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Organocatalytic Asymmetric One-Pot Sequential Conjugate Addition/Dearomative Fluorination: Synthesis of Chiral Fluorinated Isoxazol-5(4*H*)-ones

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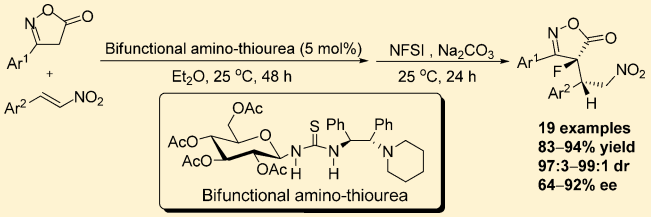
Supporting Information

ABSTRACT: A facile one-pot sequential conjugate addition/dearomative fluorination transformation of isoxazol-5(4*H*)-ones with nitroolefins and *N*-fluorobenzenesulfonimide (NFSI) has been developed. By using a bifunctional chiral tertiary amino-thiourea catalyst, a series of chiral fluorinated isoxazol-5(4*H*)-ones containing one fluorine-substituted quaternary stereocenter were obtained in high yields with high enantio- and diastereoselectivities. Further transformation of adducts could afford isoxazolidin-5-one derivatives with three contiguous stereocenters.



INTRODUCTION

Fluorinated heteroalicyclic scaffolds are important structural units because of their frequent appearance in many pharmaceuticals and biologically active compounds.[1] The development of efficient methods for the construction of these useful building blocks is of significant interest in organic chemistry. To this end, many reports have provided efficient approaches to the construction of various fluorinated heteroalicyclic compounds, such as fluorinated tetrahydropyrans, tetrahydrofurans, flavanones, cyclohexenones, thiacyclohexanes, piperidines, tetrahydropyrroloindoles, and tetrahydrofuroindoles.[2] Despite this promising progress, it is still highly desirable to broaden the diversity of fluorinated hereroalicycles and to develop new catalytic asymmetric methods to access chiral fluorinated hereroalicyclic species. Isoxazol-5(4*H*)-ones, an important class of five-membered heteroalicyclic rings, have exhibited a range of applications in organic synthesis and medicinal chemistry.[3] However, a survey of the literature reveals that the asymmetric version for the synthesis of optically active isoxazolinone derivatives is still elusive.

The asymmetric dearomatization of aromatic compounds offers straightforward access to chiral molecules with cyclic skeletons and has received much attention over the past decades.[4] Although a wide variety of catalytic asymmetric dearomatization transformations have been discovered, relatively few dearomative fluorination reactions have been reported.[5] Recently, Gaunt and co-workers provided a single elegant example of the phenol dearomatization using an asymmetric sequential transformation strategy that affords the fluorinated decalin in excellent enantioselectivity,[5a] and Gouverneur's group described an organocatalytic asymmetric fluorocyclization reaction of indoles involving an intramolecular cyclization/dearomative fluorination process.[5b] Our group reported a catalytic asymmetric one-pot sequential 1,4-addition/dearomative fluorination to afford optically active fluorinated pyrazolones.[6] Encouraged by these results and as a part of our continued interest in the stereoselective synthesis of organofluorine compounds,[7,8] we envisioned that fluorinated isoxazolinones could be constructed using isoxazol-5(4*H*)-ones as the aromatic relay partners. Herein, we report our efforts in developing this one-pot sequential process. Our studies show that this addition reaction of isoxazol-5(4*H*)-ones to nitroolefins in the presence of chiral amino-thiourea catalysts proceeds to produce aromatic isoxazol-5-ol intermediates (**Int-A**), which could be further fluorinated with concurrent dearomatization to afford the fluorinated chiral isoxazol-5(4*H*)-ones (Scheme 1).

RESULTS AND DISCUSSION

We initially investigated the reaction of 3-phenylisoxazol-5(4*H*)-one **1a** (1.3 equiv) with *trans*-*β*-nitrostyrene **2a** (1.0 equiv) and *N*-fluorobenzenesulfonimide (NFSI, 1.5 equiv) in toluene at room temperature by using saccharide-derived chiral tertiary amino-thiourea catalyst **A** (Figure 1), developed previously in our laboratory.[9] After substrate **2a** completely disappeared (monitored by TLC), the electrophilic fluorinating reagent NFSI was then added to the reaction system. In the presence of catalyst **A**, the fluorinated product **3a** was obtained in good yield (Table 1, entry 1); accordingly, the heteroaromatic isoxazol-5-ole (**Int-a**) was isolated in 27% yield. The use of 4-dimethylaminopyridine (DMAP) and 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) gave similar results (entries 2 and 3). Subsequently, several inorganic bases were employed as additives (entries 4−7). It was found that the use of Na_2CO_3 provided the best results (entry 5, 88%, 99:1 dr, 52% ee). After a series of amino-thioureas **B**−**G** were screened by using Na_2CO_3 as additive (entries 8−13), we were pleased to find that the catalyst **D**, which incorporates chiral

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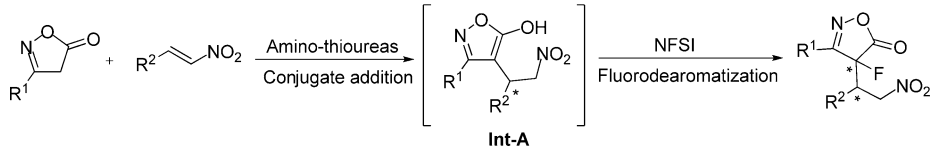
Scheme 1. One-Pot Sequential Strategy for the Synthesis of Chiral Fluorinated Isoxazol-5(4*H*)-ones



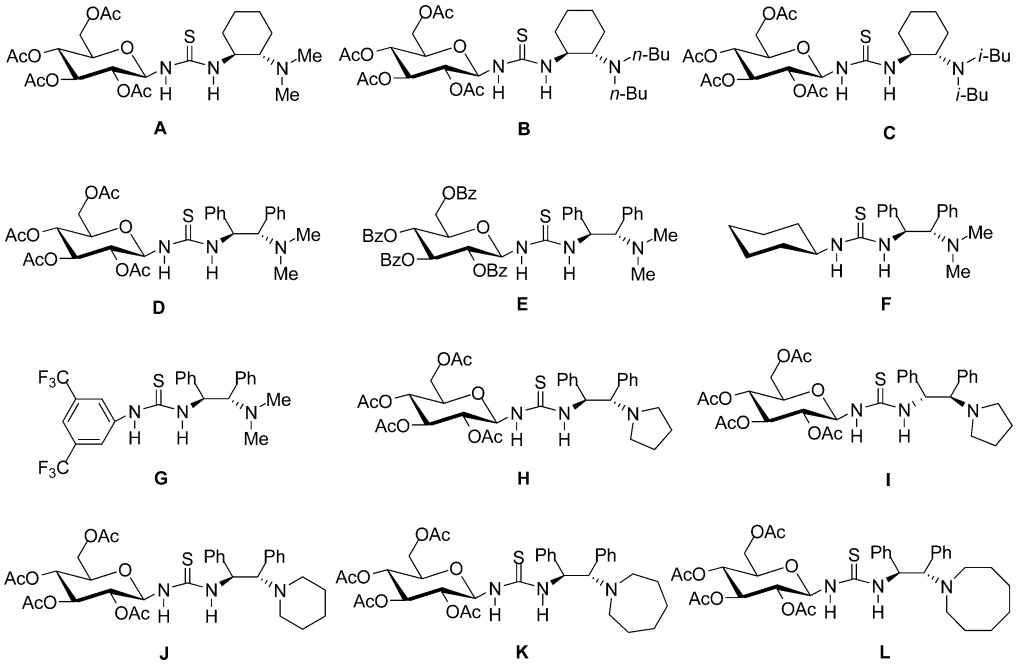


Figure 1. Bifunctional tertiary amino-thiourea catalysts tested in the one-pot sequential transformation.

1,2-diphenylethane-1,2-diamine at the thiourea backbone, affords the sequential product **3a** in 93% yield and with 54% ee (entry 10). It is very interesting that the use of catalysts **F** and **G**, which do not contain a saccharide motif, resulted in a slight decrease in enantioselectivity (entries 12 and 13). Further modifications of modular organocatalyst **D** have been made by using different cyclic tertiary amine substituents to give a series of new catalysts **H**–**L** (Figure 1). Chiral catalyst **H** promoted this one-pot sequential transformation with a good enantioselectivity of 80% ee, whereas catalyst **I** exhibited a moderate level of stereoselectivity with an opposite sense of asymmetric induction (entries 14 and 15). These results indicate that the (*S*,*S*)-configuration of 1,2-diphenylethane-1,2-diamine matched the *β*-D-glucopyranose to enhance the stereochemical control. Bifunctional catalysts **J**, **K**, and **L** with an (*S*,*S*)-configuration of the 1,2-diphenylethane-1,2-diamine moiety can also induce good enantioselectivities (entries 16–18). Subsequent optimization of other reaction parameters, such as solvent, catalyst loading, and temperature (entries 19–27) led to the discovery that the best results were obtained as the reaction was performed in Et_2O at room temperature employing 5 mol % tertiary amino-thiourea **J** as catalyst (93% yield, 99:1 dr, 86% ee; entry 24).

Under the optimized experimental conditions, the scope of the one-pot sequential transformation was investigated with a variety of isoxazol-5(4*H*)-ones **1** and nitroolefins **2**, and the results are summarized in Table 2. This asymmetric one-pot multistep reaction is compatible with a series of nitroolefin substrates, delivering the fluorinated isoxazolinones **3a**–**i** in 87–94% yields with 80–92% enantioselectivities and excellent diastereoselectivites (entries 1–9). The reaction worked well with 1- and 2-naphthalenyl-substituted nitroolefins to afford the products **3j** and **3k** in good yields and enantioselectivities with uniformly high diastereoselectivities (entries 10 and 11). Notably, the heteroaromatic substrate was also tolerated, affording the desired product **3l** in high yield and diastereoselectivity, albeit with decreased enantioselectivity (90% yield, 99:1 dr, 64% ee, entry 12). In addition, we investigated the addition reaction with alkyl-substituted nitroolefins, such as (*E*)-1-nitropent-1-ene and (*E*)-4-methyl-1-nitropent-1-ene. These substrates were found to be unsuitable for this asymmetric sequential transformation, and no product was observed. The basis for this intriguing difference in nitroolefin reactivity is not well understood at this stage. Further exploration of the substrate scope focused on the nucleophilic isoxazol-5(4*H*)-ones. It appeared that electron-donating and electron-withdrawing substituents on the aromatic ring can be tolerated, and good to high stereocontrol was observed for the products **3m**–**s** (entries 13–19). Finally, the single stereoisomer of **3i** proved to be crystalline, thus allowing the determination of the absolute configuration of two adjacent stereogenic centers to be (4*S*, 1′*S*) by means of X-ray crystallographic analysis (see the Supporting Information).[10]

These sequential products **3** are useful synthetic intermediates and can be readily transformed into isoxazolidin-5-ones, known to be important structural elements of varied pharmacologically active compounds.[11] For instance, reduction of **3b** using $NaBH_4$, followed by condensation with Boc_2O gave rise to fluorinated isoxazolidin-5-one **4** in 55% yield with moderate diastereoselectivity. Notably, three contiguous stereocenters were constructed without erosion of enantiopurity during these transformations (Scheme 2).

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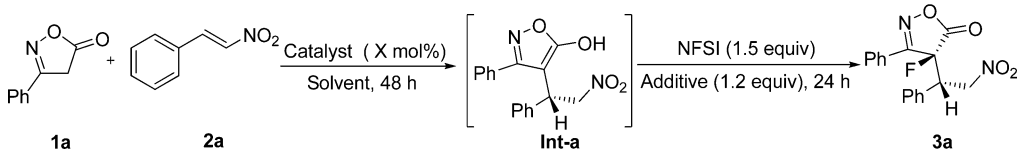
Table 1. Effect of Catalyst, Solvent, Temperature, and Other Reaction Conditions for the Sequential Reaction[a]



1a 2a Int-a 3a

entry	catalyst (mol %)	solvent	temp (°C)	additive	yield (%)	dr[b]	ee[c] (%)
1	**A** (10)	toluene	25		62	98:2	52 (−)
2	**A** (10)	toluene	25	DMAP	68	98:2	50 (−)
3	**A** (10)	toluene	25	DBU	70	98:2	48 (−)
4	**A** (10)	toluene	25	$NaHCO_3$	80	99:1	47 (−)
5	**A** (10)	toluene	25	Na_2CO_3	88	99:1	52 (−)
6	**A** (10)	toluene	25	K_2CO_3	84	>99:1	50 (−)
7	**A** (10)	toluene	25	Cs_2CO_3	76	99:1	49 (−)
8	**B** (10)	toluene	25	Na_2CO_3	89	98:2	40 (−)
9	**C** (10)	toluene	25	Na_2CO_3	89	99:1	23 (−)
10	**D** (10)	toluene	25	Na_2CO_3	93	>99:1	54 (−)
11	**E** (10)	toluene	25	Na_2CO_3	81	97:3	41 (−)
12	**F** (10)	toluene	25	Na_2CO_3	85	95:5	19 (−)
13	**G** (10)	toluene	25	Na_2CO_3	82	>99:1	39 (−)
14	**H** (10)	toluene	25	Na_2CO_3	94	>99:1	80 (−)
15	**I** (10)	toluene	25	Na_2CO_3	91	>99:1	51 (+)
16	**J** (10)	toluene	25	Na_2CO_3	93	>99:1	84 (−)
17	**K** (10)	toluene	25	Na_2CO_3	91	>99:1	84 (−)
18	**L** (10)	toluene	25	Na_2CO_3	93	>99:1	79 (−)
19	**J** (10)	CH_2Cl_2	25	Na_2CO_3	94	>99:1	64 (−)
20	**J** (10)	THF	25	Na_2CO_3	58	>99:1	48 (−)
21	**J** (10)	Et_2O	25	Na_2CO_3	93	>99:1	86 (−)
22	**J** (10)	CH_3CN	25	Na_2CO_3	78	>99:1	46 (−)
23	**J** (10)	CH_3OH	25	Na_2CO_3	57	>99:1	54 (−)
24	**J** (5)	Et_2O	25	Na_2CO_3	93	>99:1	86 (−)
25	**J** (1)	Et_2O	25	Na_2CO_3	88	>99:1	80 (−)
26[d]	**J** (5)	Et_2O	0	Na_2CO_3	70	>99:1	86 (−)
27	**J** (5)	Et_2O	40	Na_2CO_3	81	99:1	48 (−)

[a]Unless otherwise noted, all reactions were carried out with isoxazolin-5-one (**1a**) (21.0 mg, 0.13 mmol), nitrostyrene (**2a**) (14.9 mg, 0.10 mmol), tertiary amino-thiourea catalyst in solvent (1 mL) for 48 h. Then NFSI (47.3 mg, 0.15 mmol) and additive (0.12 mmol) were added at the same temperature, and stirring was maintained for 24 h. [b]Determined by ^{19}F NMR analysis of the crude product; [c]Determined by HPLC analysis; [d]After the addition of NFSI and Na_2CO_3, the reaction was performed for 72 h.

To obtain more information about this sequential transformation, we performed step-by-step control experiments. In the presence of the tertiary amino-thiourea catalyst **J**, compound **1a** was transformed into the *C*-substituted intermediate **Int-a** (Scheme 3), which was isolated in almost quantitative yield with 88% ee. Subsequent treatment of this intermediate **Int-a** with Na_2CO_3 and *N*-fluorobenzenesulfonimide in the absence of catalyst **J** afforded dearomatization−fluorination product **3a** in 90% yield with 95:5 dr and 84% ee. These results indicated that the chiral catalyst not only controls the stereochemistry in the first step but also is essential for the diastereoselective formation of the C−F bond in the subsequent transformation. On the basis of the above experimental results and other work,[6,12] a possible mechanism for the one-pot sequential 1,4-addition/dearomative fluorination transformation is proposed in Figure 2. First, the nitroolefin forms a hydrogen-binding complex with the thiourea group of the chiral catalyst, and the isoxazol-5(4*H*)-one substrate, in its enol form, is coordinated via hydrogen-binding to the amino moiety. Hydrogen-bond-assisted enol-type addition to the nitroolefin proceeds through a highly organized open transition state. In the subsequent electrophilic fluorination step, isoxazol-5-olate is reassociated with the catalyst system to form a highly organized structure followed by a hydrogen bond-assisted reaction with the fluorinating reagent.

CONCLUSION

In summary, we have developed a new one-pot sequential conjugate addition/dearomative fluorination reaction of isoxazol-5(4*H*)-ones with nitroolefins and NFSI. This transformation was cooperatively promoted by saccharide-based bifunctional organocatalysts that contain tertiary amine and thiourea moieties to activate substrates simultaneously. A series of fluorinated isoxazolin-5-ones were obtained in high yields and diastereoselectivities with good to high enantioselectivites. Further mechanistic investigation and extension of this protocol to the synthesis of bioactive products are ongoing in our laboratory.

EXPERIMENTAL SECTION

General Information. Solvents were distilled following standard procedures before use. Analytical thin-layer chromatography was performed on 0.20 mm silica gel plates. Silica gel (200−300 mesh) was used for flash chromatography. ^1H, ^{13}C, and ^{19}F NMR were recorded at 400 or 600 MHz (^1H NMR), 100 or 150 MHz (^{13}C NMR), as well as 376 MHz (^{19}F NMR). Chemical shifts were reported in ppm

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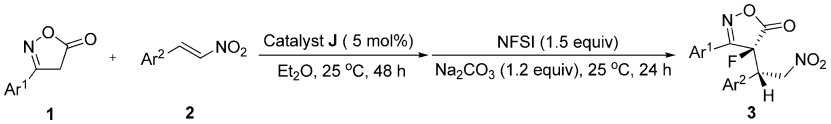
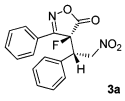
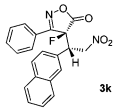
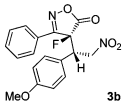
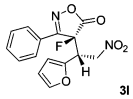
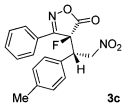
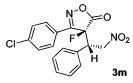
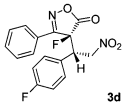
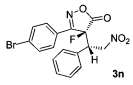
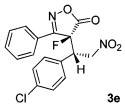
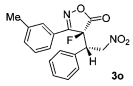
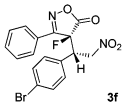
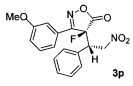
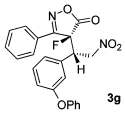
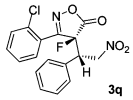
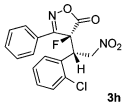
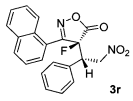
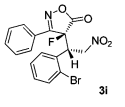
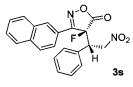
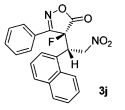
Table 2. Catalytic Asymmetric One-Pot Sequential Conjugate Addition/Dearomative Fluorination Transformation[a]



1 2 3

entry	product	yield (%)	dr[b]	ee (%)[c]	entry	product	yield (%)	dr[b]	ee (%)[c]
1	 3a	93	>99:1	86	11	 3k	84	>99:1	77
2	 3b	94	>99:1	92	12	 3l	90	>99:1	64
3	 3c	92	>99:1	90	13	 3m	92	>99:1	80
4	 3d	87	>99:1	86	14	 3n	84	>99:1	81
5	 3e	90	>99:1	81	15	 3o	92	>99:1	80
6	 3f	87	>99:1	80	16	 3p	91	>99:1	78
7	 3g	93	>99:1	80	17	 3q	88	>99:1	85
8	 3h	93	> 99:1	90	18	 3r	88	>99:1	79
9	 3i	87	97:3	90	19	 3s	85	>99:1	83
10	 3j	83	>99:1	82					

[a]Unless otherwise noted, all reactions were carried out with isoxazolin-5-one (**1**) (0.13 mmol), nitroolefins **2** (0.10 mmol), and 5 mol % of tertiary amino-thiourea catalyst **J** in Et_2O (1 mL) at 25 °C for 48 h. Then NFSI (47.3 mg, 0.15 mmol) and anhydrous Na_2CO_3 (12.7 mg, 0.12 mmol) were added at the same temperature, and stirring was maintained for 24 h. [b]Determined by ^{19}F NMR analysis of the crude product. [c]The ee value was determined by HPLC analysis, and the absolute configurations of other fluorinated products were assigned on the basis of analogy with study of **3i**.

downfield from internal Me_4Si and external CCl_3F, respectively. HRMS were recorded on a miorOTOF-QII (APCI ion source), APEXIII 7.0 TESLA FTMS (ESI ion source), or IonSpec 4.7 T FTMS (MALDI ion source).

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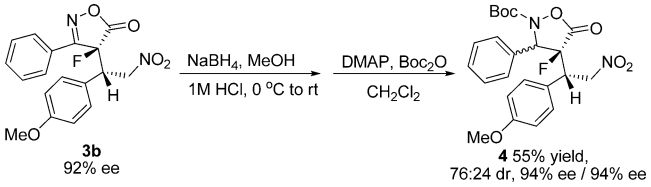
Scheme 2. Further Synthetic Transformation of Product 3b into Fluorinated Isoxazolidin-5-one 4



Materials. Unless otherwise noted, all commercially available compounds and solvents were used as provided without further purification. Organocatalysts **A**–**G**[6,9] and isoxazol-5-ones[13,14] were prepared according or in analogy to the reported procedures.

General Procedure for the Synthesis of Catalysts. To a stirred solution of (1*S*,2*S*)-1,2-diphenyl-2-(piperidin-1-yl)ethanamine[15] (5.0 mmol) in dichloromethane (20 mL) was added a solution of saccharide-derived isothiocyanate (5.0 mmol) in dry dichloromethane (20 mL) at 0 °C. The mixture was stirred at room temperature for 24 h (TLC) and concentrated. The resulting residue was purified by column chromatography on silica gel with the eluent (CH_2Cl_2/Et_3N 100/1) to give the white solid, which was dissolved in a minimal amount of dichloromethane and slowly precipitated from solution by the addition of petroleum ether at 0 °C. Filtration afforded the desired cyclic tertiary amino-thiourea **H**. The catalysts of **I**–**L** were prepared by this similar procedure.

*(2R,3R,4S,5R,6R)-2-(Acetoxymethyl)-6-(3-((1S,2S)-1,2-diphenyl-2-(pyrrolidin-1-yl)ethyl)thioureido)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**H**):* light yellow solid; 1.77 g; 54% yield; mp 104–106 °C; $[\alpha]^{20}_D$ −1.8 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.70–1.76 (m, 4H), 1.93 (s, 2H), 2.01–2.09 (m, 12H), 2.46–2.57 (m, 4H), 3.85–3.88 (m, 1H), 3.93 (d, *J* = 8.4 Hz, 1H), 4.11–4.16 (m, 1H), 4.38–4.41 (m, 1H), 4.92 (d, *J* = 7.4 Hz), 5.10 (t, *J* = 9.7 Hz), 5.31–5.34 (m, 1H), 5.73–5.85 (m, 1H), 7.10 (s, 4H), 7.15–7.19 (m, 3H), 7.22–7.25 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.3, 170.6, 169.9, 169.6, 130.0, 129.5, 128.0, 127.7, 127.3, 83.2, 73.5, 73.0, 70.8, 68.2, 61.6, 52.1, 50.3, 47.6, 23.1, 22.9, 20.7, 20.6, 20.5; IR (KBr) ν 3356, 2963, 1753, 1538, 1371, 1228, 1038, 911, 704 cm^{-1}; HRMS (ESI) found *m*/*z* 656.2637 [M + H]$^+$, calcd for $C_{33}H_{41}N_3O_9S$ + H 656.2642.

*(2R,3R,4S,5R,6R)-2-(Acetoxymethyl)-6-(3-((1R,2R)-1,2-diphenyl-2-(pyrrolidin-1-yl)ethyl)thioureido)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**I**):* light yellow solid; 1.74 g; 53% yield; mp 95–98 °C; $[\alpha]^{20}_D$ +21.2 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.69–1.73 (m, 4H), 1.98 (s, 2H), 2.01–2.09 (m, 12H), 2.38–2.51 (m, 4H), 3.78 (d, *J* = 9.5 Hz, 1H), 3.87 (d, *J* = 5.1 Hz, 1H), 4.08 (d, *J* = 11.4 Hz, 1H), 4.21–4.25 (m, 1H), 4.78–4.82 (m, 1H), 4.96–4.50 (m, 1H), 5.30–5.33 (m, 1H), 5.69 (t, *J* = 8.7 Hz, 1H), 6.27 (d, *J* = 5.3 Hz, 1H), 7.14 (d, *J* = 7.2 Hz, 2H), 7.22–7.24 (m, 4H), 7.26 (d, *J* = 7.2 Hz, 2H), 7.30 (d, *J* = 6.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.2, 170.5, 169.7, 169.6, 129.4, 128.5, 128.0, 127.8, 127.3, 82.9, 73.3, 72.7, 71.6, 71.0, 68.4, 61.7, 59.8, 49.5, 22.9, 20.6, 20.5; IR (KBr) ν 3362, 2962, 1752, 1538, 1371, 1228, 1038, 911, 704 cm^{-1}; HRMS (ESI) found *m*/*z* 656.2637 [M + H]$^+$, calcd for $C_{33}H_{41}N_3O_9S$ + H 656.2642.

*(2R,3R,4S,5R,6R)-2-(Acetoxymethyl)-6-(3-((1S,2S)-1,2-diphenyl-2-(piperidin-1-yl)ethyl)thioureido)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**J**):* light yellow solid; 1.81 g; 54% yield; mp 105–107 °C; $[\alpha]^{20}_D$ −71.2 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25–1.45 (m, 4H), 1.59 (s, 2H), 1.67 (s, 2H), 1.85–2.08 (m, 12H), 2.27–2.51 (m, 4H), 3.60 (d, *J* = 9.1 Hz, 1H), 3.83 (d, *J* = 9.7 Hz, 1H), 4.08 (d, *J* = 12.1 Hz, 1H), 4.37–4.42 (m, 1H), 4.68–4.89 (m, 1H), 5.06 (t, *J* = 9.6 Hz, 1H), 5.27 (d, *J* = 12.9 Hz, 1H), 5.75–5.92 (m, 1H), 6.50 (d, *J* = 7.0 Hz, 1H), 7.03–7.05 (m, 4H), 7.11 (s, 3H), 7.23 (d, *J* = 3.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.6, 170.7, 169.8, 169.6, 132.7, 129.7, 128.6, 127.8, 127.4, 82.9, 75.6, 73.5, 73.2, 70.4, 68.2, 61.6, 58.0, 26.4, 24.2, 20.8, 20.6, 20.5, 20.4; IR (KBr) ν 3352, 2935, 1760, 1537, 1370, 1212, 1035, 912, 702 cm^{-1}; HRMS (ESI) found *m*/*z* 670.2802 [M + H]$^+$, calcd for $C_{34}H_{43}N_3O_9S$ + H 670.2798.

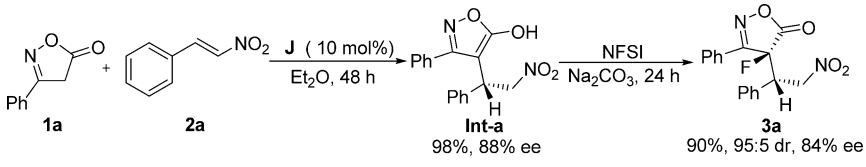
*(2R,3R,4S,5R,6R)-2-(Acetoxymethyl)-6-(3-((1S,2S)-2-(azepan-1-yl)-1,2-diphenylethyl)thioureido)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**K**):* light yellow solid; 1.54 g; 45% yield; mp 102–104 °C; $[\alpha]^{20}_D$ −46.2 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.63 (s, 5H), 1.77 (s, 2H), 1.95 (s, 2H), 2.00–2.14 (m, 12H), 2.58–2.77 (m, 4H), 3.81 (d, *J* = 8.9 Hz, 1H), 4.05 (d, *J* = 12.1 Hz, 1H), 4.38–4.40 (m, 1H), 4.75 (s, 1H), 5.04–5.11 (m, 2H), 5.23–5.29 (m, 1H), 5.83 (s, 1H), 7.06 (s, 3H), 7.12 (m, 3H), 7.24–7.26 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.6, 170.7, 169.9, 169.5, 129.5, 129.0, 128.6, 128.2, 127.6, 82.7, 73.4, 70.2, 68.2, 61.6, 58.8, 51.9, 26.3, 20.7, 20.5, 20.4, 20.3; IR (KBr) ν 3344, 2932, 1753, 1537, 1371, 1228, 1037, 911, 701 cm^{-1}; HRMS (MALDI) found *m*/*z* 684.2949 [M + H]$^+$, calcd for $C_{35}H_{45}N_3O_9S$ + H 684.2955.

*(2R,3R,4S,5R,6R)-2-(Acetoxymethyl)-6-(3-((1S,2S)-2-(azocan-1-yl)-1,2-diphenylethyl)thioureido)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**L**):* light yellow solid; 1.43 g; 41% yield; mp 120–122 °C; $[\alpha]^{20}_D$ −3.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, 3H), 1.36–1.49 (m, 3H), 1.69–1.76 (m, 2H), 1.97–2.04 (m, 12H), 2.06–2.15 (m, 8H), 3.88 (d, *J* = 9.1 Hz, 1H), 4.10 (d, *J* = 12.3 Hz, 1H), 4.16–4.22 (m, 1H), 4.30–4.33 (m, 1H), 4.99 (t, *J* = 8.9 Hz, 1H), 5.09 (t, *J* = 9.5 Hz, 2H), 5.32 (t, *J* = 8.4 Hz, 1H), 5.97–6.06 (m, 1H), 7.21 (d, *J* = 13.6 Hz, 7H), 7.32–7.44 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 183.6, 170.7, 169.9, 169.6, 130.9, 128.9, 128.6, 127.8, 127.1, 82.5, 73.3, 73.2, 73.1, 72.8, 70.6, 70.5, 68.3, 65.6, 61.8, 61.7, 45.0, 32.4, 30.6, 26.7, 20.8, 20.6, 19.2, 14.2, 13.7; IR (KBr) ν 3333, 2939, 1750, 1539, 1371, 1228, 1039, 912, 702 cm^{-1}; HRMS (MALDI) found *m*/*z* 698.3106 [M + H]$^+$, calcd for $C_{36}H_{47}N_3O_9S$ + H 698.3111.

General Procedure of Asymmetric Conjugate Addition/Dearomative Fluorination Transformation. Isoxazol-5-one (0.13 mmol), nitroolefin (0.10 mmol), and the amino-thiourea catalyst (0.005 mmol) were added to a 10 mL Schlenk equipped with a magneton. The vial was refilled with Ar three times. Et_2O (1 mL) was added, and the resulting mixture was stirred at room temperature under Ar atmosphere for 48 h (monitored by TLC). Then NFSI (0.15 mmol) and anhydrous Na_2CO_3 (0.12 mmol) were added, and the mixture was stirred at the same temperature for 24 h (monitored by TLC). The system was purified by flash chromatography with ethyl ether/petroleum ether (1/25, v/v) to afford the fluorinated product.

*4-Fluoro-(2-nitro-1-phenylethyl)-3-phenyl-4H-isoxazol-5-one (**3a**):* light brown solid; mp 78–80 °C; 30.5 mg; 93% yield; 86% ee [determined by HPLC analysis Daicel Chirapak IC, hexane/*i*-PrOH = 90/10, 220 nm UV detector, 1.0 mL/min, t_R = 9.6 min (minor) and t_R = 10.8 min (major)]; >99:1 dr [determined by ^{19}F NMR]; $[\alpha]^{20}_D$ −17.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58–4.63 (m, 1H), 5.17–5.23 (m, 1H), 5.42–5.47 (m, 1H), 6.85 (d, *J* = 7.6 Hz, 2H),7.27 (t, *J* = 7.4 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 2H), 7.69 (t, *J* = 7.3 Hz, 1H), 7.75 (d, *J* = 7.40, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7 (d, $^2J_{C-F}$ = 22.3 Hz), 161.1 (d, $^2J_{C-F}$ = 14.5 Hz), 133.0, 130.1, 129.7, 129.6, 128.4, 127.1 (d, $^3J_{C-F}$ = 1.0 Hz), 125.4 (d, $^3J_{C-F}$ = 0.8 Hz), 92.5 (d, $^1J_{C-F}$ = 205.6 Hz), 72.1 (d, $^3J_{C-F}$ = 2.7 Hz), 47.0 (d, $^2J_{C-F}$ = 23.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −162.20 (d, *J* = 6.0 Hz); IR (KBr) ν 2962, 2925, 1811, 1561, 1378, 1261, 1137, 1091, 868, 799, 695 cm^{-1}; HRMS (APCI) found *m*/*z* 329.0934 [M + H]$^+$, calcd for $C_{17}H_{13}FN_2O_4$ + H 329.0937.

Scheme 3. Step-by-Step Control Experiments



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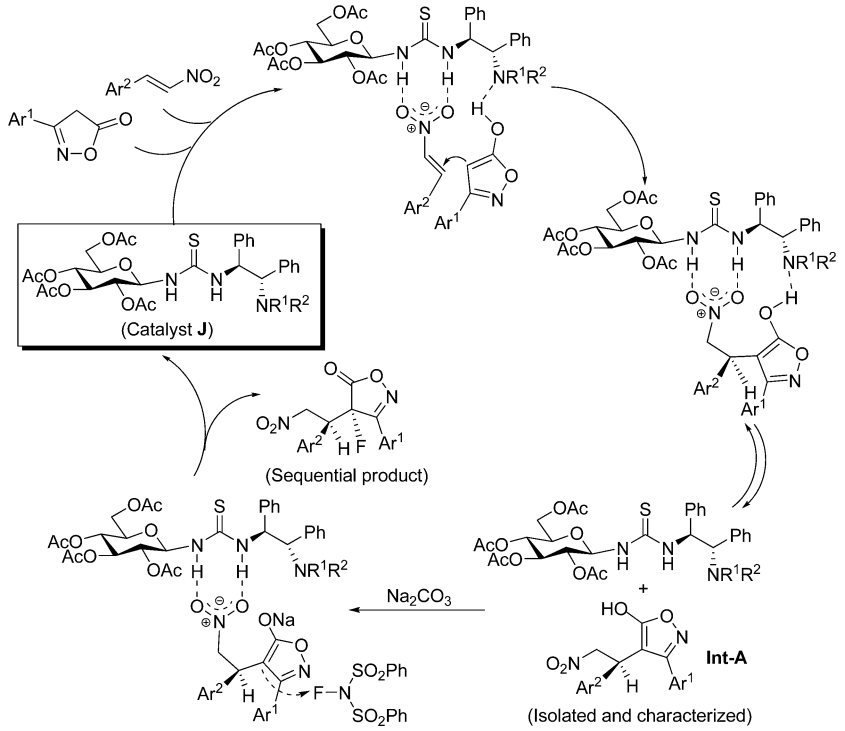

Figure 2. Proposed mechanism for the one-pot sequential transformation.

*4-Fluoro-4-(1-(4-methoxyphenyl)-2-nitroethyl)-3-phenylisoxazol-5(4H)-one (**3b**):* yellow solid; mp 148−150 °C; 33.7 mg; 94% yield; 92% ee [determined by HPLC analysis Daicel Chirapak AD, hexane/*i*-PrOH = 90/10, 220 nm UV detector, 1.0 mL/min, t_R = 8.4 min (minor) and t_R = 9.7 min (major)]; >99:1 dr [determined by ^{19}F NMR]; $[\alpha]^{20}_D$ −7.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 4.51−4.56 (m, 1H), 5.13−5.19 (m, 1H), 5.37−5.42 (m, 1H), 6.77 (s, 4H), 7.60 (t, *J* = 7.5 Hz, 2H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9 (d, $^2J_{C-F}$ = 22.5 Hz), 161.2 (d, $^2J_{C-F}$ = 14.5 Hz), 133.0, 129.7, 129.6, 129.2, 127.8, 127.1 (d, $^3J_{C-F}$ = 0.9 Hz), 125.4, 92.5 (d, $^1J_{C-F}$ = 206.5 Hz), 72.3 (d, $^3J_{C-F}$ = 2.3 Hz), 55.3, 46.2 (d, $^2J_{C-F}$ = 23.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −161.64 (d, *J* = 5.4 Hz); IR (KBr) ν 2963, 2920, 1810, 1557, 1376, 1257, 869, 799, 544 cm^{-1}; HRMS (ESI) found *m*/*z* 359.1039 [M + H]$^+$, calcd for $C_{18}H_{15}FN_2O_5$ + H 359.1043.

*4-Fluoro-4-(2-nitro-1-p-tolylethyl)-3-phenylisoxazol-5(4H)-one (**3c**):* light yellow solid; mp 104−106 °C; 31.5 mg, 92% yield; 90% ee [determined by HPLC analysis Daicel Chirapak AD, hexane/*i*-PrOH = 95/5, 220 nm UV detector, 0.8 mL/min, t_R = 9.4 min (minor) and t_R = 15.7 min (major)]; >99:1 dr [determined by ^{19}F NMR]; $[\alpha]^{20}_D$ −3.2 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H), 4.53−4.58 (m, 1H), 5.15−5.20 (m, 1H), 5.39−5.44 (m, 1H), 6.73 (d, *J* = 8.1 Hz, 2H), 7.06 (d, *J* = 7.9 Hz, 2H), 7.60 (t, *J* = 7.6 Hz, 2H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8 (d, $^2J_{C-F}$ = 22.6 Hz), 161.2 (d, $^2J_{C-F}$ = 14.6 Hz), 140.2, 133.0, 130.3, 129.7, 128.2, 127.1 (d, $^3J_{C-F}$ = 1.2 Hz), 125.5 (d, $^3J_{C-F}$ = 1.2 Hz), 92.6 (d, $^1J_{C-F}$ = 205.7 Hz), 72.2 (d, $^3J_{C-F}$ = 2.6 Hz), 46.6 (d, $^2J_{C-F}$ = 23.2 Hz), 21.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −162.01 (d, *J* = 5.6 Hz); IR (KBr) ν 2922, 1810, 1561, 1379, 1264, 1093, 870, 744, 692 cm^{-1}; HRMS (ESI) found *m*/*z* 365.0908 [M + Na]$^+$, calcd for $C_{18}H_{15}FN_2O_4$ + Na 365.0914.

*4-Fluoro-4-(1-(4-fluorophenyl)-2-nitroethyl)-3-phenylisoxazol-5(4H)-one (**3d**):* light brown solid; mp 85−88 °C; 30.1 mg, 87% yield; 86% ee [determined by HPLC analysis Daicel Chirapak AD, hexane/*i*-PrOH = 95/5, 220 nm UV detector, 0.8 mL/min, t_R = 11.0 min (minor) and t_R = 13.2 min (major)]; >99:1 dr [determined by ^{19}F NMR]; $[\alpha]^{20}_D$ −20.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ4.56−4.61 (m, 1H), 5.15−5.21 (m, 1H), 5.38−5.43 (m, 1H), 6.83−6.86 (m, 2H), 6.97 (t, *J* = 8.4 Hz, 2H), 7.61 (t, *J* = 7.5 Hz, 2H), 7.70 (t, *J* = 7.4 Hz, 1H), 7.75 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6 (d, $^2J_{C-F}$ = 22.5 Hz), 163.4 (d, $^1J_{C-F}$ = 251.0 Hz), 161.0 (d, $^2J_{C-F}$ = 14.5 Hz), 133.1, 130.4, 130.3, 129.8, 127.0 (d, $^3J_{C-F}$ = 1.2 Hz), 125.2 (d, $^3J_{C-F}$ = 1.4 Hz), 116.8 (d, $^2J_{C-F}$ = 22.0 Hz), 92.3 (d, $^1J_{C-F}$ = 206.3 Hz), 72.1 (d, $^3J_{C-F}$ = 2.8 Hz), 46.4 (d, $^2J_{C-F}$ = 23.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −106.38−−112.44 (m), −162.24 (d, *J* = 5.7 Hz); IR (KBr) ν 2962, 2932, 1811, 1605, 1562, 1513, 1378, 1236, 1137, 869, 693 cm^{-1}; HRMS (ESI) found *m*/*z* 369.0665 [M + Na]$^+$, calcd for $C_{17}H_{12}F_2N_2O_4$ + Na 369.0663.

*4-(1-(4-Chlorophenyl)-2-nitroethyl)-4-fluoro-3-phenylisoxazol-5(4H)-one (**3e**):* light yellow solid; mp 126−128 °C; 32.6 mg; 90% yield; 81% ee [determined by HPLC analysis Daicel Chirapak AD, hexane/*i*-PrOH = 95/5, 220 nm UV detector, 1.0 mL/min, t_R = 11.2 min (minor) and t_R = 13.9 min (major)]; >99:1 dr [determined by ^{19}F NMR]; $[\alpha]^{20}_D$ +1.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.55−4.60 (m, 1H), 5.15−5.21 (m, 1H), 5.38−5.43 (m, 1H), 6.79 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.61 (t, *J* = 7.6 Hz, 2H), 7.70 (t, *J* = 7.4 Hz, 1H), 7.75 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5 (d, $^2J_{C-F}$ = 22.4 Hz), 161.0 (d, $^2J_{C-F}$ = 14.5 Hz), 136.4, 135.8, 133.2, 129.9, 129.8, 129.5, 127.0 (d, $^3J_{C-F}$ = 1.1 Hz), 125.2 (d, $^3J_{C-F}$ = 1.1 Hz), 116.8 (d, $^2J_{C-F}$ = 22.0 Hz), 92.3 (d, $^1J_{C-F}$ = 206.4 Hz), 72.9 (d, $^3J_{C-F}$ = 3.0 Hz), 46.5 (d, $^2J_{C-F}$ = 23.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −162.31 (d, *J* = 5.6 Hz); IR (KBr) ν 2964, 2925, 1812, 1559, 1494, 1379, 1379, 1192, 1090, 869, 798, 688 cm^{-1}; HRMS (ESI) found *m*/*z* 358.0362 [M + Na]$^+$, calcd for $C_{17}H_{12}ClFN_2O_4$ + Na 385.0367.

*4-(1-(4-Bromophenyl)-2-nitroethyl)-4-fluoro-3-phenylisoxazol-5(4H)-one (**3f**):* light yellow solid; mp 132−134 °C; 35.4 mg, 87% yield; 80% ee [determined by HPLC analysis Daicel Chirapak AD, hexane/*i*-PrOH = 95/5, 220 nm UV detector, 0.8 mL/min, t_R = 11.8 min (minor) and t_R = 11.7 min (major)]; >99:1 dr [determined by ^{19}F NMR]; $[\alpha]^{20}_D$ +17.2 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53−4.58 (m, 1H), 5.15−5.21 (m, 1H), 5.38−5.43 (m, 1H), 6.73 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.61 (t, *J* = 7.6 Hz, 2H), 7.70 (t, *J* = 7.4 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5 (d, $^2J_{C-F}$ = 22.2 Hz), 160.9 (d, $^2J_{C-F}$ = 14.3 Hz), 133.2, 132.9, 129.9, 129.8, 127.0 (d, $^3J_{C-F}$ = 1.2 Hz), 125.2 (d, $^3J_{C-F}$ = 1.2 Hz),124.6, 92.2 (d, $^1J_{C-F}$ = 206.4 Hz), 71.9 (d, $^3J_{C-F}$ = 2.8 Hz), 46.6 (d, $^2J_{C-F}$ = 23.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −162.31 (d, *J* = 5.4 Hz); IR (KBr) ν 2963, 1811, 1724, 1559, 1261, 1074, 869, 797, 689 cm^{-1}; HRMS (APCI) found *m*/*z* 407.0037 [M + H]$^+$, calcd for $C_{17}H_{12}BrFN_2O_4$ + H 407.0042.

*4-Fluoro-4-(2-nitro-1-(3-phenoxyphenyl)ethyl)-3-phenylisoxazol-5(4H)-one (**3g**):* yellow solid; mp 80−82 °C; 39.1 mg, 93% yield; 80% ee

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[determined by HPLC analysis Daicel Chirapak IC, hexane/*i*-PrOH = 90/10, 220 nm UV detector, 1.0 mL/min, t_R = 9.7 min (minor) and t_R = 14.2 min (major)]; >99:1 dr [determined by ^{19}F NMR]; $[\alpha]^{20}_D$ +27.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.54−4.58 (m, 1H), 5.12−5.17 (m, 1H), 5.38−5.43 (m, 1H), 6.45 (s, 1H), 6.60 (d, *J* = 7.7 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 2H), 6.97−7.00 (m, 1H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 2H), 7.55 (t, *J* = 7.6 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.73 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5 (d, $^2J_{C-F}$ = 22.6 Hz), 161.1 (d, $^2J_{C-F}$ = 14.6 Hz), 158.2, 156.0, 133.0, 131.0, 130.0, 129.8, 127.0 (d, $^3J_{C-F}$ = 1.1 Hz), 124.1, 122.5, 120.2, 119.3, 118.5, 92.4 (d, $^1J_{C-F}$ = 205.7 Hz), 71.9 (d, $^3J_{C-F}$ = 2.9 Hz), 46.8 (d, $^2J_{C-F}$ = 23.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −162.46 (d, *J* = 5.6 Hz); IR (KBr) ν 3261, 2961, 2921, 2238, 1811, 1723, 1594, 1561, 1489, 1330, 1277, 1251, 1158, 750, 691 cm^{-1}; HRMS (ESI) found *m*/*z* 420.1124 [M]$^+$, calcd for $C_{23}H_{17}FN_2O_5$ 420.1121.

4-(1-(2-Chlorophenyl)-2-nitroethyl)-4-fluoro-3-phenylisoxazol-5(4H)-one (**3h**): white solid; mp 130−132 °C; 33.7 mg, 93% yield; 90% ee [determined by HPLC analysis Daicel Chirapak AD, hexane/*i*-PrOH = 95/5, 220 nm UV detector, 0.8 mL/min, t_R = 11.9 min (minor) and t_R = 12.7 min (major)]; >99:1 dr [determined by ^{19}F NMR]; $[\alpha]^{20}_D$ −10.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.04−5.10 (m, 1H), 5.36 (d, *J* = 3.8 Hz, 1H), 5.43−5.48 (m, 1H), 7.26 (d, *J* = 8.9 Hz, 2H), 7.30 (d, *J* = 7.0 Hz, 2H), 7.53 (t, *J* = 7.6 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.72 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0 (d, $^2J_{C-F}$ = 22.6 Hz), 161.3 (d, $^2J_{C-F}$ = 14.0 Hz), 135.9, 135.1, 133.0, 131.1, 130.8, 129.8, 129.4, 128.2, 127.2 (d, $^3J_{C-F}$ = 1.0 Hz), 125.3, 92.6 (d, $^1J_{C-F}$ = 205.2 Hz), 72.9 (d, $^3J_{C-F}$ = 1.5 Hz), 42.5 (d, $^2J_{C-F}$ = 27.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −161.42 (s); IR (KBr) ν 2962, 2925, 18077, 1557, 1447, 1381, 1193, 1138, 1081, 863, 760, 692 cm^{-1}; HRMS (ESI) found *m*/*z* 362.0465 [M]$^+$, calcd for $C_{17}H_{12}ClFN_2O_4$ 362.0470.

4-(1-(2-Bromophenyl)-2-nitroethyl)-4-fluoro-3-phenylisoxazol-5(4H)-one (**3i**): white solid; mp 130−132 °C; 35.4 mg, 87% yield; 90% ee [determined by HPLC analysis Daicel Chirapak AD, hexane/*i*-PrOH = 95/5, 220 nm UV detector, 0.8 mL/min, t_R = 12.2 min (minor) and t_R = 13.6 min (major)]; dr =97:3 dr [determined by ^{19}F NMR]; $[\alpha]^{20}_D$ −26.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00−5.05 (m, 1H), 5.34−5.39 (m, 1H), 5.42−5.47 (m, 1H), 7.19−7.25 (m, 2H), 7.40−7.35 (m, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 2H), 7.63 (t, *J* = 7.3 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0 (d, $^2J_{C-F}$ = 22.6 Hz), 161.3 (d, $^2J_{C-F}$ = 13.9 Hz), 134.4, 133.0, 131.3, 129.5, 128.8, 127.1 (d, $^3J_{C-F}$ = 1.4 Hz), 125.4 (d, $^3J_{C-F}$ = 1.4 Hz), 92.6 (d, $^1J_{C-F}$ = 204.6 Hz), 73.1, 45.3 (d, $^2J_{C-F}$ = 26.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −161.29 (d, *J* = 7.2 Hz), −162.34 (d, *J* = 5.6 Hz); IR (KBr) ν 2963, 2925, 1797, 1553, 1261, 1067, 863, 798, 690 cm^{-1}; HRMS (ESI) found *m*/*z* 405.9968 [M]$^+$, calcd for $C_{17}H_{12}BrFN_2O_4$ 405.9964.

4-Fluoro-4-(1-(naphthalen-1-yl)-2-nitroethyl)-3-phenylisoxazol-5(4H)-one (**3j**): yellow solid; mp 122−124 °C; 31.4 mg, 83% yield; 82% ee [determined by HPLC analysis Daicel Chirapak AD, hexane/*i*-PrOH = 95/5, 220 nm UV detector, 0.8 mL/min, t_R = 12.4 min (major) and t_R = 15.4 min (minor)]; >99:1 dr [determined by ^{19}F NMR]; $[\alpha]^{20}_D$ −76.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73−4.78 (m, 1H), 5.31−5.37 (m, 1H), 5.50−5.55 (m, 1H), 6.90−6.92 (m, 1H), 7.31 (s, 1H), 7.30−7.56 (m, 2H), 7.60−7.66 (m, 3H), 7.70−7.77 (m, 4H), 7.82 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2 (d, $^2J_{C-F}$ = 22.7 Hz), 161.2 (d, $^2J_{C-F}$ = 14.0 Hz), 133.9, 132.7, 130.9, 130.7, 129.4, 128.8, 127.0 (d, $^3J_{C-F}$ = 1.7 Hz), 126.3, 136.0, 125.7, 125.3, 125.0, 92.9 (d, $^1J_{C-F}$ = 205.0 Hz), 73.5 (d, $^3J_{C-F}$ = 1.0 Hz), 40.5 (d, $^2J_{C-F}$ = 24.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −159.22 (d, *J* = 7.6 Hz); IR (KBr) ν 2964, 2925, 1809, 1560, 1377, 1138, 1078, 1053, 867, 770, 692 cm^{-1}; HRMS (ESI) found *m*/*z* 378.1013 [M]$^+$, calcd for $C_{21}H_{15}FN_2O_4$ 378.1016.

4-Fluoro-4-(1-(naphthalen-2-yl)-2-nitroethyl)-3-phenylisoxazol-5(4H)-one (**3k**): yellow solid; mp 122−124 °C; 31.8 mg, 84% yield; 77% ee [determined by HPLC analysis Daicel Chirapak AD, hexane/*i*-PrOH = 95/5, 220 nm UV detector, 0.8 mL/min, t_R = 12.9 min (minor) and t_R = 17.3 min (major)]; >99:1 dr [determined by ^{19}F NMR]; $[\alpha]^{20}_D$ +30.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24−5.32 (m, 1H), 5.53−5.65 (m, 2H), 6.92 (t, *J* = 7.7 Hz, 1H), 7.17 (d, *J* = 8.7 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 4.5 Hz, 4H), 7.42−7.50 (m, 2H), 7.57 (m, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8 (d, $^2J_{C-F}$ = 22.5 Hz), 161.2 (d, $^2J_{C-F}$ = 14.5 Hz), 133.6, 133.0, 129.7, 129.6, 128.7, 128.0, 127.8, 127.4, 127.2 (d, $^3J_{C-F}$ = 1.1 Hz), 127.1, 126.5, 125.5 (d, $^3J_{C-F}$ = 1.0 Hz), 124.8, 92.6 (d, $^1J_{C-F}$ = 205.9 Hz), 72.2 (d, $^3J_{C-F}$ = 2.5 Hz), 47.1 (d, $^2J_{C-F}$ = 23.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −159.22 (d, *J* = 7.6 Hz); IR (KBr) ν 2962, 2928, 1810, 1724, 1560, 1378, 1284, 1137, 1065, 866, 748, 693 cm^{-1}; HRMS (ESI) found *m*/*z* 378.1014 [M]$^+$, calcd for $C_{21}H_{15}FN_2O_4$ 378.1016.

4-Fluoro-4-(1-(furan-2-yl)-2-nitroethyl)-3-phenylisoxazol-5(4H)-one (**3l**): brown oil liquid; 20.4 mg, 90% yield; 64% ee [determined by HPLC analysis Daicel Chirapak IC, hexane/*i*-PrOH = 90/10, 220 nm UV detector, 1.0 mL/min, t_R = 9.8 min (major) and t_R = 10.8 min (minor)]; >99:1 dr [determined by ^{19}F NMR]; $[\alpha]^{20}_D$ −47.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69−4.74 (m, 1H), 5.15−5.21 (m, 1H$_2$), 5.30−5.34 (m, 1H), 6.01 (d, *J* = 3.3 Hz, 1H), 6.28−6.30 (m, 1H), 7.38 (d, *J* = 1.1 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 2H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0 (d, $^2J_{C-F}$ = 22.1 Hz), 161.2 (d, $^2J_{C-F}$ = 14.2 Hz), 144.7, 142.4 (d, $^3J_{C-F}$ = 10.4 Hz), 132.9, 129.7, 127.0 (d, $^3J_{C-F}$ = 1.1 Hz), 125.1, 111.5, 111.1, 90.7 (d, $^1J_{C-F}$ = 207.0 Hz), 70.8 (d, $^2J_{C-F}$ = 1.5 Hz), 41.5 (d, $^2J_{C-F}$ = 26.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −163.50 (d, *J* = 5.4 Hz); IR (KBr) ν 2963, 2930, 1814, 1724, 1563, 1501, 1377, 1327, 1137, 1018, 869, 748, 694 cm^{-1}; HRMS (APCI) found *m*/*z* 319.0724 [M + H]$^+$, calcd for $C_{15}H_{11}FN_2O_5$ + H 319.0730.

3-(4-Chlorophenyl)-4-fluoro-4-(2-nitro-1-phenylethyl)isoxazol-5(4H)-one (**3m**): light yellow solid; mp 122−125 °C; 33.4 mg, 92% yield; 87% ee [determined by HPLC analysis Daicel Chirapak IC, hexane/*i*-PrOH = 90/10, 220 nm UV detector, 1.0 mL/min, t_R = 10.3 min (minor) and t_R = 12.0 min (major)]; >99:1 dr [determined by ^{19}F NMR]; $[\alpha]^{20}_D$ +16.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53−4.58 (m, 1H), 5.14−5.20 (m, 1H), 5.42−5.47 (m, 1H), 6.86 (d, *J* = 7.5 Hz, 2H), 7.27−7.31 (m, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4 (d, $^2J_{C-F}$ = 22.2 Hz), 160.4 (d, $^2J_{C-F}$ = 14.6 Hz), 139.5, 130.2, 130.2, 129.7, 129.4, 129.2, 128.3, 123.8 (d, $^3J_{C-F}$ = 1.0 Hz), 92.3 (d, $^1J_{C-F}$ = 205.8 Hz), 72.0 (d, $^2J_{C-F}$ = 2.6 Hz), 47.0 (d, $^2J_{C-F}$ = 23.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −162.53 (d, *J* = 6.0 Hz); IR (KBr) ν 2963, 2921, 1813, 1560, 1378, 1342, 1261, 1092, 870, 800, 702 cm^{-1}; HRMS (ESI) found: *m*/*z* 362.0469 [M]$^+$, calcd for $C_{17}H_{12}ClFN_2O_4$ 362.0470.

3-(4-Bromophenyl)-4-fluoro-4-(2-nitro-1-phenylethyl)isoxazol-5(4H)-one (**3n**): light yellow solid; mp 143−145 °C; 34.2 mg, 84% yield; 81% ee [determined by HPLC analysis Daicel Chirapak AD, hexane/*i*-PrOH = 95/5, 220 nm UV detector, 0.8 mL/min, t_R = 12.3 min (minor) and t_R = 14.1 min (major)]; >99:1 dr [determined by ^{19}F NMR]; $[\alpha]^{20}_D$ +17.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53−4.58 (m, 1H), 5.14−5.20 (m, 1H), 5.42−5.46 (m, 1H), 6.86 (d, *J* = 7.4 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4 (d, $^2J_{C-F}$ = 22.3 Hz), 160.5 (d, $^2J_{C-F}$ = 14.7 Hz), 139.1, 133.1, 132.1, 130.2, 129.7, 129.4, 129.2, 128.4 (d, $^3J_{C-F}$ = 1.2 Hz), 128.3, 128.1, 124.3 (d, $^3J_{C-F}$ = 1.1 Hz), 92.3 (d, $^1J_{C-F}$ = 205.6 Hz), 72.0 (d, $^2J_{C-F}$ = 2.6 Hz), 47.0 (d, $^2J_{C-F}$ = 23.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −162.55 (d, *J* = 5.8 Hz); IR (KBr) ν 2962, 2923, 1812, 1592, 1560, 1432, 1332, 1158, 1089, 870, 750, 699 cm^{-1}; HRMS (ESI) found *m*/*z* 405.9966 [M]$^+$, calcd for $C_{17}H_{12}BrFN_2O_4$ 405.9964.

4-Fluoro-4-(2-nitro-1-phenylethyl)-3-m-tolylisoxazol-5(4H)-one (**3o**): light yellow solid; mp 99−101 °C; 31.5 mg, 92% yield; 80% ee [determined by HPLC analysis Daicel Chirapak AD, hexane/*i*-PrOH = 95/5, 220 nm UV detector, 1.0 mL/min, t_R = 11.7 min (minor) and t_R = 12.9 min (major)]; >99:1 dr [determined by ^{19}F NMR]; $[\alpha]^{20}_D$ −6.8 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (s, 3H), 4.59−4.63 (m, 1H), 5.14−5.20 (m, 1H), 5.43−5.48 (m, 1H), 6.87 (d, *J* = 7.4 Hz, 2H), 7.26−7.30 (m, 2H), 7.34−7.36 (m, 1H), 7.55 (d, *J* = 2.4 Hz, 2H), 7.73−7.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8 (d, $^2J_{C-F}$ = 22.4 Hz), 161.2 (d, $^2J_{C-F}$ = 14.3 Hz), 139.7, 133.9, 130.1, 129.6, 129.5, 128.4, 127.4 (d, $^3J_{C-F}$ = 1.0 Hz), 125.3 (d, $^3J_{C-F}$ = 1.3 Hz), 124.3, 124.2, 92.6 (d, $^1J_{C-F}$ = 205.5 Hz), 72.1 (d, $^2J_{C-F}$ = 3.0 Hz), 47.0 (d, $^2J_{C-F}$ = 23.2 Hz), 21.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −162.19 (d, *J* = 5.6 Hz); IR (KBr) ν 2963, 2927, 1804, 1559, 1438, 1379, 1342, 1261, 1092, 882, 797,

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701 cm^{-1}; HRMS (APCI) found m/z 343.1089 $[M + H]^+$, calcd for $C_{18}H_{15}FN_2O_4$ + H 343.1094.

*4-Fluoro-3-(3-methoxyphenyl)-4-(2-nitro-1-phenylethyl)isoxazol-5(4H)-one (**3p**):* white solid; mp 147−149 °C; 32.6 mg, 91% yield; 78% ee [determined by HPLC analysis Daicel Chirapak AD, hexane/*i*-PrOH = 95/5, 220 nm UV detector, 1.0 mL/min, t_R = 11.9 min (minor) and t_R = 12.8 min (major)]; >99:1 dr [determined by ^{19}F NMR]; $[\alpha]^{20}_D$ −6.8 (*c* 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 4.61−4.66 (m, 1H), 5.17−5.23 (m, 1H), 5.42−5.47 (m, 1H), 6.87 (d, J = 7.5 Hz, 2H), 7.27 (t, J = 7.5 Hz, 2H), 7.36 (t, J = 7.3 Hz, 1H), 7.49 (d, J = 4.9 Hz, 2H), 7.54 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7 (d, $^2J_{C-F}$ = 22.4 Hz), 161.1 (d, $^2J_{C-F}$ = 14.3 Hz), 160.3, 130.8, 130.1, 129.8, 129.6, 128.5, 126.5, 119.5 (d, $^3J_{C-F}$ = 1.8 Hz), 119.4, 111.5, 92.5 (d, $^1J_{C-F}$ = 205.6 Hz), 72.1 (d, $^2J_{C-F}$ = 2.8 Hz), 55.5, 47.0 (d, $^2J_{C-F}$ = 23.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −162.19 (d, J = 5.5 Hz); IR (KBr) ν 2963, 2944, 1800, 1550, 1454, 1380, 1295, 1245, 1037, 873, 791, 703 cm^{-1}; HRMS (ESI) found m/z 358.0961 $[M]^+$, calcd for $C_{18}H_{15}FN_2O_5$ 358.0965.

*3-(2-Chlorophenyl)-4-fluoro-4-(2-nitro-1-phenylethyl)isoxazol-5(4H)-one (**3q**):* white solid; mp 126−128 °C; 31.9 mg, 88% yield; 85% ee [determined by HPLC analysis Daicel Chirapak AD, hexane/*i*-PrOH = 90/10, 220 nm UV detector, 1.0 mL/min, t_R = 12.6 min (minor) and t_R = 13.3 min (major)]; >99:1 dr [determined by ^{19}F NMR]; $[\alpha]^{20}_D$ −283.6 (*c* 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 4.29−4.34 (m, 1H), 5.15−5.21 (m, 1H), 5.33−5.38 (m, 1H), 6.87 (d, J = 7.3 Hz, 2H), 7.32 (t, J = 7.4 Hz, 2H), 7.38 (t, J = 7.3 Hz, 1H), 7.49−7.53 (m, 1H), 7.55−7.60 (m, 2H), 7.70 (d, J = 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0 (d, $^2J_{C-F}$ = 22.6 Hz), 159.4 (d, $^2J_{C-F}$ = 13.0 Hz), 134.1, 133.1, 132.0, 130.1, 130.0, 129.8, 129.7, 128.3, 127.5, 124.1 (d, $^3J_{C-F}$ = 1.2 Hz), 92.5 (d, $^1J_{C-F}$ = 202.9 Hz), 72.7 (d, $^2J_{C-F}$ = 2.2 Hz), 46.8 (d, $^2J_{C-F}$ = 23.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −154.80 (d, J = 7.6 Hz); IR (KBr) ν 2969, 2927, 1803, 1556, 1430, 1379, 1143, 1095, 860, 766, 700 cm^{-1}; HRMS (ESI) found m/z 362.0467 $[M]^+$, calcd for $C_{17}H_{12}ClFN_2O_4$ 362.0470.

*4-Fluoro-3-(naphthalen-1-yl)-4-(2-nitro-1-phenylethyl)isoxazol-5(4H)-one (**3r**):* light yellow solid; mp 103−106 °C; 33.3 mg, 88% yield; 79% ee [determined by HPLC analysis Daicel Chirapak AD, hexane/*i*-PrOH = 98/2, 220 nm UV detector, 0.6 mL/min, t_R = 20.2 min (minor) and t_R = 22.3 min (major)]; >99:1 dr [determined by ^{19}F NMR]; $[\alpha]^{20}_D$ −132.0 (*c* 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 4.47−4.50 (m, 1H), 5.20−5.26 (m, 1H), 5.41−5.46 (m, 1H), 6.74 (d, J = 7.5 Hz, 2H), 7.10 (t, J = 7.7 Hz, 2H), 7.28−7.32 (m, 1H), 7.42−7.46 (m, 1H), 7.59 (t, J = 7.4 Hz, 1H), 7.69 (t, J = 7.8 Hz, 1H), 7.83 (d, J = 8.7 Hz, 1H), 7.96 (d, J = 8.2 Hz, 1H), 8.05 (d, J = 7.3 Hz, 1H), 8.14 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4 (d, $^2J_{C-F}$ = 22.8 Hz), 161.0 (d, $^2J_{C-F}$ = 12.6 Hz), 139.1, 134.1, 133.6, 129.9, 129.7, 129.4, 129.2, 128.8, 128.5, 128.2, 128.0, 127.9, 127.1, 125.8, 125.0, 122.2 (d, $^3J_{C-F}$ = 1.3 Hz), 93.4 (d, $^1J_{C-F}$ = 205.0 Hz), 72.5 (d, $^2J_{C-F}$ = 2.4 Hz), 47.2 (d, $^2J_{C-F}$ = 23.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −156.84 (d, J = 6.7 Hz); IR (KBr) ν 2963, 2924, 1808, 1724, 1560, 1513, 1377, 1260, 1092, 869, 802, 776, 703 cm^{-1}; HRMS (ESI) found m/z 378.1021 $[M]^+$, calcd for $C_{21}H_{15}FN_2O_4$ 378.1016.

*4-Fluoro-3-(naphthalen-2-yl)-4-(2-nitro-1-phenylethyl)isoxazol-5(4H)-one (**3s**):* white solid; mp 150−152 °C; 32.2 mg, 85% yield; 83% ee [determined by HPLC analysis Daicel Chirapak AD, hexane/*i*-PrOH = 98/2, 220 nm UV detector, 0.5 mL/min, t_R = 38.7 min (minor) and t_R = 42.4 min (major)]; >99:1 dr [determined by ^{19}F NMR]; $[\alpha]^{20}_D$ +59.0 (*c* 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 4.72−4.77 (m, 1H), 5.18−5.24 (m, 1H), 5.50−5.55 (m, 1H), 6.85 (d, J = 7.6 Hz, 2H), 7.25 (t, J = 7.6 Hz, 2H), 7.54−7.56 (m, 1H), 7.68−7.70 (m, 1H), 7.72−7.74 (m, 2H), 7.96−8.00 (m, 2H), 8.05 (d, J = 7.7 Hz, 1H), 8.33 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8 (d, $^2J_{C-F}$ = 22.6 Hz), 161.1 (d, $^2J_{C-F}$ = 14.7 Hz), 139.1, 135.1, 132.8, 130.9 (d, $^3J_{C-F}$ = 2.5 Hz), 130.1, 129.9, 129.6, 129.4, 129.3, 129.1, 129.0, 128.4, 128.1, 127.6, 122.8 (d, $^3J_{C-F}$ = 1.1 Hz), 122.4, 92.8 (d, $^1J_{C-F}$ = 206.2 Hz), 72.1 (d, $^2J_{C-F}$ = 3.0 Hz), 47.2 (d, $^2J_{C-F}$ = 23.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −162.43 (d, J = 5.4 Hz); IR (KBr) ν 2959, 2931, 1797, 1726, 1560, 1456, 1382, 1344, 1276, 1122, 1069, 880, 818, 753, 705 cm^{-1}; HRMS (ESI) found m/z 378.1019 $[M]^+$, calcd for $C_{21}H_{15}FN_2O_4$ 378.1016.

Step-by-Step Procedure for Asymmetric Conjugate Addition, then Dearomative Fluorination Transformation. Isoxazol-5-one **1a** (42 mg, 0.26 mmol), *trans*-β-nitrostyrene **2a** (30 mg, 0.20 mmol), and the amino-thiourea catalyst **J** (6.7 mg, 0.01 mmol) were added to a 10 mL Schlenk equipped with a magneton. The vial was refilled with Ar three times. Et_2O (2 mL) was added, and the resulting mixture was stirred at room temperature under Ar atmosphere for 48 h (monitored by TLC). The reaction was concentrated and purified by flash chromatography with ethyl ether/petroleum ether (1/15, v/v) to afford the addition intermediate (**Int-a**): light brown solid; mp 44−46 °C; 60.8 mg, 98% yield; 88% ee [determined by HPLC analysis Daicel Chirapak IA, hexane/*i*-PrOH = 80/20, 254 nm UV detector, 0.8 mL/min, t_R = 4.4 min (minor) and t_R = 6.1 min (major)]; $[\alpha]^{20}_D$ −2.4 (*c* 1.0, CH_2Cl_2); ^1H NMR (400 MHz, DMSO) δ 4.53−4.57 (m, 1H), 5.12−5.17 (m, 1H), 5.35−5.42 (m, 1H), 7.27−7.30 (m, 1H), 7.34 −7.40 (m, 4H), 7.50 (s, 2H), 7.60−7.62 (d, J = 6.7 Hz, 3H), 12.96 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 171.5, 162.9, 139.5, 131.8, 129.8, 129.4, 129.1, 128.2, 128.0, 127.9, 127.3, 76.8, 38.4; IR (KBr) ν 3431, 2932, 1669, 1612, 1554, 1487, 1378, 1159, 1032, 760, 698 cm^{-1}; HRMS (ESI) found m/z 310.0957 $[M]^+$, calcd for $C_{17}H_{14}N_2O_4$ 310.0954.

To a solution of **Int-a** (46.5 mg, 0.15 mmol) in Et_2O (2 mL) were added NFSI (63 mg, 0.2 mmol) and anhydrous Na_2CO_3 (22 mg, 0.2 mmol). The mixture was stirred at room temperature for 24 h (monitored by TLC). The reaction was quenched with water (5 mL) and extracted with EtOAc (5 mL × 3), and the organic layer was washed with brine (5 mL × 3) and dried over Na_2SO_4. The organics were filtered, concentrated, and purified by flash chromatography with ethyl ether/petroleum ether to afford the fluorinated product **3a**. 44.3 mg; 90% yield; 84% ee [determined by HPLC analysis Daicel Chirapak IC, hexane/*i*-PrOH = 90/10, 220 nm UV detector, 1.0 mL/min, t_R = 9.6 min (minor) and t_R = 10.8 min (major)]; 95:5 dr [determined by ^{19}F NMR].

Procedure for Further Synthetic Transformation. To a solution of **3b** (71.7 mg, 0.2 mmol) in anhydrous CH_3OH (3 mL) was slowly added $NaBH_4$ (75.7 mg, 20.0 mmol) in batches at 0 °C under argon atmosphere. After 8 h (monitored by TLC) at room temperature, 1 N HCl was added, the reaction was quenched with EtOAc (5 mL × 3), and the organic layer was washed with brine (5 mL × 3) and dried over Na_2SO_4. The organics were filtered and concentrated. The solid obtained was directly for next reaction.

To a solution of the above intermediate and DMAP (24.4 mg, 0.2 mmol) in THF (5 mL) was added Boc_2O (65.6 mg, 0.3 mmol) at 0 °C under argon atmosphere. After 12 h (monitored by TLC) at room temperature, the mixture was concentrated and purified by flash chromatography (petroleum ether/ethyl acetate = 20:1) to obtain the product **4**: yellow solid; mp 48−51 °C; 50.6 mg, 55% yield; 76:24 dr [determined by HPLC analysis Daicel Chirapak IC, hexane/*i*-PrOH = 90/10, 220 nm UV detector, 1.0 mL/min, major diastereomer: t_R = 11.773 min and t_R = 14.543 min, 94% ee; minor diastereomer: t_R = 13.1 min and t_R = 16.7 min, 94% ee]; $[\alpha]^{20}_D$ −9.8 (*c* 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.54 (s, 9H, $O(CH_3)_3$), 3.78 (s, 3H, OCH_3), 5.03−5.09 (m, 1H, CH_2NO_2), 5.14−5.19 (m, 1H, CH_2NO_2), 6.49 (s, 1H, CH), 6.81 (d, J = 8.3 Hz, 2H, Ar−H), 6.97 (d, J = 8.3 Hz, 2H, Ar−H), 7.54 (d, J = 4.8 Hz, 3H, Ar−H), 7.86 (d, J = 7.2 Hz, 2H, Ar−H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 155.3 (d, $^2J_{C-F}$ = 17.9 Hz), 151.3, 131.6, 130.6, 129.7, 129.4, 128.1, 127.3 (d, $^3J_{C-F}$ = 2.9 Hz), 114.6, 105.9 (d, $^1J_{C-F}$ = 214.0 Hz), 96.1 (d, $^2J_{C-F}$ = 14.8 Hz), 84.5, 74.6 (d, $^3J_{C-F}$ = 3.6 Hz), 55.2, 46.2 (d, $^2J_{C-F}$ = 23.2 Hz), 27.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −170.47 (d, J = 8.2 Hz); IR (KBr) ν 2964, 2935, 1745, 1560, 1515, 1374, 1278, 1256, 1158, 1031, 991, 848, 769, 694 cm^{-1}; HRMS (ESI) found m/z 461.1641 $[M]^+$, calcd for $C_{23}H_{25}FN_2O_7$ 461.1646.

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra and HPLC analytic results for the products **3a−s**, **Int-a**, and **4**, as well as crystallographic data for compound **3i** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(10) The relative and absolute configuration of compound **3i** was confirmed by X-ray crystal structure analysis. CCDC 879309 (**3i**) contains the supplementary crystallographic data for this paper (see the Supporting Information). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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