


Article

Synthesis of 2-Oxazolines from Ring Opening Isomerization of 3-Amido-2-Phenyl Azetidines

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Abstract: Chiral 2-oxazolines are valuable building blocks and famous ligands for asymmetric catalysis. The most common synthesis involves the reaction of an amino alcohol with a carboxylic acid. In this paper, an efficient synthesis of 2-oxazolines has been achieved via the stereospecific isomerization of 3-amido-2-phenyl azetidines. The reactions were studied in the presence of both Brønsted and Lewis acids, and Cu(OTf)₂ was found to be the most effective.

Keywords: azetidine; oxazoline; isomerization; amide; acid



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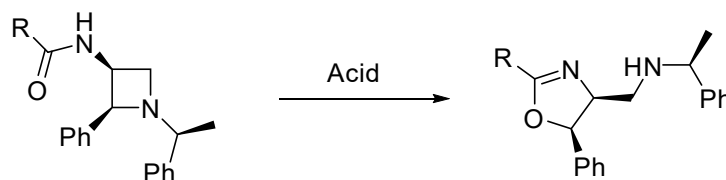


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1. Introduction

2-Oxazolines are very important five-membered heterocycles existing in numerous medicinally active compounds and natural products [1–6]. They are also widely applied as synthetic intermediates, protecting, activating and directing groups in organic synthesis. In addition, the optically active 2-oxazolines are valuable chiral building blocks and famous ligands for asymmetric catalysis [7–11]. There are numerous methods that have been developed for the preparation of 2-oxazolines [12–15]. The most common process for their preparation involves the reaction of an amino alcohol with a carboxylic acid [16,17]. In this way, oxazoline amines can be accessed from commercially available β -amino alcohols and suitably protected α -amino acids [18].

Recently, we reported the synthesis of chiral 4,5-dihydrothiazol-2-amines and 4,5-dihydrooxazol-2-amines through an unexpected ring opening reaction of azetidines [19]. Based on this strategy, we now extend our research work and report herein the asymmetric synthesis of 2-oxazolines via the stereospecific isomerization of 3-amido-2-phenyl azetidines in the presence of acid (Scheme 1).



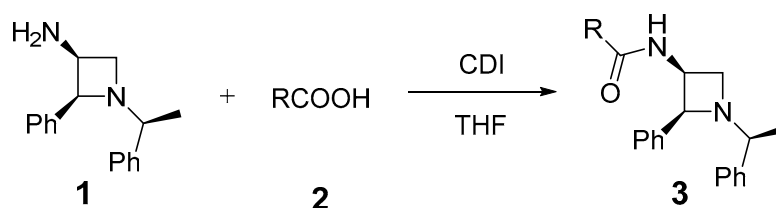
Scheme 1. Isomerization of 3-amido-2-phenyl azetidines to 2-oxazolines.

2. Results

Chiral 3-amino-2-phenyl azetidine **1** was prepared as previously reported by our group [20]. The coupling of 3-amino-2-phenyl azetidine **1** with acids **2** led to the corresponding amides **3**, which were obtained in 77% to 95% yields (Scheme 2; see Supplementary Materials).

The isomerization of amide **3a** was examined in different conditions (Scheme 3, Table 1). The results (Table 1) showed that the isomerization of **3a** did not occur at reflux in 1,2-dichloroethane (Table 1, entry 1) or in toluene (Table 1, entry 2) without additive or in the

presence of bases such as DABCO, *t*-BuOK and NaH (Table 1, entries 3–5). Nevertheless, isomerization of amide **3a** to 2-oxazoline **4a** occurred in the presence of acids, including Lewis acids and Brønsted acids but excepting acetic acid (Table 1, entries 6–16). In search for a better additive, we explored Brønsted acids such as HClO₄, CF₃SO₃H, CH₃COOH and CF₃COOH (TFA). It was found that TFA was the suitable additive for this transformation and the yield of **4a** could achieve up to 91% in 1,2-dichloroethane for about half an hour (Table 1, entry 10). However, prolonging the reaction time to over 2 h resulted in some degradation (Table 1, entry 11). Moreover, among the Lewis acids, Cu(OTf)₂ turned out to be the most efficient for this transformation, allowing the formation of **4a** in a 93% yield (Table 1, entry 14).



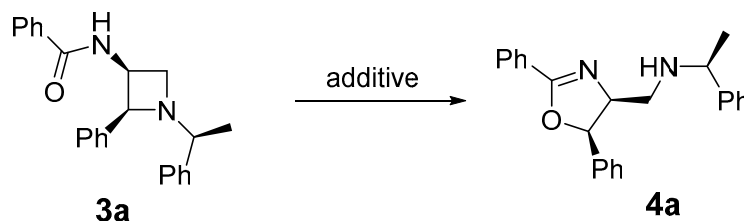
Scheme 2. Synthesis of 3-amido-2-phenyl azetidines

Table 1. Isomerization of amide **3a**¹.

Entry	Additive (Equiv.)	Solvent	Time (h)	Yield (%) ²
1	-	ClCH ₂ CH ₂ Cl	6	n.r.
2	-	Toluene	6	n.r.
3	DABCO (1)	ClCH ₂ CH ₂ Cl	6	n.r.
4	<i>t</i> -BuOK (1)	THF	6	n.r.
5	NaH (1)	THF	6	n.r.
6	HClO ₄ (1)	ClCH ₂ CH ₂ Cl	0.5	87
7	CF ₃ SO ₃ H (1)	ClCH ₂ CH ₂ Cl	0.5	65
8	CH ₃ COOH (1)	CH ₂ Cl ₂	12	n.r.
9	CF ₃ COOH (1)	CH ₂ Cl ₂	12	37
10	CF ₃ COOH (1)	ClCH ₂ CH ₂ Cl	0.5	91
11	CF ₃ COOH (1)	ClCH ₂ CH ₂ Cl	2	86
12	CF ₃ COOH (0.75)	ClCH ₂ CH ₂ Cl	0.5	71
13	TMSOTf (1)	ClCH ₂ CH ₂ Cl	4	72
14	Cu(OTf) ₂ (1)	ClCH ₂ CH ₂ Cl	4	93
15	Cu(OTf) ₂ (0.5)	ClCH ₂ CH ₂ Cl	4	90
16	BF ₃ ·Et ₂ O (1)	ClCH ₂ CH ₂ Cl	6	87

¹ The reactions were conducted with amide **3a** (1 mmol) in solvent (10 mL) in the presence of additive at reflux.

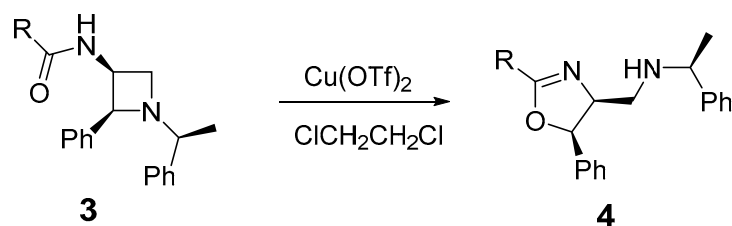
² Isolated yields.



Scheme 3. Isomerization of amide **3a** in different conditions.

After optimizing the reaction conditions, we extended the substrate scope and different amides were examined (Scheme 4, Table 2). The amides with aryl, heteroaryl and alkyl groups were successfully isomerized to 2-oxazolines in the presence of Cu(OTf)₂ in high yields (Table 2, entries 1–9 and 13–16). However, those substrates with 2-hydroxyl or 2-amino groups could not be isomerized, presumably due to their coordination to Cu(OTf)₂.

Nevertheless, these substrates could be isomerized to 2-oxazolines in the presence of CF_3COOH in good yields (Table 2, entries 10–12).



Scheme 4. Substrate scope of the isomerization of amides **3**.

Table 2. Isomerizations of various amides in the presence of $\text{Cu}(\text{OTf})_2$ ¹.

Entry	R	Product	Yield (%) ²
1	3a: C_6H_5-	4a	96
2	3b: 4-MeOC ₆ H ₄ -	4b	94
3	3c: 2-MeOC ₆ H ₄ -	4c	93
4	3d: 4-O ₂ NC ₆ H ₄ -	4d	94
5	3e: 2-O ₂ NC ₆ H ₄ -	4e	91
6	3f: 4-ClC ₆ H ₄ -	4f	79
7	3g: 2-ClC ₆ H ₄ -	4g	85
8	3h: 4-pyridyl	4h	82
9	3i: 2-pyridyl	4i	87
10 ³	3j: 2-HOC ₆ H ₄ -	4j	87
11 ³	3k: 2-H ₂ NC ₆ H ₄ -	4k	82
12 ³	3l: 1-hydroxynaphthalen-2-yl	4l	88
13	3m: thiophen-2-yl	4m	90
14	3n: furan-2-yl	4n	84
15	3o: Me-	4o	85
16	3p: $\text{C}_6\text{H}_5\text{CH}_2-$	4p	83

¹ Reactions were conducted with amide **3** (1 mmol) at reflux for 4 h in $\text{ClCH}_2\text{CH}_2\text{Cl}$ (10 mL) in the presence of $\text{Cu}(\text{OTf})_2$ (0.5 mmol). ² Isolated yields. ³ Reactions were conducted in the presence of CF_3COOH (1.5 mmol) at reflux for 30 min.

A proposed mechanism for this transformation is shown below (Scheme 5). The isomerization of amides **3** occurred regioselectively by presumably an $\text{S}_{\text{N}}2$ nucleophilic attack at the more active C2 but not the less-hindered C4 of the azetidine ring, thus the stereochemistry of 2-oxazolines **4** was shown to be *cis* [21]. This is also supported by comparison of the coupling constant (10 Hz) between H4 and H5 with reported *cis*-2-oxazolines [22,23]. In addition, all the structures of 2-oxazolines were established by ¹H and ¹³C NMR, high resolution mass spectra (HRMS), IR. Furthermore, the absolute configuration of **4l** was further confirmed by X-ray analysis (Figure 1).

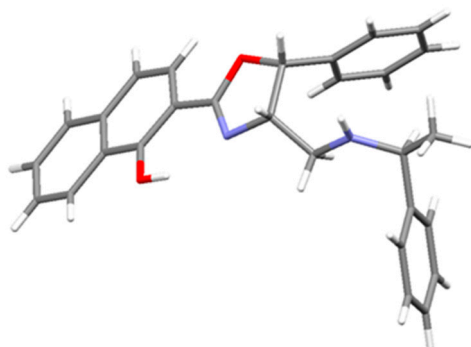
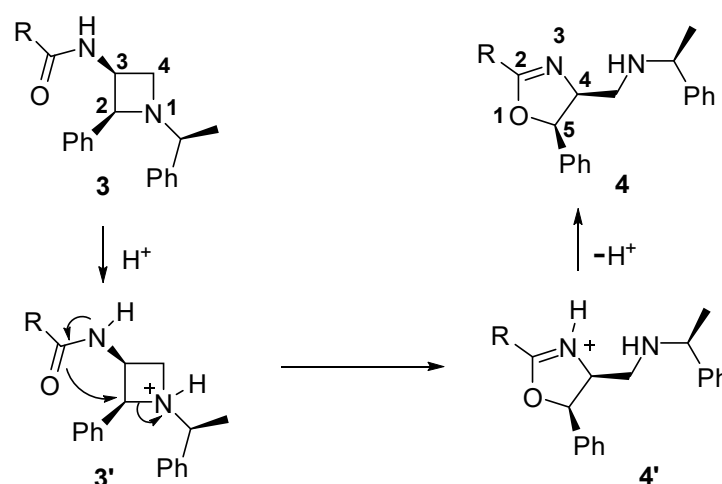


Figure 1. Structure of **4l**.



Scheme 5. Proposed mechanism.

3. Materials and Methods

3.1. General Information

All reactants and reagents were commercially available and were used without further purification. ^1H and ^{13}C NMR spectra were recorded on a Bruker Advance III 400 MHz spectrometer (Billerica, MA, USA). Chemical shifts are reported in δ values (ppm) relative to an internal reference (0.03% *v/v*) of tetramethylsilane (TMS) for ^1H NMR or the solvent signal, chloroform (CDCl_3), for ^{13}C NMR. IR data was obtained with an IRAffinity-1 spectrometer (Shimadzu, Kyoto, Japan). High resolution mass spectrometry (HRMS) was conducted with a high-resolution LCT Premier XE mass spectrometer in positive ESI mode (Waters, MA, USA). Melting points were measured on a digital melting point apparatus and are uncorrected.

3.2. General Procedure for the Isomerization of Amide 3

A mixture of amide **3** (1 mmol), $\text{Cu}(\text{OTf})_2$ (0.5 mmol) in 1,2-dichloroethane (10 mL) was refluxed for 4 h. The mixture was washed with water (10 mL), saturated NaHCO_3 (10 mL), and dried over Na_2SO_4 . The solvent was removed under reduced pressure. The residue was purified by gradient column chromatography on silica gel with PE/EA (5:1–2:1) as eluent to give oxazoline **4**.

(S)-N-(((4S,5R)-2,5-diphenyl-4,5-dihydrooxazol-4-yl)methyl)-1-phenylethanamine (**4a**)

Yellow oil, 96% yield, $[\alpha]_{\text{D}}^{20} = -322.0$ (c 1.0 $\text{CH}_3\text{COOC}_2\text{H}_5$); ^1H NMR (400 MHz, CDCl_3) $\delta = 8.02$ (d, $J = 7.4$ Hz, 2H), 7.59–7.00 (m, 13H), 5.79 (d, $J = 9.9$ Hz, 1H), 4.68 (q, $J = 7.2$ Hz, 1H), 3.46 (q, $J = 6.4$ Hz, 1H), 2.43–2.14 (m, 3H), 1.16 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 23.72, 49.35, 58.29, 69.67, 83.13, 126.36, 126.49, 126.89, 127.53, 128.21, 128.35, 128.38, 128.42, 128.44, 131.60, 136.41, 144.86, 163.76$; IR (KBr) ν 3061, 3028, 2963, 2924, 1651, 1603, 1580, 1495, 1450, 1368, 1333, 1277, 1246, 1209, 1175, 1128, 1082, 1065, 1024, 964, 781, 760, 696, 540 cm^{-1} ; HRMS m/z $[\text{M} + \text{H}]^+$ calcd. for $[\text{C}_{24}\text{H}_{25}\text{N}_2\text{O}]^+$ 357.1961, found 357.1962.

(S)-N-(((4S,5R)-2-(4-methoxyphenyl)-5-phenyl-4,5-dihydrooxazol-4-yl)methyl)-1-phenylethanamine (**4b**)

Yellow solid, 94% yield, mp: 71–74 °C, $[\alpha]_{\text{D}}^{20} = -273.8$ (c 1.0 $\text{CH}_3\text{COOC}_2\text{H}_5$); ^1H NMR (400 MHz, CDCl_3) $\delta = 7.96$ (d, $J = 8.8$ Hz, 2H), 7.37–7.07 (m, 10H), 6.92 (d, $J = 8.9$ Hz, 2H), 5.73 (d, $J = 9.9$ Hz, 1H), 4.61 (dt, $J = 9.8, 7.0$ Hz, 1H), 3.81 (s, 3H), 3.41 (q, $J = 6.5$ Hz, 1H), 2.28 (d, $J = 7.0$ Hz, 2H), 1.69 (br s, 1H), 1.12 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 23.99, 49.55, 55.38, 58.23, 69.85, 83.10, 113.80, 120.08, 126.42, 126.46, 126.74, 128.12, 128.31, 128.33, 130.16, 136.69, 145.50, 162.28, 163.51$; IR (KBr) ν 3061, 3026, 2961, 2930, 2837,

1647, 1609, 1512, 1495, 1452, 1420, 1368, 1335, 1310, 1256, 1167, 1076, 1030, 966, 841, 741, 700, 685 cm^{-1} ; HRMS m/z $[M + H]^+$ calcd. for $[\text{C}_{25}\text{H}_{27}\text{N}_2\text{O}_2]^+$ 387.2067, found 387.2067.

(S)-N-(((4S,5R)-2-(2-methoxyphenyl)-5-phenyl-4,5-dihydrooxazol-4-yl)methyl)-1-phenylethanimine (4c)

Yellow oil, 93% yield, $[\alpha]_{\text{D}}^{20} = -204.5$ (c 1.0 $\text{CH}_3\text{COOC}_2\text{H}_5$); ^1H NMR (400 MHz, CDCl_3) $\delta = 7.80$ (d, $J = 7.2$ Hz, 1H), 7.44 (t, $J = 7.3$ Hz, 1H), 7.39–7.06 (m, 10H), 6.98 (d, $J = 7.9$ Hz, 2H), 5.76 (d, $J = 9.9$ Hz, 1H), 4.80–4.74 (m, 1H), 3.90 (s, 4H), 3.52–3.45 (m, 1H), 2.39–2.27 (m, 2H), 1.21 (d, $J = 6.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 23.31, 49.09, 55.99, 58.38, 69.43, 82.44, 111.71, 116.89, 120.35, 126.45, 126.64, 127.10, 128.13, 128.32, 128.41, 131.40, 132.58, 136.43, 143.87, 158.61, 162.87$; IR (KBr) ν 3061, 3028, 2961, 2924, 2837, 1653, 1636, 1578, 1560, 1491, 1458, 1437, 1331, 1283, 1258, 1123, 1043, 1024, 968, 754, 700, 592 cm^{-1} ; HRMS m/z $[M + H]^+$ calcd. for $[\text{C}_{25}\text{H}_{27}\text{N}_2\text{O}_2]^+$ 387.2067, found 387.2064.

(S)-N-(((4S,5R)-2-(4-nitrophenyl)-5-phenyl-4,5-dihydrooxazol-4-yl)methyl)-1-phenylethanimine (4d)

White solid, 94% yield, mp: 68–71 $^\circ\text{C}$, $[\alpha]_{\text{D}}^{20} = -145.8$ (c 1.0 $\text{CH}_3\text{COOC}_2\text{H}_5$); ^1H NMR (400 MHz, CDCl_3) $\delta = 8.29$ (d, $J = 8.9$ Hz, 2H), 8.19 (d, $J = 8.9$ Hz, 2H), 7.42–7.30 (m, 3H), 7.28–7.11 (m, 7H), 5.85 (d, $J = 10.1$ Hz, 1H), 4.72 (dt, $J = 10.0, 7.1$ Hz, 1H), 3.45 (q, $J = 6.5$ Hz, 1H), 2.38–2.21 (m, 2H), 2.02 (br s, 1H), 1.16 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 23.72, 49.16, 58.25, 70.20, 83.83, 123.62, 126.28, 126.41, 126.91, 128.38, 128.44, 128.46, 129.42, 133.31, 135.79, 144.99, 149.64, 161.93$; IR (KBr) ν 3082, 3061, 3030, 2959, 2924, 2873, 1653, 1647, 1599, 1524, 1493, 1452, 1410, 1348, 1277, 1107, 1076, 1014, 961, 866, 851, 762, 702 cm^{-1} ; HRMS m/z $[M + H]^+$ calcd. for $[\text{C}_{24}\text{H}_{24}\text{N}_3\text{O}_3]^+$ 402.1812, found 402.1812.

(S)-N-(((4S,5R)-2-(2-nitrophenyl)-5-phenyl-4,5-dihydrooxazol-4-yl)methyl)-1-phenylethanimine (4e)

White solid, 91% yield, mp: 44–47 $^\circ\text{C}$, $[\alpha]_{\text{D}}^{20} = -314.7$ (c 1.0 $\text{CH}_3\text{COOC}_2\text{H}_5$); ^1H NMR (400 MHz, CDCl_3) $\delta = 7.90$ –7.79 (m, 2H), 7.68–7.53 (m, 2H), 7.39–7.06 (m, 10H), 5.80 (d, $J = 10.0$ Hz, 1H), 4.66 (dt, $J = 9.8, 7.0$ Hz, 1H), 3.44 (q, $J = 6.5$ Hz, 1H), 2.44–2.12 (m, 2H), 1.47 (br s, 1H), 1.12 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 24.00, 49.00, 58.11, 69.98, 84.57, 123.14, 123.96, 126.34, 126.42, 126.74, 128.28, 128.32, 128.40, 131.12, 131.61, 132.49, 135.43, 145.30, 149.13, 161.28$; IR (KBr) ν 3327, 3063, 3028, 2963, 2926, 2833, 1661, 1607, 1576, 1537, 1493, 1450, 1368, 1352, 1279, 1244, 1209, 1107, 1059, 1032, 957, 852, 762, 736, 700, 681, 650 cm^{-1} ; HRMS m/z $[M + H]^+$ calcd. for $[\text{C}_{24}\text{H}_{24}\text{N}_3\text{O}_3]^+$ 402.1812, found 402.1812.

(S)-N-(((4S,5R)-2-(4-chlorophenyl)-5-phenyl-4,5-dihydrooxazol-4-yl)methyl)-1-phenylethanimine (4f)

Yellow oil, 79% yield, $[\alpha]_{\text{D}}^{20} = -171.0$ (c 1.0 $\text{CH}_3\text{COOC}_2\text{H}_5$); ^1H NMR (400 MHz, CDCl_3) $\delta = 7.94$ (d, $J = 8.5$ Hz, 2H), 7.39 (d, $J = 8.5$ Hz, 2H), 7.36–7.08 (m, 10H), 5.76 (d, $J = 10.0$ Hz, 1H), 4.64 (dt, $J = 9.9, 7.0$ Hz, 1H), 3.42 (q, $J = 6.5$ Hz, 1H), 2.28 (d, $J = 7.0$ Hz, 2H), 1.57 (br s, 1H), 1.12 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 23.95, 49.39, 58.22, 70.06, 83.44, 126.12, 126.37, 126.43, 126.78, 128.26, 128.35, 128.75, 129.77, 136.33, 137.77, 145.45, 162.82$; IR (KBr) ν 3318, 3061, 3028, 2965, 2924, 1651, 1599, 1491, 1452, 1402, 1368, 1333, 1277, 1244, 1170, 1128, 1092, 1074, 1015, 964, 841, 760, 731, 700, 677, 550, 534 cm^{-1} ; HRMS m/z $[M + H]^+$ calcd. for $[\text{C}_{24}\text{H}_{24}\text{ClN}_2\text{O}]^+$ 391.1572, found 391.1572.

(S)-N-(((4S,5R)-2-(2-chlorophenyl)-5-phenyl-4,5-dihydrooxazol-4-yl)methyl)-1-phenylethanimine (4g)

Yellow oil, 84.8% yield, $[\alpha]_{\text{D}}^{20} = -259.2$ (c 1.0 $\text{CH}_3\text{COOC}_2\text{H}_5$); ^1H NMR (400 MHz, CDCl_3) $\delta = 7.80$ (dd, $J = 7.7, 1.6$ Hz, 1H), 7.46 (dd, $J = 8.0, 0.8$ Hz, 1H), 7.39–7.06 (m, 12H), 5.79 (d, $J = 10.1$ Hz, 1H), 4.69 (dt, $J = 10.0, 6.9$ Hz, 1H), 3.43 (q, $J = 6.6$ Hz, 1H), 2.39–2.20 (m, 2H), 1.54 (br s, 1H), 1.13 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 24.05, 49.39, 58.18, 70.12, 83.55, 126.43, 126.44, 126.63, 126.72, 127.45, 128.17, 128.30, 128.32, 130.77, 131.45, 131.74, 133.53, 136.05, 145.37, 162.47$; IR (KBr) ν 3323, 3061, 3028, 2961, 1651, 1593, 1493,

1477, 1452, 1435, 1368, 1331, 1279, 1240, 1132, 1096, 1036, 961, 914, 762, 735, 700, 654 cm^{-1} ; HRMS m/z $[M + H]^+$ calcd. for $[\text{C}_{24}\text{H}_{24}\text{ClN}_2\text{O}]^+$ 391.1572, found 391.1575.

(S)-1-phenyl-N-(((4S,5R)-5-phenyl-2-(pyridin-4-yl)-4,5-dihydrooxazol-4-yl)methyl)ethanamine (**4h**)

Yellow oil, 82% yield, $[\alpha]_{\text{D}}^{20} = -302.7$ (c 1.0 $\text{CH}_3\text{COOC}_2\text{H}_5$); ^1H NMR (400 MHz, CDCl_3) $\delta = 8.74$ (d, $J = 5.9$ Hz, 2H), 7.85 (d, $J = 5.9$ Hz, 2H), 7.40–7.09 (m, 10H), 5.82 (d, $J = 10.1$ Hz, 1H), 4.70 (dt, $J = 10.0, 7.1$ Hz, 1H), 3.44 (q, $J = 6.5$ Hz, 1H), 2.39–2.20 (m, 2H), 1.97 (br s, 1H), 1.15 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 23.78, 49.16, 58.22, 70.09, 83.63, 122.05, 126.30, 126.41, 126.88, 128.37, 128.42, 134.88, 135.83, 145.06, 150.38, 162.03$; IR (KBr) ν 3061, 3030, 2963, 2924, 1655, 1599, 1558, 1493, 1452, 1410, 1368, 1339, 1277, 1210, 1128, 1094, 1080, 1063, 991, 961, 837, 760, 745, 700, 681 cm^{-1} ; HRMS m/z $[M + H]^+$ calcd. for $[\text{C}_{23}\text{H}_{24}\text{N}_3\text{O}]^+$ 358.1914, found 358.1914.

(S)-1-phenyl-N-(((4S,5R)-5-phenyl-2-(pyridin-2-yl)-4,5-dihydrooxazol-4-yl)methyl)ethanamine (**4i**)

Yellow oil, 87% yield, $[\alpha]_{\text{D}}^{20} = -261.0$ (c 1.0 $\text{CH}_3\text{COOC}_2\text{H}_5$); ^1H NMR (400 MHz, CDCl_3) $\delta = 8.74$ (d, $J = 4.2$ Hz, 1H), 8.06 (d, $J = 7.9$ Hz, 1H), 7.79 (td, $J = 7.8, 1.6$ Hz, 1H), 7.48–7.35 (m, 1H), 7.35–7.01 (m, 10H), 5.85 (d, $J = 10.1$ Hz, 1H), 4.89–4.67 (m, 1H), 3.52 (q, $J = 6.5$ Hz, 1H), 3.25 (s, 1H), 2.43–2.12 (m, 2H), 1.19 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 23.31, 49.11, 58.32, 69.63, 83.76, 124.09, 125.81, 126.36, 126.59, 127.01, 128.30, 128.34, 128.36, 135.87, 136.79, 144.34, 146.37, 150.03, 162.96$; IR (KBr) ν 3314, 3059, 3028, 2961, 2924, 1653, 1647, 1582, 1570, 1493, 1468, 1452, 1439, 1368, 1341, 1246, 1117, 1098, 1043, 993, 962, 799, 745, 700, 621 cm^{-1} ; HRMS m/z $[M + H]^+$ calcd. for $[\text{C}_{23}\text{H}_{24}\text{N}_3\text{O}]^+$ 358.1914, found 358.1913.

2-((4S,5R)-5-phenyl-4-(((S)-1-phenylethyl)amino)methyl)-4,5-dihydrooxazol-2-yl)phenol (**4j**)

White solid, 87% yield, mp: 76–79 °C, $[\alpha]_{\text{D}}^{20} = -256.6$ (c 1.0 $\text{CH}_3\text{COOC}_2\text{H}_5$); ^1H NMR (400 MHz, CDCl_3) $\delta = 11.96$ (s, 1H), 7.74 (dd, $J = 7.8, 1.5$ Hz, 1H), 7.43–7.14 (m, 9H), 7.11 (d, $J = 7.0$ Hz, 2H), 7.03 (d, $J = 8.3$ Hz, 1H), 6.87 (t, $J = 7.3$ Hz, 1H), 5.75 (d, $J = 9.9$ Hz, 1H), 4.68 (dt, $J = 9.8, 6.9$ Hz, 1H), 3.39 (q, $J = 6.6$ Hz, 1H), 2.34–2.22 (m, 2H), 1.11 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 23.89, 49.25, 58.14, 68.82, 82.51, 110.43, 116.85, 118.84, 126.36, 126.49, 126.93, 128.31, 128.46, 128.53, 133.70, 135.59, 145.18, 160.00, 165.44$; IR (KBr) ν 3061, 3028, 2961, 2924, 2849, 1643, 1616, 1491, 1454, 1368, 1352, 1312, 1258, 1231, 1155, 1130, 1070, 1032, 961, 756, 700, 571, 540 cm^{-1} ; HRMS m/z $[M + H]^+$ calcd. for $[\text{C}_{24}\text{H}_{25}\text{N}_2\text{O}_2]^+$ 373.1911, found 373.1909.

2-((4S,5R)-5-phenyl-4-(((S)-1-phenylethyl)amino)methyl)-4,5-dihydrooxazol-2-yl)aniline (**4k**)

Yellow oil, 82% yield, $[\alpha]_{\text{D}}^{20} = -285.7$ (c 1.0 $\text{CH}_3\text{COOC}_2\text{H}_5$); ^1H NMR (400 MHz, CDCl_3) $\delta = 7.79$ (d, $J = 7.1$ Hz, 1H), 7.35–7.11 (m, 11H), 6.66 (dd, $J = 13.6, 7.6$ Hz, 2H), 6.04 (s, 2H), 5.65 (d, $J = 9.9$ Hz, 1H), 4.68 (dt, $J = 9.7, 7.1$ Hz, 1H), 3.41 (q, $J = 6.5$ Hz, 1H), 2.36–2.13 (m, 2H), 1.44 (br s, 1H), 1.11 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 23.91, 49.76, 58.21, 70.06, 81.32, 108.70, 115.75, 116.14, 126.46, 126.49, 126.85, 128.35, 128.41, 129.91, 132.37, 136.66, 145.54, 148.80, 164.07$; IR (KBr) ν 3466, 3296, 3061, 3028, 2961, 2924, 1636, 1609, 1595, 1560, 1490, 1454, 1368, 1348, 1319, 1263, 1161, 1078, 1053, 970, 914, 750, 700, 569, 538 cm^{-1} ; HRMS m/z $[M + H]^+$ calcd. for $[\text{C}_{24}\text{H}_{26}\text{N}_3\text{O}]^+$ 372.2070, found 372.2070.

2-((4S,5R)-5-phenyl-4-(((S)-1-phenylethyl)amino)methyl)-4,5-dihydrooxazol-2-yl)naphthalen-1-ol (**4l**)

Dark green solid, 88% yield, mp: 79–81 °C, $[\alpha]_{\text{D}}^{20} = +166.9$ (c 1.0 $\text{CH}_3\text{COOC}_2\text{H}_5$); ^1H NMR (400 MHz, CDCl_3) $\delta = 13.11$ (br s, 1H), 8.42 (d, $J = 8.2$ Hz, 1H), 7.77 (d, $J = 7.8$ Hz, 1H), 7.72 (d, $J = 8.7$ Hz, 1H), 7.57 (td, $J = 7.0, 1.4$ Hz, 1H), 7.51 (td, $J = 6.9, 1.3$ Hz, 1H), 7.40–7.05 (m, 11H), 5.81 (d, $J = 9.8$ Hz, 1H), 4.74 (dt, $J = 9.8, 6.9$ Hz, 1H), 3.43 (q, $J = 6.6$ Hz,

1H), 2.37–2.28 (m, 2H), 1.13 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 23.87, 49.32, 58.13, 68.52, 82.68, 103.37, 118.20, 123.47, 123.70, 124.75, 125.54, 126.37, 126.51, 126.90, 127.54, 128.44, 128.50, 128.52, 135.62, 136.28, 145.18, 158.85, 166.38$; IR (KBr) $\nu 3061, 3030, 2959, 2924, 2851, 1628, 1599, 1578, 1466, 1450, 1408, 1391, 1304, 1260, 1140, 1078, 964, 810, 756, 700\text{ cm}^{-1}$; HRMS m/z $[\text{M} + \text{H}]^+$ calcd. for $[\text{C}_{28}\text{H}_{27}\text{N}_2\text{O}_2]^+$ 423.2067, found 423.2064.

(S)-1-phenyl-N-(((4S,5R)-5-phenyl-2-(thiophen-2-yl)-4,5-dihydrooxazol-4-yl)methyl)ethanamine (**4m**)

Yellow oil, 90% yield, $[\alpha]_{\text{D}}^{20} = -256.6$ (c 1.0 $\text{CH}_3\text{COOC}_2\text{H}_5$); ^1H NMR (400 MHz, CDCl_3) $\delta = 7.67$ (d, $J = 2.2$ Hz, 1H), 7.48 (d, $J = 4.5$ Hz, 1H), 7.41–7.03 (m, 11H), 5.77 (d, $J = 9.8$ Hz, 1H), 4.62 (q, $J = 7.1$ Hz, 1H), 3.51–3.27 (m, 1H), 2.34–2.24 (m, 2H), 1.53 (br s, 1H), 1.11 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 24.01, 49.28, 58.21, 70.05, 83.67, 126.43, 126.74, 127.71, 128.26, 128.33, 130.19, 130.21, 130.66, 136.18, 145.38, 159.54$; IR (KBr) $\nu 3323, 3082, 3061, 3026, 2963, 2924, 1649, 1522, 1493, 1452, 1433, 1369, 1329, 1277, 1217, 1128, 1082, 1059, 1018, 959, 851, 760, 716, 700, 650\text{ cm}^{-1}$; HRMS m/z $[\text{M} + \text{H}]^+$ calcd. for $[\text{C}_{22}\text{H}_{23}\text{N}_2\text{OS}]^+$ 363.1526, found 363.1526.

(S)-N-(((4S,5R)-2-(furan-2-yl)-5-phenyl-4,5-dihydrooxazol-4-yl)methyl)-1-phenylethanamine (**4n**)

White solid, 84% yield, mp: 45–48 °C; $[\alpha]_{\text{D}}^{20} = -279.1$ (c 1.0 $\text{CH}_3\text{COOC}_2\text{H}_5$); ^1H NMR (400 MHz, CDCl_3) $\delta = 7.57$ (s, 1H), 7.42–7.09 (m, 10H), 7.02 (d, $J = 3.1$ Hz, 1H), 6.51 (s, 1H), 5.74 (d, $J = 9.9$ Hz, 1H), 4.69–4.69 (m, 1H), 3.45 (q, $J = 6.4$ Hz, 1H), 2.29 (d, $J = 6.9$ Hz, 2H), 2.00 (br s, 1H), 1.13 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 23.70, 49.24, 58.20, 69.69, 83.35, 111.63, 114.90, 126.38, 126.47, 126.80, 128.30, 128.34, 135.96, 142.71, 145.12, 145.56, 156.15$; IR (KBr) $\nu 3318, 3061, 3028, 2963, 2924, 2855, 1674, 1580, 1560, 1493, 1481, 1452, 1402, 1331, 1229, 1169, 1092, 1011, 962, 885, 754, 700, 631, 596, 552\text{ cm}^{-1}$; HRMS m/z $[\text{M} + \text{H}]^+$ calcd. for $[\text{C}_{22}\text{H}_{23}\text{N}_2\text{O}_2]^+$ 347.1754, found 347.1754.

(S)-N-(((4S,5R)-2-methyl-5-phenyl-4,5-dihydrooxazol-4-yl)methyl)-1-phenylethanamine (**4o**)

Yellow solid, 85% yield, mp: 44–47 °C; $[\alpha]_{\text{D}}^{20} = -252.6$ (c 1.0 $\text{CH}_3\text{COOC}_2\text{H}_5$); ^1H NMR (400 MHz, CDCl_3) $\delta = 7.37$ –7.04 (m, 10H), 5.57 (d, $J = 10.0$ Hz, 1H), 4.44–4.37 (m, 1H), 3.39 (q, $J = 6.5$ Hz, 1H), 2.24–2.10 (m, 2H), 2.07 (d, $J = 0.8$ Hz, 3H), 1.10 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 14.06, 23.82, 49.41, 58.14, 69.48, 83.12, 126.24, 126.40, 126.69, 128.05, 128.25, 136.43, 145.43, 164.76$; IR (KBr) $\nu 3320, 3061, 3026, 2967, 2928, 1680, 1603, 1493, 1452, 1387, 1369, 1310, 1229, 1130, 1078, 1028, 974, 914, 760, 700, 623, 592, 538\text{ cm}^{-1}$; HRMS m/z $[\text{M} + \text{H}]^+$ calcd. for $[\text{C}_{19}\text{H}_{23}\text{N}_2\text{O}]^+$ 295.1805, found 295.1801.

(S)-N-(((4S,5R)-2-benzyl-5-phenyl-4,5-dihydrooxazol-4-yl)methyl)-1-phenylethanamine (**4p**)

White solid, 83% yield, mp: 103–106 °C, $[\alpha]_{\text{D}}^{20} = -248.0$ (c 1.0 $\text{CH}_3\text{COOC}_2\text{H}_5$); ^1H NMR (400 MHz, CDCl_3) $\delta = 7.44$ –7.15 (m, 11H), 7.08–7.02 (m, 4H), 5.56 (d, $J = 10.0$ Hz, 1H), 4.47–4.40 (m, 1H), 3.69 (q, $J = 14.6$ Hz, 2H), 3.37 (q, $J = 6.5$ Hz, 1H), 2.21–2.05 (m, 2H), 1.52 (br s, 1H), 1.10 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 23.99, 35.08, 49.41, 58.17, 69.41, 83.25, 126.20, 126.40, 126.72, 127.10, 128.00, 128.19, 128.30, 128.65, 129.06, 135.07, 136.32, 145.33, 166.20$; IR (KBr) $\nu 3302, 3057, 3028, 2985, 2932, 2857, 1663, 1603, 1558, 1495, 1449, 1267, 1244, 1219, 1167, 1142, 1126, 1076, 1055, 1028, 993, 972, 920, 822, 784, 736, 723, 700, 575, 538\text{ cm}^{-1}$; HRMS m/z $[\text{M} + \text{H}]^+$ calcd. for $[\text{C}_{25}\text{H}_{27}\text{N}_2\text{O}]^+$ 371.2118, found 371.2118.

4. Conclusions

In conclusion, we have developed a new isomerization of amides **3** that leads to 2-oxazoles **4** in a completely highly regio- and stereoselective isomerization manner. Further application of these 2-oxazoles in catalytic asymmetric reaction is currently underway in our laboratory.

Supplementary Materials: The supplementary materials in the text are available online. CCDC 2059257 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif (accessed on 6 February 2021), or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033.

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