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Organocatalytic Enantioselective Vinylogous Henry Reaction of 3,5-Dimethyl-4-nitroisoxazole with Trifluoromethyl Ketones

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Abstract The enantioselective vinylogous Henry reaction of 3,5-dimethyl-4-nitroisoxazole with trifluoromethyl ketones employing a bi-functional squaramide organocatalyst has been developed. A series of isoxazole bearing trifluoromethyl-substituted tertiary alcohols, 2-substituted (*R*)-1,1,1-trifluoro-3-(3-methyl-4-nitroisoxazol-5-yl)propan-2-ols, were obtained under these mild reaction conditions in good yields and moderate to good enantioselectivities

Key words asymmetric synthesis, isoxazole, trifluoromethyl ketone, squaramide organocatalyst, vinylogous Henry reaction

Figure 1 Representative examples of isoxazole-containing drugs

Compounds containing fluorine atoms¹ find wide applications in agrochemicals,² medicinal chemistry,³ clinical imaging,⁴ and material science.⁵ The presence of the trifluoromethyl (CF_3) group in a molecule can significantly improve its properties, such as lipophilicity and pharmacokinetics.⁶ Therefore many protocols have recently been reported for the enantioselective addition of various nucleophiles to trifluoromethyl ketones⁷ leading to tertiary alcohols containing an $\alpha\text{-CF}_3$ group and thus a tetrasubstituted stereocenter, either in the presence of a transition-metal catalyst⁸ or an organocatalyst.⁹

On the other hand, the isoxazole moiety is an important class of heterocycles present in many bioactive compounds.¹⁰ For example, the anti-arthritis drug leflunomide (**I**) and the anti-inflammatory drug parecoxib (**II**) bear an isoxazole unit as the core structure (Figure 1).

In 2016, Fan and co-workers reported the organocatalyzed asymmetric vinylogous Michael reaction of 3,5-dimethyl-4-nitroisoxazole (**1**) with aromatic α,β -unsaturated aldehydes [Scheme 1 (a)].¹¹ Owing to the synthetic and biological significance of the CF_3 group and the isoxazole unit, we now report an enantioselective vinylogous Henry reaction of 3,5-dimethyl-4-nitroisoxazole (**1**) with trifluoromethyl ketones [Scheme 1 (b)]. To the best of our knowledge, there is no report on the enantioselective version of a such transformation.¹²

Scheme 1 3,5-Dimethyl-4-nitroisoxazole as a substrate in asymmetric vinylogous Henry reactions

In order to achieve our goal, we began with optimization studies for this reaction. We envisioned that the use of chiral bases or bifunctional hydrogen bonding catalysts¹³ may lead to high enantioselectivity.

In our first attempt we chose 3,5-dimethyl-4-nitroisoxazole (**1**) as the nucleophile and 2,2,2-trifluoroacetophenone (**2a**) as the acceptor in the presence of 5 mol% of the chiral basic catalyst **4a** and dichloromethane as solvent (Table 1, Figure 2). By stirring at room temperature we observed a moderate conversion and a very low ee value of

Table 1 Optimization of the Reaction Conditions^a

Entry	Catalyst	Yield (%) ^b	ee (%) ^c
1	4a	49	16
2	4b	18	12
3	4c	— ^d	—
4	4d	— ^d	—
5	4e	22	24
6	4f	71	53
7	4g	14	62
8	4h	22	13
9	4i	8	19
10	4j	9	71
11	4k	17	69
12 ^e	4k	85	79

^a Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), CH₂Cl₂ (2 mL).

^b Yield of isolated product.

^c Determined by HPLC.

^d No reaction.

^e Firstly **2a** and catalyst stirred for 1 h in CH₂Cl₂ (0.075 mL, concentration 4 M), and then **1** was added.

the desired product **3a** (entry 1). Employing the bifunctional organocatalysts **4b–e** under the same reaction conditions did not result in good enantioselectivities (entries 2–5). When a thiourea catalyst **4f** was tested a much better yield with improved ee was obtained (entry 6). Switching to the squaramide derived catalyst **4g** the yield decreased, but the ee significantly improved to 62% (entry 7). Other squaramide catalysts **4h–k** were then tested and it turned out that the catalyst **4k** is the best one for this reaction leading to the best ee of 69% but only 17% yield (entry 8–11). Further optimization, screening different solvents, such as toluene, DCE, THF, and acetonitrile, in combination with catalyst **4k**, did not improve the results. Interestingly, when the trifluoromethyl ketone **2a** and catalyst **4k** are stirred in 0.075 mL of dichloromethane (concentration 4 M) for 1 hour and then the isoxazole **1** is added, the reaction is much faster leading to the desired product in 85% yield and 79% ee after 3 days (entry 12).

With the optimized conditions in hand, next the substrate scope of the asymmetric addition of 3,5-dimethyl-4-nitroisoxazole (**1**) to the trifluoromethyl ketones **2** for a wide range of both electron-withdrawing and electron-donating substituents at different positions was evaluated (Scheme 2).

It was observed that this protocol is applicable to a variety of trifluoromethyl ketones bearing electron-withdrawing substituents at different positions, thus leading to the formation of the desired products **3b–h** with high yields and good ee. The trifluoromethyl ketones **2j–m** bearing electron-donating substituents also worked very well to provide the desired α -hydroxy trifluoromethyl compounds **3j–m** in good yields and ee values. We have also used substrates containing a thiophen-2-yl substituent successfully, leading to the formation of **3n** with good yield (87%) and a moderate ee value of 59%. Notably, 58% ee and 77% yield of **3o** were obtained for the challenging aliphatic substrate **2o**.

Figure 2 Catalyst screening for the vinylogous Henry reaction

Scheme 2 Substrate scope of the vinylogous Henry reaction. *Reagents and conditions*: **1** (0.4 mmol), **2** (0.6 mmol), CH_2Cl_2 (0.15 mL); **2** and catalyst **4k** were stirred for 1 h in CH_2Cl_2 (concentration 4 M), and then **1** was added. The ee was determined by HPLC with a chiral stationary phase (value in brackets after one recrystallization).

To explore the scalability of this vinylogous Henry reaction, a gram-scale reaction of 3,5-dimethyl-4-nitroisoxazole (**1**) and 2,2,2-trifluoroacetophenone (**2a**) was carried out under the optimized conditions, and the corresponding product **3a** was obtained with the expected good yield and enantioselectivity (Scheme 3).

Scheme 3 Gram-scale synthesis of **3a**

The absolute configuration of adduct **3g** was determined as *R* by single crystal X-ray structure analysis (Figure 3).¹⁴

Figure 3 Determination of the absolute configuration of **3g** by X-ray crystal structure analysis¹⁴

By knowing the absolute configuration we proposed a possible transition state for the enantioselective vinylogous addition of 3,5-dimethyl-4-nitroisoxazole (**1**) to the trifluoromethyl ketones **2**. It is assumed that the nitroisoxazole is deprotonated by the tertiary amine of the catalyst. Simultaneously, the trifluoromethyl ketone is activated by H-bonding with the squaramide moiety to undergo a *Si*-face attack of the anion to afford the (*R*)-enantiomer of the product (Scheme 4).

Scheme 4 Proposed transition state for the enantioselective addition of the nitroisoxazole **1** to the trifluoromethyl ketones

In conclusion, we have developed an efficient organocatalytic protocol for the enantioselective vinylogous Henry reaction of 3,5-dimethyl-4-nitroisoxazole with trifluoromethyl ketones. The resulting products bearing a CF₃ group attached to a tetrasubstituted stereocenter were obtained in very good yields and moderate to good enantioselectivities under mild reaction conditions. The ee values were improved by a single crystallization.

Unless otherwise noted, all commercially available compounds were used without further purification. Anhyd CH₂Cl₂ was purified by distillation over CaH₂. The products were purified by column chromatography on Merck silica gel 60, particle size 0.040–0.063 mm (230–240 mesh, flash). For TLC analysis, Merck precoated TLC plates (silica gel 60 GF254 0.25 mm) were used. Visualization of the developed TLC plates was performed with UV irradiation (254 nm). Optical rotation values were measured on a Perkin-Elmer 241 polarimeter. HRMS were acquired on a ThermoFisher Scientific LTQ-Orbitrap XL. IR spectra were taken on a PerkinElmer Spectrum 100 FT-IR spectrophotometer. ¹H NMR and ¹³C NMR spectra were recorded at r.t. on Inova 400 or Agilent VNMRs 600 spectrometers. ¹H NMR spectra are measured relative to the solvent residual peak (CDCl₃, δ = 7.26) as external standard. Analytical HPLC was performed on a Hewlett-Packard 1100 Series instrument or Agilent 1100 instrument using chiral stationary phases [Daicel AS, Daicel AD, Daicel IA, Daicel IB, Daicel IG]. The melting points were obtained with a LLG MPM-H2 apparatus. The bifunctional squaramide catalyst **4k** was synthesized according to the literature.¹⁵ Racemic compounds were prepared by using Et₃N as catalyst.

2-Substituted (*R*)-1,1,1-Trifluoro-3-(3-methyl-4-nitroisoxazol-5-yl)propan-2-ols **3a–o**; General Procedure

A 10-mL glass tube equipped with a stirring bar was charged with trifluoromethyl ketone **2** (0.6 mmol, 1.5 equiv), catalyst **4k** (0.02 mmol, 5 mol%), and CH₂Cl₂ (0.15 mL, 4.0 M). The resulting solution was stirred at r.t. for 1 h, then 3,5-dimethyl-4-nitroisoxazole **1** (0.4 mmol, 1.0 equiv) was added and the mixture was stirred for 72 h. The crude was purified by flash chromatography (*n*-pentane/EtOAc 9:1) to provide the desired products **3** as colorless solids or viscous oils.

(*R*)-1,1,1-Trifluoro-3-(3-methyl-4-nitroisoxazol-5-yl)-2-phenylpropan-2-ol (**3a**)

Colorless solid; yield: 108 mg (85%); mp 112–113 °C; [α]_D²⁵ +75.3 (c 1, CHCl₃).

HPLC [Chiralpak IA, *n*-heptane/*i*-PrOH (9:1), 0.7 mL/min, 254 nm]: *t*_R (major) = 16.5 min, *t*_R (minor) = 17.7 min; 79% ee.

IR (ATR): 3354, 2939, 2290, 1950, 1741, 1606, 1522, 1382, 1155, 815, 737 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): δ = 2.48 (s, 3 H, CH₃), 3.61 (s, 1 H, OH), 4.06–4.12 (m, 2 H, CH₂), 7.36–7.40 (m, 3 H, ArH), 7.55–7.56 (m, 2 H, ArH).

¹³C NMR (125 MHz, CDCl₃): δ = 11.5, 33.9, 83.2, 124.6 (d, *J*_{C-F} = 237 Hz), 125.9 (2 C), 128.6 (2 C), 128.8, 129.4, 134.3, 155.4, 168.3.

HRMS (ESI): *m/z* calcd for C₁₃H₁₁N₂O₄F₃: 316.0671; found: 316.0651.

(*R*)-2-(4-Bromophenyl)-1,1,1-trifluoro-3-(3-methyl-4-nitroisoxazol-5-yl)propan-2-ol (**3b**)

Colorless solid; yield: 141 mg (89%); mp 136–137.1 °C; [α]_D²⁵ +90.1 (c 1, CHCl₃).

HPLC [Chiralpak AD, *n*-heptane/EtOH (7:3), 1.0 mL/min, 254 nm]: *t*_R (major) = 5.4 min, *t*_R (minor) = 7.2 min; 76% ee.

IR (ATR): 3353, 2983, 2315, 2096, 1741, 1606, 1522, 1382, 1154, 815 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): δ = 2.50 (s, 3 H, CH₃), 3.64 (s, 1 H, OH), 4.01 (d, *J* = 12 Hz, 1 H, CH₂), 4.12 (d, *J* = 12 Hz, 1 H, CH₂), 7.44 (d, *J* = 12 Hz, 2 H, ArH), 7.51–7.54 (m, 2 H, ArH).

¹³C NMR (125 MHz, CDCl₃): δ = 11.5, 33.7, 83.1, 124.0, 124.3 (d, *J*_{C-F} = 237 Hz), 127.1, 127.9 (2 C), 131.2 (2 C), 133.2, 155.5, 167.7.

HRMS (ESI): *m/z* calcd for C₁₃H₁₀N₂O₄BrF₃: 393.9776; found: 393.9776.

(*R*)-2-(3-Bromophenyl)-1,1,1-trifluoro-3-(3-methyl-4-nitroisoxazol-5-yl)propan-2-ol (**3c**)

Colorless solid; yield: 138 mg (87%); mp 99.1–100 °C; [α]_D²⁵ +27.6 (c 1, CHCl₃).

HPLC [Chiralpak IA, *n*-heptane/EtOH (9:1), 1.0 mL/min, 230 nm]: *t*_R (major) = 8.0 min, *t*_R (minor) = 8.7 min; 43% ee.

IR (ATR): 3378, 2929, 2300, 2107, 1740, 1601, 1521, 1376, 1153, 950, 891, 786, 727 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): δ = 2.51 (s, 3 H, CH₃), 3.66 (s, 1 H, OH), 3.99 (d, *J* = 12 Hz, 1 H, CH₂), 4.13 (d, *J* = 12 Hz, 1 H, CH₂), 7.28 (t, *J* = 6 Hz, 1 H, ArH), 7.49–7.54 (m, 2 H, ArH), 7.73 (s, 1 H, ArH).

¹³C NMR (125 MHz, CDCl₃): δ = 11.6, 33.8, 83.1, 122.9, 124.3 (d, *J*_{C-F} = 236 Hz), 124.7, 127.1, 129.4, 130.1, 132.7, 136.4, 155.6, 167.6.

HRMS (ESI): m/z calcd for $C_{13}H_{10}N_2O_4BrF_3$: 393.9776; found: 393.9775.

(R)-2-(2-Bromophenyl)-1,1,1-trifluoro-3-(3-methyl-4-nitroisoxazol-5-yl)propan-2-ol (3d)

Viscous oil; yield: 128 mg (81%); $[\alpha]_D^{25} +44.7$ (c 1, $CHCl_3$).

HPLC [Chiralpak IA, *n*-heptane/EtOH (7:3), 0.5 mL/min, 254 nm]: t_R (major) = 10.3 min, t_R (minor) = 8.7 min; 69% ee.

IR (ATR): 3352, 2919, 2344, 2092, 1743, 1601, 1527, 1393, 1166, 743 cm^{-1} .

1H NMR (600 MHz, $CDCl_3$): δ = 2.51 (s, 3 H, CH_3), 4.20 (d, J = 18 Hz, 1 H, CH_2), 4.38 (s, 1 H, OH), 4.75 (d, J = 18 Hz, 1 H, CH_2), 7.23–7.25 (m, 1 H, ArH), 7.34–7.37 (m, 1 H, ArH), 7.66 (dd, J = 3, 6 Hz, 1 H, ArH), 7.72 (d, J = 12 Hz, 1 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.6, 32.9, 83.2, 120.5, 122.8, 124.4 (d, J_{C-F} = 239 Hz), 127.8, 130.4, 131.0, 132.9, 136.2, 155.4, 168.3.

HRMS (ESI): m/z calcd for $C_{13}H_{10}N_2O_4BrF_3$: 393.9776; found: 393.9785.

(R)-1,1,1-Trifluoro-2-(4-fluorophenyl)-3-(3-methyl-4-nitroisoxazol-5-yl)propan-2-ol (3e)

Colorless solid; yield: 125 mg (93%); mp 88.8–90.2 °C; $[\alpha]_D^{25} +23.0$ (c 1, $CHCl_3$).

HPLC [Chiralpak AS, *n*-heptane/EtOH (97:3), 1.0 mL/min, 254 nm]: t_R (major) = 10.7 min, t_R (minor) = 13.1 min; 74% ee.

IR (ATR): 3375, 3001, 2428, 2295, 2124, 1977, 1740, 1600, 1514, 1372, 1161, 935, 822, 739 cm^{-1} .

1H NMR (600 MHz, $CDCl_3$): δ = 2.49 (s, 3 H, CH_3), 3.66 (s, 1 H, OH), 4.02 (d, J = 12 Hz, 1 H, CH_2), 4.11 (d, J = 12 Hz, 1 H, CH_2), 7.05–7.09 (m, 2 H, ArH), 7.54–7.56 (m, 2 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.5, 33.9, 83.1, 115.6 (d, J_{C-F} = 19 Hz, 2 C), 124.4 (d, J_{C-F} = 237 Hz), 128.1 (d, J_{C-F} = 8 Hz, 2 C), 130.0 (d, J_{C-F} = 3 Hz), 132.2, 155.6, 164.0, 167.9.

HRMS (ESI): m/z calcd for $C_{13}H_{10}N_2O_4F_4$: 334.0577; found: 334.0587.

(R)-1,1,1-Trifluoro-2-(3-fluorophenyl)-3-(3-methyl-4-nitroisoxazol-5-yl)propan-2-ol (3f)

Colorless solid; yield: 119 mg (89%); mp 94.7–95.6 °C; $[\alpha]_D^{25} +57.6$ (c 1, $CHCl_3$).

HPLC [Chiralpak AS, *n*-heptane/EtOH (97:3), 1.0 mL/min, 254 nm]: t_R (major) = 10.7 min, t_R (minor) = 12.5 min; 59% ee.

IR (ATR): 3402, 2952, 2317, 2095, 1741, 1610, 1520, 1378, 1158, 1011, 796, 720 cm^{-1} .

1H NMR (600 MHz, $CDCl_3$): δ = 2.50 (s, 3 H, CH_3), 3.72 (s, 1 H, OH), 4.00 (d, J = 12 Hz, 1 H, CH_2), 4.13 (d, J = 12 Hz, 1 H, CH_2), 7.07–7.10 (m, 1 H, ArH), 7.29–7.31 (m, 1 H, ArH), 7.34 (d, J = 6 Hz, 1 H, ArH), 7.36–7.39 (m, 1 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.5, 33.9, 83.2, 113.7 (d, J_{C-F} = 20 Hz), 116.5 (d, J_{C-F} = 18 Hz), 121.7, 124.3 (d, J_{C-F} = 237 Hz), 130.2 (d, J_{C-F} = 8 Hz), 136.8 (d, J_{C-F} = 6 Hz), 155.6, 161.9, 163.9, 167.7.

HRMS (ESI): m/z calcd for $C_{13}H_{10}N_2O_4F_4$: 334.0577; found: 334.0582.

(R)-2-(4-Chlorophenyl)-1,1,1-trifluoro-3-(3-methyl-4-nitroisoxazol-5-yl)propan-2-ol (3g)

Colorless solid; yield: 127 mg (90%); mp 131.5–132.7 °C; $[\alpha]_D^{25} +65.7$ (c 1, $CHCl_3$).

HPLC [Chiralpak IA, *n*-heptane/*i*-PrOH (9:1), 1.0 mL/min, 230 nm]: t_R (major) = 10.6 min, t_R (minor) = 12.3 min; 80% ee.

IR (ATR): 3363, 2986, 2371, 2102, 1915, 1741, 1607, 1524, 1381, 1162, 818, 739 cm^{-1} .

1H NMR (600 MHz, $CDCl_3$): δ = 2.50 (s, 3 H, CH_3), 3.62 (s, 1 H, OH), 4.01 (d, J = 12 Hz, 1 H, CH_2), 4.12 (d, J = 12 Hz, 1 H, CH_2), 7.36–7.38 (m, 2 H, ArH), 7.50 (d, J = 6 Hz, 2 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.5, 33.7, 83.3, 124.3 (d, J_{C-F} = 237 Hz), 127.2, 127.6 (2 C), 128.8 (2 C), 132.7, 135.7, 155.5, 167.7.

HRMS (ESI): m/z calcd for $C_{13}H_{10}N_2O_4ClF_3$: 350.0281; found: 350.0280.

(R)-1,1,1-Trifluoro-3-(3-methyl-4-nitroisoxazol-5-yl)-2-[4-(trifluoromethyl)phenyl]propan-2-ol (3h)

Colorless solid; yield: 145 mg (94%); mp 138–139.1 °C; $[\alpha]_D^{25} +96.8$ (c 1, $CHCl_3$).

HPLC [Chiralpak IB, *n*-heptane/EtOH (9:1), 0.7 mL/min, 254 nm]: t_R (major) = 9.0 min, t_R (minor) = 8.5 min; 72% ee.

IR (ATR): 3394, 2937, 2295, 2105, 1740, 1600, 1514, 1379, 1077, 797, 726 cm^{-1} .

1H NMR (600 MHz, $CDCl_3$): δ = 2.50 (s, 3 H, CH_3), 3.74 (s, 1 H, OH), 4.03 (d, J = 12 Hz, 1 H, CH_2), 4.19 (d, J = 12 Hz, 1 H, CH_2), 7.66 (m, 2 H, ArH), 7.72 (m, 2 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.5, 33.7, 83.3, 122.7, 124.3 (d, J_{C-F} = 237 Hz), 124.5, 125.6 (d, J_{C-F} = 4 Hz, 2 C), 126.8 (2 C), 131.8, 138.0, 155.6, 167.4.

HRMS (ESI): m/z calcd for $C_{14}H_{10}N_2O_4F_6$: 384.0545; found: 384.0542.

(R)-1,1,1-Trifluoro-3-(3-methyl-4-nitroisoxazol-5-yl)-2-(perfluorophenyl)propan-2-ol (3i)

Colorless solid; yield: 138 mg (89%); mp 100.2–100.4 °C; $[\alpha]_D^{25} +72.0$ (c 1, $CHCl_3$).

HPLC [Chiralpak AD, *n*-heptane/*i*-PrOH (97:3), 0.7 mL/min, 230 nm]: t_R (major) = 13.2 min, t_R (minor) = 15.9 min; 53% ee.

IR (ATR): 3354, 3319, 2945, 2311, 2109, 1928, 1740, 1610, 1497, 1378, 1139, 979, 816, 663 cm^{-1} .

1H NMR (600 MHz, $CDCl_3$): δ = 2.50 (s, 3 H, CH_3), 4.14 (t, J = 6 Hz, 1 H, OH), 4.26–4.33 (m, 2 H, CH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.5, 32.4, 83.2, 122.8, 124.7, 137.3 (2 C), 139.0 (2 C), 145.1, 146.7, 155.8, 167.2.

HRMS (ESI): m/z calcd for $C_{13}H_6N_2O_4F_8$: 406.0200; found: 406.0211.

(R)-1,1,1-Trifluoro-2-(4-methoxyphenyl)-3-(3-methyl-4-nitroisoxazol-5-yl)propan-2-ol (3j)

Colorless solid; yield: 110 mg (79%); mp 129.4–130.5 °C; $[\alpha]_D^{25} -82.4$ (c 1, $CHCl_3$).

HPLC [Chiralpak IA, *n*-heptane/EtOH (7:3), 0.7 mL/min, 230 nm]: t_R (major) = 9.8 min, t_R (minor) = 11.5 min; 77% ee.

IR (ATR): 3387, 2931, 2320, 2101, 1741, 1600, 1519, 1379, 1159, 1036, 947, 813, 729 cm^{-1} .

1H NMR (600 MHz, $CDCl_3$): δ = 2.49 (s, 3 H, CH_3), 3.49 (s, 1 H, OH), 3.80 (s, 3 H, OCH_3), 4.07 (s, 2 H, CH_2), 6.88–6.90 (m, 2 H, ArH), 7.46 (d, J = 12 Hz, 2 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.5, 33.8, 55.2, 83.2, 113.9 (2 C), 121.9, 124.6 (d, J_{C-F} = 236 Hz), 126.1, 127.4 (2 C), 155.4, 160.2, 168.3.

HRMS (ESI): m/z calcd for $C_{14}H_{13}N_2O_5F_3$: 346.0777; found: 346.0779.

(R)-1,1,1-Trifluoro-2-(3-methoxyphenyl)-3-(3-methyl-4-nitro-isoxazol-5-yl)propan-2-ol (3k)

Viscous oil; yield: 106 mg (76%); $[\alpha]_D^{25} +47.0$ (c 1, CHCl₃).

HPLC [Chiralpak IG, *n*-heptane/*i*-PrOH (97:3), 1.0 mL/min, 230 nm]: t_R (major) = 17.3 min, t_R (minor) = 15.5 min; 47% ee.

IR (ATR): 3430, 2949, 2328, 2093, 1600, 1512, 1414, 1161, 1042, 827, 730 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): δ = 2.49 (s, 3 H, CH₃), 3.61 (s, 1 H, OH), 3.79 (s, 3 H, OCH₃), 4.07 (s, 2 H, CH₂), 6.89–6.91 (m, 1 H, ArH), 7.10–7.11 (m, 2 H, ArH), 7.30 (t, J = 6 Hz, 1 H, ArH).

¹³C NMR (125 MHz, CDCl₃): δ = 11.5, 33.9, 55.2, 83.2, 112.1, 114.6, 118.1, 124.6 (d, J_{C-F} = 237 Hz), 129.6, 132.1, 136.0, 155.4, 159.6, 168.1.

HRMS (ESI): m/z calcd for C₁₄H₁₃N₂O₅F₃: 346.0777; found: 346.0776.

(R)-1,1,1-Trifluoro-2-(2-methoxyphenyl)-3-(3-methyl-4-nitro-isoxazol-5-yl)propan-2-ol (3l)

Viscous oil; yield: 106 mg (76%); $[\alpha]_D^{25} -80.5$ (c 1, CHCl₃).

HPLC [Chiralpak AD, *n*-heptane/*i*-PrOH (9:1), 0.7 mL/min, 254 nm]: t_R (major) = 12.3 min, t_R (minor) = 13.9 min; 79% ee.

IR (ATR): 3417, 2960, 2325, 2086, 1603, 1512, 1408, 1163, 1021, 753 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): δ = 2.49 (s, 3 H, CH₃), 3.92 (s, 3 H, OCH₃), 4.00 (d, J = 12 Hz, 1 H, CH₂), 4.32 (d, J = 12 Hz, 1 H, CH₂), 6.19 (br s, 1 H, OH), 6.98–7.02 (m, 2 H, ArH), 7.35–7.38 (m, 1 H, ArH), 7.39 (d, J = 12 Hz, 1 H, ArH).

¹³C NMR (125 MHz, CDCl₃): δ = 11.6, 32.7, 56.3, 78.4 (d, J_{C-F} = 25 Hz), 112.7, 121.6, 121.9, 124.8 (d, J_{C-F} = 239 Hz), 127.7, 128.9, 130.1, 155.2, 157.8, 168.9.

HRMS (ESI): m/z calcd for C₁₄H₁₃N₂O₅F₃: 346.0777; found: 346.0779.

(R)-1,1,1-Trifluoro-3-(3-methyl-4-nitroisoxazol-5-yl)-2-(*p*-tolyl)-propan-2-ol (3m)

Colorless solid; yield: 111 mg (84%); mp 118–118.8 °C; $[\alpha]_D^{25} +81.7$ (c 1, CHCl₃).

HPLC [Chiralpak AS, *n*-heptane/EtOH (97:3), 1.0 mL/min, 254 nm]: t_R (major) = 10.1 min, t_R (minor) = 12.0 min; 76% ee.

IR (ATR): 3377, 2929, 2315, 2104, 1741, 1605, 1521, 1379, 1152, 1033, 935, 811, 734 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): δ = 2.34 (s, 3 H, CH₃), 2.49 (s, 3 H, CH₃), 3.49 (s, 1 H, OH), 4.04–4.10 (m, 2 H, CH₂), 7.18 (d, J = 6 Hz, 2 H, ArH), 7.42 (d, J = 6 Hz, 2 H, ArH).

¹³C NMR (125 MHz, CDCl₃): δ = 11.5, 21.1, 33.9, 77.3, 124.6 (d, J_{C-F} = 237 Hz), 125.9 (2 C), 127.4, 129.3 (2 C), 131.3, 139.4, 155.5, 168.3.

HRMS (ESI): m/z calcd for C₁₄H₁₃N₂O₄F₃: 330.0827; found: 330.0835.

(R)-1,1,1-Trifluoro-3-(3-methyl-4-nitroisoxazol-5-yl)-2-(thiophen-2-yl)propan-2-ol (3n)

Colorless solid; yield: 105 mg (87%); mp 119.4–120.5 °C; $[\alpha]_D^{25} +56.7$ (c 1, CHCl₃).

HPLC [Chiralpak IA, *n*-heptane/EtOH (7:3), 0.7 mL/min, 230 nm]: t_R (major) = 7.8 min, t_R (minor) = 10.5 min; 59% ee.

IR (ATR): 3287, 2945, 2317, 2101, 1741, 1602, 1522, 1383, 1148, 928, 821, 705 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): δ = 2.52 (s, 3 H, CH₃), 3.78 (s, 1 H, OH), 4.00 (d, J = 12 Hz, 1 H, CH₂), 4.12 (d, J = 12 Hz, 1 H, CH₂), 7.04 (dd, J = 4, 6 Hz, 1 H, thiophen), 7.18 (d, J = 4 Hz, 1 H, thiophen), 7.34 (dd, J = 4, 6 Hz, 1 H, thiophen).

¹³C NMR (125 MHz, CDCl₃): δ = 11.6, 34.9, 76.6, 121.2, 124.0 (d, J_{C-F} = 237 Hz), 126.2, 127.1, 127.5, 138.0, 155.5, 167.6.

HRMS (ESI): m/z calcd for C₁₁H₉N₂O₄F₃S: 322.0235; found: 322.0235.

(R)-2-Benzyl-1,1,1-trifluoro-3-(3-methyl-4-nitroisoxazol-5-yl)propan-2-ol (3o)

Colorless solid; yield: 101 mg (77%); mp 66.0–67.6 °C; $[\alpha]_D^{25} +28.3$ (c 1, CHCl₃).

HPLC [Chiralpak AS, *n*-heptane/EtOH (95:5), 0.5 mL/min, 254 nm]: t_R (major) = 21.7 min, t_R (minor) = 24.3 min; 58% ee.

IR (ATR): 3507, 3034, 2936, 1606, 1521, 1422, 1369, 1279, 1157, 1099, 910, 829, 708 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): δ = 2.52 (s, 3 H, CH₃), 3.01 (d, J = 12 Hz, 1 H, CH₂Ph), 3.10 (s, 1 H, OH), 3.25 (d, J = 12 Hz, 1 H, CH₂Ph), 3.54 (d, J = 18 Hz, 1 H, CH₂), 3.67 (d, J = 18 Hz, 1 H, CH₂), 7.29–7.35 (m, 5 H, ArH).

¹³C NMR (125 MHz, CDCl₃): δ = 11.5, 31.3, 40.1, 76.1 (d, J_{C-F} = 34 Hz), 125.1 (d, J_{C-F} = 356 Hz), 127.8, 128.7 (2 C), 129.3, 130.6 (2 C), 132.8, 155.6, 168.7.

HRMS (ESI): m/z calcd for C₁₄H₁₃N₂O₄F₃: 330.0827; found: 330.0836.

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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0036-1590928>.

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