# A Facile Synthesis of Oxazolines, Thiazolines, and Imidazolines Using α,α-Difluoroalkylamines

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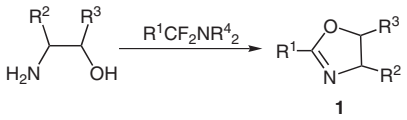
**Abstract:** β-Amino alcohols, β-amino thiols, and β-diamines can be converted to the corresponding oxazoline, thiazoline, and imidazoline derivatives, respectively, by reaction with α,α-difluoroalkylamines under mild conditions. The reaction is applicable for the synthesis of optically active heterocyclic compounds.

**Key words:** α,α-difluoroalkylamine, heterocycle, amino alcohol, oxazoline, thiazoline, imidazoline

Nitrogen-containing five-membered heterocyclic compounds such as oxazolines, thiazolines, and imidazolines are of great interest to organic chemists, because they are present in various natural compounds having interesting bioactivities.[1] Furthermore, the optically active heterocyclic compounds have been successfully used in asymmetric synthesis as chiral templates[2] or ligands.[3] Many methods for their synthesis have been developed, including cyclization of carboxyamide derivatives,[4] and acid-catalyzed condensation of amino compounds with carboxylic acid,[5] ester,[6] nitrile,[7] or benzimidate.[8] The cyclization reaction from *N*-acylamino alcohols or halides using a dehydration reagent or a base has been most frequently used for their synthesis. However, the method includes the problem of epimerization during the cyclization.[9] The acid-catalyzed cyclization of the *N*-acylamino alcohols can avoid the problem but the reaction is generally carried out at high temperature and the method requires multi-step procedures from the starting amines.[2c,10] Though the acid-catalyzed condensation of the amines with the carboxylic acid or its derivatives is more direct and favored for their synthesis, high temperature and/or long reaction time is generally required. Therefore, a new method for the direct conversion of the amines to the heterocyclic compounds under mild conditions has been desired. Recently, we reported a synthesis of (fluoroalkyl)amides by the deoxyfluorination of N-protected amino alcohols using α,α-difluoroalkylamine.[11] During the course of the study, we found that N-unprotected β-amino alcohols were converted to the corresponding oxazolines by reaction with the α,α-difluoroalkylamines under mild conditions (Equation 1). For instance, the reaction of 2-aminoethanol and 2-amino-2-methylpropan-1-ol with *N*,*N*-diethyl-α,α-difluoro-3-methylbenzylamine (DFMBA) was completed in one hour at 40 °C to give the corresponding oxazolines **1a** and **1b** in 85 and 60% yield, respectively (Table 1). Under the reaction conditions, deoxyfluorination of the hydroxy group did not take place.[12]

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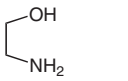
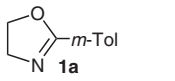
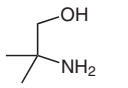
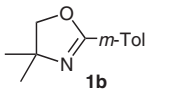
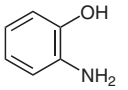
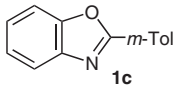
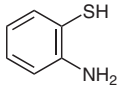
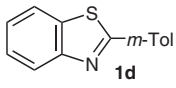
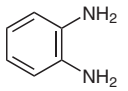
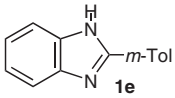
**Equation 1**

**Table 1** Synthesis of Heterocyclic Compounds Using DFMBA[a]

| Substrate | Conditions | Product | Yield (%)[b] |
|---|---|---|---|
|  | 40 °C, 1 h |  **1a** | 85 |
|  | 40 °C, 1 h |  **1b** | 60 |
|  | 40 °C, 1 h |  **1c** | 90 |
|  | 20 °C, 1 h |  **1d** | 94 |
|  | 83 °C, 1 h[c] |  **1e** | 63 |

[a] Unless otherwise stated, the reaction was carried out in $CH_2Cl_2$.
[b] Isolated yield based on DFMBA.
[c] 1,2-Dichloroethane was used as solvent.

The reaction of DFMBA was applied for the synthesis of oxazole **1c**, thiazole **1d**, and imidazole **1e**. The reaction with 2-aminophenol and 2-aminothiophenol proceeded at 20–40 °C to give **1c** and **1d** in high yields, respectively. On the other hand, the reaction with *o*-phenylenediamine was sluggish and higher temperature (83 °C) was required to complete the reaction and **1e** was obtained in moderate yield as shown in Table 1.

Various α,α-difluoroalkylamines, such as *N*-(α,α-difluorobenzyl)pyrrolidine (DFBP), *N*-(difluoromethyl)morpholine (DFMM), *N*-(1,1-difluoro-2,2-dimethylpropyl)-pyrrolidine (DFMPP), *N*,*N*-diethyl(α,α-difluoro-4-meth-

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oxybenzyl)amine (DFMOBA), and *N*,*N*′-(α,α,α′,α′-tetrafluoro-α,α′-*m*-xylene)dipyrrolidine (TFXDP) can be prepared from the corresponding amides in two steps,[13] and were applied for the synthesis of heterocyclic compounds (Figure 1).

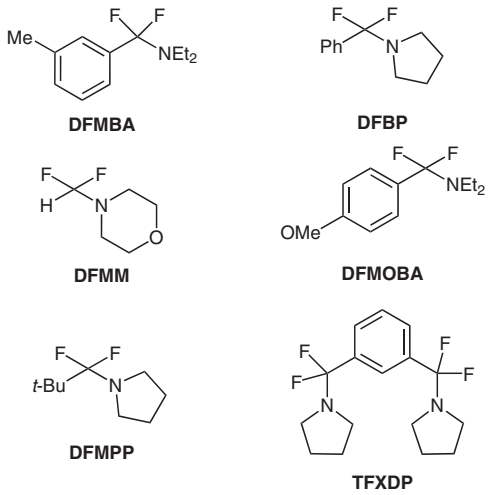
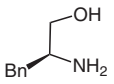
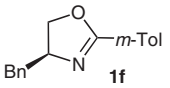
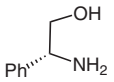
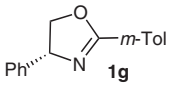
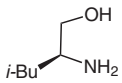
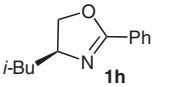
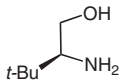
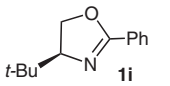
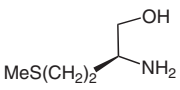
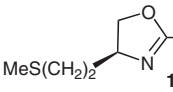
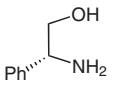
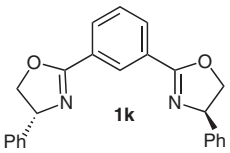



**Figure 1** α,α-Difluoroalkylamines prepared

Recently, optically active oxazolines have been successfully used in asymmetric synthesis as the chiral ligands.[2] Various kinds of optically active amino alcohols and their precursors are commercially available and we used them for the synthesis of the optically active oxazolines by reaction with DFMBA, DFBP or TFXDP. The reaction proceeded without racemization and the optical purity of the starting materials was completely kept in the products.[14] By choosing the α,α-difluoroalkylamine and the amino alcohol, various optically active oxazolines **1f–j** can be prepared in 73–85% yield (Table 2). (*R*,*R*)-1,3-Benzenebis(4-phenyl-4,5-dihydro-2-oxazole) (**1k**), which was used as chiral ligand in asymmetric synthesis,[15] can be directly prepared from (*R*)-2-amino-2-phenylethanol and TFXDP in 79% yield.

Heterocyclic compounds having an ester substituent on their ring easily racemize and it is difficult to synthesize them without losing the enantiomeric purity of the starting amino precursors. Next, we applied our method for the synthesis of optically active oxazoline and thiazoline derivatives having an ester group on the ring. When L-serine methyl ester hydrochloride was used, $Et_3N$ was initially added at low temperature to generate free amino alcohol, which was used in situ for the reaction with DFBP. By this method, the corresponding optically active oxazoline derivative **1l** was obtained in 86% yield (98% ee). Similarly, 2-methoxyphenyloxazoline derivative **1p** was obtained in pure form using DFMOBA in high yield (Table 3). A thiazoline derivative **1o**, which was used as a key intermediate for synthesis of β-lactam antibiotics,[16] was previously prepared from *N*-formyl-L-cysteine ethyl ester under acidic conditions. However, racemization took place during the reaction and the optically purity of the resulting **1o** was 70% ee.[17] In the reaction of L-cysteine ethyl ester hydrochloride with DFMM, it was critical to add $Et_3N$ after the addition of DFMM. By this method, **1o** could be obtained in 89% yield without racemization (99% ee). When $Et_3N$ was added before DFMM to generate the free amino thiol, the optically purity of the resulting **1o** was low. Under the same conditions, optically pure thiazoline derivatives **1m** and **1n** were obtained in high yields from L-cysteine ethyl ester hydrochloride using DFMPP and DFBP, respectively. An oxazoline **1r** was previously prepared from L-threonine methyl ester in three steps[2c] and used for asymmetric synthesis as a chiral template.[2c,18] It could be directly prepared from L-threonine methyl ester using DFMOBA in 89% yield (>99% ee).

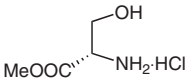
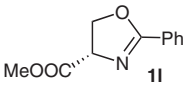
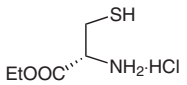
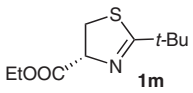
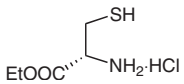
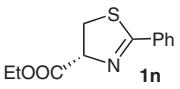
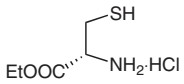
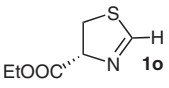
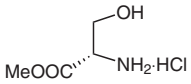
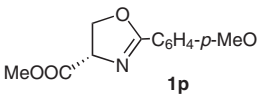
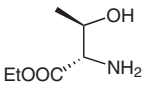
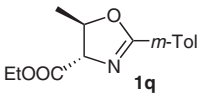
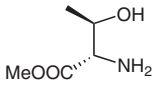
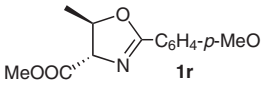
**Table 2** Synthesis of Optically Active Oxazolines Using α,α-Difluoroalkylamines[a]

| Amino alcohol | Fluoroamine | Product | Yield (%)[b] |
|---|---|---|---|
|  | DFMBA |  **1f** | 85 (>95) |
|  | DFMBA |  **1g** | 82 (99) |
|  | DFBP |  **1h** | 74 (98) |
|  | DFBP[c] |  **1i** | 78 (97) |
|  | DFBP |  **1j** | 73 (98) |
|  | TFXDP[d] |  **1k** | 79 (99) |

[a] Unless otherwise stated, the reaction was carried out in $CH_2Cl_2$ at 40 °C for 1 h.
[b] Isolated yield based on α,α-difluoroalkylamine used. In parentheses, ee (%) value determined by HPLC using a chiral column.
[c] The reaction was carried out in 1,2-dichloroethane at 60 °C for 1 h.
[d] The reaction was carried out at 40 °C for 2 h.

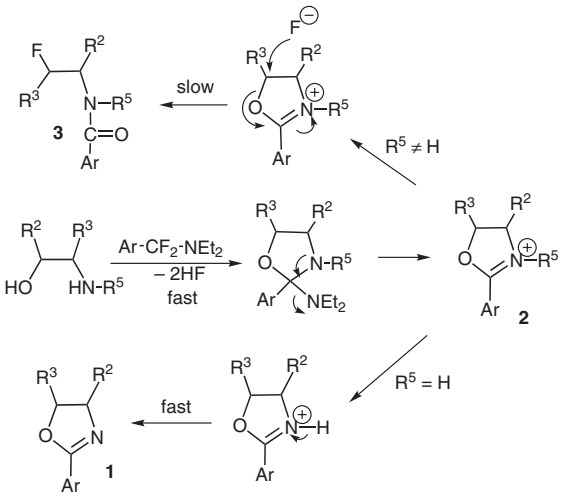
Though the reaction of N-protected amino alcohols with DFMBA gave the fluorinated products,[11] the reaction of unprotected amino alcohols with DFMBA gave the oxazolines. This difference can be explained as follows: In the reaction of the amino alcohol with DFMBA, an oxazolinium salt **2** was formed quickly at first. When the N-protected amino alcohol was used ($R^5 \neq H$), the liberated fluoride attacks at an oxygen attached carbon to give the N-acylated fluoroalkylamine **3**. This step is slow and relatively high temperature is required. On the other hand, when the N-unprotected amino alcohol was used ($R^5 = H$), deprotonation from the oxazolinium intermedi-

**Table 3** Synthesis of Optically Active Heterocyclic Compounds Using α,α-Difluoroalkylamines[a]

| Amino acids | Fluoroamine | Product | Yield (%)[b] |
|---|---|---|---|
|  | DFBP |  **1l** | 86 (98) |
|  | DFMPP |  **1m** | 81 (>99) |
|  | DFBP |  **1n** | 92 (95) |
|  | DFMM |  **1o** | 89 (99) |
|  | DFMOBA |  **1p** | 93 (>99) |
|  | DFMBA |  **1q** | 84 (>99) |
|  | DFMOBA |  **1r** | 89 (>99) |

[a] The reaction conditions are given in the text.
[b] Isolated yield based on α,α-difluoroalkylamine used. In parentheses, ee % value determined by HPLC using chiral column.

ate takes place to give the oxazoline **1**. This step is fast and it takes place at lower temperature. Therefore, under the present conditions, the unprotected amino alcohol is selectively converted to the oxazoline **1** without the formation of N-acylated fluoroalkylamine **3** (Scheme 1).



**Scheme 1**

In summary, we succeeded in the synthesis of various five-membered heterocyclic compounds, such as oxazoline, thiazoline, and imidazoline derivatives, from amino alcohols, amino thiols, and diamines respectively by the reaction with α,α-difluoroalkylamines. As the reaction proceeds under mild conditions, it can be applied to the synthesis of optically active heterocyclic compounds which have been used as templates or ligands in asymmetric synthesis.

IR spectra were recorded using a JASCO FT/IR-410 spectrophotometer. The $^1$H NMR (270 MHz) and $^{13}$C NMR (68 MHz) spectra were recorded in $CDCl_3$ on a JEOL JNM-A270II FT NMR spectrometer and the chemical shifts δ are referred to tetramethylsilane. The EI low- and high-resolution mass spectra were measured on a JEOL JMS-700TZ, JMS-FABmate or JMS-HX110 spectrometer. Enantiomeric excess was determined by HPLC (TOSOH SD-801) using CHIRALCEL OD-H (0.46 cm ∅ × 25 cm) and hexane–propan-2-ol as eluents. Optical rotation was measured with a Horiba High Sensitive Polarimeter. The $Et_3N{\cdot}3HF$ was prepared by the addition of freshly distilled $Et_3N$ to anhyd HF in Teflon™ PFA vessel at 0 °C.[13] 2-Aminoethanol, 2-methyl-2-aminopropan-1-ol, 2-aminopropan-1-ol, 2-aminophenol, *o*-phenylenediamine were purchased from Tokyo Chemical Industry Co., Ltd. 2-Aminothiophenol was obtained from Kanto Chemical Co., Inc. (*S*)-2-Amino-3,3-dimethylbutan-1-ol was obtained from Mitsubishi Gas Chemical Co., Inc. (*S*)-2-Amino-3-phenylpropan-1-ol, (*R*)-2-amino-2-phenylethanol, (*S*)-2-amino-4-methylpentan-1-ol, and (*S*)-2-amino-4-methylthiobutan-1-ol were prepared by reduction of L-phenylalanine, D-phenylglycine, L-leucine, L-methionine, respectively,[19] and the original amino acids were obtained from Tokyo Chemical Industry Co., Ltd.

### *N*,*N*-Diethyl-α,α-difluoro-3-methylbenzylamine (DFMBA); Typical Procedure

DFMBA was prepared by a modification of reported procedure.[13] To a $CH_2Cl_2$ (50 mL) solution of *N*,*N*-diethyl-3-methylbenzamide (13.8 g, 72 mmol), was added dropwise at 0 °C a $CH_2Cl_2$ (20 mL)

solution of oxalyl chloride (9.9 g, 78 mmol) and the mixture was stirred at 40 °C for 2 h. The mixture was cooled again to 0 °C, and $Et_3N{\cdot}3HF$ (8.7 g, 53 mmol) and $Et_3N$ (10.1 g, 100 mmol) were added successively. The mixture was stirred at r.t. for 2 h and a generated precipitate was removed by filtration. The precipitate was washed with $CH_2Cl_2$ (100 mL) and the combined filtrate was concentrated under reduced pressure. Hexane (100 mL) was added to the residue and the generated solid was removed by filtration again. The solid was washed with hexane (50 mL) and the filtrate was concentrated under reduced pressure. Distillation of the residue gave DFMBA (12.6 g) in 82% yield; bp 81–83 °C/4 mmHg. Glassware can be used, but all operations should be carried out under minimum exposure to moisture.

$^1$H NMR ($CDCl_3$): δ = 1.07 (t, *J* = 7.1 Hz, 6 H), 2.39 (s, 3 H), 2.92 (q, *J* = 7.0 Hz, 4 H), 7.17–7.41 (m, 4 H).

**_N_-(α,α-Difluorobenzyl)pyrrolidine (DFBP)**

DFBP was prepared from *N*-benzoylpyrrolidine as in the case of DFMBA in 76% yield; clear liquid; bp 95–99 °C/5 mmHg.

$^1$H NMR ($CDCl_3$): δ = 1.80–1.84 (m, 4 H), 2.94–2.97 (m, 4 H), 7.41–7.43 (m, 3 H), 7.61–7.63 (m, 2 H).

**_N_-(Difluoromethyl)morpholine (DFMM)**

DFMM was prepared from *N*-formylmorpholine as in the case of DFMBA in 80% yield; clear liquid; bp 49–52 °C/20 mmHg.

$^1$H NMR ($CDCl_3$): δ = 2.87 (t, *J* = 5.0 Hz, 4 H), 3.73 (t, *J* = 5.4 Hz, 4 H), 5.93 (t, *J* = 62.5 Hz, 1 H).

**_N_-(1,1-Difluoro-2,2-dimethylpropyl)pyrrolidine (DFMPP)**

DFMPP was prepared from *N*-pivaloylpyrrolidine as in the case of DFMBA in 77% yield; clear liquid; bp 48–49 °C/7 mmHg.

$^1$H NMR ($CDCl_3$): δ = 1.13 (s, 9 H), 1.76–1.80 (m, 4 H), 3.03–3.07 (m, 4 H).

***N*,*N*-Diethyl(α,α-difluoro-4-methoxybenzyl)amine (DFMOBA)**

DFMOBA was prepared from *N*,*N*-diethyl-4-methoxybenzamide as in the case of DFMBA in 91% yield; clear liquid; bp 116–119 °C/5 mmHg.

$^1$H NMR ($CDCl_3$): δ = 1.05 (t, *J* = 7.2 Hz, 6 H), 2.89 (q, *J* = 7.2 Hz, 4 H), 3.83 (s, 3 H), 6.91 (d, *J* = 8.8 Hz, 2 H), 7.52 (d, *J* = 8.8 Hz, 2 H).

***N*,*N*′-(α,α,α′,α′-Tetrafluoro-α,α′-*m*-xylene)dipyrrolidine (TFXDP)**

TFXDP was prepared from 1,1′-isophthaloylbispyrrolidine using 2.2 equiv of oxalyl chloride, 1.5 equiv of $Et_3N{\cdot}3HF$, and 2.8 equiv of $Et_3N$ to the amide as in the case of DFMBA in 67% yield; clear liquid; bp 175–179 °C/5 mmHg.

$^1$H NMR ($CDCl_3$): δ = 1.84–1.87 (m, 8 H), 3.02 (br s, 8 H), 7.51–7.53 (m, 1 H), 7.74–7.76 (m, 2 H), 7.91 (s, 1 H).

**2-(*m*-Tolyl)-4,5-dihydrooxazole (1a); Typical Procedure**

To a $CH_2Cl_2$ solution (4 mL) of 2-aminoethanol (146 mg, 2.4 mmol) at –20 °C was added DFMBA (426 mg, 2 mmol) in $CH_2Cl_2$ (2 mL) and the mixture was stirred at –20 °C for 5 min and at 40 °C for 1 h. The mixture was poured into aq sat. $K_2CO_3$ (20 mL) and extracted with $Et_2O$ (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), and concentrated under reduced pressure. Purification by column chromatography (silica gel, hexane–$Et_2O$) gave **1a** (274 mg) in 85% yield.

IR (neat): 1650, 1358, 1193 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 2.38 (s, 3 H), 4.06 (t, *J* = 9.6 Hz, 2 H), 4.31 (t, *J* = 9.6 Hz, 2 H), 7.26–7.31 (m, 2 H), 7.71–7.81 (m, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 21.18, 54.82, 67.46, 125.17, 127.56, 128.16, 128.68, 131.97, 137.97, 164.71.

HRMS (EI): *m*/*z* calcd for $C_{10}H_{11}NO$ ($M^+$): 161.0841; found: 161.0848.

**4,4-Dimethyl-2-(*m*-tolyl)-4,5-dihydrooxazole (1b)**

The reaction was carried out as in the case of **1a** using 2-methyl-2-aminopropan-1-ol, and **1b** was obtained in 60% yield.

IR (neat): 2967, 1650, 1312, 1193 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 1.38 (s, 6 H), 2.37 (s, 3 H), 4.10 (s, 2 H), 7.26–7.29 (m, 2 H), 7.70–7.79 (m, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 21.18, 28.42 (2 C), 67.49, 79.05, 125.24, 127.92, 128.17, 128.78, 131.93, 138.02, 162.20.

HRMS (EI): *m*/*z* calcd for $C_{12}H_{15}NO$ ($M^+$): 189.1154; found: 189.1150.

**2-(*m*-Tolyl)benzoxazole (1c)**

The reaction was carried out as in the case of **1a** using 2-aminophenol, and **1c** was obtained in 90% yield; white solid; mp 81 °C (Lit.[20] mp 81–82 °C).

IR (KBr): 1551, 1453, 1245 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 2.46 (s, 3 H), 7.32–7.45 (m, 4 H), 7.57–7.60 (m, 1 H), 7.76–7.79 (m, 1 H), 8.04–8.11 (m, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 21.33, 110.53, 119.96, 124.52, 124.75, 125.00, 127.03, 128.19, 128.81, 132.34, 138.73, 142.12, 150.75, 163.25.

HRMS (EI): *m*/*z* calcd for $C_{14}H_{11}NO$ ($M^+$): 209.0841; found: 209.0834.

**2-(*m*-Tolyl)benzothiazole (1d)**

The reaction was carried out at 20 °C for 1 h as in the case of **1a** using 2-aminothiophenol, and **1d** was obtained in 94% yield; white solid; mp 69–70 °C (Lit.[21] mp 67–68 °C).

IR (KBr): 1485, 1435, 1313 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 2.46 (s, 3 H), 7.30–7.52 (m, 4 H), 7.86–7.95 (m, 3 H), 7.86 (d, *J* = 7.7 Hz, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 21.34, 121.59, 123.17, 123.20, 124.86, 125.11, 126.27, 127.99, 128.91, 131.80, 133.54, 138.87, 154.14, 168.32.

HRMS (EI): *m*/*z* calcd for $C_{14}H_{11}NS$ ($M^+$): 225.0612; found: 225.0610.

**2-(*m*-Tolyl)-1*H*-benzimidazole (1e)**

The reaction was carried out in 1,2-dichloroethane at 83 °C for 1 h using *o*-phenylenediamine, and **1e** was obtained in 63% yield; white solid; mp 211–212 °C (Lit.[22] mp 217.0–219.0 °C).

IR (KBr): 3434, 2879, 1447, 1404 cm$^{-1}$.

$^1$H NMR (DMSO-$d_6$): δ = 2.42 (s, 3 H), 7.19–7.64 (m, 6 H), 7.95–8.02 (m, 2 H), 12.85 (s, 1 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 21.02, 115.00 (2 C), 122.00 (2 C), 123.56 (2 C), 126.98 (2 C), 128.79, 130.06, 130.44, 138.11, 151.29.

HRMS (EI): *m*/*z* calcd for $C_{14}H_{12}N_2$ ($M^+$): 208.1000; found: 208.0994.

**(*S*)-4-Benzyl-2-(*m*-tolyl)-4,5-dihydrooxazole (1f)**

The reaction was carried out as in the case of **1a** using (*S*)-2-amino-3-phenylpropan-1-ol, and **1f** was obtained in 85% yield (>95%ee); $[\alpha]_D^{23}$ +8.6 (*c* = 1.0, $CHCl_3$).

IR (neat): 2921, 1649, 1357, 1194 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 2.38 (s, 3 H), 2.73 (dd, *J* = 13.7, 8.9 Hz, 1 H), 3.27 (dd, *J* = 13.7, 5.0 Hz, 1 H), 4.13 (dd, *J* = 8.4, 8.5 Hz, 1 H), 4.32 (dd, *J* = 8.6, 9.2 Hz, 1 H), 4.55–4.60 (m, 1 H), 7.24–7.33 (m, 7 H), 7.72–7.79 (m, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 21.21, 41.83, 67.84, 71.78, 125.31, 126.46, 127.61, 128.20, 128.52 (2 C), 128.81, 129.21 (2 C), 132.09, 138.00, 138.03, 164.11.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{17}NO$ ($M^+$): 251.1310; found: 251.1308.

**(*R*)-4-Phenyl-2-(*m*-tolyl)-4,5-dihydrooxazole (1g)**

The reaction was carried out as in the case of **1a** using (*R*)-2-amino-2-phenylethanol, and **1g** was obtained in 82% yield (99% ee); $[\alpha]_D^{23}$ +28.0 (*c* = 1.0, $CHCl_3$).

IR (neat): 2922, 1649, 1357, 1194 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 2.40 (s, 3 H), 4.28 (t, *J* = 8.1 Hz, 1 H), 4.79 (dd, *J* = 7.1, 10.3 Hz, 1 H), 5.38 (dd, *J* = 7.1, 10.3 Hz, 1 H), 7.26–7.36 (m, 7 H), 7.81–7.90 (m, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 21.23, 70.10, 74.82, 125.53, 126.75 (2 C), 127.42, 127.58, 128.27, 128.73 (2 C), 129.06, 132.30, 138.13, 142.42, 164.88.

HRMS (EI): *m*/*z* calcd for $C_{16}H_{15}NO$ ($M^+$): 237.1154; found: 237.1150.

**(*S*)-4-Isobutyl-2-phenyl-4,5-dihydrooxazole (1h)**

The reaction was carried out as in the case of **1a** using (*S*)-2-amino-4-methylpentan-1-ol and DFBP, and **1h** was obtained in 74% yield (98% ee); $[\alpha]_D^{21}$ –76.9 (*c* = 1.0, $CHCl_3$) {Lit.[23] $[\alpha]_D^{23}$ –79.9 (*c* = 0.95, $CHCl_3$)}.

IR (neat): 2956, 1651, 1358, 1063 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 0.96–1.00 (m, 6 H), 1.38–1.41 (m, 1 H), 1.70–1.83 (m, 2 H), 3.99 (dd, *J* = 7.8, 7.8 Hz, 1 H), 4.33–4.36 (m, 1 H), 4.51 (dd, *J* = 9.3, 7.8 Hz, 1 H), 7.37–7.46 (m, 3 H), 7.92–7.96 (m, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 22.67, 22.91, 25.49, 45.59, 65.16, 73.08, 127.98, 128.17, 128.23 (2 C), 131.11 (2 C), 163.20.

HRMS (EI): *m*/*z* calcd for $C_{13}H_{17}NO$ ($M^+$): 203.1310; found: 203.1308.

**(*S*)-4-*tert*-Butyl-2-phenyl-4,5-dihydrooxazole (1i)**

The reaction was carried out in 1,2-dichloroethane at 60 °C for 1 h using (*S*)-2-amino-3,3-dimethylbutan-1-ol and DFBP, and **1i** was obtained in 78% yield (97% ee); white solid; mp 31 °C (Lit.[24] mp 32–33 °C; $[\alpha]_D^{22}$ –80.39 (*c* = 1.02, $CHCl_3$) {Lit.[24] $[\alpha]_D^{20}$ –99.4 (*c* = 1.3, $CHCl_3$)}.

IR (KBr): 2956, 1653, 1356, 1086 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 0.95 (s, 9 H), 4.05 (dd, *J* = 5.1, 6.7 Hz, 1 H), 4.24 (dd, *J* = 5.7, 5.7 Hz, 1 H), 4.35 (dd, *J* = 5.7, 6.7 Hz, 1 H), 7.38–7.46 (m, 3 H), 7.94–7.97 (m, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 25.86 (3 C), 34.03, 68.69, 76.19, 128.00, 128.21 (2 C), 128.23 (2 C), 131.07, 163.18.

HRMS (EI): *m*/*z* calcd for $C_{13}H_{17}NO$ ($M^+$): 203.1310; found: 203.1305.

**(*S*)-4-(Methylthioethyl)-2-phenyl-4,5-dihydrooxazole (1j)**

The reaction was carried out as in the case of **1a** using (*S*)-2-amino-4-methylthiobutan-1-ol and DFBP, and **1j** was obtained in 73% yield (98% ee); $[\alpha]_D^{23}$ –91.6 (*c* = 1.10, acetone) {Lit.[25] $[\alpha]_D^{23}$ –80.96 (*c* = 1.0, acetone)}.

IR (neat): 2915, 1650, 1359 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 1.88–2.02 (m, 2 H), 2.13 (s, 3 H), 2.64–2.71 (m, 2 H), 4.06 (dd, *J* = 7.5, 7.5 Hz, 1 H), 4.41–4.55 (m, 2 H), 7.37–7.48 (m, 3 H), 7.92–7.96 (m, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 15.52, 30.65, 35.41, 65.71, 72.32, 127.67, 128.19 (2 C), 128.25 (2 C), 131.27, 163.70.

HRMS (EI): *m*/*z* calcd for $C_{12}H_{15}NOS$ ($M^+$): 221.0874; found: 221.0875.

**(*R*,*R*)-1,3-Benzenebis(4-phenyl-4,5-dihydro-2-oxazole) (1k)**

To a $CH_2Cl_2$ solution (7 mL) of (*R*)-2-amino-2-phenylethanol (165 mg, 1.2 mmol) at –20 °C was added TFXDP (160 mg, 0.5 mmol) in $CH_2Cl_2$ (1 mL) and the mixture was stirred at r.t. for 10 min. Then the mixture was warmed to 40 °C and stirred for 2 h. The mixture was then poured into aq sat. $K_2CO_3$ (20 mL) and extracted with $Et_2O$ (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), and concentrated under reduced pressure. Purification by column chromatography (silica gel, hexane–$Et_2O$) gave **1k** (145 mg) in 79% yield (99% ee); $[\alpha]_D^{23}$ +83.0 (*c* = 1.0, $CHCl_3$) {Lit.[15b] for (*S*,*S*)-isomer $[\alpha]_D^{25}$ –74.4 (*c* = 1.04, $CHCl_3$)}; white solid; mp 128–129 °C (Lit.[15a] mp 129–130 °C).

IR (KBr): 2901, 1654, 1454, 983 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 4.30 (dd, *J* = 8.3, 8.4 Hz, 2 H), 4.82 (dd, *J* = 8.4, 10.1 Hz, 2 H), 5.41 (dd, *J* = 8.3, 10.1 Hz, 2 H), 7.26–7.38 (m, 10 H), 7.52 (t, *J* = 7.8 Hz, 1 H), 8.20 (dd, *J* = 1.6, 7.8 Hz, 2 H), 8.69 (t, *J* = 1.6 Hz, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 70.21 (2 C), 74.97 (2 C), 126.73 (4 C), 127.66 (2 C), 127.97, 128.52 (2 C), 128.56, 128.76 (4 C), 131.37 (2 C), 142.18 (2 C), 164.07 (2 C).

**Methyl (*S*)-2-Phenyl-4,5-dihydrooxazole-4-carboxylate (1l)**

To a $CH_2Cl_2$ solution (4 mL) of L-serine methyl ester hydrochloride (373 mg, 2.4 mmol) at –20 °C was added $Et_3N$ (606 mg, 6 mmol), and the mixture was stirred at r.t. for 30 min. Then the mixture was cooled to –20 °C again and DFBP (394 mg, 2 mmol) in $CH_2Cl_2$ (2 mL) was added. The mixture was warmed to 20 °C and stirred for 2 h. The mixture was poured into aq sat. $K_2CO_3$ (20 mL) and extracted with $Et_2O$ (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), and concentrated under reduced pressure. Purification by column chromatography (silica gel, hexane–$Et_2O$) gave **1l** (352 mg) in 86% yield (98% ee); $[\alpha]_D^{23}$ +122.7 (*c* = 1.0, $CHCl_3$) {Lit.[26] $[\alpha]_D^{20}$ +117.2 (*c* = 0.053, $CHCl_3$)}.

IR (neat): 2953, 1742, 1642, 1361 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 3.83 (s, 3 H), 4.57–4.74 (m, 2 H), 4.96 (dd, *J* = 10.6, 7.9 Hz, 1 H), 7.39–7.51 (m, 3 H), 7.97–8.01 (m, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 52.61, 68.40, 69.50, 126.76, 128.27 (2 C), 128.51 (2 C), 131.82, 166.30, 171.51.

HRMS (EI): *m*/*z* calcd for $C_{11}H_{11}NO_3$ ($M^+$): 205.0739; found: 205.0738.

**Ethyl (*S*)-2-*tert*-Butyl-4,5-dihydrothiazole-4-carboxylate (1m)**

To a $CH_2Cl_2$ suspension (4 mL) of L-cysteine ethyl ester hydrochloride (445 mg, 2.4 mmol) at –20 °C, was added DFMPP (354 mg, 2 mmol) in $CH_2Cl_2$ (2 mL) and the mixture was stirred at r.t. for 30 min. Then the mixture was cooled to –20 °C again and $Et_3N$ (182 mg, 1.8 mmol) was added. The mixture was warmed to 40 °C and stirred for 1 h. The mixture was poured into aq sat. $K_2CO_3$ (20 mL) and extracted with $Et_2O$ (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), and concentrated under reduced pressure. Purification by column chromatography (silica gel, hexane–$Et_2O$) gave **1m** (348 mg) in 81% yield (>99% ee); $[\alpha]_D^{23}$ +82.5 (*c* = 1.0, $CHCl_3$).

IR (neat): 2967, 1741, 1613, 1184 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 1.27 (s, 9 H), 1.30 (t, *J* = 7.2 Hz, 3 H), 3.46–3.51 (m, 2 H), 4.24 (q, *J* = 7.2 Hz, 2 H), 5.07 (dd, *J* = 9.3, 8.1 Hz, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 13.92, 29.01 (3 C), 35.16, 37.99, 61.20, 77.81, 170.81, 183.13.

HRMS (EI): *m*/*z* calcd for $C_{10}H_{17}NO_2S$ ($M^+$): 215.0980; found: 215.0985.

**Ethyl (*S*)-2-Phenyl-4,5-dihydrothiazole-4-carboxylate (1n)**

The reaction was carried out as in the case of **1m** using DFBP, and **1n** was obtained in 92% yield (95% ee); $[\alpha]_D^{23}$ +47.6 (*c* = 1.0, EtOH) {Lit.[27] $[\alpha]_D^{23.8}$ +14.6 (*c* = 1.098, EtOH)}.

IR (neat): 2981, 1739, 1602, 1188 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 1.33 (t, *J* = 7.2 Hz, 3 H), 3.61–3.73 (m, 2 H), 4.29 (q, *J* = 7.2 Hz, 2 H), 5.27 (dd, *J* = 9.2, 9.2 Hz, 1 H), 7.27–7.49 (m, 3 H), 7.86–7.88 (m, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 14.14, 35.36, 61.73, 78.58, 128.42 (2 C), 128.57 (2 C), 131.58, 132.66, 170.76, 170.79.

HRMS (EI): *m*/*z* calcd for $C_{12}H_{13}NO_2S$ ($M^+$): 235.0667; found: 235.0670.

**Ethyl (*S*)-4,5-Dihydrothiazole-4-carboxylate (1o)**

The reaction was carried out as in the case of **1m** using DFMM, and **1o** was obtained in 89% yield (99% ee); $[\alpha]_D^{21}$ +191.2 (*c* = 1.2, $CHCl_3$).

IR (neat): 2982, 1738, 1570, 1191 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 1.33 (t, *J* = 4.9 Hz, 3 H), 3.45–3.57 (m, 2 H), 4.25–4.31 (m, 2 H), 5.10 (ddd, *J* = 6.5, 6.5, 1.7 Hz, 1 H), 8.04 (d, *J* = 1.7 Hz, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 14.07, 33.19, 61.83, 77.78, 159.40, 170.38.

HRMS (EI): *m*/*z* calcd for $C_6H_9NO_2S$ ($M^+$): 159.0354; found: 159.0358.

**Methyl (*S*)-2-(4-Methoxyphenyl)-4,5-dihydrooxazole-4-carboxylate (1p)**

The reaction was carried out as in the case of **1l** using DFMOBA, and **1p** was obtained in 93% yield (>99% ee); $[\alpha]_D^{23}$ +100 (*c* = 1.0, $CHCl_3$); white solid; mp 115–119 °C.

IR (KBr): 1738, 1601, 1447, 1187 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 3.81 (s, 3 H), 3.84 (s, 3 H), 4.57 (dd, *J* = 7.1, 5.9 Hz, 1 H), 4.93 (dd, *J* = 7.1, 5.3 Hz, 1 H), 4.66 (dd, *J* = 5.6, 5.6 Hz, 1 H), 6.90 (d, *J* = 6.0 Hz, 2 H), 7.92 (d, *J* = 6.0 Hz, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 52.23, 54.96, 68.21, 69.08, 113.34 (2 C), 119.04, 129.99 (2 C), 162.14, 165.62, 171.44.

HRMS (EI): *m*/*z* calcd for $C_{12}H_{13}NO_4$ ($M^+$): 235.0844; found: 235.0849.

**Ethyl (4*S*,5*R*)-5-Methyl-2-(*m*-tolyl)-4,5-dihydrooxazole-4-carboxylate (1q)**

The reaction was carried out as in the case of **1a** using D-threonine ethyl ester, and **1q** was obtained in 84% yield (>99% ee); $[\alpha]_D^{23}$ +98.5 (*c* = 1.0, $CHCl_3$).

IR (neat): 2979, 1739, 1641, 1196 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 1.32 (t, *J* = 7.2 Hz, 3 H), 1.52 (d, *J* = 6.3 Hz, 3 H), 2.37 (s, 3 H), 4.26 (q, *J* = 7.2 Hz, 2 H), 4.45 (d, *J* = 7.4 Hz, 1 H), 4.94–4.99 (m, 1 H), 7.28–7.32 (m, 2 H), 7.76–7.84 (m, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 14.03, 20.85, 21.05, 61.45, 75.02, 78.75, 125.52, 127.00, 128.08, 129.00, 132.42, 137.93, 165.56, 171.02.

HRMS (EI): *m*/*z* calcd for $C_{14}H_{17}NO_3$ ($M^+$): 247.1208; found: 247.1212.

**Methyl (4*S*,5*R*)-2-(4-Methoxyphenyl)-5-methyl-4,5-dihydrooxazole-4-carboxylate (1r)**

The reaction was carried out as in the case of **1q** using DFMOBA, and **1r** was obtained in 89% yield (>99%ee); $[\alpha]_D^{23}$ +75 (*c* = 1.0, $CHCl_3$) {Lit.[2c] $[\alpha]_D^{23}$ +69.4 (*c* = 2.0, $CHCl_3$)}; white solid; mp 86–87 °C (Lit.[2c] mp 86–87 °C).

IR (KBr): 1735, 1637, 1253 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 1.52 (d, *J* = 6.3 Hz, 3 H), 3.80 (s, 3 H), 3.85 (s, 3 H), 4.44 (d, *J* = 7.4 Hz, 1 H), 4.94–4.98 (m, 1 H), 6.90 (d, *J* = 9.0 Hz, 2 H), 7.93 (d, *J* = 8.9 Hz, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 21.00, 52.63, 55.37, 75.11, 78.68, 113.65 (2 C), 119.69, 130.32 (2 C), 162.41, 165.31, 171.83.

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