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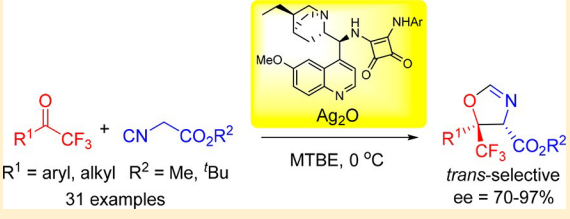
Additional Information

Enantioselective Synthesis of 5-Trifluoromethyl-2-oxazolines under Dual Silver/Organocatalysis

Pablo Martínez-Pardo,[†] Gonzalo Blay,*[†] Carlos Vila,[†] Amparo Sanz-Marco,[†] M. Carmen Muñoz,[‡] and Jose R. Pedro*,[†]

[†]Departament de Química Orgànica, Facultat de Química, Universitat de València, Burjassot, València 46100, Spain
[‡]Departament de Física Aplicada, Universitat Politècnica de València, València 46022, Spain

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.



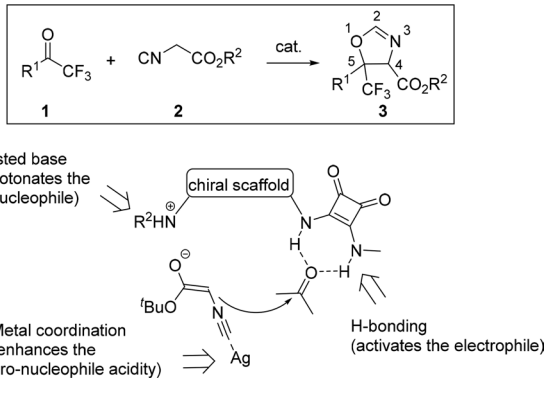
INTRODUCTION

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, to a lesser 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 nonfluorinated 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 nonproteinogenic 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 a 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, on the basis of 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-

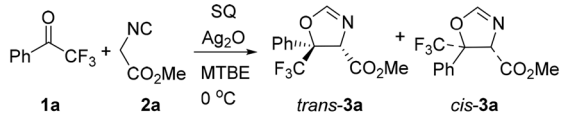
squaramide organocatalyst and Ag^+ as Lewis acid (Scheme 1).[5d]

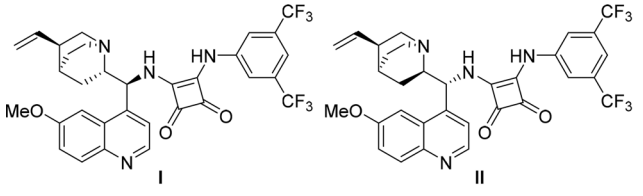
Following this approach,[14] we tested the reaction of trifluoroacetophenone (1a) and methyl isocyanoacetate (2a) in the presence of several bifunctional squaramides (SQ, 10 mol %) and Ag_2O (5 mol %) in methyl *tert*-butyl ether (MTBE) at 0 °C (Table 1, see also Tables S1–S3 in the Supporting Information). The reaction did not proceed in the absence of Ag_2O (Table 1, entry 1). On the other hand, all of 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 of 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).

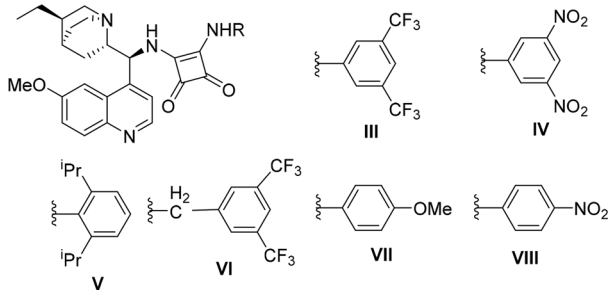
A strong concentration effect was also found, with the diastereo- and enantioselectivity of the reaction increasing with the dilution of the reaction mixture (Table 2, entries 1–3). The use of a 1:2 squaramide/Ag_2O ratio increased the diastereoselectivity but unfortunately lowered the enantioselectivity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

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, while 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

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

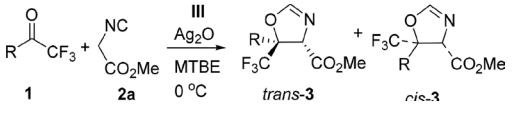
[a]1a (0.25 mmol), 2a (0.33 mmol), SQ (0.026 mmol), Ag_2O (0.0125 mmol), MTBE (2 mL), 0 °C. [b]Yield of isolated product. [c]Determined by ^{1}H NMR. [d]Determined by HPLC over chiral chromatography phases. [e]Reaction carried out in the absence of silver salt. No advance was observed after the indicated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

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).

Table 3. Enantioselective Reaction of Trifluoromethylketones and Methyl Isocyanoacetate. Substrate Scope[a]



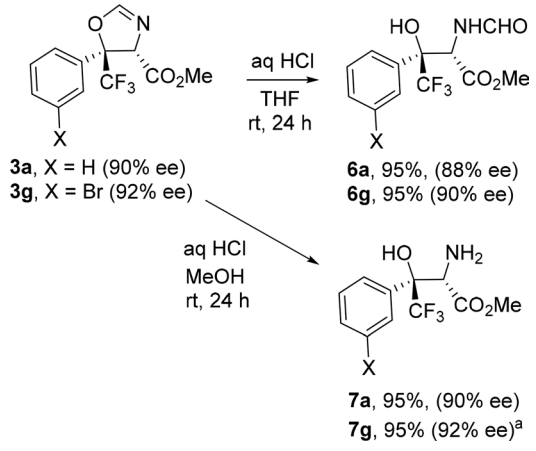
entry	1	R	*t* (h)	3	yield[b] (%)	*trans*:*cis*[c]	ee$_{trans}$[d] (%)
1	1a	Ph	4	3a	>95	96:4	90
2	1b	4-MeC_6H_4	5	3b	>95	94:6	87
3	1c	4-MeOC_6H_4	3.5	3c	88	96:4	85
4	1d	4-ClC_6H_4	4	3d	>95	80:20	84
5	1e	3-MeC_6H_4	5	3e	>95	94:6	90
6	1f	3-MeOC_6H_4	4	3f	94	92:8	88
7	1g	3-BrC_6H_4	3.5	3g	95	86:14	92
8	1h	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.

(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).

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]

Scheme 2. Hydrolysis of Oxazolines 3a and 3g



[a]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 the Supporting Information). *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]

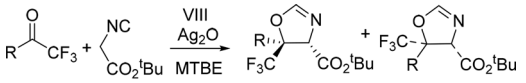
Finally, the reaction of several trifluoromethylketones 1 with methyl 2-isocyano-2-phenylacetate (2c) to give oxazolines 5 bearing two contiguous quaternary stereocenters was achieved in the presence of squaramide VIII and Ag_2O (Table 5).[18] In this case, the reaction worked better under higher concentration 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).

Furthermore, oxazoline 3m, prepared in 82% ee from methyl isocyanoacetate and 1,1,1-trifluoroacetone (Table 1, entry 13), upon treatment with aqueous HCl in methanol for 72 h, could be transformed into amino alcohol 7m (82% ee), a known

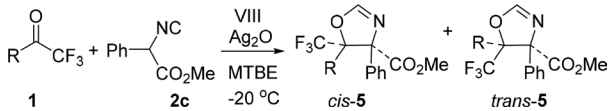
Table 4. Enantioselective Reaction of Trifluoromethylketones and *tert*-Butyl Isocyanoacetate. Substrate Scope[a]



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$_6$H$_4$	7	4b	87	66:34	93/96
3	1c	4-MeOC$_6$H	7	4c	>95	63:37	84/77
4	1d	4-ClC$_6$H$_4$	1	4d	>95	53:47	96/90
5	1e	3-MeC$_6$H	6	4e	94	76:24	97/87
6	1f	3-MeOC$_6$H$_4$	4	4f	84	72:28	97/85
7	1g	3-BrC$_6$H$_4$	1	4g	>95	64:36	97/90
8	1h	2-MeOC$_6$H$_4$	12	4h	80	94:6	94/70
9	1i	2-BrC$_6$H$_4$	3	4i[e]	>95	99:1	91/nd
10	1j	3,4-Cl$_2$C$_6$H$_3$	1	4j	>95	53:47	94/85
11	1k	2-thienyl	1	4k	>95	62:38	97/91
12	1l	CH$_2$CH$_2$Ph	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).

Table 5. Enantioselective Reaction of Trifluoromethylketones and Methyl 2-Isocyano-2-phenylacetate. Substrate Scope[a]

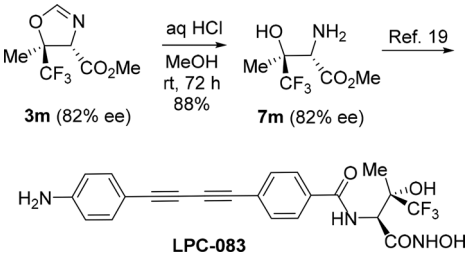


entry	1	R	*t* (d)	5	yield[b] (%)	*trans*:*cis*[c]	ee$_{cis}$[d] (%)
1	1a	Ph	1	5a	89	15:85	90
2	1c	4-MeOC$_6$H$_4$	3	5c	42	21:79	89
3	1d	4-ClC$_6$H$_4$	1	5d	>95	10:90	89
4	1n	4-BrC$_6$H$_5$	2	5n	82	13:87	89
5	1e	3-MeC$_6$H$_4$	1	5e	86	1:99	90
6	1f	3-MeOC$_6$H$_4$	3	5f	86	15:85	89
7	1g	3-BrC$_6$H$_4$	7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

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 and 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 an internal standard (δ 7.26 and 77.0 ppm, respectively) and at 282 MHz for ^{19}F NMR using $CFCl_3$ as an 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-(dimethylamino)propyl)-squaramide as a substitute 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, $J_{C\square F}$ = 1.6 Hz), 123.8 (C, q, $J_{C\square F}$ = 283 Hz), 87.6 (C, q, $J_{C\square F}$ = 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); ^{1}H 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{^{1}H} 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, $J_{C\square F}$ = 1.6 Hz), 123.8 (C, q, $J_{C\square F}$ = 283 Hz), 87.5 (C, q, $J_{C\square F}$ = 30 Hz), 74.0 (CH), 52.1 (CH_3), 21.0 (CH_3); ^{19}F{^{1}H} 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; ^{1}H 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{^{1}H} 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); ^{1}H 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{^{1}H} NMR (75 MHz, $CDCl_3$) δ 167.2 (C), 160.3 (C), 155.7 (CH), 127.3 (CH, q, $J_{C\square F}$ = 1.9 Hz), 123.8 (C, q, $J_{C\square F}$ = 283 Hz), 122.4 (C), 113.8 (CH), 87.5 (C, q, $J_{C\square F}$ = 30 Hz), 74.0 (CH), 55.2 (CH_3), 52.3 (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 $C_{13}H_{13}F_3NO_4^+$: 304.0791, found: 304.0795. ***cis***-3c (minor diastereomer): representative signals taken from the NMR spectra of the diastereomer mixture; ^{1}H 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{^{1}H} 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, $J_{C\square F}$ = 1.6 Hz), 123.6 (C, q, $J_{C\square F}$ = 283 Hz), 87.2 (C, q, $J_{C\square F}$ = 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, $J_{C\square F}$ = 283 Hz), 87.7 (C, q, $J_{C\square F}$ = 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, $J_{C\square F}$ = 1.8 Hz), 123.8 (C, q, $J_{C\square F}$ = 283 Hz), 122.9 (CH, q, $J_{C\square F}$ = 1.9 Hz), 87.6 (C, q, $J_{C\square F}$ = 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, $J_{C\square F}$ = 283 Hz), 118.1 (CH, q, $J_{C\square F}$ = 2.2 Hz), 114.9 (CH), 111.9 (CH, q, $J_{C\square F}$ = 1.7 Hz), 87.5 (C, q, $J_{C\square F}$ = 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, $J_{C\square F}$ = 1.7 Hz), 125.4 (C, q, $J_{C\square F}$ = 283 Hz), 124.6 (CH, q, $J_{C\square F}$ = 1.7 Hz), 122.6 (C), 86.9 (C, q, $J_{C\square F}$ = 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, $J_{C\square F}$ = 283 Hz), 120.9 (CH), 119.8 (C), 110.3 (CH), 86.9 (C, q, $J_{C\square F}$ = 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. *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 °C) 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 °C) 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, $J_{C\square F}$ = 283 Hz), 120.8 (C), 88.8 (C, q, $J_{C\square F}$ = 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, $J_{C\square F}$ = 1.8 Hz), 125.4 (CH, q, $J_{C\square F}$ = 1.7 Hz), 125.2

(C, q, $J_{C\square F}$ = 283 Hz), 86.6 (C, q, $J_{C\square F}$ = 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, $J_{C\square F}$ = 2.1 Hz), 123.2 (C, q, $J_{C\square F}$ = 283 Hz), 86.3 (C, q, $J_{C\square F}$ = 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, $J_{C\square F}$ = 283 Hz), 85.7 (C, q, $J_{C\square F}$ = 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, $J_{C\square F}$ = 283 Hz), 83.9 (C, q, $J_{C\square F}$ = 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 °C until consumption of the trifluoroacetophenone 1 (TLC). After this time, the reaction mixture was filtered through a short pad of silica gel and concenterd under reduced pressure. A small aliquot was analyzed by ^1H 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); ^1H 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); $^{13}C\{^1H\}$ 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, $J_{C\square F}$ = 2.0 Hz), 123.9 (C, q, $J_{C\square F}$ = 284 Hz), 87.6 (C, q, $J_{C\square F}$ = 30 Hz), 82.7 (C), 74.6 (CH), 27.1 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −80.3 (s, CF_3); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{17}F_3NO_3^+$: 316.1155, found: 316.1154. ***cis***-4a (minor diastereomer): $[\alpha]_D^{25}$ +77.2 (*c* 0.23, $CHCl_3$, 90% ee); ^1H 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); $^{13}C\{^1H\}$ 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, $J_{C\square F}$ = 283 Hz), 126.4 (CH), 123.0 (C, q, $J_{C\square F}$ = 283 Hz), 87.9 (C, q, $J_{C\square F}$ = 30.7 Hz), 83.6 (C), 77.4 (CH), 27.7 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −75.0 (s, CF_3); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{17}F_3NO_3^+$: 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 °C; $[\alpha]_D^{25}$ +153.3 (*c* 0.96, $CHCl_3$, 93% ee); ^1H 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); $^{13}C\{^1H\}$ 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, $J_{C\square F}$ = 1.7 Hz), 123.9 (C, q, $J_{C\square F}$ = 283 Hz), 87.6 (C, q, $J_{C\square F}$ = 30 Hz), 82.6 (C), 74.5 (CH), 27.1 (CH_3), 21.0 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −80.4 (s, CF_3); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{19}F_3NO_3^+$: 330.1312, found: 330.1316. ***cis***-4b (minor diastereomer): colorless oil; $[\alpha]_D^{25}$ +84.8 (*c* 1.09, $CHCl_3$, 96% ee); ^1H 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); $^{13}C\{^1H\}$ 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, $J_{C\square F}$ = 283 Hz), 87.9 (C, q, $J_{C\square F}$ = 30.1 Hz), 83.5 (C), 27.7 (CH_3), 21.1 (CH_3); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ −75.1 (s, CF_3); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{19}F_3NO_3^+$: 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); ^1H 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* = 18 Hz, CH), 3.79 (3H, s, CH_3), 1.08 (9H, s, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.5 (C), 160.4 (C), 155.3 (CH), 127.9 (CH, q, $J_{C\square F}$ = 1.8 Hz), 123.9 (C, q, $J_{C\square F}$ = 284 Hz), 122.9 (C), 113.8 (CH), 87.5 (C, q, $J_{C\square F}$ = 29 Hz), 82.7 (C), 74.5 (CH), 55.3 (CH_3), 27.3 (CH_3); $^{19}F\{^1H\}$ 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); ^1H 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, $J_{C\square F}$ = 283 Hz), 114.1 (CH), 87.8 (C, q, $J_{C\square F}$ = 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, $J_{C\square F}$ = 1.9 Hz), 123.7 (C, q, $J_{C\square F}$ = 283 Hz), 87.5 (C, q, $J_{C\square F}$ = 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, $J_{C\square F}$ = 283 Hz), 87.5 (C, q, $J_{C\square F}$ = 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, $J_{C\square F}$ = 2.0 Hz), 123.9 (C, q, $J_{C\square F}$ = 283 Hz), 123.5 (CH, q, $J_{C\square F}$ = 1.9 Hz), 87.6 (C, q, $J_{C\square F}$ = 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, $J_{C\square F}$ = 283 Hz), 87.9 (C, q, $J_{C\square F}$ = 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, $J_{C\square F}$ = 283 Hz), 118.6 (CH, q, $J_{C\square F}$ = 2.0 Hz), 114.8 (CH), 112.5 (CH, q, $J_{C\square F}$ = 1.8 Hz), 87.5 (C, q, $J_{C\square F}$ = 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, $J_{C\square F}$ = 283 Hz), 118.5 (CH), 115.1 (CH), 112.2 (CH), 87.9 (C, q, $J_{C\square F}$ = 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]$^+$ calcd 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); ^1H 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, $J_{C\square F}$ = 1.8 Hz), 125.1 (CH, q, $J_{C\square F}$ = 2.0 Hz), 123.6 (C, q, $J_{C\square F}$ = 283 Hz), 122.6 (C), 86.9 (C, q, $J_{C\square F}$ = 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); ^1H 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, $J_{C\square F}$ = 283 Hz), 87.2 (C, q, $J_{C\square F}$ = 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 °C; $[\alpha]_D^{25}$ +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{^{1}H} 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, $J_{C\square F}$ = 283 Hz), 120.6 (CH), 120.5 (C), 110.4 (CH), 87.0 (C, q, $J_{C\square F}$ = 30 Hz), 81.5 (C), 74.2 (CH), 54.7 (CH_3), 27.3 (CH_3); ^{19}F{^{1}H} 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); ^{1}H 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{^{1}H} 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, $J_{C\square F}$ = 283), 123.0 (C), 120.6 (CH), 111.9 (CH), 87.6 (C, q, $J_{C\square F}$ = 32 Hz), 82.4 (C), 75.5 (CH), 55.2 (CH_3), 27.8 (CH_3); ^{19}F{^{1}H} 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 °C; $[\alpha]_D^{25}$ +190.2 (*c* 0.54, $CHCl_3$, 91% ee); (two possible rotamers are observed) ^{1}H 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{^{1}H} 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, $J_{C\square F}$ = 30 Hz), 82.6 (CH), 74.0 (CH), 27.2 (CH_3); ^{19}F{^{1}H} 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 Supporting Information.

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); ^{1}H 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{^{1}H} 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, $J_{C\square F}$ = 1.9 Hz), 125.8 (CH, q, $J_{C\square F}$ = 1.7 Hz), 123.5 (C, q, $J_{C\square F}$ = 283 Hz), 86.5 (C, q, $J_{C\square F}$ = 30 Hz), 83.4 (C), 74.6 (CH), 27.3 (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 $C_{15}H_{15}Cl_2F_3NO_3^+$: 384.0376, found: 384.0371. ***cis***-4j (minor diastereomer): $[\alpha]_D^{25}$ +68.2 (*c* 0.45, $CHCl_3$, 85% ee); ^{1}H 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{^{1}H} 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, $J_{C\square F}$ = 283 Hz), 86.9 (C, q, $J_{C\square F}$ = 30.8 Hz), 84.1 (CH), 77.4 (CH), 27.7 (CH_3); ^{19}F{^{1}H} 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); ^{1}H 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{^{1}H} NMR (75 MHz, $CDCl_3$) δ 165.0 (C), 154.6 (CH), 132.8 (C), 127.5 (CH), 127.3 (CH, q, $J_{C\square F}$ = 2.0 Hz, Ar), 126.5 (CH), 123.3 (C, q, $J_{C\square F}$ = 283 Hz), 86.3 (C, q, $J_{C\square F}$ = 32 Hz), 82.9 (C), 75.0 (CH), 27.3 (CH_3). ^{19}F{^{1}H} 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); ^{1}H 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{^{1}H} 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, $J_{C\square F}$ = 283 Hz), 86.4 (C, q, $J_{C\square F}$ = 32 Hz), 83.7 (C), 78.2 (CH), 27.7 (CH_3); ^{19}F{^{1}H} 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 (300 MHz, $CDCl_3$) δ ^{1}H NMR (300 MHz, $CDCl_3$) 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{^{1}H} 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, $J_{C\square F}$ = 282 Hz), 85.7 (C, q, $J_{C\square F}$ = 30 Hz), 83.4 (C), 72.1 (CH), 31.3 (CH_2), 28.6 (CH_2), 27.9 (CH_3); ^{19}F{^{1}H} 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{^{1}H} 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, $J_{C\square F}$ = 284.3 Hz), 86.9 (C, q, $J_{C\square F}$ = 29 Hz), 83.2 (CH), 73.2 (C), 35.7 (CH_2), 28.4 (CH_2), 27.7 (CH_3); ^{19}F{^{1}H} 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 °C. After 5 min, methyl 2-isocyano-2-phenylacetate (2c, 40 μL, 0.33 mmol) was added and the mixture was stirred at −20 °C until consumption of the trifluoroacetophenone 1 (TLC). After this time, the reaction mixture was filtered through a short pad of silica gel and concenterd 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, NCHO), 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-F} = 283 Hz), 92.6 (C, q, J_{C-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, NCHO), 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, NCHO), 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-F} = 283 Hz), 112.9 (CH), 92.6 (C, q, J_{C-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, NCHO), 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, NCHO), 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-F} = 283 Hz), 92.2 (C, q, J_{C-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, NCHO), 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-F} = 283 Hz), 123.3 (C), 92.3 (C, q, J_{C-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, NCHO), 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, NCHO), 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-F} = 283 Hz), 92.6 (C, q, J_{C-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, NCHO), 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-F} = 287 Hz), 120.0 (CH), 114.6 (CH), 113.4 (C), 92.4 (C, q, J_{C-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, NCHO), 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, NCHO), 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-F} = 283 Hz), 121.7 (C), 92.0 (C, q, J_{C-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). Aqueous HCl (6 M, six 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. Saturated aqueous

$NaHCO_3$ (1 mL) and water (10 mL) were added, and the mixture 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, t_r = 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); ^{1}H 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{^{1}H} 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, $J_{C\square F}$ = 283 MHz), 78.20 (C, q, $J_{C\square F}$ = 30 Hz), 53.5 (CH), 52.9 (CH_3); ^{19}F{^{1}H} 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; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.85 (d, J = 10.5 Hz, CH), 3.54 (3H, s, CH_3); ^{19}F{^{1}H} 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 a procedure similar to that used for the synthesis of compound 6a, from compound 3g (42.3 mg, 0.12 mmol) was obtained formamide 6g as a 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{^{1}H} 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, $J_{C\square F}$ = 285 MHz), 122.9 (C), 77.8 (C, q, $J_{C\square F}$ = 29 MHz), 53.6 (CH), 53.1 (CH_3); ^{19}F{^{1}H} 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{^{1}H} 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). Aqueous HCl (6 M, six 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. Saturated aqueous $NaHCO_3$ (1 mL) and water (10 mL) were added, and the mixture 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 a 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{^{1}H} NMR (75 MHz, $CDCl_3$) δ 171.3 (C), 135.1 (C), 128.8 (CH), 128.0 (CH), 126.3 (CH, q, $J_{C\square F}$ = 2.0 Hz), 125.2 (C, q, $J_{C\square F}$ = 283 Hz), 76.4 (C, q, $J_{C\square F}$ = 27 Hz), 57.3 (CH), 52.0 (CH_3); ^{19}F{^{1}H} 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{^{1}H} NMR (75 MHz, $CDCl_3$) δ 56.5(CH), 52.9 (CH_3); ^{19}F{^{1}H} 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 a procedure similar to that used 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{^{1}H} NMR (75 MHz, $CDCl_3$) δ 170.8 (C), 137.3 (C), 132.0 (CH), 129.7 (CH, q, $J_{C\square F}$ = 1.6 Hz), 129.5 (CH), 125.1 (CH, q, $J_{C\square F}$ = 1.6 Hz), 124.9 (C, q, $J_{C\square F}$ = 289 Hz), 75.9 (C, q, $J_{C\square F}$ = 27 Hz), 57.1 (CH), 52.2 (CH_3); ^{19}F{^{1}H} 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 Supporting Information. ***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{^{1}H} NMR (282 MHz, $CDCl_3$) δ −76.6 (s, CF_3).

Methyl 2-Amino-4,4,4-trifluoro-3-hydroxy-3-methylbutanoate (7m). Following a procedure similar to that used 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 at7 °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{^{1}H} NMR (75 MHz, $CDCl_3$) δ 172.2 (C), 125.8 (C, q, $J_{C\square F}$ = 285 MHz), 72.6 (C, q, $J_{C\square F}$ = 31 Hz), 55.7 (br, CH), 52.5 (CH_3), 18.1 (CH_3); ^{19}F{^{1}H} 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; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (3H, s, CH_3), 1.44 (3H, s, CH_3); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ −78.6 (s, CF_3).

ASSOCIATED CONTENT

AUTHOR INFORMATION

Corresponding Authors

*E-mail: gonzalo.blay@uv.es.

*E-mail: jose.r.pedro@uv.es.

ORCID

Gonzalo Blay: 0000-0002-7379-6789

Carlos Vila: 0000-0001-9306-1109

José R. Pedro: 0000-0002-6137-866X

Notes

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

(18) The absolute stereochemistry of compound 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 made their purification by this technique difficult. In a reduced number of cases, the reaction products contained trace amounts of residual isocyanoacetates or their byproducts. See the NMR spectra in the Supporting Information for the possible presence of small amounts of contaminants.