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Catalytic enantioselective synthesis of carboxy-substituted 2-isoxazolines by cascade oxa-Michael-cyclization

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Abstract

An efficient quinidine-based phase-transfer-catalyzed enantioselective cascade oxa-Michael–cyclization reaction of hydroxylamine with various β-carboxy-substituted α,β-unsaturated ketones has been achieved for the preparation of chiral carboxy-substituted 2-isoxazolines. This cascade reaction provided the desired products in good yields (up to 98%) with excellent enantioselectivities (91−96% ee). In addition, the cascade reaction was effectively applied to the first catalytic asymmetric synthesis of the herbicide (*S*)-methiozolin.

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Introduction

2-Isoxazolines are an important class of heterocycles found in natural products,[1] pharmaceuticals[2] and agrochemicals[3] displaying a variety of potent biological activities. In addition, 2-isoxazolines have been widely used as versatile synthons[4] and chiral ligands[5] in synthetic organic chemistry. For this reason, 2-isoxazoline synthesis has attracted significant attention.[6] In particular, the asymmetric synthesis of optically pure 2-isoxazolines has been a subject of active research.[7] As an example of the importance of enantiopure 2-isoxazolines (Fig. 1), biological evaluation of the antiparasitic isoxazoline Bravecto (fluralaner) revealed that only the *S* enantiomer of Bravecto is active and the *R* enantiomer is inactive.[8]

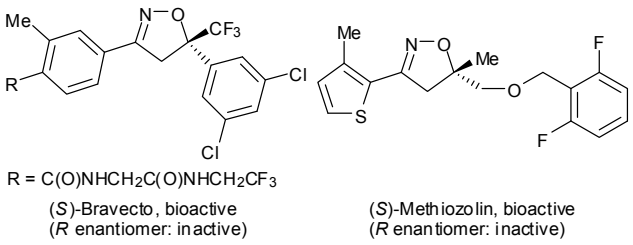

Fig. 1 Examples of bioactive chiral 2-isoxazolines.

In addition, in our previous paper,[9] it was reported that only the (*S*)-methiozolin, which was synthesized from enantiopure (*S*)-[5-methyl-3-(3-methylthiophen-2-yl)-4,5-

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dihydroisoxazol-5-yl]methanol prepared by chiral prep-HPLC separation, displayed herbicidal activities against grass weeds. Interestingly, (*R*)-methiozolin showed no herbicidal activities. Methiozolin has been commercialized as a racemic herbicide displaying an efficacious and toxicologically favorable activity against grass weed in turf grass.[10] Therefore, owing to the environment-friendly and atom-economic importance, development of an enantioselective route for the efficient synthesis of (*S*)-methiozolin is highly desirable. Here, we report an asymmetric phase-transfer-catalyzed cascade oxa-Michael–cyclization reaction of various β-carboxy-substituted α,β-unsaturated ketones with hydroxylamine that affords the desired chiral carboxy-substituted 2-isoxazolines in good yields with excellent enantioselectivities (Scheme 1). The cascade reaction is effectively applied to the first catalytic asymmetric synthesis of (*S*)-methiozolin. Although the enantioselective phase-transfer-catalyzed cascade synthesis[11−13] of chiral trifluoromethyl-substituted 2-isoxazolines with β-trifluoromethyl-substituted α,β-unsaturated ketones and hydroxylamine has been well developed by Shibata's group,[7d] to the best our knowledge, the use of β-carboxy-substituted α,β-unsaturated ketones as substrates in the cascade reaction has not been reported. In particular, the carboxy group in the cascade product can be transformed to versatile functional groups.

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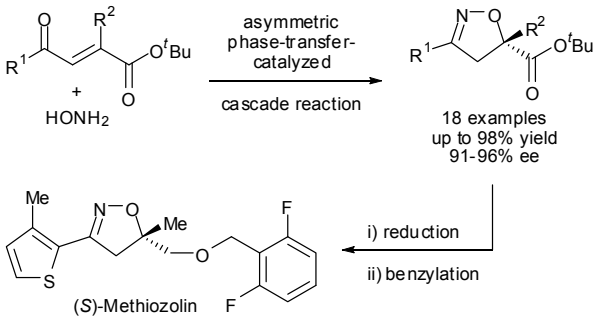

Scheme 1 Enantioselective phase-transfer-catalyzed cascade reaction of β-carboxy-substituted α,β-unsaturated ketones with hydroxylamine and its application to synthesis of (*S*)-methiozolin.

Results and discussion

To explore the feasibility of the enantioselective phase-transfer-catalyzed cascade oxa-Michael-cyclization reactions of β-carboxy-substituted α,β-unsaturated ketones with hydroxylamine,[14] the cascade reactions of (*E*)-*tert*-butyl 2-methyl-4-oxo-4-phenylbut-2-enoate (**1a**) and hydroxylamine with potassium hydroxide as the base additive in toluene at −30 °C were performed in the presence of quinidine-based phase-transfer catalysts **I**−**VIII**, respectively (Table 1, entries 1−8). Among all the catalysts assayed, catalyst **VIII** proved to be the best and provided the corresponding cascade product **2a** in 68% yield and 73% ee. Varying the solvent revealed that methyl *tert*-butyl ether (MTBE) was ideal for the cascade reaction under otherwise identical conditions,

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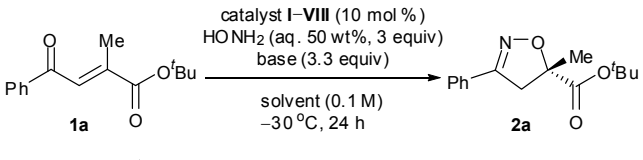
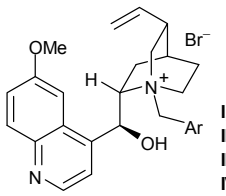
affording **2a** in 94% yield and 83% ee (Table 1, entries 9−13). Finally, among the base additives tested, cesium carbonate was ideal for the cascade reaction to provide the desired cascade product **2a** in 92% yield and 93% ee. (Table 1, entries 14−17). When the loadings of hydroxylamine and cesium carbonate were decreased to 2 equiv and 2.2 equiv, respectively, **2a** was obtained in 94% ee, but with a considerably decreased yield of 54% (Table 1, entry 18). In addition, lowering the reaction temperature to −40 °C provided **2a** in 95% ee, with a drastically decreased yield of 15% (Table 1, entry 19).

Table 1 Optimization of the enantioselective phase-transfer-catalyzed cascade oxa-Michael-cyclization reactions of (*E*)-*tert*-butyl 2-methyl-4-oxo-4-phenylbut-2-enoate (**1a**) with hydroxylamine[a]





I, Ar = 4-$(CF_3)C_6H_4$ **V**, Ar = 3,5-$(1\text{-Naph})_2C_6H_3$
II, Ar = 9-Anthracyl **VI**, Ar = 3,5-$(2\text{-Naph})_2C_6H_3$
III, Ar = 3,5-$^t Bu_2C_6H_3$ **VII**, Ar = 3,5-$(CF_3)_2C_6H_3$
IV, Ar = 3,5-$Ph_2C_6H_3$ **VIII**, Ar = 2,5-$(CF_3)_2C_6H_3$

Entry	Catalyst	Base[b]	Solvent	Yield[c] (%)	ee[d] (%)
1	**I**	KOH	toluene	75	28
2	**II**	KOH	toluene	77	25
3	**III**	KOH	toluene	76	61
4	**IV**	KOH	toluene	61	46

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5	**V**	KOH	toluene	71	44
6	**VI**	KOH	toluene	71	68
7	**VII**	KOH	toluene	67	54
8	**VIII**	KOH	toluene	68	73
9	**VIII**	KOH	CH_2Cl_2	78	71
10	**VIII**	KOH	$CHCl_3$	65	71
11	**VIII**	KOH	THF	78	76
12	**VIII**	KOH	Et_2O	82	66
13	**VIII**	KOH	MTBE	94	83
14	**VIII**	Na_2CO_3	MTBE	n.r.[e]	
15	**VIII**	K_2CO_3	MTBE	19	90
16	**VIII**	Rb_2CO_3	MTBE	63	93
17	**VIII**	Cs_2CO_3	MTBE	92	93
18[f]	**VIII**	Cs_2CO_3	MTBE	54	94
19[g]	**VIII**	Cs_2CO_3	MTBE	15	95

[a]Procedure: $HONH_2$ (0.6 mmol) was added to a mixture of **1a** (0.2 mmol), catalyst (0.02 mmol), and base (0.66 mmol) in 2 mL of the solvent in one portion. The mixture was stirred at −30 °C for 24 h. [b]KOH was used as 50 wt% aqueous solution. Na_2CO_3, K_2CO_3, Rb_2CO_3, and Cs_2CO_3 were solids and used as such. [c]Isolated yield. [d]Determined by chiral HPLC analysis (Chiralpak AD-H). [e]No reaction. [f]2 equiv of $HONH_2$ and 2.2 equiv of Cs_2CO_3 were used. [g]At −40 °C.

Subsequently, the scope of the β-carboxy-substituted α,β-unsaturated ketones in the enantioselective phase-transfer-catalyzed cascade oxa-Michael–cyclization reactions with hydroxylamine was explored under the optimized conditions (Tables 2 and 3). First,

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the reactions of hydroxylamine with a series of 4-substituted (*E*)-*tert*-butyl 2-methyl-4-oxobut-2-enoate **1** bearing aryl, electron-deficient aryl, electron-rich aryl, heteroaryl, and substituted heteroaryl substituents gave the corresponding cascade products **2a**–**2i** in good yields and excellent enantioselectivities (Table 2).[15] Further investigation of the enantioselective phase-transfer-catalyzed cascade reactions with hydroxylamine was then carried out with an assortment of 2-substituted (*E*)-*tert*-butyl 4-oxo-4-phenylbut-2-enoate **1** bearing alkyl, substituted alkyl, protected hydroxyalkyl, benzyl-protected mercaptoalkyl, and doubly *N*-protected aminoalkyl substituents (Table 3). In all cases, the desired cascade products **2j**–**2r** were obtained in good yields and excellent enantioselectivities.

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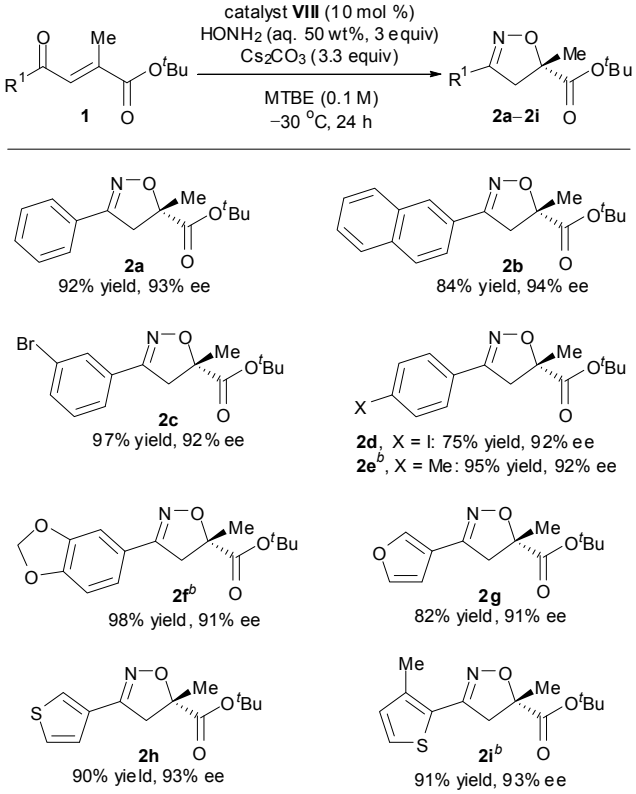
Table 2 Enantioselective phase-transfer-catalyzed cascade oxa-Michael–cyclization reactions of hydroxylamine with various 4-substituted (*E*)-*tert*-butyl 2-methyl-4-oxobut-2-enoates **1**[a]



[a]Procedure: $HONH_2$ (0.6 mmol) was added to a mixture of **1** (0.2 mmol), catalyst **VIII** (0.02 mmol), and Cs_2CO_3 (0.66 mmol) in MTBE (2 mL) in one portion. The mixture was stirred either at −20 or −30 °C for 24 h. Enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AD-H). [b]At −20 °C.

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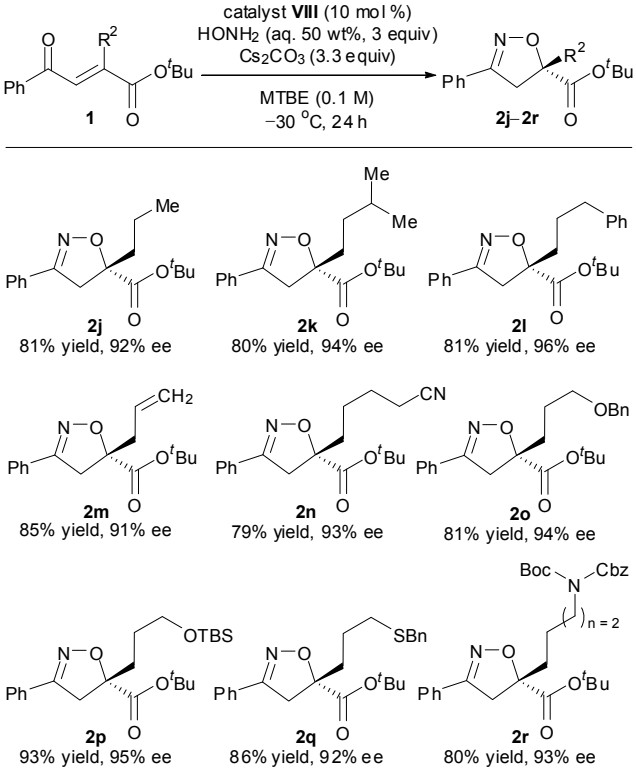
Table 3 Enantioselective phase-transfer-catalyzed cascade oxa-Michael–cyclization reactions of hydroxylamine with various 2-substituted (*E*)-*tert*-butyl 4-oxo-4-phenylbut-2-enoates **1**[a]



[a]Procedure: $HONH_2$ (0.6 mmol) was added to a mixture of **1** (0.2 mmol), catalyst **VIII** (0.02 mmol), and Cs_2CO_3 (0.66 mmol) in MTBE (2 mL) in one portion. The mixture was stirred at −30 °C for 24 h. Enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AD-H).

To further investigate the feasibility of scaling-up the cascade reaction, the enantioselective phase-transfer-catalyzed cascade reaction was carried out on a large scale, as shown in Scheme 2. The reaction successfully provided the desired cascade

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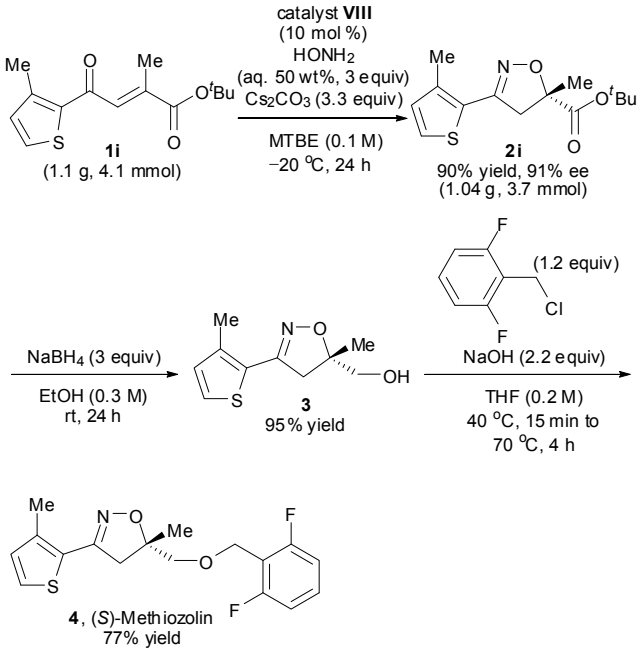
product **2i** in 90% yield and 91% ee. The cascade product **2i** was transformed to (*S*)-methiozolin (**4**) in two steps. Reduction of **2i** with sodium borohydride in ethanol at room temperature resulted in the formation of alcohol **3** in 95% yield. Benzylation of **3** with 2-(chloromethyl)-1,3-difluorobenzene and sodium hydroxide in tetrahydrofuran provided (*S*)-methiozolin (**4**) in 77% yield.[9]



Scheme 2 Synthesis of (*S*)-methiozolin via a large-scale enantioselective phase-transfer-catalyzed cascade reaction.

The absolute stereochemical assignment of all cascade products was based on the absolute stereochemistry of **3**, which was determined to be the *S* configuration by

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comparing the specific rotation of **3** with that reported in the literature.[9] Based on the absolute stereochemistry of the cascade products, the proposed transition state of the cascade reaction is depicted in Fig. 2. The substrate is presumably captured by the catalyst via hydrogen bonding between the carbonyl oxygen in the substrate and the chiral secondary hydroxyl group in the catalyst. The anionic hydroxylamine nucleophile, which is generated by the deprotonation of hydroxylamine by the base additive, would form an ion pair with the ammonium cation in the catalyst and be thus optimally positioned between the catalyst and the substrate. Therefore, the oxa-Michael reaction of the anionic hydroxylamine nucleophile takes place from the *Si* face of the substrate to afford the oxa-Michael intermediate. The subsequent intramolecular imine formation provides the desired cascade product.

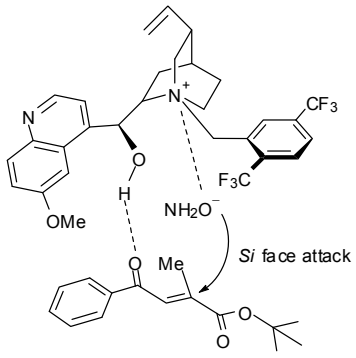

Fig. 2 Proposed transition state of the cascade reaction.

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Conclusion

In conclusion, the enantioselective phase-transfer-catalyzed cascade oxa-Michael–cyclization reaction of β-carboxy-substituted α,β-unsaturated ketones with hydroxylamine has been achieved by using the quinidine-based phase-transfer catalyst **VIII** and cesium carbonate as the base additive. The cascade reaction provided the highly enantioenriched carboxy-substituted 2-isoxazolines as the cascade products in good yields (up to 98%) with excellent enantioselectivities (91−96% ee). This is the only example of the use of β-carboxy-substituted α,β-unsaturated ketones as a substrate in the enantioselective phase-transfer-catalyzed cascade oxa-Michael–cyclization reaction with hydroxylamine. In addition, the cascade reaction was effectively applied to the first catalytic asymmetric synthesis of the herbicide (*S*)-methiozolin. Thus, the developed strategy provides a convenient synthetic route for generating various chiral carboxy-substituted 2-isoxazolines. Further applications of these species in the synthesis of bioactive compounds are being studied.

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Experimental

General

^{1}H and ^{13}C NMR spectra were recorded on a 500 MHz spectrometer with tetramethylsilane as the internal reference. Mass spectroscopic data were obtained from the Korea Basic Science Institute (Daegu) with a JEOL JMS 700 high resolution mass spectrometer. Enantiomeric excess values were determined by HPLC analysis with chiral stationary phase column (Chiralpak AD-H). β-Carboxy-substituted α,β-unsaturated ketones **1** were prepared according to the reported procedures.[16]

Preparation of catalysts I−VIII.

Catalysts **I**−**VII** were prepared according to the reported procedures.[17]

1-[2,5-Bis(trifluoromethyl)benzyl]-2-[(*S*)-hydroxy(6-methoxyquinolin-4-yl)methyl]-8-vinyl-1-azoniabicyclo[2.2.2]octane bromide (catalyst VIII).

2,5-Bis(trifluoromethy)benzyl bromide (0.47 mL, 2.6 mmol) was added to a solution of quinidine (648 mg, 2 mmol) in THF (10 mL, 0.2 M) at rt, and then the mixture was allowed to stir at reflux. After 12 h, the mixture was cooled to rt. The solvent was removed and the residue was purified by silica gel column chromatography (SiO_2, 7% MeOH in $CHCl_3$) to provide the catalyst **VIII** in 63% yield (798 mg, 1.26 mmol) as a

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white solid. mp 177−178 °C; $[\alpha]_D^{24}$ 122.2 (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.64 (d, *J* = 4.5 Hz, 1H), 7.96−7.94 (m, 2H), 7.91−7.89 (m, 1H), 7.83 (d, *J* = 4.5 Hz, 1H), 7.30 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.81 (d, *J* = 4.5 Hz, 1H), 6.57 (s, 1H), 6.43 (d, *J* = 13.0 Hz, 1H), 6.07−6.00 (m, 1H), 5.47 (d, *J* = 12.0 Hz, 1H), 5.29−5.22 (m, 2H), 4.79−4.75 (m, 1H), 4.17 (s, 1H), 4.05−4.02 (m, 1H), 3.96 (s, 3H), 3.41−3.37 (m, 1H), 2.90−2.83 (m, 1H), 2.58−2.48 (m, 2H), 2.06 (s, 1H), 1.96 (s, 1H), 1.92−1.83 (m, 2H), 1.08−1.03 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 146.8, 143.7, 142.4, 135.3, 134.4 (q, $^2J_{C\text{-}F}$ = 6.2 Hz), 134.2 (q, $^2J_{C\text{-}F}$ = 10.0 Hz), 133.9, 131.2, 128.8 (q, $^3J_{C\text{-}F}$ = 5.0 Hz), 127.8, 126.5, 125.8, 123.9 (q, $^1J_{C\text{-}F}$ = 91.2 Hz), 121.8, 121.7 (q, $^1J_{C\text{-}F}$ = 88.7 Hz), 120.6, 118.0, 100.9, 69.1, 65.7, 58.0, 56.5, 55.9, 55.3, 37.7, 26.5, 23.7, 21.7; FTIR (neat) 3182, 2949, 1621, 1508, 1422, 1304, 1240, 1173, 1125, 1095, 1045, 826, 747 cm^{-1}; HRMS (FAB) calcd for $[M–Br]^+$ $C_{29}H_{29}F_6N_2O_2$ 551.2133, found 551.2131.

Typical procedure for the synthesis of racemic carboxy-substituted 2-isoxazolines 2. Hydroxylamine (50 wt% in H_2O) (0.6 mmol) was added to a mixture of substrate **1** (0.2 mmol), hexadecyltrimethylammonium bromide (0.06 mmol), and potassium hydroxide (2 mmol) in $ClCH_2CH_2Cl$ (2 mL) in one portion. The mixture was stirred at rt for 0.5 h. The mixture was quenched by 1 N HCl and extracted with CH_2Cl_2. The organic layer

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was washed with brine and dried with $MgSO_4$. Filtration, concentration, and purification by flash column chromatography (SiO_2, 5−20% EtOAc in hexanes) provided the corresponding racemic carboxy-substituted 2-isoxazolines **2**.

Typical procedure for the enantioselective phase-transfer-catalyzed cascade oxa-Michael−cyclization reactions of hydroxylamine to β-carboxy-substituted α,β-unsaturated ketones.

Hydroxylamine (50 wt% in H_2O) (0.6 mmol) was added to a mixture of substrate **1** (0.2 mmol), catalyst **VIII** (0.02 mmol), and cesium carbonate (0.66 mmol) in MTBE (2 mL) in one portion. The mixture was stirred either at −20 or −30 °C for 24 h. The mixture was quenched by 1 N HCl and extracted with EtOAc. The organic layer was washed with brine and dried with $MgSO_4$. Filtration, concentration, and purification by flash column chromatography (SiO_2, 5−20% EtOAc in hexanes) provided the corresponding cascade products **2**.

(*S*)-*tert*-Butyl 5-methyl-3-phenyl-4,5-dihydroisoxazole-5-carboxylate (2a). White solid (48 mg, 92%); mp 48−49 °C; $[\alpha]_D^{24}$ 174.4 (*c* 1, $CHCl_3$, 93% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67−7.65 (m, 2H), 7.41−7.38 (m, 3H), 3.84 (d, *J* = 17.0 Hz, 1H), 3.15 (d, *J* = 17.0 Hz, 1H), 1.66 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

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170.8, 155.9, 130.1, 129.2, 128.6, 126.6, 86.5, 82.3, 44.3, 27.7, 23.5; FTIR (neat) 2983, 2931, 1726, 1446, 1364, 1301, 1151, 1098, 906, 757, 686 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{15}H_{19}NO_3$ 261.1365, found 261.1367; HPLC (Chiralpak AD-H, hexane/IPA = 95/5, 0.9 mL/min, λ = 254 nm) t_R = 7.9 min (minor isomer), 13.3 min (major isomer).

(*S*)-*tert*-Butyl 5-methyl-3-(naphthalen-2-yl)-4,5-dihydroisoxazole-5-carboxylate (2b). White solid (52 mg, 84%); mp 137−138 °C; $[\alpha]_D^{24}$ 205.4 (*c* 1, $CHCl_3$, 94% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 9.0, 1.5 Hz, 1H), 7.89 (d, *J* = 1.5 Hz, 1H), 7.85−7.83 (m, 3H), 7.54−7.49 (m, 2H), 3.96 (d, *J* = 17.0 Hz, 1H), 3.28 (d, *J* = 17.0 Hz, 1H), 1.70 (s, 3H), 1.51 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 156.1, 133.9, 132.8, 128.4, 128.2, 127.7, 127.0, 126.8, 126.8, 126.6, 123.4, 86.7, 82.3, 44.3, 27.8, 23.6; FTIR (neat) 2922, 2853, 1724, 1461, 1369, 1302, 1260, 1156, 1089, 917, 826, 752 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{19}H_{21}NO_2$ 311.1521, found 311.1522; HPLC (Chiralpak AD-H, hexane/IPA = 92/8, 0.9 mL/min, λ = 254 nm) t_R = 7.9 min (minor isomer), 16.9 min (major isomer).

(*S*)-*tert*-Butyl 3-(3-bromophenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (2c). White solid (66 mg, 97%); mp 59−60 °C; $[\alpha]_D^{24}$ 137.0 (*c* 1, $CHCl_3$, 92% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 7.79 (t, *J* = 1.5 Hz, 1H), 7.59 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.53 (dq, *J* = 8.0, 1.0 Hz, 1H), 7.27 (t, *J* = 8.0 Hz, 1H), 3.80 (d, *J* = 17.0 Hz, 1H), 3.11 (d, *J* =

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17.0 Hz, 1H), 1.66 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 154.8, 132.9, 131.2, 130.1, 129.5, 125.1, 122.7, 86.9, 82.4, 44.0, 27.7, 23.5; FTIR (neat) 2980, 2933, 1741, 1719, 1553, 1367, 1307, 1148, 1088, 908, 841, 786 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{15}H_{18}BrNO_3$ 339.0470, found 339.0473; HPLC (Chiralpak AD-H, hexane/IPA = 90/10, 0.9 mL/min, λ = 254 nm) t_R = 5.7 min (minor isomer), 8.1 min (major isomer).

(*S*)-*tert*-Butyl 3-(4-iodophenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (2d). Yellow solid (58 mg, 75%); mp 92−93 °C; $[\alpha]_D^{24}$ 133.2 (*c* 1, $CHCl_3$, 92% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75−7.73 (m, 2H), 7.39−7.36 (m, 2H), 3.80 (d, *J* = 17.0 Hz, 1H), 3.10 (d, *J* = 17.0 Hz, 1H), 1.65 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 155.2, 137.7, 128.6, 128.0, 96.2, 86.9, 82.4, 43.9, 27.7, 23.5; FTIR (neat) 2982, 2930, 1721, 1587, 1434, 1366, 1311, 1153, 1105, 1005, 913, 817 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{15}H_{18}NO_3I$ 387.0331, found 387.0329; HPLC (Chiralpak AD-H, hexane/IPA = 90/10, 0.9 mL/min, λ = 254 nm) t_R = 9.1 min (minor isomer), 14.6 min (major isomer).

(*S*)-*tert*-Butyl 5-methyl-3-*p*-tolyl-4,5-dihydroisoxazole-5-carboxylate (2e). White solid (52 mg, 95%); mp 67−68 °C; $[\alpha]_D^{24}$ 167.1 (*c* 1, $CHCl_3$, 92% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56−7.53 (m, 2H), 7.21−7.19 (m, 2H), 3.81 (d, *J* = 17.0 Hz, 1H), 3.13 (d, *J* = 17.0 Hz, 1H), 2.37 (s, 3H), 1.65 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (125 MHz,

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$CDCl_3$) δ 170.9, 155.9, 140.3, 129.3, 126.6, 126.4, 86.4, 82.3, 44.5, 27.8, 23.5, 21.3; FTIR (neat) 2984, 2934, 1722, 1432, 1368, 1308, 1260, 1156, 1093, 909, 814 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{16}H_{21}NO_2$ 275.1521, found 275.1521; HPLC (Chiralpak AD-H, hexane/EtOH = 92/8, 0.9 mL/min, λ = 254 nm) t_R = 9.6 min (minor isomer), 13.1 min (major isomer).

(*S*)-*tert*-Butyl 3-(benzo[d][1,3]dioxol-5-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (2f). White solid (60 mg, 98%); mp 76−77 °C; $[\alpha]_D^{24}$ 150.9 (*c* 1, $CHCl_3$, 91% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 1.5 Hz, 1H), 7.01 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.00 (s, 2H), 3.78 (d, *J* = 17.0 Hz, 1H), 3.09 (d, *J* = 17.0 Hz, 1H), 1.64 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 155.6, 149.3, 148.0, 123.3, 121.4, 108.1, 106.4, 101.4, 86.5, 82.3, 44.5, 27.8, 23.5; FTIR (neat) 2982, 2902, 1726, 1507, 1456, 1367, 1302, 1220, 1155, 1103, 1038, 898, 807 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{16}H_{19}NO_5$ 305.1263, found 305.1260; HPLC (Chiralpak AD-H, hexane/IPA = 90/10, 0.9 mL/min, λ = 254 nm) t_R = 9.1 min (minor isomer), 15.7 min (major isomer).

(*S*)-*tert*-Butyl 3-(furan-3-yl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (2g). Yellow solid (41 mg, 82%); mp 42−43 °C; $[\alpha]_D^{23}$ 179.3 (*c* 1, $CHCl_3$, 91% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.44 (dd, *J* = 1.5, 1.5 Hz, 1H), 6.76 (dd, *J* = 1.5, 1.0

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Hz, 1H), 3.69 (d, J = 16.5 Hz, 1H), 3.01 (d, J = 16.5 Hz, 1H), 1.63 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 149.6, 144.1, 142.2, 116.6, 108.0, 86.1, 82.3, 44.7, 27.7, 23.3; FTIR (neat) 3126, 2987, 2936, 1723, 1454, 1369, 1318, 1275, 1152, 1109, 870, 799 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{13}H_{17}NO_4$ 251.1158, found 251.1161; HPLC (Chiralpak AD-H, hexane/IPA = 95/5, 0.9 mL/min, λ = 254 nm) t_R = 8.5 min (minor isomer), 11.5 min (major isomer).

(*S*)-*tert*-Butyl 5-methyl-3-(thiophen-3-yl)-4,5-dihydroisoxazole-5-carboxylate (2h). White solid (48 mg, 90%); mp 71−72 °C; $[\alpha]_D^{23}$ 184.4 (*c* 1, $CHCl_3$, 93% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (dd, J = 5.0, 1.0 Hz, 1H), 7.19 (dd, J = 3.5, 1.0 Hz, 1H), 7.05 (dd, J = 5.0, 3.5 Hz, 1H), 3.84 (d, J = 17.0 Hz, 1H), 3.15 (d, J = 17.0 Hz, 1H), 1.65 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 151.7, 131.6, 128.4, 128.3, 127.2, 86.8, 82.4, 45.0, 27.7, 23.4; FTIR (neat) 3108, 2990, 2932, 1720, 1439, 1366, 1309, 1202, 1149, 1102, 910, 839, 713 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{13}H_{17}NO_3S$ 267.0929, found 267.0931; HPLC (Chiralpak AD-H, hexane/EtOH = 95/5, 0.9 mL/min, λ = 254 nm) t_R = 9.1 min (minor isomer), 12.0 min (major isomer).

(*S*)-*tert*-Butyl 5-methyl-3-(3-methylthiophen-2-yl)-4,5-dihydroisoxazole-5-carboxylate (2i). White solid (51 mg, 91%); mp 62−63 °C; $[\alpha]_D^{23}$ 181.0 (*c* 1, $CHCl_3$, 93% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, J = 5.0 Hz, 1H), 6.91 (d, J = 5.0 Hz,

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1H), 3.84 (d, J = 17.0 Hz, 1H), 3.16 (d, J = 17.0 Hz, 1H), 2.46 (s, 3H), 1.64 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 151.9, 139.1, 131.8, 126.0, 125.5, 85.9, 82.3, 46.7, 27.7, 23.3, 16.3; FTIR (neat) 3104, 2976, 2918, 1719, 1438, 1370, 1305, 1154, 910, 843, 740 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{14}H_{19}NO_3S$ 281.1086, found 281.1086; HPLC (Chiralpak AD-H, hexane/IPA = 95/5, 0.9 mL/min, λ = 254 nm) t_R = 5.6 min (minor isomer), 7.4 min (major isomer).

(*S*)-*tert*-Butyl 3-phenyl-5-propyl-4,5-dihydroisoxazole-5-carboxylate (2j). White solid (47 mg, 81%); mp 50−51 °C; $[\alpha]_D^{23}$ 113.3 (*c* 1, $CHCl_3$, 92% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67−7.65 (m, 2H), 7.41−7.38 (m, 3H), 3.77 (d, J = 17.0 Hz, 1H), 3.18 (d, J = 17.0 Hz, 1H), 1.94 (t, J = 8.0 Hz, 2H), 1.49 (s, 9H), 1.47−1.35 (m, 2H), 0.97 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 155.8, 130.0, 129.3, 128.6, 126.6, 89.5, 82.3, 42.2, 39.1, 27.8, 17.2, 14.1; FTIR (neat) 2967, 2928, 2874, 1721, 1446, 1365, 1328, 1230, 1149, 915, 837, 760, 691 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{17}H_{23}NO_3$ 289.1678, found 289.1676; HPLC (Chiralpak AD-H, hexane/IPA = 95/5, 0.9 mL/min, λ = 254 nm) t_R = 7.8 min (minor isomer), 13.4 min (major isomer).

(*S*)-*tert*-Butyl 5-isopentyl-3-phenyl-4,5-dihydroisoxazole-5-carboxylate (2k). White solid (51 mg, 80%); mp 98−99 °C; $[\alpha]_D^{23}$ 104.9 (*c* 1, $CHCl_3$, 94% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67−7.65 (m, 2H), 7.41−7.38 (m, 3H), 3.78 (d, J = 17.0 Hz, 1H),

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3.17 (d, J = 17.0 Hz, 1H), 2.02−1.90 (m, 2H), 1.61−1.53 (m, 1H), 1.50 (s, 9H), 1.31−1.20 (m, 2H), 0.90 (d, J = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 155.9, 130.1, 129.3, 128.6, 126.6, 89.7, 82.3, 42.1, 34.9, 32.7, 28.1, 27.9, 22.4, 22.3; FTIR (neat) 2961, 2870, 1720, 1448, 1365, 1300, 1258, 1153, 1066, 916, 758, 690 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{19}H_{27}NO_3$ 317.1991, found 317.1992; HPLC (Chiralpak AD-H, hexane/IPA = 90/10, 0.9 mL/min, λ = 254 nm) t_R = 5.5 min (minor isomer), 7.4 min (major isomer).

(*S*)-*tert*-Butyl 3-phenyl-5-(3-phenylpropyl)-4,5-dihydroisoxazole-5-carboxylate (2l). White solid (59 mg, 81%); mp 100−101 °C; $[\alpha]_D^{23}$ 74.2 (*c* 1, $CHCl_3$, 96% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65−7.63 (m, 2H), 7.40−7.37 (m, 3H), 7.28−7.25 (m, 2H), 7.19−7.15 (m, 3H), 3.75 (d, J = 17.0 Hz, 1H), 3.15 (d, J = 17.0 Hz, 1H), 2.66 (t, J = 7.5 Hz, 2H), 1.99 (t, J = 8.0 Hz, 2H), 1.79−1.65 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 155.8, 141.5, 130.1, 129.2, 128.6, 128.3, 128.3, 126.6, 125.8, 89.4, 82.3, 42.3, 36.4, 35.6, 27.8, 25.5; FTIR (neat) 2976, 2930, 1721, 1597, 1447, 1366, 1297, 1244, 1152, 1128, 915, 747, 690 cm^{-1}; HRMS (FAB) calcd for $[M+H]^+$ $C_{23}H_{28}NO_3$ 366.2069, found 366.2073; HPLC (Chiralpak AD-H, hexane/IPA = 90/10, 0.9 mL/min, λ = 254 nm) t_R = 7.5 min (minor isomer), 11.4 min (major isomer).

(*S*)-*tert*-Butyl 5-allyl-3-phenyl-4,5-dihydroisoxazole-5-carboxylate (2m). White

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solid (49 mg, 85%); mp 39−40 °C; $[\alpha]_D^{23}$ 126.0 (*c* 1, $CHCl_3$, 91% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 7.67−7.64 (m, 2H), 7.41−7.38 (m, 3H), 5.81−5.73 (m, 1H), 5.22−5.16 (m, 2H), 3.76 (d, *J* = 17.0 Hz, 1H), 3.23 (d, *J* = 17.0 Hz, 1H), 2.75−2.67 (m, 2H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 156.0, 131.2, 130.1, 129.1, 128.6, 126.7, 119.9, 88.8, 82.6, 41.5, 41.1, 27.8; FTIR (neat) 2976, 2931, 1725, 1599, 1368, 1283, 1257, 1152, 1001, 907, 759, 691 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{17}H_{21}NO_3$ 287.1521, found 287.1520; HPLC (Chiralpak AD-H, hexane/IPA = 95/5, 0.9 mL/min, λ = 254 nm) t_R = 7.1 min (minor isomer), 12.4 min (major isomer).

(*S*)-*tert*-Butyl 5-(4-cyanobutyl)-3-phenyl-4,5-dihydroisoxazole-5-carboxylate (2n). Yellow oil (52 mg, 79%); $[\alpha]_D^{24}$ 90.8 (*c* 1, $CHCl_3$, 93% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 7.66−7.64 (m, 2H), 7.42−7.39 (m, 3H), 3.77 (d, *J* = 17.0 Hz, 1H), 3.21 (d, *J* = 17.0 Hz, 1H), 2.37 (t, *J* = 7.5 Hz, 2H), 2.06−1.94 (m, 2H), 1.77−1.71 (m, 2H), 1.65−1.55 (m, 2H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 155.8, 130.1, 128.9, 128.6, 126.5, 119.2, 88.8, 82.6, 42.6, 35.9, 27.7, 25.1, 22.9, 16.8; FTIR (neat) 2930, 2246, 1724, 1447, 1360, 1255, 1152, 1099, 911, 840, 759, 692 cm^{-1}; HRMS (FAB) calcd for $[M+H]^+$ $C_{19}H_{25}N_2O_3$ 329.1865, found 329.1867; HPLC (Chiralpak AD-H, hexane/IPA = 80/20, 0.9 mL/min, λ = 254 nm) t_R = 9.6 min (minor isomer), 18.2 min (major isomer).

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(*S*)-*tert*-Butyl 5-[3-(benzyloxy)propyl]-3-phenyl-4,5-dihydroisoxazole-5-carboxylate (2o). White solid (64 mg, 81%); mp 48−49 °C; $[\alpha]_D^{23}$ 64.8 (*c* 1, $CHCl_3$, 94% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65−7.63 (m, 2H), 7.41−7.37 (m, 3H), 7.34−7.30 (m, 4H), 7.29−7.25 (m, 1H), 4.49 (s, 2H), 3.77 (d, *J* = 17.0 Hz, 1H), 3.51 (t, *J* = 6.5 Hz, 2H), 3.20 (d, *J* = 17.0 Hz, 1H), 2.12−2.02 (m, 2H), 1.78−1.64 (m, 2H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 155.8, 138.3, 130.0, 129.1, 128.5, 128.2, 127.4, 127.4, 126.5, 89.2, 82.3, 72.7, 69.6, 42.2, 33.7, 27.8, 24.2; FTIR (neat) 2980, 2928, 2865, 1720, 1453, 1365, 1332, 1215, 1149, 1126, 916, 841, 762, 733, 691 cm^{-1}; HRMS (FAB) calcd for $[M+H]^+$ $C_{24}H_{30}NO_4$ 396.2175, found 396.2173; HPLC (Chiralpak AD-H, hexane/IPA = 88/12, 0.9 mL/min, λ = 254 nm) t_R = 9.8 min (minor isomer), 16.6 min (major isomer).

(*S*)-*tert*-Butyl 5-[3-(*tert*-butyldimethylsilyloxy)propyl]-3-phenyl-4,5-dihydroisoxazole-5-carboxylate (2p). Colorless oil (78 mg, 93%); $[\alpha]_D^{23}$ 56.9 (*c* 1, $CHCl_3$, 95% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67−7.64 (m, 2H), 7.41−7.38 (m, 3H), 3.79 (d, *J* = 17.0 Hz, 1H), 3.64 (dt, *J* = 6.0, 1.0 Hz, 2H), 3.20 (d, *J* = 17.0 Hz, 1H), 2.05−2.01 (m, 2H), 1.66−1.61 (m, 1H), 1.58−1.53 (m, 1H), 1.49 (s, 9H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 155.8, 130.0, 129.2, 128.5, 126.5, 89.4, 82.2, 62.5, 42.2, 33.5, 27.8, 27.1, 25.8, 18.1, −5.4; FTIR (neat) 2929,

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2857, 1726, 1447, 1360, 1253, 1151, 1096, 912, 833, 756 cm^{-1}; HRMS (FAB) calcd for $[M+H]^+$ $C_{23}H_{38}NO_4Si$ 420.2570, found 420.2573; HPLC (Chiralpak AD-H, hexane/IPA = 90/10, 0.9 mL/min, λ = 254 nm) t_R = 4.3 min (minor isomer), 5.6 min (major isomer).

(*S*)-*tert*-Butyl 5-[3-(benzylthio)propyl]-3-phenyl-4,5-dihydroisoxazole-5-carboxylate (2q). White solid (71 mg, 86%); mp 69−70 °C; $[\alpha]_D^{23}$ 42.7 (*c* 1, $CHCl_3$, 92% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 7.65−7.63 (m, 2H), 7.42−7.39 (m, 3H), 7.30−7.27 (m, 4H), 7.24−7.19 (m, 1H), 3.73 (d, *J* = 17.0 Hz, 1H), 3.69 (s, 2H), 3.13 (d, *J* = 17.0 Hz, 1H), 2.46 (t, *J* = 7.0 Hz, 2H), 2.08−1.96 (m, 2H), 1.72−1.60 (m, 2H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 155.8, 138.3, 130.1, 129.1, 128.7, 128.6, 128.4, 126.9, 126.6, 89.1, 82.5, 42.5, 36.1, 35.9, 31.1, 27.8, 23.5; FTIR (neat) 2987, 2920, 1718, 1598, 1453, 1366, 1296, 1259, 1150, 913, 756, 690 cm^{-1}; HRMS (FAB) calcd for $[M+H]^+$ $C_{24}H_{30}NO_3S$ 412.1946, found 412.1949; HPLC (Chiralpak AD-H, hexane/IPA = 80/20, 0.9 mL/min, λ = 254 nm) t_R = 8.5 min (minor isomer), 18.0 min (major isomer).

(*S*)-*tert*-Butyl 5-{4-[(benzyloxycarbonyl)(*tert*-butoxycarbonyl)amino]butyl}-3-phenyl-4,5-dihydroisoxazole-5-carboxylate (2r). White solid (88 mg, 80%); mp 72−73 °C; $[\alpha]_D^{23}$ 42.9 (*c* 1, $CHCl_3$, 93% ee); ^1H NMR (500 MHz, $CDCl_3$) δ 7.66−7.63 (m, 2H), 7.42−7.38 (m, 3H), 7.37−7.33 (m, 4H), 7.32−7.28 (m, 1H), 7.32−7.28 (m, 1H),

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5.20 (s, 2H), 3.74 (d, J = 17.0 Hz, 1H), 3.63 (t, J = 7.5 Hz, 2H), 3.15 (d, J = 17.0 Hz, 1H), 2.00−1.90 (m, 2H), 1.65−1.59 (m, 2H), 1.48 (s, 9H), 1.45 (s, 9H), 1.42−1.32 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 155.8, 153.7, 152.0, 135.4, 130.1, 129.1, 128.6, 128.4, 128.2, 128.1, 126.6, 89.2, 82.7, 82.4, 68.2, 46.1, 42.2, 36.5, 28.8, 27.8, 27.8, 21.0; FTIR (neat) 2981, 2934, 1752, 1727, 1709, 1455, 1357, 1286, 1152, 1131, 1106, 1069, 907, 755, 690 cm^{-1}; HRMS (FAB) calcd for $[M+Na]^+$ $C_{31}H_{40}N_2O_7Na$ 575.2733, found 575.2731; HPLC (Chiralpak AD-H, hexane/IPA = 82/18, 0.9 mL/min, λ = 254 nm) t_R = 8.9 min (minor isomer), 17.7 min (major isomer).

Large-scale enantioselective phase-transfer-catalyzed cascade oxa-Michael–cyclization reaction for the synthesis of (*S*)-methiozolin (4).

Hydroxylamine (50 wt% in H_2O) (0.75 mL, 12.3 mmol) was added to a mixture of (*E*)-*tert*-butyl 2-methyl-4-(3-methylthiophen-2-yl)-4-oxobut-2-enoate (**1i**) (1.1 g, 4.1 mmol), catalyst **VIII** (259 mg, 0.41 mmol), and cesium carbonate (4.4 g, 13.5 mmol) in MTBE (41 mL) in one portion. The mixture was stirred at −20 °C for 24 h. The mixture was quenched by 1 N HCl and extracted with EtOAc. The organic layer was washed with brine and dried with $MgSO_4$. Filtration, concentration, and purification by flash column chromatography (SiO_2, 8% EtOAc in hexanes) afforded the cascade product **2i** in 90%

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yield (1.04 g, 3.7 mmol) and 91% ee as a white solid.

(*S*)-[5-Methyl-3-(3-methylthiophen-2-yl)-4,5-dihydroisoxazol-5-yl]methanol (3). Sodium borohydride (419 mg, 11 mmol) was added to (*S*)-*tert*-butyl 5-methyl-3-(3-methylthiophen-2-yl)-4,5-dihydroisoxazole-5-carboxylate (**2i**) (1.04 g, 3.7 mmol) in EtOH (12 mL). The mixture was stirred at rt for 24 h. The mixture was quenched by saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine and dried with $MgSO_4$. Filtration, concentration, and purification by flash column chromatography (SiO_2, 40% EtOAc in hexanes) provided the alcohol **3** in 95% yield (738 mg, 3.5 mmol) as a white solid. mp 106–107 °C; $[\alpha]_D^{23}$ 57.0 (*c* 1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 5.0 Hz, 1H), 6.90 (d, *J* = 5.0 Hz, 1H), 3.72 (d, *J* = 12.0 Hz, 1H), 3.57 (dd, *J* = 12.0, 7.5 Hz, 1H), 3.51 (d, *J* = 16.5 Hz, 1H), 3.04 (d, *J* = 16.5 Hz, 1H), 2.45 (s, 3H), 2.01 (s, 1H), 1.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 138.8, 131.8, 126.2, 125.9, 86.8, 67.0, 44.4, 22.4, 16.3; FTIR (neat) 3337, 2931, 2858, 1576, 1435, 1341, 1188, 1075, 939, 901, 754 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{10}H_{13}NO_2S$ 211.0667, found 211.0666.

(*S*)-5-[(2,6-Difluorobenzyloxy)methyl]-5-methyl-3-(3-methylthiophen-2-yl)-4,5-dihydroisoxazole (4).

Sodium hydroxide (307 mg, 7.7 mmol) was added to (*S*)-[5-methyl-3-(3-

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methylthiophen-2-yl)-4,5-dihydroisoxazol-5-yl]methanol (**3**) (738 mg, 3.5 mmol) in THF (17 mL). The mixture was stirred at 40 °C for 15 min. After addition of 2,6-difluorobenzyl chloride (680 mg, 4.2 mmol), the mixture was stirred at 70 °C for 4 h. After cooling to rt, the mixture was quenched by ice water and extracted with EtOAc. The organic layer was washed with 1 N HCl and brine, and dried with $MgSO_4$. Filtration, concentration, and purification by flash column chromatography (SiO_2, 7% EtOAc in hexanes) provided (*S*)-methiozolin (**4**) in 77% yield (905 mg, 2.7 mmol) as a white solid. mp 43−44 °C; $[\alpha]_D^{23}$ 56.1 (*c* 1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29−7.23 (m, 2H), 6.90−6.85 (m, 3H), 4.69 (t, *J* = 1.0 Hz, 2H), 3.58−3.50 (m, 2H), 3.43 (d, *J* = 16.5 Hz, 1H), 2.98 (d, *J* = 16.5 Hz, 1H), 2.43 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8 (dd, $^1J_{C\text{-}F}$ = 248.7, 7.5 Hz), 152.4, 138.6, 131.8, 130.2 (dd, $^3J_{C\text{-}F}$ = 10.0, 10.0 Hz), 126.4, 125.7, 113.4 (dd, $^2J_{C\text{-}F}$ = 20.0, 20.0 Hz), 111.2 (dd, $^2J_{C\text{-}F}$ = 20.0, 6.2 Hz), 85.8, 74.1, 60.7 (t, $^3J_{C\text{-}F}$ = 2.5 Hz), 45.4, 23.0, 16.2; FTIR (neat) 3070, 2933, 2887, 1629, 1595, 1469, 1428, 1330, 1228, 1096, 1053, 863, 789, 710 cm^{-1}; HRMS (EI) calcd for $[M]^+$ $C_{17}H_{17}F_2NO_2S$ 337.0948, found 337.0950.

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Conflicts of interest

The authors declare the following competing financial interest(s): The authors are listed as inventors on a pending patent application related to technology described in this work.

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Electronic supplementary information (ESI) available: Copies of ^{1}H NMR and ^{13}C NMR spectra of all new compounds. Chiral HPLC analysis data of **2a**−**2r**.

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14. We performed the enantioselective phase-transfer-catalyzed cascade reaction of (*E*)-*tert*-butyl 2-methyl-4-oxo-4-phenylbut-2-enoate (**1a**) as the substrate with hydroxylamine under the same reaction conditions as those previously reported for the enantioselective phase-transfer-catalyzed cascade reaction of β−trifluoromethyl-substituted α,β-unsaturated ketones as the substrate with hydroxylamine (Ref. 7d**)**. The reaction provided the desired cascade product **2a** in 90% yield but with a low ee of 59%.

15. Under the optimized conditions in Table 2, the cascade reactions with 4-alkyl substituted (*E*)-*tert*-butyl 2-methyl-4-oxobut-2-enoates as the substrate provided the desired products in low yields, but with high enantioselectivities (for example, R^1 = cyclopropyl: 20% yield, 87% ee; R^1 = cyclohexyl: 18% yield, 94% ee).

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[Table of Contents Entry]

Enantioselective phase-transfer-catalyzed cascade synthesis of chiral carboxy-substituted 2-isoxazolines was achieved. The cascade reaction was applied to synthesis of herbicide (*S*)-methiozolin.