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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 2270–2275

Synthesis of non-symmetric bisoxazoline compounds. An easy way to reach tailored chiral ligands

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Received 7 July 2006; accepted 25 July 2006
Available online 23 August 2006

Abstract—Bisoxazoline compounds have been used as chiral catalyst ligands in a wide variety of reactions. A great deal of effort has been aimed at the synthesis of C_2-symmetric bisoxazolines but very few references exist for non-symmetric ones. As part of our studies into the possible usefulness of non-symmetric bisoxazolines, we report an easy method for the synthesis of bisoxazoline compounds bearing different substituents in each oxazoline ring.

1. Introduction

Bisoxazoline compounds have become increasingly important as chiral ligands in the asymmetric catalysis of a wide variety of organic reactions.[1,2] Several synthetic methods have been described for the synthesis of these types of ligands[3–13] but they are all dedicated to C_2-symmetric bisoxazolines.

Our group has worked on the modification of bisoxazoline compounds in order to make them suitable for immobilization onto different supports such as silica,[14] polymers,[15] and clays,[16] as well as on the use of such catalysts in cyclopropanation reactions.

These studies have shown that the surface has a significant effect when using clay-immobilized bisoxazoline complexes in solvents with low dielectric constants. Reversal of enantioselectivity with respect to homogeneous phase reactions and a preference for *cis* cyclopropanes were observed.[17] These results were rationalized on the basis of an increased steric interaction between the clay surface with the Cu–carbene intermediate and the incoming styrene.

The above effect could be improved if it were possible to make the clay play the role of a bulky substituent of the ligand. Initial attempts to achieve this were made using pyridineoxazoline (Pyox) ligands[18] (Fig. 1). Promising results were obtained in that a cis-preference was observed in cyclopropanation reactions when using clay-immobilized pyox–Cu complexes with styrene as a solvent, although reversal of the enantioselectivity was not observed.

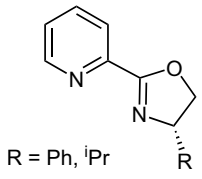

Figure 1. Pyridineoxazoline used as a ligand for the immobilization of copper complexes on clays.

These results encouraged us to design new bisoxazoline ligands with the same structural pattern. In order to achieve this goal we needed to establish a new synthetic method for bisoxazoline compounds bearing one unsubstituted oxazoline (R = H) (Fig. 2) to minimize the distance between the clay and the copper complex.

Based on our previous experience in the synthesis of bisoxazoline compounds,[19] we herein report the use of a similar synthetic pathway to obtain non-symmetric (C_1-symmetric) bisoxazoline ligands. This approach gave a wide variety of new bisoxazoline compounds that could prove very interesting as clay-immobilized chiral ligands.

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doi:10.1016/j.tetasy.2006.07.031

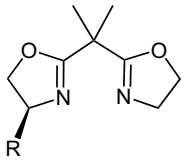

Figure 2. Non-symmetric bisoxazoline compounds.

2. Results and discussion

The synthesis of non-symmetric bisoxazolines is based on the separate synthesis of each oxazoline ring (Fig. 3).

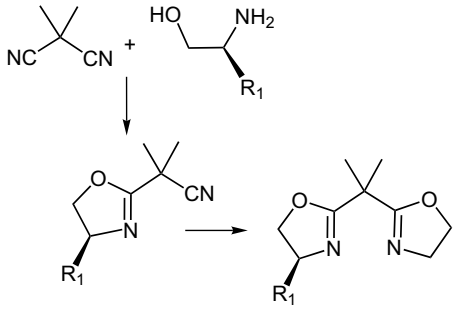

Figure 3. Non-symmetric bisoxazoline formation.

The chemistry for synthesising oxazoline compounds starting from dimethylmalononitrile is well known, but the problem was how to synthesize one oxazoline ring while leaving a nitrile group untouched.

Our group recently described an efficient method for the synthesis of C_2-symmetric bisoxazolines. Bisoxazolines were synthesized in a one-step reaction from the corresponding amino alcohol and dimethylmalononitrile using a variety of Zn catalysts.[19] Taking advantage of this information we decided to try these catalysts in the synthesis of oxazoline compound **2** (Fig. 4).

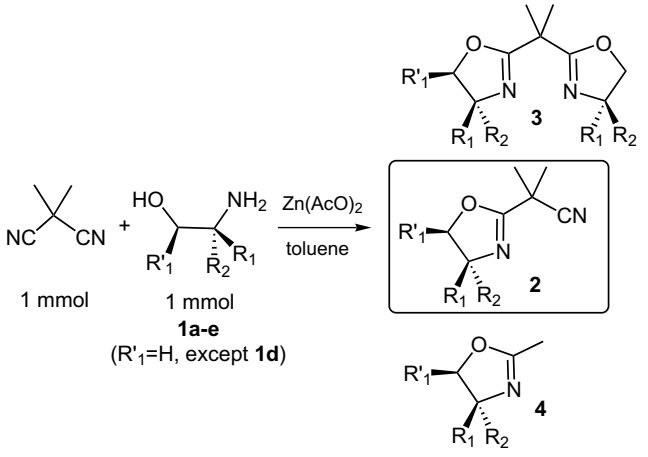

Figure 4. Synthesis of oxazoline compounds **2** from starting materials: (**1a**) $R_1 = H$, $R_2 = H$; (**1b**) $R_1 = Phe$, $R_2 = H$; (**1c**) $R_1 = {}^tBu$, $R_2 = H$; (**1d**) R_1, $R'_1 =$ indanyl, $R_2 = H$; (**1e**) $R_1 = Me$, $R_2 = H$; (**1f**) $R_1 = Phe$, $R_2 = Me$.

The reaction of equimolecular amounts of 2,2-dimethylmalononitrile and amino alcohol with $ZnCl_2$ or $Zn(OTf)_2$ led to C_2-symmetric bisoxazolines **3** as the major reaction products, regardless of the starting amino alcohol (Table 1).

Table 1. Results of the reaction of equimolecular amounts of 2,2-dimethylmalononitrile and amino alcohols **1a**–**f** using $Zn(OAc)_2$ (20%) in toluene at 110 °C

2	Time (h)	Yield (%) 2[a]	Yield (%) 3	Yield (%) 4
2a	22	81	0	0
2b	6	84	4	8
2c	21	91	0	0
2d	6	75	4	17
2e	24	61	5	0
2f	24	90	0	7

[a] Yields calculated by ^1H NMR spectroscopy.

In this case, $Zn(OAc)_2$ was found to be the best catalyst for obtaining oxazoline **2**, although the formation of bisoxazoline **3** and small amounts of a new by-product identified as methyl oxazoline **4**, was sometimes observed.

In all cases, good yields of product **2** were obtained. Small amounts of either bisoxazoline **3** or methyl oxazoline **4** were observed in most cases. The exceptions were when $R_1 = {}^tBu$ and H, in which case only product **2** was obtained.

Problems associated with the solubility of 2-ethanolamine in toluene and the lower stability of the unsubstituted oxazoline ring led to difficulties in scaling up reactions using 2-ethanolamine **1a** as the starting material. Other solvents (e.g., THF and dioxane) were tried in order to improve the synthetic method. The solubility of 2-ethanolamine was higher in THF but the reaction temperature was not sufficiently high enough to give good results. When using dioxane, we were unable to obtain the desired product. We therefore decided to synthesize the unsubstituted ring in the second reaction step.

Formation of the second oxazoline ring from compound **2** was carried out without the need for further purification of product **2**. In this case, $Zn(OTf)_2$ (Fig. 5) was used as a catalyst, as we knew that this was the best one for the synthesis of bisoxazoline compounds.[19]

Surprisingly, the desired product **5** was not the only one observed. The formation of bisoxazoline **3** was also observed, indicating that oxazoline formation is a reversible process under the reaction conditions used. A similar situation was described by Kim et al.[20] in the synthesis of chiral tripodal oxazolines.

The results for the synthesis of compound **5** are given in Table 2. We observed that reaction times and conversions were strongly dependent on the starting oxazoline **2**. Non-symmetric bisoxazolines were obtained in good-to-moderate yields. Chromatographic purification provided pure products **5**.

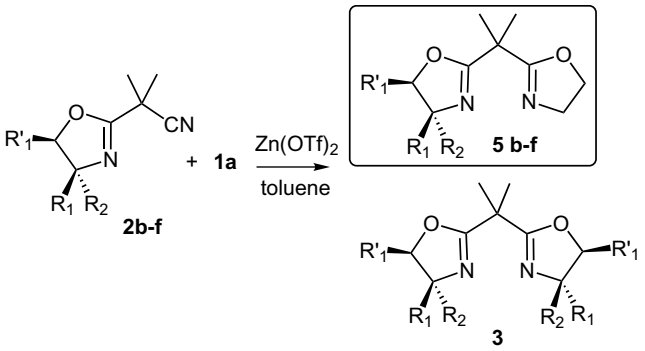

Figure 5. Formation of non-symmetric bisoxazoline **5** compounds starting from oxazoline compounds **2b–f** and ethanolamine **1a**. (b) $R_1 = Phe$, $R_2 = H$; (c) $R_1 = {}^tBu$, $R_2 = H$; (d) R_1, $R'_1 =$ indanyl, $R_2 = H$; (f) $R_1 = Phe$, $R_2 = Me$.

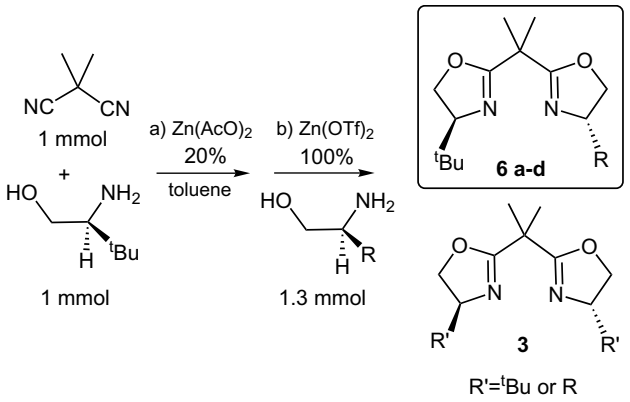

Figure 6. Formation of non-symmetric bisoxazoline **6** compounds starting from dimethylmalononitrile and the corresponding amino alcohols **1** in a two-step one-pot procedure. (a) R = Phe, (b) R = Bn, (c) R = Me, (d) R = Bn–O–CH_2.

Table 2. Results in the reaction of equimolecular amounts of **2b–f** and ethanolamine **1a** using $Zn(OTf)_2$ in toluene at 110 °C

Product	Time (days)	Yield **5** (%)[a]	**5/3**[a]
5b	2	62	6
5c	7	71	12
5d	2	50	4
5f	3	64	8.6

[a] Calculated by ^1H NMR spectroscopy.

Table 3. Results of the one-pot synthesis of non-symmetric bisoxazolines **6** after three days of reaction

Product	Yield **6** (%)[a]	**6/3**[a]
7a	50	2.3
7b	76	15
7c	70	3.6
7d	72	3

[a] Calculated by ^1H NMR spectroscopy.

In order to prove the versatility of this method we decided to use amino alcohols other than ethanolamine in order to obtain new bisoxazoline compounds with different substituents at the 4- and 4′-positions. We fixed the presence of a *tert*-butyl group in one of the oxazoline rings due to the better enantioselectivity that is usually associated with the presence of this bulky substituent.

We also tried to improve the synthetic methodology by working with a one-pot process, that is, adding $Zn(OTf)_2$ and the second amino alcohol to the initial reaction mixture and carrying out the work up only after bisoxazoline formation (Fig. 6).

In all cases, we obtained a mixture of C_2-symmetric bisoxazolines **3** and the desired product **6**, which could be purified by column chromatography. Once again, conversions and product ratios were found to be dependent on the starting amino alcohol but, in most cases, fairly good yields of the target compound were obtained (Table 3).

3. Conclusions

We have designed a simple, general, and convenient method for the synthesis of non-symmetric bisoxazolines. In two-step one-pot reactions using dimethylmalononitrile, two different amino alcohols and $Zn(OAc)_2$ and $Zn(OTf)_2$ as catalysts, we were able to obtain a wide variety of new bisoxazoline compounds. Fourteen new products, considering bisoxazolines and their precursors, have been synthesized and fully characterized. This method opens the way to increase the molecular diversity of chiral bisoxazolines for catalytic applications.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra ($CDCl_3$, δ ppm, J Hz) were obtained using a Bruker AV-400 instrument with TMS as the standard. Quantitative elemental analyses were performed on a Perkin–Elmer 2400 instrument. Polarimetry was carried out using a Jasco P-1020 instrument.

Enantiomerically pure amino alcohols were commercially available except for (*S*)-2-methylphenylglycinol and (*R*)-2-amino-3-(benzyloxy)-1-propanol, which were obtained from the corresponding amino acids by Meyers' method.[21]

4.2. General procedure for the synthesis of products 2a–f

The synthesis of 2-[(4*S*)-4-*tert*-butyl-4,5-dihydro-1,3-oxazol-2-yl]-2-methylpropanenitrile **2c** is representative.

A 250-mL two-necked round-bottomed flask fitted with a reflux condenser was charged with 2,2-dimethylmalononitrile (941.1 mg, 10 mmol), zinc acetate (20% 367 mg) and toluene (80 ml). The solution was stirred for 5 min and a solution of L-*tert*-leucinol **1c** (1.172 g, 10 mmol) in toluene (20 ml) was added. The solution was then heated at reflux. The reaction mixture was allowed to cool and then washed

with brine (1×100 ml) and $NaHCO_3$ (2×100 ml), dried over $MgSO_4$ and the solvent evaporated to give 1.765 g (9.1 mmol, 91%) of pure **2c**. ^{1}H NMR: 4.21 (dd, $J = 10.09$, 8.80 Hz, 1H), 4.11 (dd, $J = 8.80$, 7.50 Hz, 1H), 3.83 (dd, $J = 10.09$, 7.50 Hz, 1H), 1.58 (s, 3H), 1.57 (s, 3H), 0.82 (s, 9H). ^{13}C NMR: 24.37, 24.57, 32.29, 32.82, 68.91, 74.59, 120.33, 163.77. Anal. Calcd for $C_{11}H_{18}N_2O$: C, 68.01; H, 9.34; N, 14.42. Found C, 67.87; H, 9.33; N, 14.52.

4.2.1. 2-(4,5-Dihydro-1,3-oxazol-2-yl)-2-methylpropane nitrile 2a. 2-(4,5-Dihydro-1,3-oxazol-2-yl)-2-methyl propanenitrile was prepared analogously to **2c** in 81% yield. ^{1}H NMR: 4.36 (t, $J = 9.52$ Hz, 2H), 3.89 (t, $J = 9.52$ Hz, 2H), 1.63 (s, 6H). ^{13}C NMR: 24.03, 37.91, 41.77, 60.36, 121.43, 168.46. Anal. Calcd for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.28. Found C, 60.91; H, 7.35; N, 20.20.

4.2.2. 2-Methyl-2-[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxa-zol-2-yl]propanenitrile 2b. 2-Methyl-2-[(4*S*)-phenyl-4,5-dihydro-1,3-oxazol-2-yl]propanenitrile was prepared analogously to **2c** to give 84% of the target compound. Purification of the crude product was not necessary. ^{1}H NMR: 7.26 (m, 2H), 7.15 (m, 3H) 5.18 (dd, $J = 10.16$, 8.18 Hz, 1H), 4.68 (dd, $J = 10.16$, 8.56 Hz, 1H), 4.17 (dd, $J = 8.56$, 8.18 Hz, 1H), 1.68 (s, 6H). ^{13}C NMR: 24.40, 32.39, 68.50, 73.6, 120.10, 125.45, 126.89, 127.86, 140.33, 165.49.

4.2.3. 2-{(3a*S*,8a*R*)-8,8a-dihydro-3a*H*-indeno[1,2-*d*][1,3]-oxazol-2-yl}-2-methylpropanenitrile 2d. 2-{(3a*S*,8a*R*)-8,8a-Dihydro-3a*H*-indeno[1,2-*d*][1,3]oxazol-2-yl}-2-methyl-propanenitrile was prepared analogously to **2c** to give 75% of the target compound. Purification of the crude product was not necessary. ^{1}H NMR: 7.46–7.40 (m, 1H), 7.24–7.14 (m, 3H), 5.53 (d, $J = 7.94$ Hz, 1H), 5.37 (ddd, $J = 7.94$, 7.07, 1.64 Hz, 1H), 3.39 (dd, $J = 18.04$, 7.07 Hz, 1H), 3.20 (dd, $J = 18.04$, 1.64 Hz, 1H), 1.55 (s, 3H), 1.51 (s, 3H). ^{13}C NMR: 165.53, 141.00, 139.49, 128.79, 127.58, 125.66, 125.37, 121.19, 84.53, 76.76, 39.62, 33.33, 25.32, 25.28.

4.2.4. 2-Methyl-2-[(4*S*)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]propanenitrile 2e. 2-Methyl-2-[(4*S*)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]propanenitrile was prepared analogously to **2c** to give 61% of the target compound. Purification of the crude product was not necessary. ^{1}H NMR: 4.39 (dd, $J = 9.35$, 8.24 Hz, 1H), 4.22–4.11 (m, 1H), 3.83 (dd, $J = 8.24$, 7.70 Hz, 1H), 1.58 (s, 6H), 1.21 (d, $J = 6.65$ Hz, 3H). ^{13}C NMR: 18.78, 22.92, 30.87, 59.44, 72.84, 118.87, 162.65.

4.2.5. 2-Methyl-2-[(4*S*)-4-methyl-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]propanenitrile 2f. 2-Methyl-2-[(4*S*)-4-methyl-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]propanenitrile was prepared analogously to **2c** to give 90% of the target compound. Purification of the crude product was not necessary. ^{1}H NMR: 7.32–7.14 (m, 5H), 4.34 (d, $J = 8.24$ Hz, 1H), 4.28 (d, $J = 8.24$ Hz, 1H), 1.65 (s, 6H), 1.54 (s, 3H). ^{13}C NMR: 25.45, 29.38, 33.42, 73.16, 81.30, 121.26, 125.11, 127.19, 128.64, 146.14, 164.49.

4.3. General stepwise procedure for the synthesis of bisoxazolines 5 from oxazolines 2b–e

The synthesis of (4*S*)-4-*tert*-butyl-2-[1-(4,5-dihydro-1,3-oxazol-2-yl)-1-methylethyl]-4,5-dihydro-1,3-oxazole **5c** is representative. A 250-mL two-necked round-bottomed flask fitted with a reflux condenser was charged with 2-[(4*S*)-4-*tert*-butyl-4,5-dihydro-1,3-oxazol-2-yl]-2-methylpropanenitrile **2c** (1.941 g, 10 mmol) in anhydrous toluene (10 ml) and zinc triflate (4 g, 11 mmol). The system was purged with argon and anhydrous toluene (90 ml) was added. The solution was stirred for 5 min and ethanolamine (794 mg, 13 mmol) was added. The solution was heated at reflux for 7 days. The reaction mixture was allowed to cool and was then washed with brine (1×100 ml) and $NaHCO_3$ (2×100 ml), dried over $MgSO_4$ and the solvent evaporated to give 71% of the target compound **5c**. The crude product was purified by column chromatography (Al_2O_3; hexane/ethyl acetate, 6:4, 0.4% NEt_3).

4.3.1. (4*S*)-4-*tert*-Butyl-2-[1-(4,5-dihydro-1,3-oxazol-2-yl)-1-methylethyl]-4,5-dihydro-1,3-oxazole 5c. $[\alpha]_D = -44.6$ (*c* 1, CH_2Cl_2). ^{1}H NMR: 4.18 (m, 2H), 4.09 (m, 1H), 4.02 (m, 1H), 3.77 (m, 3H), 1.44 (s, 3H), 1.43 (s, 3H), 0.79 (s, 9H) ^{13}C NMR: 170.19, 168.49, 75.27, 69.11, 67.95, 54.32, 38.58, 33.91, 25.62, 24.40, 24.35. Anal. Calcd for $C_{13}H_{22}N_2O_2$: C, 65.51; H, 9.30; N, 11.75. Found C, 65.34; H, 9.32; N, 11.78.

4.3.2. (4*S*)-2-[1-(4,5-Dihydro-1,3-oxazol-2-yl)-1-methyl ethyl]-4-phenyl-4,5-dihydro-1,3-oxazole 5b. (4*S*)-2-[1-(4,5-Dihydro-1,3-oxazol-2-yl)-1-methylethyl]-4-phenyl-4,5-dihydro-1,3-oxazole was prepared analogously to **5c** from 2,2-dimethylmalononitrile, (*S*)-(+)-2-phenylglycinol, and ethanolamine **2b** to give 62% of the target compound in a reaction time of 48 h. The crude product was purified by column chromatography (Al_2O_3; hexane/ethyl acetate, 6:4, 0.4% NEt_3). $[\alpha]_D = -124.6$ (*c* 1, CH_2Cl_2). ^{1}H NMR: 7.30–7.24 (m, 2H), 7.22–7.14 (m, 3H), 5.13 (dd, $J = 10.12$, 7.74 Hz, 1H), 4.57 (dd, $J = 10.12$, 8.33 Hz, 1H), 4.25 (dd, $J = 9.63$, 9.63 Hz, 2H), 4.05 (dd, $J = 8.33$, 7.74 Hz, 1H), 3.83 (dd, $J = 9.63$, 9.63 Hz, 2H), 1.53 (s, 3H), 1.52 (s, 3H). ^{13}C NMR: 170.43, 170.01, 142.39, 128.69, 127.50, 126.65, 75.57, 69.46, 68.02, 54.40, 38.82, 24.47, 24.36. Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found C, 69.81; H, 7.07; N, 10.82.

4.3.3. (3a*S*,8a*R*)-2-[1-(4,5-Dihydro-1,3-oxazol-2-yl)-1-methylethyl]-8,8a-dihydro-3a*H*-indeno[1,2-*d*][1,3] oxazole 5d. (3a*S*,8a*R*)-2-[1-(4,5-Dihydro-1,3-oxazol-2-yl)-1-methylethyl]-8,8a-dihydro-3a*H*-indeno[1,2-*d*][1,3] oxazole was prepared analogously to **5c** from 2,2-dimethylmalononitrile, (1*S*)-amino-(2*R*)-indanol, and ethanolamine to give 50% of the target compound in a reaction time of 48 h. The crude product was purified by column chromatography (Al_2O_3; hexane/ethyl acetate, 2:8, 0.4% NEt_3). $[\alpha]_D = -206.3$ (*c* 1, EtOH). ^{1}H NMR: 7.48–7.40 (m, 1H), 7.23–7.12 (m, 3H), 5.49 (d, $J = 8.02$ Hz, 1H), 5.29 (ddd, $J = 8.02$, 7.15, 1.55 Hz, 1H), 4.18 (dd, $J = 9.47$, 9.47 Hz, 2H) (m, 2H), 3.79 (dd, $J = 9.47$, 9.47 Hz, 2H) (m, 2H), 3.34 (dd, $J = 17.84$, 7.15 Hz, 1H), 3.12 (dd, $J = 17.84$, 1.55 Hz, 1H), 1.43 (s, 3H), 1.36 (s, 3H). ^{13}C NMR:

170.01, 169.15, 141.75, 139.78, 128.41, 127.36, 125.71, 125.17, 83.35, 76.57, 68.04, 54.38, 39.84, 38.62, 24.41, 24.09. Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found C, 71.00; H, 6.72; N, 10.35.

4.3.4. (4*S*)-2-[1-(4,5-Dihydro-1,3-oxazol-2-yl)-1-methylethyl]-4-methyl-4-phenyl-4,5-dihydro-1,3-oxazole (5). (4*S*)-2-[1-(4,5-Dihydro-1,3-oxazol-2-yl)-1-methylethyl]-4-methyl-4-phenyl-4,5-dihydro-1,3-oxazole was prepared analogously to **5c** from 2,2-dimethylmalononitrile, (*S*)-(+)-2-methyl-2-phenylglycinol, and ethanolamine to give 64% of the target compound in a reaction time of 72 h. The crude product was purified by column chromatography (Al_2O_3; hexane/ethyl acetate, 7:3, 0.4% NEt_3). $[\alpha]_D = +4.6$ (*c* 1, EtOH). ^{1}H NMR: 7.32–7.23 (m, 4H), 7.20–7.13 (m, 1H), 4.28–4.18 (m, 3H), 4.15 (d, $J = 8.11$ Hz, 1H), 3.82 (dd, $J = 9.50$, 9.50 Hz, 2H), 1.55 (s, 3H), 1.53 (s, 3H), 1.52 (s, 3H). ^{13}C NMR: 170.13, 168.23, 146.80, 128.45, 126.88, 125.34, 80.85, 72.46, 68.07, 54.42, 38.69, 28.73, 24.46, 24.42. Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found C, 70.55; H, 7.38; N, 10.28.

4.4. General one-pot procedure for the synthesis of bisoxazolines 6

The synthesis of (4*S*)-4-*tert*-butyl-2-{1-methyl-1-[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]ethyl}-4,5-dihydro-1,3-oxazole **6a** is representative.

A 250-mL two-necked round-bottomed flask fitted with a reflux condenser was charged with 2,2-dimethylmalononitrile (941.1 mg, 10 mmol), zinc acetate (20% 367 mg), and toluene (80 ml). The solution was stirred for 5 min and a solution of L-*tert*-leucinol **1c** (1.172 g, 10 mmol) in toluene (20 ml) was added. The solution was heated at reflux for one day. The system was then allowed to cool. Zinc triflate (4 g, 11 mmol) and (*S*)-(+)-2-phenylglycinol (1.78 g, 13 mmol) were added. The solution was again heated at reflux for 3 days. The system was allowed to cool. The reaction was then washed with brine (1×100 ml) and $NaHCO_3$ (2×100 ml), dried over $MgSO_4$ and the solvent evaporated to give 50% of the target compound **6a**. The crude product was purified by column chromatography (Al_2O_3; hexane/ethyl acetate, 8:2, 0.4% NEt_3).

4.4.1. (4*S*)-4-*tert*-Butyl-2-{1-methyl-1-[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]ethyl}-4,5-dihydro-1,3-oxazole 6a. $[\alpha]_D = -173.3$ (*c* 1, CH_2Cl_2). ^{1}H NMR: 7.28–7.22 (m, 2H), 7.21–7.15 (m, 3H), 5.10 (dd, $J = 10.07$, 7.52 Hz, 1H), 4.53 (dd, $J = 10.07$, 8.40 Hz, 1H), 4.12 (dd, $J = 9.98$, 8.76 Hz, 1H), 4.05 (dd, $J = 8.76$, 7.00 Hz, 1H) 4.03 (dd, $J = 8.40$, 7.52 Hz, 1H), 3.81 (dd, $J = 9.98$, 7.00 Hz, 1H), 1.52 (s, 3H), 1.49 (s, 3H), 0.82 (s, 9H). ^{13}C NMR: 170.59, 168.52, 142.61, 128.67, 127.53, 126.77, 75.51, 75.44, 69.54, 69.13, 38.84, 33.96, 25.68, 24.65, 24.34. Anal. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.33; N, 8.91. Found C, 72.61; H, 8.35; N, 8.89.

4.4.2. (4*S*)-4-Benzyl-2-{1-[(4*S*)-4-*tert*-butyl-4,5-dihydro-1,3-oxazol-2-yl]-1-methylethyl}-4,5-dihydro-1,3-oxazole 6b. (4*S*)-4-Benzyl-2-{1-[(4*S*)-4-*tert*-butyl-4,5-dihydro-1,3-oxazol-2-yl]-1-methylethyl}-4,5-dihydro-1,3-oxazole was prepared analogously to **6a** from 2,2-dimethylmalononitrile, L-*tert*-leucinol, and (*S*)-2-amino-3-phenyl-1-propanol to give 76% of the target compound in a reaction time of 72 h. The crude product was purified by column chromatography (Al_2O_3; hexane/ethyl acetate, 7:3, 0.4% NEt_3). $[\alpha]_D = -91.1$ (*c* 1, CH_2Cl_2). ^{1}H NMR: 7.26–7.18 (m, 2H), 7.18–7.10 (m, 3H), 4.33 (m, 1H), 4.13–4.06 (m, 2H), 4.03 (dd, $J = 8.63$, 6.89 Hz, 1H), 3.93 (dd, $J = 8.41$, 6.87 Hz, 1H), 3.78 (dd, $J = 10.00$, 6.89 Hz, 1H), 3.04 (dd, $J = 13.69$, 4.63 Hz, 1H), 2.58 (dd, $J = 13.69$, 8.71 Hz, 1H), 1.44 (s, 3H), 1.41 (s, 3H), 0.80 (s, 9H). ^{13}C NMR: 169.67, 168.50, 137.78, 129.45, 128.44, 126.45, 75.30, 71.96, 69.08, 67.08, 41.36, 38.59, 33.94, 25.64, 24.44, 24.23. Anal. Calcd for $C_{20}H_{28}N_2O_2$: C, 73.14; H, 8.59; N, 8.53. Found C, 73.09; H, 8.57; N, 8.55.

4.4.3. (4*S*)-4-*tert*-Butyl-2-{1-methyl-1-[(4*S*)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]ethyl}-4,5-dihydro-1,3-oxazole 6c. (4*S*)-4-*tert*-Butyl-2-{1-methyl-1-[(4*S*)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl]ethyl}-4,5-dihydro-1,3-oxazole was prepared analogously to **6a** from 2,2-dimethylmalononitrile, L-*tert*-leucinol, and (*S*)-(+)-2-amino-1-propanol to give 70% of the target compound in a reaction time of 72 h. The crude product was purified by column chromatography (Al_2O_3; hexane/ethyl acetate, 8:2, 0.4% NEt_3). Yield 63%. $[\alpha]_D = -86.9$ (*c* 0.785, CH_2Cl_2). ^{1}H NMR: 4.30 (dd, $J = 9.17$, 8.07 Hz, 1H), 4.17–4.04 (m, 3H), 3.82 (dd, $J = 9.98$, 6.92 Hz, 1H), 3.78–3.71 (m, 1H), 1.49 (s, 3H), 1.48 (s, 3H), 1.21 (d, $J = 6.58$ Hz, 3H), 0.84 (s, 9H). ^{13}C NMR: 169.02, 168.56, 75.29, 74.37, 69.09, 61.39, 38.50, 33.95, 25.63, 24.45, 24.36, 21.32. Anal. Calcd for $C_{14}H_{24}N_2O_2$: C, 66.63; H, 9.59; N, 11.10. Found C, 66.65; H, 9.60; N, 11.09.

4.4.4. (4*S*)-4-[(Benzyloxy)methyl]-2-{1-[(4*S*)-4-*tert*-butyl-4,5-dihydro-1,3-oxazol-2-yl]-1-methylethyl}-4,5-dihydro-1,3-oxazole 6d. (4*S*)-4-[(Benzyloxy)methyl]-2-{1-[(4*S*)-4-*tert*-butyl-4,5-dihydro-1,3-oxazol-2-yl]-1-methylethyl}-4,5-dihydro-1,3-oxazole was prepared analogously to **6a** from 2,2-dimethylmalononitrile, L-*tert*-leucinol, and (*R*)-2-amino-3-(benzyloxy)propan-1-ol to give 72% of the target compound in a reaction time of 72 h. The crude product was purified by column chromatography (Al_2O_3; hexane/ethyl acetate, 7:3, 0.4% NEt_3). Yield 44%. $[\alpha]_D = -96.9$ (*c* 1, CH_2Cl_2). ^{1}H NMR: 7.28–7.16 (m, 5H), 4.48 (d, $J = 12.14$ Hz, 1H), 4.45 (d, $J = 12.14$ Hz, 1H), 4.29–4.17 (m, 2H), 4.16–4.07 (m, 1H), 4.07 (dd, $J = 10.02$, 8.70 Hz, 1H), 4.00 (dd, $J = 8.70$, 6.89 Hz, 1H), 3.77 (dd, $J = 10.02$, 6.89 Hz, 1H), 3.64–3.59 (m, 1H), 3.36–3.28 (m, 1H), 1.43 (s, 6H), 0.78 (s, 9H). ^{13}C NMR: 169.99, 167.69, 137.44, 127.63, 126.90, 126.87, 74.54, 72.62, 71.34, 70.39, 68.34, 65.10, 37.92, 33.19, 24.89, 23.71, 23.64. Anal. Calcd for $C_{21}H_{30}N_2O_3$: C, 70.36; H, 8.44; N, 7.81. Found C, 70.39; H, 8.47; N, 7.79.

Acknowledgments

This work was made possible by the generous financial support of the CICYT (Project CTQ2005-08016). I.V. wishes

to thank the MEC for a grant. We thank DSM-Deretil for furnishing us with pure (*S*)-2-methylphenylglycine.

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