# An Efficient and General One-Pot Method for the Synthesis of Chiral Bis(oxazoline) and Pyridine Bis(oxazoline) Ligands

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**Abstract:** An expeditious method for the synthesis of chiral box and pybox ligands is reported. The approach is based on a one-pot condensation reaction of chiral β-amino alcohols with a dinitrile using stoichiometric or catalytic amounts of zinc triflate. Yields greater than 90% are obtained in many cases without the need for further purification of the product.

**Key words:** bis(oxazolines), pybox, synthesis, zinc triflate, toluene, chiral ligands

Chiral bis(oxazolines) (box) are widely used in the asymmetric catalysis of an increasing variety of organic reactions including cyclopropanations, Diels–Alder, ene, aziridination, allylic substitutions, Mukaiyama–Michael, Mukaiyama aldol reactions,[1,2] to mention just a few. Box systems bearing a one-carbon spacer between the two oxazoline rings are the most frequently used.

Since 1997 many attempts have also been made to support box ligands in heterogeneous systems.[3]

The introduction of a third coordinating atom into the link between the two oxazoline rings has led to the development of tridentate bis(oxazoline) ligands, among which pyridine bis(oxazoline) (pybox) derivatives represent the best known examples. These ligands have been successfully used in the same types of reactions as bis(oxazolines),[1,4] and our group has described for the first time the support of this family of ligands.[5]

Interest in box and pybox ligands has increased due to the wide variety of new compounds that have been synthesized. Modifications include different substituents on the oxazoline rings or variation of the nature and size of the spacer between oxazoline rings. Such changes open new possibilities for catalytic applications of these materials.

Recently, we have focused our attention in the synthesis of these ligands in order not only to improve yields but also to have a general method to design tailored box and pybox ligands.

If we review synthetic methods for box ligands, most of them follow a general route in which the first step is the condensation of the chiral amino alcohol with nitriles or acid derivatives to form the bis(hydroxy)amide derivative. The hydroxyl groups are then activated and the resulting intermediate is cyclized to provide the bis(oxazoline) ligand. Several activating agents have been described to favor the cyclization,[6–8] but most of the papers describing non-commercial bis(oxazolines) ligands use the Evans method.[9]

It is worth noting that this method consists of a two-step process in which several purifications are needed, with overall yields that can reach 80%, but are often lower.

A convenient synthesis of bis(oxazoline) ligands was described by Lehn[10] and Pfalz.[6] The treatment of malononitrile with anhydrous HCl in ethanol afforded the corresponding imidate salt. Condensation with an optically active β-amino alcohol in dichloromethane furnished the bis(oxazoline) in good yields. Unfortunately, this method does not work with other spacers, for instance when the methylene spacer is alkyl-substituted.

Bolm and coworkers[11] reported the condensation of phthalonitrile and 1,2-ethanedinitrile with an excess (1:3) of several β-amino alcohols using chlorobenzene as solvent and catalytic amounts of $ZnCl_2$ (5%). The best results were obtained for bis(oxazolines) bearing a phenylene spacer between the oxazoline rings, but moderate yields were obtained when the spacer was an ethylene group. The need for an excess of the amino alcohol, the moderate yields, the need for purification of the reaction mixture and the frequent loss of the starting enantiomerically pure amino alcohol are significant drawbacks of this method.

The same method has also been used for the synthesis of pybox ligands[12] but the yields were no higher than 65%. Pybox ligands have traditionally been prepared in multistep processes by the method reported by Nishiyama.[13] The need for several purifications of the intermediate products results in yields no higher than 70%.

Other synthetic methods have been reported but the yields always range from moderate to low.[14]

The aim of this paper is to describe a general method for the one-pot synthesis of these types of ligands with high or quantitative yields, without loss of chiral amino alcohol and avoiding the need for product purification.

Optimization of the synthetic conditions was started by applying the Bolm[11] method for 2,2-bis[4-(*S*)-phenyl-1,3-oxazolinyl)propane] (**1**). Condensation of 2,2-dimethylmalononitrile (1 mmol) with (*S*)-phenylglycinol (3 mmol)

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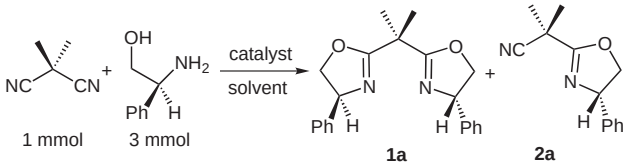
using $ZnCl_2$ (5%) in chlorobenzene furnished a mixture of the desired product **1a** and oxazoline **2a** (Scheme 1). Chromatographic purification of the reaction mixture was needed and a poor yield (28%) of bis(oxazoline) was obtained. The reaction does not progress due to the formation of a strong bis(oxazoline) **1a**–$ZnCl_2$ complex. Bis(oxazoline) competes favorably for the catalyst with the nitrile group of oxazoline **2a** in the reaction medium and the reaction stops.[15] The amount of catalyst should therefore be increased to obtain good yields of the bis(oxazoline).

Another drawback of Bolm's conditions is the use of an excess of amino alcohol, which is the most expensive and difficult reagent to obtain. We therefore aimed to find new conditions in which good yields were obtained, if possible without the need for excess enantiomerically pure amino alcohol and in a greener medium.




**Scheme 1**

We first decided to change the solvent and use a non-chlorinated and less toxic one. The long reaction times led us to work with reaction temperatures over 100 °C and we chose toluene as the solvent because of its appropriate boiling point and the good solubility of the reactants. We fixed a 1:2 ratio of 2,2-dimethylmalononitrile and amino alcohol, and tested different amounts of $ZnCl_2$ in toluene. Under these conditions only oxazoline **2a** was obtained. The reduced activity of $ZnCl_2$ in toluene is certainly due to solubility problems, so we considered other Zn salts that would be more soluble in toluene.

The use of $Zn(OAc)_2$ gave a complex reaction mixture containing oxazoline **2a**, bis(oxazoline) **1a** and a new product. Chromatographic purification enabled us to identify that product as 2-methyl-4-phenyloxazoline. Finally, $Zn(OTf)_2$ turned out to be the best catalyst for this reaction. The results obtained with several proportions of the catalyst are gathered in Table 1. When substoichiometric amounts of catalyst were used, oxazoline **2a** appeared and purification was required to obtain bis(oxazoline) **1a**. Only near stoichiometric amounts of zinc triflate gave pure bis(oxazoline) **1a** in very good yields (Figure 1).

We therefore achieved the synthesis of the desired product in just one step, with an easy work up and almost quantitative yield.[16]

This method was subsequently applied to the synthesis of several box systems using other enantiomerically pure β-amino alcohols, such as (*S*)-valinol, (*S*)-phenylglycinol, (*S*)-*tert*-leucinol, (*S*)-phenylalaninol, (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol and (*S*)-2-methylphenylglycinol,[17,18] the latter leading to a non-previously described box (Scheme 2).[19]

**Table 1** Results Using Zinc Triflate in the Condensation of 2,2-Dimethylmalononitrile and (*S*)-Phenylglycinol in Toluene

| Amount of $Zn(OTf)_2$ (%) | Ratio of **2a**:**1a** | Box yield (%)[a] |
|---|---|---|
| 5 | –[b] | 0 |
| 30 | 7:1 | 12 |
| 60 | 1:2.5 | 65 |
| 100 | –[c] | 95 |

[a] Determined by $^1H$ NMR.
[b] Only oxazoline **2** was observed.
[c] Only bis(oxazoline) **1** was observed.

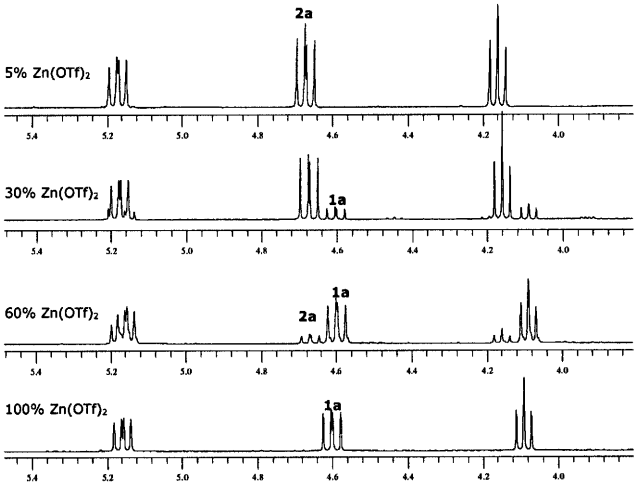
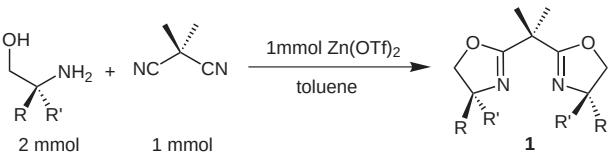



**Figure 1** $^1H$ NMR signals showing **1a**:**2a** ratio in synthesis reactions with several amounts of $Zn(OTf)_2$




R' = H and R = Ph (**a**), $CH_2Ph$ (**b**), $^iPr$ (**c**), $^tBu$ (**d**), Me (**e**), Indanyl (**f**)
R' = Me and R = Ph (**g**),

**Scheme 2**

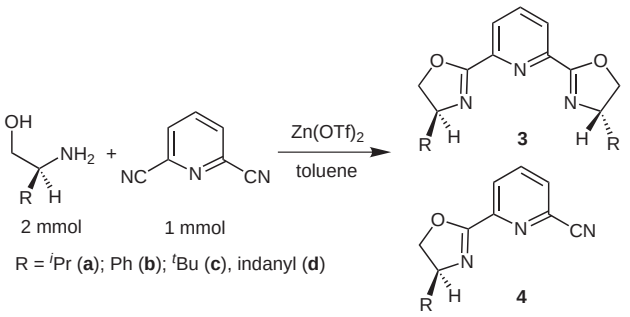
It can be seen from the results in Table 2 that excellent yields were obtained in all cases, even when a quaternary amino alcohol was used. The only change required in this case being an increase in reaction time.

To test this method we decided to try the synthesis of pybox systems (Scheme 3).

We first tried to optimize synthetic conditions using smaller amounts of $Zn(OTf)_2$. As the need of using stoichiometric amounts in box synthesis was due to the formation of strong catalyst–box complex we thought that it could not be the case with pybox ligands.

**Table 2** Synthesis of Box Ligands with Stoichiometric Amounts of Zinc Triflate in Toluene[20]

| Entry | Box ligand | Reaction time (d) | Box (yield, %) |
|---|---|---|---|
| 1 | **1a** | 2 | 95 |
| 2 | **1b** | 2 | 100 |
| 3 | **1c** | 2 | 90 |
| 4 | **1d** | 3 | 90 |
| 5 | **1e** | 2 | 75 |
| 6 | **1f** | 2 | 100 |
| 7 | **1g** | 3 | 85 |




**Scheme 3**

We started with the synthesis of *i*-Pr-pybox (**3a**) and results showed that 5% of catalyst was enough to obtain excellent yields of pybox product **3a** and no pyridine oxazoline **4a** is observed (Table 3 and Figure 2)

The same study was carried out with the rest of pybox ligands. Table 4 gathers the best conditions for each one, best conditions meaning those in which no pyridine oxazoline (**4**) was observed, the minimum amount of catalyst was used and good yields were obtained.[21]

In all cases good yields were achieved in one-pot reactions and pybox ligands were isolated with no need of further purification.

We have described here an easy, efficient, general method for the synthesis of box and pybox ligands in just one step. This method gives high yields using a wide variety of different chiral amino alcohols in stoichiometric amounts. Only catalytic amounts of $Zn(OTf)_2$ are needed in the case of pybox syntheses, which makes the process economically interesting. In the case box ligands, even if a stoichiometric amount of $Zn(OTf)_2$ is necessary, the fact that excess enantiomerically pure β-amino alcohol is not required may be economically advantageous in many cases, given the relative prices of catalyst and some chiral amino alcohols.

Furthermore, the need for product purification is avoided and the method is environmentally friendly (improved atom economy, use of a non-chlorinated solvent, reduced amount of reaction solvent because there is only one synthetic step, and solvents not used in purification steps).

**Table 3** Synthesis of Pybox Ligand **3a** with Zinc Triflate in Toluene

| Amount of $Zn(OTf)_2$ (%) | Ratio of **3a**:**4a**[a] | Pybox yield (%)[a] |
|---|---|---|
| 0.1 | 1:5 | 6 |
| 0.5 | 3.8:1 | 63 |
| 1 | –[b] | 70 |
| 5 | –[b] | 85 |

[a] Determined by $^1$H NMR.
[b] Only pybox **3** was observed.

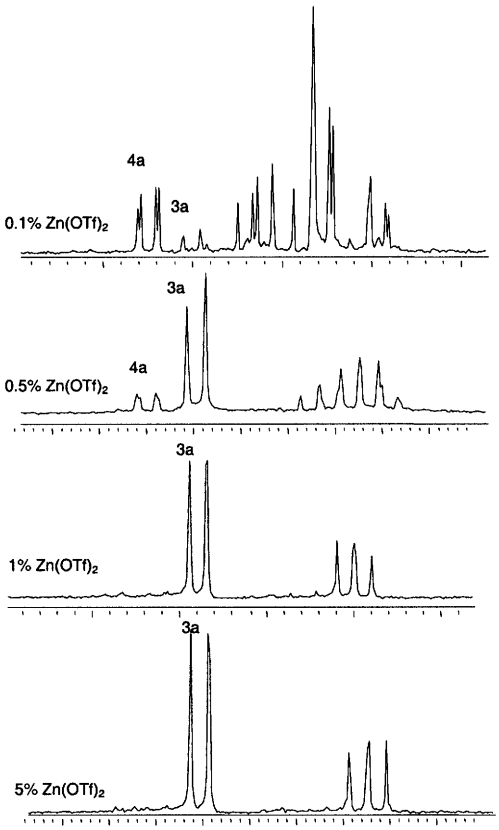



**Figure 2** $^1$H NMR signals showing **3**:**4** ratio in synthesis reactions of **3a** with several amounts of $Zn(OTf)_2$

**Table 4** Optimized Conditions for the Synthesis of Pybox Ligands with Zinc Triflate in Toluene[a,20]

| Entry | R | Amount of $Zn(OTf)_2$ (%) | Yield (%) |
|---|---|---|---|
| 1 | **3a** | 5 | 85 |
| 2 | **3b** | 10 | 75 |
| 3 | **3c** | 10 | 85 |
| 4 | **3d** | 5 | 85 |

[a] Reaction time 2 d.

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(15) The $^1$H NMR signals of the box-$ZnCl_2$ complex were observed.
(16) **General Procedure for the Preparation of Box.**
A 100-mL two-necked round-bottomed flask fitted with a reflux condenser was charged with 2,2-dimethyl malononitrile (564 mg, 6 mmol) and zinc triflate (**2**, 177.4 mg, 6 mmol). The system was purged with argon and anhyd toluene (40 mL) was added. The solution was stirred during 5 min and a solution of the β-amino alcohol (12 mmol) in anhyd toluene (20 mL) was added. The solution was heated under reflux for 48 h [72 h when *tert*-leucinol and (*S*)-2-methylphenylglycinol were used]. The system was allowed to cool. The reaction was then washed with brine (3 × 75 mL) and $NaHCO_3$ (3 × 70 mL), dried with $MgSO_4$ and the solvent evaporated to give pure product.
(17) (*S*)-2-Methylphenylglycinol was obtained from (*S*)-2-methylphenylglycine by the Meyers method: McKennon, M. J.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 3568.
(18) (*S*)-2-Methylphenylglycinol: $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, 3 H), 2.06 (br s, 3 H), 3.59 (dd, 2 H, $J_1$ = 10.68 Hz, $J_2$ = 13.11 Hz), 7.19 (t, 1 H, $J$ = 6.57 Hz), 7.35 (dd, 2 H, $J$ = 6.57 Hz, $J$ = 8.08 Hz), 7.45 (d, 2 H, $J$ = 8.08 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 27.09, 56.38, 71.71, 125.29, 126.85, 128.49, 146.31. $[\alpha]_D^{25}$ 10.97 (*c* 0.75, HCl 1 N). Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.40; H, 8.65; N, 9.31.
(19) 2,2-Bis[4-(*S*)-methyl-4-phenyl-1,3-oxazolinyl]propane: $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.61 (s, 3 H), 1.65 (s, 3 H), 4.25 (dd, 2 H, $J_1$ = 8.08 Hz, $J_2$ = 25.00 Hz), 7.19 (m, 1 H), 7.30 (m, 2 H), 7.35 (m, 2 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 24.47, 28.69, 38.78, 72.47, 80.84, 125.38, 126.85, 128.42, 146.75, 168.50. $[\alpha]_D^{25}$ –5.98 (*c* 1, $CH_2Cl_2$). Anal. Calcd for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 76.06; H, 7.76; N, 7.56..
(20) $^1$H NMR and $[\alpha]_D$ data for box and pybox ligands bearing phenyl, benzyl, isopropyl, *tert*-butyl or indanyl groups were compared with those described in the literature.[7,9,13a,22–24] Purity of those products was verified by elemental analysis.
(21) **General Procedure for the Preparation of Pybox.**
A 100-mL two-necked round-bottomed flask fitted with a reflux condenser was charged pyridine-2,6-dicarbonitrile (774 mg, 6 mmol) and the adequate amount of zinc triflate **(**5% mol for **3a** and **3d** and 10% mol for **3b** and **3c**). The system was purged with argon and anhyd toluene (40 mL) was added. The solution was stirred during 5 min and a solution of the β-amino alcohol (12 mmol) in anhyd toluene (20 mL) was added. The solution was heated under reflux for 48 h. The system was allowed to cool, and reaction was diluted with 50 mL of EtOAc. The solution was then washed with brine (3 × 75 mL) and $NaHCO_3$ (3 × 70 mL), dried with $MgSO_4$ and the solvent evaporated to give pure product.
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