Notes

An Efficient and Versatile Method for the Synthesis of Optically Active 2-Oxazolines: An Acid-catalyzed Condensation of Ortho Esters with Amino Alcohols

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A variety of methods have been reported for the synthesis of enantiomerically pure 2-oxazolines which currently play an important role in asymmetric synthesis as chiral auxiliaries[1] and more recently as ligands[2] for catalytic asymmetric reactions. Commonly employed literature procedures for the preparation of chiral 2-oxazolines include condensation of 2-amino alcohols with alkyl imidates,[1] cyclization of hydroxyl amides,[1,3] one-pot reaction of carboxylic acids with 2-amino alcohols via the amide-*O*-phosphonium salts,[4] and coupling of nitriles with amino alcohols in the presence of zinc chloride[5] or potassium carbonate.[6] Regarding the preparation of 2*H*-2-oxazolines, a general and efficient method[7] which utilizes DMF−DMA has already been reported.

We had previously described a facile method for the preparation of chiral 2-alkyl-2-oxazolines which involved condensation of ortho esters with 2-amino alcohols in the absence of a catalyst to give good yields of the products.[8]

Table 1. Preparation of Optically Active 2-Oxazolines by Condensation of Ortho Esters with Amino Alcohols

entry	ortho ester **1**	amino alcohol **2**	catalyst	react. time, h	2-oxazoline cpd no.	2-oxazoline abs config	2-oxazoline yield,[a] %
1	**1a**	**2a**	none	6	**3a**	(4*R*)	88
2	**1a**	**2a**	AcOH	2	**3a**	(4*R*)	96
3	**1b**	**2a**	AcOH	2	**3a**	(4*R*)	92
4	**1b**	**2b**	AcOH	2	**3b**	(4*S*)	87
5	**1a**	**2c**	AcOH	2	**3c**	(4*S*)	93
6	**1b**	**2d**	AcOH	2	**3d**	(4*S*,5*R*)	91
7	**1c**	**2a**	AcOH	2	**4a**	(4*R*)	99
8	**1c**	**2c**	AcOH	2	**4b**	(4*S*)	98
9	**1c**	**2d**	AcOH	2	**4c**	(4*S*,5*R*)	98
10	**1e**	**2a**	TFA	1.5	**5a**	(4*R*)	89
11	**1e**	**2d**	TFA	3.5	**5b**	(4*S*,5*R*)	88
12	**1d**	**2d**	TFA	3.5	**5b**	(4*S*,5*R*)	96
13	**1e**	**2e**	TFA	3.5	**5c**	(4*S*,5*S*)	97
14	**1f**	**2a**	TFA	5	**6a**	(4*R*)	66
15	**1f**	**2c**	TFA	7	**6b**	(4*S*)	71
16	**1f**	**2d**	TFA	5	**6c**	(4*S*,5*R*)	69
17	**1f**	**2e**	TFA	4.5	**6d**	(4*S*,5*S*)	75

[a] Yields are of the purified materials.

However, this method has received little attention except for a paper[9] in which 2-oxazolines were prepared in the presence of hydrogen chloride as a catalyst. We have routinely used ortho esters, as received commercially and without further purification, with 1,2-dichloroethane as the solvent to prepare oxazolines. The utility and reproducibility of this procedure is demonstrated by the reaction of triethyl orthoacetate (**1a**) and (*R*)-(−)-phenylglycinol (**2a**) without catalyst (Table 1, entry 1). However, the reaction failed to produce oxazolines when DMF, which is known to decompose slightly at its boiling point to give dimethylamine,[10] was employed as a solvent. It was, therefore, assumed that acidic contaminants may have catalyzed the cyclization in 1,2-dichloroethane by protonation of the ortho esters to the oxonium ion. This possibility, along with the mechanism which is essentially the same as proposed by Neilson,[9] led us to consider acid catalysts in the reaction. It was envisaged that carboxylic acids would be suitable as catalysts, since strong mineral acids might possibly reduce the nucleophilicity of 2-amino alcohols by salt formation, although they may be better catalysts for protonating ortho esters. We also felt that in some cases, acids with lower pK_a's than a carboxylic acid would be required as the basicity of an ortho ester decreases. This reasoning may be supported by the data on the heats of formation of dialkoxycarbocations from ortho esters in strong acids as

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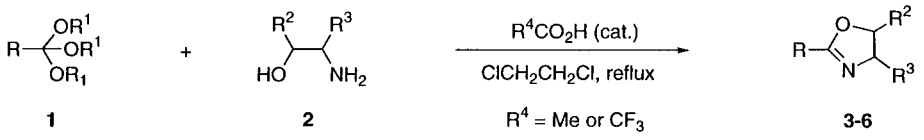
Scheme 1



1 2 3-6

1	R	R^1
a	Me	Et
b	Me	Me
c	Et	Et
d	Ph	Et
e	Ph	Me
f	H	Et
g	H	Me

2	R^2	R^3
a	H	—Ph
b	H	····*t*-Bu
c	H	····CH_2Ph
d	····Ph	····Me
e	—Ph	····CH_2OMe

3	R	R^2	R^3
a	Me	H	—Ph
b	Me	H	····*t*-Bu
c	Me	H	····CH_2Ph
d	Me	····Ph	····Me

4	R	R^2	R^3
a	Et	H	—Ph
b	Et	H	····CH_2Ph
c	Et	····Ph	····Me

5	R	R^2	R^3
a	Ph	H	—Ph
b	Ph	····Ph	····Me
c	Ph	—Ph	····CH_2OMe

6	R	R^2	R^3
a	H	H	—Ph
b	H	H	····CH_2Ph
c	H	····Ph	····Me
d	H	—Ph	····CH_2OMe

well as those of acid-catalyzed hydrolyses of ortho esters.[11] Thus, acetic acid was chosen for the reaction of aliphatic ortho esters that bear no electron-withdrawing substituents at α position, whereas trifluoroacetic acid was utilized for the reaction of orthoformates and orthobenzoates.

Table 1 summarizes the results of the acid-catalyzed cyclizations. When **1a** was heated to reflux with **2a** in the presence of catalytic amount of acetic acid in 1,2-dichloroethane, the reaction was completed within 2 h (Table 1, entry 2), whereas the corresponding reaction without a catalyst required a longer reaction time (Table 1, entry 1). Furthermore, the acid-catalyzed reaction was cleaner which was reflected in the yields of oxazolines, **3**−**6**. Similarly, condensation of **1a** or trimethyl orthoacetate (**1b**) with (*S*)-(+)-*tert*-leucinol (**2b**), (*S*)-(−)-phenylalaninol (**2c**), and (1*R*,2*S*)-(−)-norephedrine (**2d**) afforded the corresponding chiral 2-oxazolines, **3b**, **3c**, and **3d**, respectively, in excellent yields (Table 1, entries 4−6). Reaction with **2d** (Table 1, entry 6) also showed a distinct improvement over that reported in the literature[9] (2 h, 91% vs 16 h, 78%). When the solvent was replaced by the low boiling dichloromethane in the reaction of **2b**, longer reaction time (68 h) was required to attain a comparable yield of **3b**, while triethyl orthoacetate gave slightly better results than trimethyl orthoacetate. The efficacy of the acid catalyst also was further evident in the reaction of triethyl orthopropionate (**1c**) with amino alcohols **2a**, **2c**, and **2d** to furnish **4a**, **4b**, and **4c**, respectively, in essentially quantitative yields (Table 1, entries 7−9).

As predicted, preparation of (4*R*)-2,4-diphenyl-2-oxazoline (**5a**) was achieved in excellent yield using the more acidic trifluoroacetic acid as the catalyst for the reaction of trimethyl orthobenzoate (**1e**) with **2a** (Table 1, entry 10). The corresponding reaction using acetic acid resulted in a low yield (47%) of **5a**, and the reaction time was longer (3.5 h). Other chiral 2-phenyl-2-oxazolines, **5b** and **5c**, were similarly prepared in excellent yields (Table 1, entries 12 and 13). Again, the triethyl ortho ester seems to be a better reagent than the corresponding trimethyl analogue (Table 1, entry 12 vs 11). Noteworthy is the reaction of **1e** with (1*S*,2*S*)-2-amino-3-methoxy-1-phenyl-1-propanol (**2e**) which competes favorably with that of ethyl benzimidate hydrochloride[12] [Table 1, entry 13, 3.5 h, 97% (lit.,[12] 18 h, 87%)].

Neilson et al.[9] suggested that the low yield of 2,5-diphenyl-2-oxazoline in an analogous reaction may be ascribed to steric factors which were stated to inhibit resonance stabilization of dialkoxyphenylcarbocations by the phenyl group.[11a,b] Since 2-phenyl-2-oxazolines were formed essentially quantitatively in the present reactions, it is unlikely that steric factors are responsible for the low yield of the 2-phenyl-2-oxazoline.

To further apply this methodology to the synthesis of 2*H*-2-oxazolines, the reaction of triethyl orthoformate (**1f**) with **2a** was first attempted using acetic acid as a catalyst. As anticipated, only a trace of 4-phenyl-2-oxazoline (**6a**) was detected in the reaction mixture after 1.5 h in refluxing 1,2-dichloroethane. It was also found that catalytic sulfuric acid was not very effective, since **6a** formed in a low yield (approximately 30%) after 8 h of reflux. Other catalysts, including Lewis acids and molecular sieves, showed no improvement over sulfuric acid. Preparation of optically active 2*H*-2-oxazolines, **6**(**a**−**d**), was achieved in moderate to good yields using catalytic trifluoroacetic acid by condensation of **1f** with **2a**, **2c**, **2d**, and **2e**, respectively, (Table 1, entries 14−17). When trimethyl orthoformate (**1g**) was used instead of the triethyl analogue (**1f**), **6b** was obtained in a lower yield (47%) even after heating for 24 h.

The optical purity of the products, **3**−**6**, depended on that of the amino alcohols employed and was comparable to that of the corresponding 2-oxazolines reported in the literature, as assessed by comparison of the optical rotations. The efficiency, simplicity, and versatility should make this procedure the method of choice for the preparation of optically active 2-oxazolines, particularly

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of 2-alkyl and 2-phenyl derivatives, which are obtained in essentially quantitative yield.

Experimental Section

General. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were measured in $CDCl_3$ with TMS as an internal standard. Wherever necessary, NMR assignments were made with the aid of COSY and DEPT experiments. 1,2-Dichloroethane was stored over 4 A molecular sieves prior to use. All other reagents and solvents obtained from commercial sources were used without further purification. Amino alcohols, **2a**−**c**, were prepared according to the general literature procedure:[13a] **2a**; mp 76.0−76.5 °C; $[\alpha]^{22}_D$ −26.1° (*c* 5.36, MeOH) [lit.[14] mp 75−78 °C; $[\alpha]^{20}_D$ −27.1° (*c* 5.36, MeOH)], **2b**; bp 88−90 °C/12 Torr; $[\alpha]^{22}_D$ +36.6° (*c* 1.45, EtOH) [lit.[15] mp 33−35 °C; $[\alpha]^{26}_D$ +37° (*c* 1.5, EtOH)], **2c**; mp 95−96 °C; $[\alpha]^{25}_D$ −24.1° (*c* 1.37, EtOH) [lit.[16] mp 91−93 °C; $[\alpha]^{22}_D$ −25.7° (*c* 1.37, EtOH)]. (1*R*,2*S*)-(−)-Norephedrine and (1*S*,2*S*)-(+)-2-amino-3-methoxy-1-phenyl-1-propanol were purchased from Aldrich. All reactions were carried out under a dry atmosphere of argon except for one without an acid catalyst. Glassware were generally oven-dried.

General Procedure for the Preparation of 2-Methyl-2-oxazolines. Method A: Using Triethyl Orthoacetate (1a) and Acetic Acid as a Catalyst. A solution of amino alcohol (1.0 equiv), **1a** (1.2 equiv), and acetic acid (2−4 mol %) in 1,2-dichloroethane (2 mL/mmol) was heated at reflux for 2 h under argon. After cooling to ambient temperature, the volatiles were removed by rotary evaporation, and the residual oil was treated with hexane (25−30 mL/g) and dried over anhydrous $MgSO_4$. Filtration followed by rotary evaporation afforded the crude product which was distilled or subjected to Kugelrohr distillation under reduced pressure to give the pure compound.

Method B: Using Trimethyl Orthoacetate (1b) and Acetic Acid as a Catalyst. The procedure is the same as that described in method A except for **1b** (1.2 equiv) was used instead of **1a**.

Method C: Using Triethyl Orthoacetate without Catalyst. A solution of amino alcohol (1.0 equiv), and **1a** (1.2 equiv) in 1,2-dichloroethane (2 mL/mmol) was heated at reflux for 6 h under argon. The reaction mixture was worked up as described in method A to yield a pure product.

(4*R*)-2-Methyl-4-phenyl-2-oxazoline (3a). According to the general procedure (method A), (*R*)-(−)-**2a** (2.74 g, 20.0 mmol) was allowed to react with **1a** (3.89 g, 24.0 mmol) in the presence of acetic acid (50 μL, 4 mol %). Kugelrohr distillation (53−54 °C, 120 mTorr) afforded the title compound (3.09 g, 96%) as a colorless oil: $[\alpha]^{23}_D$ +101.7° (*c* 3.72, $CHCl_3$) [lit.[3] $[\alpha]^{23}_D$ +107.9° (*c* 3.75, $CHCl_3$)]; IR (neat) 1672 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.09 (d, 3H, J = 1.46 Hz), 4.08 (t, 1H, J = 8.30 Hz), 4.60 (dd, 1H, J = 8.30, 10.3 Hz), 5.16 (m, 1H), 7.23−7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.9, 69.8, 74.6, 126.5, 127.5, 128.7, 142.4, 165.7. Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.40; H, 6.97; N, 8.62.

(4*S*)-4-*tert*-Butyl-2-methyl-2-oxazoline (3b). A. Following the above procedure (method B), (*S*)-(+)-**2b** (10.40 g, 88.7 mmol), **1b** (11.73 g, 97.6 mmol), and acetic acid (150 μL, 3 mol %) furnished 9.89 g (79%) of **3b** as a colorless liquid after distillation under reduced pressure: bp 78−79 °C/55 Torr (lit.[17] bp 140−145 °C); $[\alpha]^{23}_D$ −100.5° (*c* 3.95, THF) [lit.[17] $[\alpha]_D$ −99.7° (*c* 3.0, THF)]; IR (neat) 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (s, 9H), 1.97 (d, 3H, J = 1.46 Hz), 3.79−3.85 (m, 1H), 4.01 (t, 1H, J = 8.30 Hz), 4.15 (dd, 1H, J = 8.30, 10.3 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0, 26.0, 33.7, 68.8, 76.2, 164.4. Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 67.78; H, 10.81; N, 9.72. **B.** By the same procedure, (*S*)-(+)-**2b** (3.49 g, 29.8 mmol), prepared by reduction[13b] of *tert*-leucine with lower optical purity, **1b** (3.49 g, 29.8 mmol), and acetic acid (30 μL, 2 mol %) gave 3.65 g (87%) of **3b** after distillation as a colorless liquid: bp 76−78 °C/52 Torr; $[\alpha]^{27}_D$ −67.0° (*c* 3.32, THF).

(4*S*)-4-Benzyl-2-methyl-2-oxazoline (3c). According to the general procedure (method A), (*S*)-(−)-**2c** (3.02 g, 20.0 mmol) was allowed to react with **1a** (3.89 g, 24.0 mmol) in the presence of acetic acid (50 μL, 4 mol %). Kugelrohr distillation (63−65 °C, 120 mTorr) afforded the title compound (3.27 g, 93%) as a colorless oil: $[\alpha]^{25}_D$ −49.3° (*c* 2.83, $CHCl_3$) [lit.[18] $[\alpha]^{24}_D$ −50.7° (*c* 2.83, $CHCl_3$); lit.[3] $[\alpha]^{23}_D$ −47.9° (*c* 1.70, MeOH)]; IR (neat) 1676 cm^{-1} [lit.[18] IR 1675 cm^{-1}; lit.[3] IR 1670 cm^{-1}]; ^{1}H NMR ($CDCl_3$) δ 1.96 (d, 3H, J = 1.46 Hz), 2.64 (dd, 1H, J = 8.30, 13.7 Hz), 3.08 (dd, 1H, J = 5.37, 13.7 Hz), 3.92 (dd, 1H, J = 7.33, 8.30 Hz), 4.16 (t, 1H, J = 8.30 Hz), 4.31−4.39 (m, 1H), 7.18−7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.9, 41.8, 67.4, 71.8, 126.4, 127.8, 128.5, 129.2, 138.0, 165.0. Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.14; H, 7.67; N, 7.92.

(4*S*,5*R*)-2,4-Dimethyl-5-phenyl-2-oxazoline (3d). Following the general procedure (method B), (1*R*,2*S*)-(−)-**2d** (3.02 g, 20.0 mmol), **1b** (4.30 g, 35.8 mmol), and acetic acid (50 μL, 4 mol %) gave 3.17 g (91%) of **3d** after Kugelrohr distillation (48−50 °C, 50 mTorr) as a colorless liquid: $[\alpha]^{24}_D$ −247° (*c* 3.43, $CHCl_3$); IR (neat) 1678 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.76 (d, 3H, J = 7.33 Hz), 2.10 (d, 3H, J = 1.46 Hz), 4.37−4.45 (m, 1H), 5.57 (d, 1H, J = 9.77 Hz), 7.17−7.20 (m, 2H), 7.26−7.37 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 14.1, 17.8, 65.0, 84.0, 126.1, 127.8, 128.3, 137.1, 164.0. Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 74.97; H, 7.66; N, 7.77.

General Procedure for the Preparation of 2-Ethyl-2-oxazolines. Method D: Using Triethyl Orthopropionate (1c) and Acetic Acid as a Catalyst. A solution of amino alcohol (1.0 equiv), **1c** (1.2 equiv), and acetic acid (4−6 mol %) in 1,2-dichloroethane (2 mL/mmol) was heated at reflux for 2 h under argon. After cooling to ambient temperature, the volatiles were removed by rotary evaporation, and the residual oil was treated with hexane (30−35 mL/g) and dried over anhydrous $MgSO_4$. Filtration followed by rotary evaporation afforded the crude product which was subjected to Kugelrohr distillation under reduced pressure to give the pure compound.

(4*R*)-2-Ethyl-4-phenyl-2-oxazoline (4a). Following the general procedure (method D), (*R*)-(−)-**2a** (2.06 g, 15.0 mmol), **1c** (3.17 g, 18.0 mmol), and acetic acid (50 μL, 6 mol %) gave 2.60 g (99%) of **4a** after Kugelrohr distillation (65 °C, 150 mTorr) as a colorless oil: $[\alpha]^{23}_D$ +86.5° (*c* 3.37, $CHCl_3$); IR (neat) 1666 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3H, J = 7.81 Hz), 2.40 (dq, 2H, J = 0.98, 7.81 Hz), 4.06 (dd, 1H, J = 7.81, 8.30 Hz), 4.58 (dd, 1H, J = 8.30, 10.3 Hz), 5.15 (m, 1H), 7.22−7.28 (m, 3H), 7.31−7.35 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 10.5, 21.5, 69.8, 74.6, 126.5, 127.5, 128.6, 142.6, 169.9. Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.38; H, 7.62; N, 7.97.

(4*S*)-4-Benzyl-2-ethyl-2-oxazoline (4b). Following the general procedure (method D), (*S*)-(−)-**2c** (1.36 g, 9.0 mmol), **1c** (1.90 g, 10.8 mmol), and acetic acid (20 μL, 4 mol %) gave 1.67 g (98%) of **4b** after Kugelrohr distillation (65 °C, 70 mTorr) as a colorless oil: $[\alpha]^{25}_D$ −35.9° (*c* 2.34, $CHCl_3$) [lit.[18] $[\alpha]^{24}_D$ −37.0° (*c* 2.29, $CHCl_3$)]; IR (neat) 1666 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.18 (t, 3H, J = 7.33 Hz), 2.27 (dq, 2H, J = 0.98, 7.33 Hz), 2.63 (dd, 1H, J = 8.79, 13.7 Hz), 3.10 (dd, 1H, J = 4.88, 13.7 Hz), 3.94 (dd, 1H, J = 7.33, 8.30 Hz), 4.14 (br t, 1H), 4.36 (m, 1H), 7.19−7.26 (m, 3H), 7.27−7.31 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 10.3, 21.5, 41.7, 67.1, 71.5, 126.4, 128.4, 129.2, 137.9, 169.1. Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.91; H, 8.12; N, 7.31.

(4*S*,5*R*)-2-Ethyl-4-methyl-5-phenyl-2-oxazoline (4c). Following the general procedure (method D), (1*R*,2*S*)-(−)-**2d** (3.02 g, 20.0 mmol), **1c** (4.23 g, 24.0 mmol), and acetic acid (50 μL, 4 mol %) gave 3.71 g (98%) of **4c** after Kugelrohr distillation (68−70 °C, 130 mTorr, lit.[8a] bp 95−97 °C, 2 Torr) as a colorless oil: $[\alpha]^{25}_D$ −223° (*c* 10.5, ethanol) [lit.[8a] $[\alpha]^{24}_D$ +220.9° (*c* 10.48, ethanol) for (4*R*,5*S*)-isomer]; IR (neat) 1672 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.76 (d, 3H, J = 6.84 Hz), 1.28 (t, 3H, J = 7.32 Hz), 2.42 (q, 2H, J = 7.32 Hz), 4.42 (m, 1H), 5.56 (d, 1H, J = 9.77 Hz), 7.18 (d, 2H, J = 7.81 Hz), 7.26−7.36 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 10.4, 17.8, 21.6, 64.8, 83.7, 126.0, 127.7, 128.2, 137.2,

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168.0. Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.76; H, 8.15; N, 7.37.

General Procedure for the Preparation of 2-Phenyl-2-oxazolines. Method E: Using Triethyl Orthobenzoate (1d) and Trifluoroacetic Acid as a Catalyst. A solution of amino alcohol (1.0 equiv), **1d** (1.0 equiv), and trifluoroacetic acid (17 mol %) in 1,2-dichloroethane (3 mL/mmol) was heated at reflux for 3.5 h under argon. After cooling, the reaction mixture was poured, with vigorous stirring, into ice cold 20% $KHCO_3$ (1.5 mL/mmol), and the organic layer was separated. The aqueous layer was extracted with two 10 mL portions of CH_2Cl_2. The combined organic layer and the extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to leave a yellow oil. The residue was dissolved in hexane (40−50 mL/g) and dried over anhydrous $MgSO_4$. Filtration followed by rotary evaporation afforded the crude product which was subjected to Kugelrohr distillation under reduced pressure to give the pure compound.

General Procedure for the Preparation of 2-Phenyl-2-oxazolines. Method F: Using Trimethyl Orthobenzoate (1e) and Trifluoroacetic Acid as a Catalyst. The procedure is the same as that described in method E except for **1e** was used instead of **1d**.

(4*R*)-2,4-Diphenyl-2-oxazoline (5a). Following the general procedure (method F), (*R*)-(−)-**2a** (2.06 g, 15.0 mmol), **1e** (2.73 g, 15.0 mmol), and trifluoroacetic acid (0.2 mL, 17 mol %) gave 2.99 g (89%) of **5a** after Kugelrohr distillation (102−105 °C, 40 mTorr) as a colorless oil which upon cooling crystallized: mp 32.0−32.5 °C (lit.[3] mp 112 °C); $[\alpha]^{24}_D$ +17.4° (*c* 1.96, MeOH), $[\alpha]^{22}_D$ +38.6° (*c* 1.09, $CHCl_3$) [lit.[3] $[\alpha]^{23}_D$ +12.0° (*c* 1.55, MeOH); lit.[4] $[\alpha]_D$ +36.4° (*c* 1.04, $CHCl_3$)]; IR (Nujol) 1644 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.28 (t, 1H, J = 8.30 Hz), 4.80 (dd, 1H, J = 8.30, 10.3 Hz), 5.39 (dd, 1H, J = 8.30, 10.3 Hz), 7.26−7.38 (m, 5H), 7.42 (m, 2H), 7.49−7.53 (m, 1H), 8.02−8.06 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 70.1, 74.8, 126.7, 127.4, 127.6, 128.3, 128.4, 128.7, 131.5, 142.4, 164.7. Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.87; H, 6.03; N, 6.21.

(4*S*,5*R*)-4-Methyl-2,5-diphenyl-2-oxazoline (5b). Following the general procedure (method E), (1*R*,2*S*)-(−)-**2d** (1.51 g, 10.0 mmol), **1d** (2.36 g, 10.5 mmol), and trifluoroacetic acid (130 μL, 17 mol %) gave 2.27 g (96%) of **5b** after Kugelrohr distillation (102−105 °C, 40 mTorr) as a colorless oil: $[\alpha]^{24}_D$ −355° (*c* 3.23, $CHCl_3$); IR (neat) 1648 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (d, 3H, J = 6.84 Hz), 4.66 (dq, 1H, J = 6.84, 9.77 Hz), 5.76 (d, 1H, J = 9.77 Hz), 7.25−7.37 (m, 5H), 7.42−7.46 (m, 2H), 7.49−7.53 (m, 1H), 8.04−8.06 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 17.8, 65.5, 84.1, 126.2, 127.7, 127.9, 128.3, 128.4, 131.5, 137.2, 163.0. Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.84; H, 6.55; N, 5.82.

(4*S*,5*S*)-4-(Methoxymethyl)-2,5-diphenyl-2-oxazoline (5c). Following the general procedure (method F), (1*S*,2*S*)-(+)-**2e** (1.05 g, 5.8 mmol), **1e** (1.06 g, 5.8 mmol), and trifluoroacetic acid (75 μL, 17 mol %) gave 1.51 g (97%) of **5c** after Kugelrohr distillation (110 °C, 50 mTorr) as a colorless oil: $[\alpha]^{24}_D$ +61.4° (*c* 2.05, $CHCl_3$); IR (neat) 1648 cm^{-1} (lit.[12] IR 1650 cm^{-1}); ^1H NMR ($CDCl_3$) δ 3.44 (s, 3H), 3.61 (dd, 1H, J = 6.84, 9.76 Hz), 3.73 (dd, 1H, J = 4.39, 9.76 Hz), 4.33 (dt, 1H, J = 4.39, 6.84 Hz), 5.49 (d, 1H, J = 6.84 Hz), 7.27−7.39 (m, 5H), 7.40−7.44 (m, 2H), 7.47−7.52 (m, 1H), 8.03−8.06 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 59.4, 74.4, 75.0, 83.6, 125.6, 127.6, 128.1, 128.3, 128.5, 128.7, 131.5, 140.9, 164.1. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.45; H, 6.56; N, 5.17.

General Procedure for the Preparation of 2*H*-2-oxazolines. Method G: Using Triethyl Orthoformate (1f) and Trifluoroacetic Acid as a Catalyst. A solution of amino alcohol (1.0 equiv), **1f** (1.1 equiv), and trifluoroacetic acid (17−20 mol %) in 1,2-dichloroethane (3 mL/mmol) was heated at reflux for 4.5−7 h under argon. After cooling, the reaction mixture was poured, with vigorous stirring, into ice cold 20% $KHCO_3$ (1.5 mL/mmol), and the organic layer was separated. The aqueous layer was extracted with two 10 mL portions of CH_2Cl_2. The combined organic layer and the extracts were washed with saturated brine (20 mL), dried over anhydrous $MgSO_4$ or Na_2SO_4, filtered, and evaporated under reduced pressure to leave a yellow oil. The residue was dissolved in hexane (100−150 mL/g) and dried over anhydrous $MgSO_4$ or K_2CO_3. Filtration followed by rotary evaporation afforded the crude product which was subjected to Kugelrohr distillation under reduced pressure to give the pure compound.

(4*R*)-4-Phenyl-2-oxazoline (6a). Following the general procedure (method G), (*R*)-(−)-**2a** (2.06 g, 15.0 mmol), **1f** (2.34 g, 15.8 mmol), and trifluoroacetic acid (0.2 mL, 17 mol %) gave 1.46 g (66%) of **6a** after Kugelrohr distillation (45−48 °C, 120 mTorr, lit.[7] bp 40−45 °C, 50 mTorr) as a colorless oil: $[\alpha]^{22}_D$ +128° (*c* 1.66, $CHCl_3$) [lit.[7] $[\alpha]^{24}_D$ +133° (*c* 1.60, $CHCl_3$)]; IR (neat) 1628 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.05 (dd, 1H, J = 8.30, 8.30 Hz), 4.57 (dd, 1H, J = 8.30, 10.3 Hz), 5.19 (ddd, 1H, J = 1.95, 8.30, 10.3 Hz), 7.02 (d, 1H, J = 1.95 Hz), 7.23−7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 68.8, 73.4, 126.5, 127.6, 128.7, 141.7, 155.4. Anal. Calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.32; H, 6.25; N, 9.47.

(4*S*)-4-Benzyl-2-oxazoline (6b). Following the general procedure (method G), (*S*)-(−)-**2c** (1.51 g, 10.0 mmol), **1f** (1.63 g, 11.0 mmol), and trifluoroacetic acid (130 μL, 17 mol %) gave 1.15 g (71%) of **6b** after Kugelrohr distillation (58−60 °C, 120 mTorr, lit.[7] bp 55 °C, 50 mTorr) as a colorless oil: $[\alpha]^{22}_D$ −76.4° (*c* 1.51, $CHCl_3$) [lit.[7] $[\alpha]^{24}_D$ −77.9° (*c* 1.47, $CHCl_3$)]; IR (neat) 1628 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.67 (dd, 1H, J = 8.30, 13.7 Hz), 3.08 (dd, 1H, J = 5.86, 13.7 Hz), 3.92 (dd, 1H, J = 7.81, 8.30 Hz), 4.15 (dd, 1H, J = 8.79, 9.28 Hz), 4.38 (m, 1H), 6.81 (d, 1H, J = 1.95 Hz), 7.20−7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 41.6, 66.5, 70.5, 126.5, 128.5, 129.2, 137.7, 154.8. Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.62; H, 7.02; N, 8.67.

(4*S*,5*R*)-4-Methyl-5-phenyl-2-oxazoline (6c). Following the general procedure (method G), (1*R*,2*S*)-(−)-**2d** (1.51 g, 10.0 mmol), **1f** (1.63 g, 11.0 mmol), and trifluoroacetic acid (130 μL, 17 mol %) gave 1.12 g (69%) of **6c** after Kugelrohr distillation (53−55 °C, 120 mTorr, lit.[7] bp 80 °C, 50 mTorr) as a colorless oil: $[\alpha]^{22}_D$ −227° (*c* 2.32, $CHCl_3$) [lit.[7] $[\alpha]^{24}_D$ −228° (*c* 2.30, $CHCl_3$)]; IR (neat) 1632 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (d, 3H, J = 6.84 Hz), 4.43 (m, 1H), 5.55 (d, 1H, J = 9.76 Hz), 7.01 (d, 1H, J = 1.95 Hz), 7.20−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 17.7, 64.1, 82.8, 126.2, 127.9, 128.3, 136.5, 153.9. Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.45; H, 6.99; N, 8.65.

(4*S*,5*S*)-4-(Methoxymethyl)-5-phenyl-2-oxazoline (6d). Following the general procedure (method G), (1*S*,2*S*)-(+)-**2e** (0.99 g, 5.5 mmol), **1f** (0.89 g, 6.0 mmol), and trifluoroacetic acid (85 μL, 20 mol %) gave 0.79 g (75%) of **6d** after Kugelrohr distillation (65−70 °C, 80 mTorr, lit.[7] bp 75 °C, 50 mTorr) as a colorless oil: $[\alpha]^{24}_D$ −195° (*c* 1.73, $CHCl_3$) [lit.[7] $[\alpha]^{24}_D$ +195° (*c* 1.63, $CHCl_3$)]; IR (neat) 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.42 (s, 3H), 3.54 (dd, 1H, J = 6.35, 9.76 Hz), 3.64 (dd, 1H, J = 4.40, 9.76 Hz), 4.13 (m, 1H), 5.29 (d, 1H, J = 7.33 Hz), 7.01 (d, 1H, J = 1.95 Hz), 7.28−7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 59.3, 73.5, 73.9, 82.3, 126.5, 128.3, 128.8, 140.3, 155.0. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.21; H, 6.95; N, 7.38.

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