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Application of a Ritter-type Reaction to the Synthesis of Chiral Indane-derived C_2-Symmetric Bis(oxazolines)

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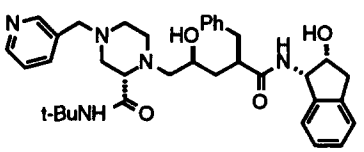
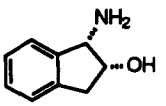
*Summary: Bis(oxazolines) **4**, **6**, **8**, **9**, **10**, and **11** are prepared in a highly regio- and diastereo-selective manner from dinitriles and indanediol **3** in a Ritter-type reaction initiated by trifluoromethanesulfonic acid.*

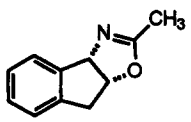
Chiral 2,2'-bis(oxazoline)alkanes and 2-oxazolines have recently been used as ligands in a wide range of transition-metal catalyzed processes.[1] To date the most general approach to these compounds has been *via* an acid derivative or nitrile and the appropriate amino alcohol.[2] As part of the synthesis of the orally active HIV protease inhibitor *Indinavir* [3] we have developed a highly efficient synthesis of the key amino indanol **1** from either indene oxide or diol using a Ritter–type reaction which proceeds *via* oxazoline **2**.[4]



Indinavir

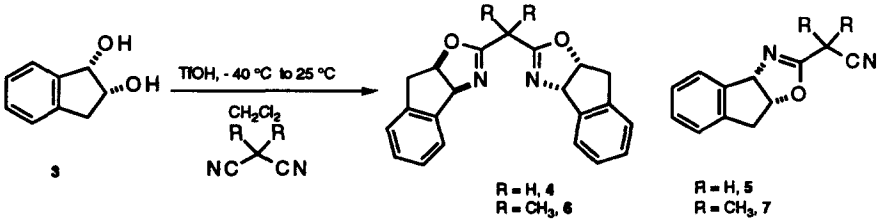


1



2

We reasoned that substitution of malononitrile for acetonitrile should give rise to a C_2-symmetric bis(*cis*-oxazoline) **4** (Scheme). This in fact was the case. When TfOH was added to a mixture of malononitrile and 1*S*, 2*R*-indandiol[4] **3** in dichloromethane at -40 °C the bis(oxazoline) **4** was isolated in 60% yield upon warming the solution to room temperature.[5] The nitrile **5** was isolated in ~10% yield and the only other product observed was 2-indanone.



3

R = H, **4**
R = CH_3, **6**

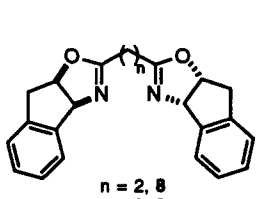
R = H, **5**
R = CH_3, **7**

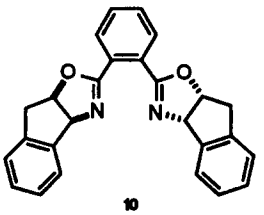
Scheme

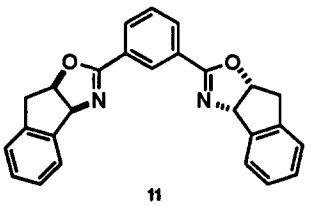
By reducing the concentration and stoichiometry of diol **3** the yield of the nitrile **5** could be increased to 80%. Significantly we have regio- and stereo-selectively introduced two nitrogen atoms and assembled the C_2-symmetric bis(oxazoline) in a single step from simple di-oxygenated materials. On the basis of these results, we next examined dimethylmalononitrile as a partner in this reaction. In this case, the bis(oxazoline) **6** was obtained in a modest 30% yield, the major product being oxazoline **7**. The low yield of **6** presumably reflects the steric hindrance of the neopentyl-type center.

We have demonstrated that this reaction is not restricted to the use of malononitrile derivatives. The dinitrile can be varied providing easy access to bis(oxazoline) ligands having different cone-angles and electronic properties. For example, succinonitrile gave the ethano-bridged ligand **8** and glutaronitrile gave **9** in 54 and 63% isolated

yield respectively. Similarly, 1,2-dicyanobenzene gave bis(oxazoline) **10** in 51% yield and 1,3-dicyanobenzene gave bis(oxazoline) **11** in 49% yield.[6]







These bis(oxazolines) contain a conformationally constrained phenyl glycinol unit[7] which we have recently shown provides high levels of diastereocontrol in Diels-Alder reactions in contrast to acyclic analogues.[8] The facile synthesis of the ligands described in this paper now allows for investigation of the aminoindanol sub-unit as a stereocontrol element in catalytic processes.

In summary, we have described a novel approach for the construction of bis(oxazoline) ligands in a single step from readily available materials. The simplicity of this reaction allows for rapid construction of ligands having different steric and electronic properties. We are currently investigating the use of these ligands in asymmetric Diels–Alder reactions and other catalytic processes. The results from these studies will be reported in due course.

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5. **General Procedure:** To a suspension of *1S,2R*-indan diol (15 mmol) and dinitrile (5 mmol) in dichloromethane (30 mL) at -40 °C was added dropwise trifluoromethanesulfonic acid (45 mmol) to give a homogeneous solution. The reaction was allowed to reach room temperature overnight. The dark solution was cooled to 5 °C and then poured into ice-cold saturated Na_2CO_3. The layers were separated, and the organic layer was washed with sat. Na_2CO_3, then water. The organic phase was dried (Na_2SO_4) and evaporated. Column chromatography on silica gel (ethyl acetate/ hexane) and crystallization (acetonitrile) gave the analytically pure bis(oxazoline). Representative data: **4** $[\alpha]_D^{22}$ -377 (c = 1, CH_2Cl_2); m.p. 215-217 °C; Found: C, 75.98; H, 5.69; N, 8.47; $C_{21}H_{18}N_2O_2$ requires: C, 76.34; H, 5.49; N, 8.48; ^1H NMR (300MHz, $CDCl_3$) δ 7.51-7.42(2H, m), 7.31-7.21(6H, m), 5.57(2H, d, *J* = 9), 5.35(2H, dt, *J* = 9, 1.5), 3.40(2H, dd, *J* = 18, 7.5), 3.28(2H, s), 3.18(2H, dd, *J* = 18, 1). **6** $[\alpha]_D^{22}$ -453 (c = 1, CH_2Cl_2); m.p. 189-190 °C; Found: C, 76.90; H, 6.13; N, 7.68; $C_{23}H_{22}N_2O_2$ requires: C, 77.01; H, 6.19; N, 7.82. ^1H NMR (300MHz, $CDCl_3$) δ 7.52-7.45 (2H, m), 7.30-7.19(6H, m), 5.51(2H, d, *J* = 9), 5.23(2H, dt, *J* = 9, 2.5), 3.29(2H, dd, *J* = 17, 7), 2.93(2H, d, *J* = 17), 1.42(6H, s). The ligands **4** and **6** were found to be identical in all respects to those prepared independently from *1S,2R*-1-amino indan-2-ol, thus establishing both the absolute and relative stereochemistry.
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