93, $CHCl_3$, for the diastereomer mixture); ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (1H, s, N=CHO), 7.39 (2H, d, *J* = 8.7 Hz, Ar), 7.13-6.96 (7H, m, Ar), 3.98 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.5 (C), 153.1 (CH), 134.9 (C), 134.0 (C), 129.5 (C), 129.1 (CH), 128.6 (CH), 128.0 (CH), 127.8 (CH), 127.3 (CH), 123.5 (C, q, $J_{C\text{-}F}$ = 283 Hz), 92.2 (C, q, $J_{C\text{-}F}$ = 29 Hz), 86.1 (C), 53.5 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –73.2 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{14}ClF_3NO_3^+$: 384.0609, found: 384.0609. ***trans*-5d** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture, ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (2H, d, *J* = 8.1 Hz, Ar), 7.52 (2H, d, *J* = 9.0 Hz, Ar), 3.2 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –71.5 (s, CF_3).

*Methyl 5-(4-bromophenyl)-4-phenyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**5n**):* Yellow oil (87.5 mg, 82% from 63.1 mg of **5n**). HPLC (Chiralpak IC, hexane:*i*PrOH 90:10, 1 mL/min): ***trans*-5n** (minor diastereomer): both enantiomers 3.6 min; ***cis*-5n** (major diastereomer, 89% ee): major enantiomer, t_r = 10.5 min, minor enantiomer, t_r = 8.6 min; dr *trans:cis* = 13:87. ***cis*-5n** (major diastereomer): $[\alpha]_D^{25}$ –12.0 (*c* 0.82, $CHCl_3$, 89% *ee*, for the diastereomer mixture); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (1H, s, N=CHO), 7.26 (2H, d, *J* = 8.5 Hz, Ar), 7.17 (2H, d, *J* = 9.0 Hz, Ar), 7.04-6.90 (5H, m, Ar), 3.91 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.5 (C), 153.1 (CH), 134.0 (C), 130.8 (CH), 129.7 (CH), 129.4 (CH), 128.7 (CH), 128.1 (CH), 127.3 (CH), 123.4 (C, q, $J_{C\text{-}F}$ = 283 Hz), 123.3 (C), 92.3 (C, q, $J_{C\text{-}F}$ = 29 Hz), 86.1 (C), 53.5 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –73.1 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{14}BrF_3NO_3^+$: 428.0104, found: 428.0107. ***trans*-5n** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture, ^1H NMR (300 MHz, $CDCl_3$) δ 7.81-7.78 (2H, m, Ar), 7.37 (1H, s, N=CHO), 3.14 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –72.4 (s, CF_3).

*Methyl 4-phenyl-5-(m-tolyl)-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**5e**):* Yellow oil (78.5 mg, 86% from 47.0 mg of **1e**). HPLC (Chiralpak IC, hexane:*i*PrOH 90:0, 1 mL/min): ***cis*-5e** (major diastereomer, 90% ee): major enantiomer, t_r = 11.4 min, minor enantiomer, t_r = 8.5 min; dr *trans:cis* = 1:99. ***cis*-5e** (major diastereomer): $[\alpha]_D^{25}$ –6.5 (*c* 0.69, $CHCl_3$, 90% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (1H, s, N=CHO), 7.26-7.22 (2H, unresolved m, Ar), 7.04 (5H, s, Ar), 6.98 (1H, t, *J* = 7.7 Hz, Ar), 6.91 (1H, br d, *J* = 7.5 Hz, Ar), 3.97 (3H, s, CH_3), 2.17 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.7 (C), 153.3 (CH), 137.1 (C), 134.4 (C), 130.5 (C), 129.4 (CH), 128.3 (CH), 127.7 (CH), 127.5 (CH), 127.4 (CH), 124.6 (C), 123.7 (C, q, $J_{C\text{-}F}$ = 283 Hz), 92.6 (C, q, $J_{C\text{-}F}$ = 29 Hz), 86.1 (C), 53.3 (CH_3), 21.2 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –72.8 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{17}F_3NO_3^+$: 364.1155, found: 364.1157.

*Methyl 5-(3-methoxyphenyl)-4-phenyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**5f**):* Yellow oil (75.4 mg, 86% from 51.0 mg of **1f**). HPLC (Chiralpak IC, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-5f** (minor diastereomer): major enantiomer, t_r = 7.5 min, minor enantiomer, t_r = 10.1 min, ***cis*-5f** (major diastereomer, 89%): major enantiomer, t_r = 19.6 min, minor enantiomer, t_r = 12.5 min; dr *trans:cis* = 15:85. ***cis*-5f** (major diastereomer): $[\alpha]_D^{25}$ +5.40 (*c* 0.72, $CHCl_3$, for the diastereomer mixture); ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (1H, s, N=CHO), 7.10-6.90 (8H, m, Ar), 6.65 (1H, ddd, *J* = 7.4, 2.6, 1.7 Hz, Ar), 3.98 (3H, s, CH_3), 3.65 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.6 (C), 158.7 (C), 153.2 (CH), 134.4 (C), 131.9 (C), 128.7 (CH), 128.4 (CH), 127.8 (CH), 127.4 (CH), 123.6 (C, q, $J_{C\text{-}F}$ = 287 Hz), 120.0 (CH), 114.6 (CH), 113.4 (C), 92.4 (C, q, $J_{C\text{-}F}$ = 28 Hz), 86.1 (C), 55.1 (CH_3), 53.4 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –72.9 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{17}F_3NO_4^+$: 380.1104, found 380.1107. ***trans*-5f** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture, ^1H NMR (300 MHz, $CDCl_3$) δ 7.93-7.90 (1H, m, Ar), 7.45 (1H, s, N=CHO), 3.85 (3H, s, CH_3), 3.18 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –72.3 (s, CF_3).

*Methyl 5-(3-bromophenyl)-4-phenyl-5-(trifluoromethyl)-4,5-dihydrooxazole-4-carboxylate (**5g**):* Yellow oil (86.8 mg, 81% from 63.0 mg of **1g**). HPLC (Chiralpak IC, hexane:*i*PrOH 90:10, 1 mL/min): ***trans*-5g** (minor diastereomer): major enantiomer, t_r = 7.0 min, minor enantiomer, t_r = 5.7 min; ***cis*-5g** (major diastereomer, 88% ee): minor enantiomer, t_r = 10.1 min, major enantiomer, t_r = 14.3 min; dr *trans:cis* = 2:98. ***cis*-5g**

(major diastereomer): $[\alpha]_D^{25}$ –15.4 (*c* 0.92, $CHCl_3$, for the diastereomer mixture); ^1H NMR (300 MHz, $CDCl_3$) 7.51 (1H, s, Ar), 7.36 (1H, s, N=CHO), 7.32 (1H, br d, *J* = 8.0 Hz, Ar), 7.17 (1H, d, *J* = 9.0 Hz), 7.03-6.92 (5H, m, Ar), 6.88 (1H, t, *J* = 8.1 Hz, Ar), 3.91 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.4 (C), 153.1 (CH), 133.8 (C), 132.8 (C), 131.9 (CH), 130.6 (br, CH), 129.0 (CH), 128.7 (CH), 128.0 (CH), 127.3 (CH), 126.4 (CH), 123.4 (C, q, $J_{C\text{-}F}$ = 283 Hz), 121.7 (C), 92.0 (C, q, $J_{C\text{-}F}$ = 29 Hz), 86.2 (C), 53.5 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –72.8 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{14}BrF_3NO_3^+$: 428.0104, found: 428.0107. ***trans*-5g** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture, ^1H NMR (300 MHz, $CDCl_3$) δ 8.12 (1H, s, Ar), 7.93 (1H, d, *J* = 9.2 Hz, Ar), 7.80-7.70 (2H, m, Ar), 3.15 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –71.5 (s, CF_3).

*Methyl (2S,3S)-4,4,4-trifluoro-2-formamido-3-hydroxy-3-phenylbutanoate (**6a**):* 6 M Aqueous HCl (6 drops) was added to a solution of compound **3a** (54.0 mg, 0.20 mmol) in THF (1 mL). The reaction mixture was stirred at rt for 24 h. The mixture was basified with saturated aqueous $NaHCO_3$ (1 mL), water was added (10 mL), extracted with EtOAc (3 × 20 mL), washed with brine (20 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded compound **6a** as a colorless oil (58.0 mg, 95%). HPLC (Chiracel OD-H, hexane:*i*PrOH 90:10, 1 mL/min): ***trans*-6a** (major diastereomer, 88% ee); major enantiomer, t_r = 14.0 min, minor enantiomer, t_r = 11.0 min; ***cis*-6a** (minor diastereomer), major enantiomer, tr = 8.5 min, minor enantiomer, tr = 7.9 min; dr *trans:cis* = 96:4. ***trans*-6a** (major diastereomer): $[\alpha]_D^{25}$ –23.6 (*c* 0.68, $CHCl_3$, for the diastereomer mixture); ^1H NMR (300 MHz, $CDCl_3$) δ 8.24 (1H, dd, *J* = 1.2, 0.7 Hz, CHO), 7.59-7.57 (2H, m, Ar), 7.42-7.40 (3H, m, Ar), 6.79 (1H, d, *J* = 9.0 Hz, NH), 5.57 (1H, dd, *J* = 9.0, 0.6 Hz, CH), 4.68 (1H, bs, OH), 3.47 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.0 (C), 160.7 (CH), 134.4 (C), 129.6 (CH), 128.6 (CH), 126.1 (CH), 123.9 (C, q, $J_{C\text{-}F}$ = 283 MHz), 78.20 (C, q, $J_{C\text{-}F}$ = 30 Hz), 53.5 (CH), 52.9 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –75.8 (s, CF_3); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{13}F_3NO_4^+$: 292.0791, found: 292.0798. ***cis*-6a** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture, ^1H NMR (300 MHz, $CDCl_3$) δ 4.85 (d, *J* = 10.5 Hz, CH), 3.54 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –76.4 (s, CF_3).

*Methyl (2S,3S)-3-(3-bromophenyl)-4,4,4-trifluoro-2-formamido-3-hydroxybutanoate (**6g**):* Following the same procedure for the synthesis of compound **6a**, from compound **3g** (42.3 mg, 0.12 mmol) was obtained formamide **6g** as colorless oil (42.6 mg, 95%). HPLC (Chiralpak AY-H, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-6g** (major diastereomer, 91% ee): major enantiomer, t_r = 21.9 min, minor enantiomer, t_r = 29.6 min; ***cis*-6g** (minor diastereomer): major enantiomer, t_r = 10.9 min, minor enantiomer, t_r = 8.7 min; dr *trans:cis* = 83:17. ***trans*-6g** (major diastereomer): $[\alpha]_D^{25}$ +5.41 (*c* 0.72, $CHCl_3$, for the diastereomer mixture); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (1H, dd, *J* = 1.0, 0.7 Hz, CHO), 7.77 (1H, bs, Ar), 7.57-7.50 (2H, m, Ar), 7.29 (1H, t, *J* = 8.0 Hz, Ar), 6.75 (1H, d, *J* = 8.8 Hz, NH), 5.52 (1H, d, *J* = 9.0 Hz, CH), 4.85 (1H, bs, OH), 3.55 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 169.7 (C), 160.8 (CH), 136.8 (C), 132.7 (CH), 130.0 (CH), 129.5 (CH), 124.9 (CH), 123.7 (C, q, $J_{C\text{-}F}$ = 285 MHz), 122.9 (C), 77.8 (C, q, $J_{C\text{-}F}$ = 29 MHz), 53.6 (CH), 53.1 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –75.2 (s, CF_3). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{12}BrF_3NO_4^+$: 369.9896, found: 369.9883. ***cis*-6g** (minor diastereomer): ^{1}H NMR (300 MHz, $CDCl_3$) representative signals taken from the NMR spectra of the diastereomer mixture, δ 7.93 (1H, s, CHO), 7.82 (1H, t, *J* = 1.7 Hz, Ar), 6.16 (1H, d, *J* = 9.0 Hz, NH), 5.42 (1H, d, *J* = 9.0 Hz, CH), 3.87 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –71.5 (s, CF_3).

*Methyl (2S,3S)-2-amino-4,4,4-trifluoro-3-hydroxy-3-phenylbutanoate (**7a**):* 6M Aqueous HCl (6 drops) was added to a solution of compound **3a** (28.6 mg, 0.11 mmol) in MeOH (1 mL). The reaction mixture was stirred at rt for 24 h. The mixture was basified with saturated aqueous $NaHCO_3$ (1 mL), water was added (10 mL), extracted with EtOAc (3 × 20 mL), washed with brine (20 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure aforded compound **7a** as colorless oil (27.6 mg, 95%). HPLC (Chiralpak AY-H, hexane:*i*PrOH 95:5, 1 mL/min): ***trans*-7a** (major diastereomer, 90% ee): major enantiomer, t_r = 15.8 min, minor enantiomer, t_r = 17.3 min; ***cis*-7a** (minor diastereomer): major enantiomer, t_r = 11.8 min; minor enantiomer, t_r = 9.6 min; dr *trans:cis* 92:8. ***trans*-7a** (major diastereomer): $[\alpha]_D^{25}$ +47.9 (*c* 1.23, $CHCl_3$, for the diastereomer mixture); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61-7.54 (2H, m, Ar), 7.38-7.35 (3H, m, Ar), 4.33 (1H, s, CH), 3.29 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 171.3 (C), 135.1 (C), 128.8 (CH), 128.0 (CH), 126.3 (CH, q, $J_{C\text{-}F}$ = 2.0 Hz), 125.2 (C, q, $J_{C\text{-}F}$ = 283 Hz), 76.4 (C, q, $J_{C\text{-}F}$ = 27 Hz), 57.3 (CH), 52.0 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –75.9 (s, CF_3). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for

$C_{11}H_{13}F_3NO_3^+$: 264.0842, found: 264.0851. ***cis*-7a** (minor diastereomer): ^{1}H NMR (300 MHz, $CDCl_3$) representative signals taken from the NMR spectra of the diastereomer mixture, δ 7.65-7.60 (2H, m, Ar), 7.45-7.31 (3H, m, Ar), 4.07 (1H, s, CH), 3.83 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 56.5(CH), 52.9 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –75.0 (s, CF_3).

*Methyl 2-amino-3-(3-bromophenyl)-4,4,4-trifluoro-3-hydroxybutanoate (**7g**):* Following the same procedure for the synthesis of compound **7a**, from compound **3g** (22.7 mg, 0.064 mmol), was obtained **7g** (21.0 mg, 95%). HPLC (Chiralpak AD-H, hexane:*i*PrOH 98:2, 0.7 mL/min): ***trans*-7g**: (major diastereomer, 92% ee): major enantiomer, t_r = 36.5 min, minor enantiomer, t_r = 34.9 min. ***cis*-7g** (minor diastereomer): major enantiomer, t_r = 32.8 min, minor enantiomer, t_r = 28.9 min; dr *trans:cis* 93:7. ***trans*-7g**: (major diastereomer): $[\alpha]_D^{25}$ +49.1 (*c* 0.68, $CHCl_3$, for the diastereomer mixture); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (1H, t, *J* = 1.9 Hz, Ar), 7.55-7.48 (2H, m, Ar), 7.24 (1H, t, *J* = 7.9 Hz, Ar), 4.32 (1H, s, CH), 3.35 (3H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.8 (C), 137.3 (C), 132.0 (CH), 129.7 (CH, q, $J_{C\text{-}F}$ = 1.6 Hz), 129.5 (CH), 125.1 (CH, q, $J_{C\text{-}F}$ = 1.6 Hz), 124.9 (C, q, $J_{C\text{-}F}$ = 289 MHz), 75.9 (C, q, $J_{C\text{-}F}$ = 27 Hz), 57.1 (CH), 52.2 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –75.6 (s, CF_3). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{12}BrF_3NO_3^+$: 341.9947, found: 341.9948. For the X-ray structure of ***trans*-7g** see Figure S2 in the SI. ***cis*-7g** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (1H, br s, Ar), 7.56-7.44 (2H, m, Ar), 7.31 (1H, t, J = 8.0 Hz, Ar), 4.00 (1H, s, CH), 3.84 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –76.6 (s, CF_3).

*Methyl 2-amino-4,4,4-trifluoro-3-hydroxy-3-methylbutanoate (**7m**):* Following the same procedure for the synthesis of compound **7a**, from compound **3m** (56.2 mg, 0.16 mmol) after 72 h was obtained **7m** (60.2 mg, 88%). GLC (Supelco β-dex-225, T_{column}= 60 °C (1 min) to 150 °C at 7 °C/min, and to 220 °C at 16 °C/min, ***trans*-7m** (major diastereomer, 82%): major enantiomer t_r = 12.3 min, minor enantiomer t_r = 13.2 min; ***cis*-7m** (minor diastereomer): enantiomer 1, t_r = 17.7 min, enantiomer 2, t_r = 17.8 min; dr *trans:cis* = 97:3; ***trans*-7m**: (major diastereomer): $[\alpha]_D^{25}$ –38.2 (*c* 0.98, $CHCl_3$, 82% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.79 (4H, s, CH, CH_3 overlapped), 1.32 (3H, s, CH_3); ^{1}H NMR (300 MHz, DMSO-d_6, for **7m**·HCl) δ 8.82 (3H, br s, NH_3), 7.47 (1H, br s, OH), 4.10 (1H, s, CH-N), 3.75 (3H, s, CH_3), 1.39 (3H, s, CH_3);[19] $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 172.2 (C), 125.8 (C, q, $J_{C\text{-}F}$ = 285 MHz), 72.6 (C, q, $J_{C\text{-}F}$ = 31 Hz), 55.7

(br, CH), 52.5 (CH_3), 18.1 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –80.6 (s, CF_3). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_6H_{11}F_3NO_3^+$: 202.0686, found: 202.0684. ***cis*-7m** (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture, ^1H NMR (300 MHz, $CDCl_3$) δ 3.83 (3H, s, CH_3), 1.44 (3H, s, CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ –78.6 (s, CF_3).

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI:10.1021/acs.joc.xxxxxx.

Copies of ^1H, ^{13}C and ^{19}F NMR spectra, HPLC chromatograms and X-ray crystallographic data of **4i** and **7g** (PDF)

X-ray crystallographic data of **4i a**nd **7g** (CIF).

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Notes

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(15) Caution has to be taken during the purification of the reaction products to avoid alteration of the ee values due to the self-disproportionation of enantiomers phenomenon. See: (a) Soloshonok, V. A. Remarkable amplification of the self-disproportionation of enantiomers on achiral-phase chromatography columns. *Angew. Chem. Int. Ed.* **2006**, *45*, 766. (b) Soloshonok, V. A.; Roussel, C.; Kitagawa, O.; Sorochinsky, A. E. Self-disproportionation of enantiomers via achiral chromatography: a warning and an extra dimension in optical purifications. *Chem. Rev.* **2012**, *41*, 4180.

(16) The structure and absolute stereochemistry of compounds **7g** and **4i** were determined by X-ray analysis, CCDC 1844051-1844052, respectively, see SI.

(17) The absolute stereochemistry of the minor *cis*-**3** and *cis*-**4** oxazolines could not be determined. Based on our previous results with ketones (see ref. 5d) we assume they may have the (4*S*,5*R*) configuration.

(18) The absolute stereochemistry of compounds **5** could not be determined.

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(20) Compounds **3** and **4** showed some tendency to hydrolyze during column chromatography, which in some cases difficulted their purification by this technique. In a reduced number of cases, the reaction products contained trace amounts of residual isocyanoacetates or their byproducts. See NMR spectra in the SI for possible presence of small amounts of contaminants.