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Spotlight 66

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Bisoxazoline (BOX) Ligand-Metal Complexes: An Emerging Chiral Catalyst

Compiled by Ramkrishna Basak

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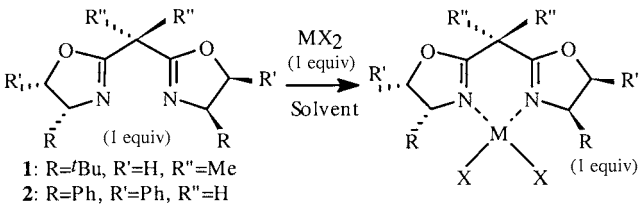
C_2-symmetric chiral bisoxazoline (BOX) ligand-metal complexes have emerged as an effective catalyst for carrying out a wide range of enantioselective reactions.[1] The presence of a C_2-symmetric axis in the bisoxazoline ligands minimizes the number of possible transition states in a particular reaction.[2] Of the various chiral bisoxazoline ligands used, ligands (**1**–**7**) with a one carbon bridging between the oxazoline rings are most frequently utilized. Several research groups have utilized these bisoxazoline ligands in combination with a wide range of mild Lewis acids as catalysts for carrying out different enantioselective reactions.[4–13] Recently, chiral BOX-metal(II) complexes covalently anchored to silica and mesoporous MCM-41 have been used as a new heterogenous catalyst for enantioselective Friedel–Crafts hydroxylation.[14] An intriguing feature of the BOX-metal(II) complexes is that the metal(II)-derived chiral Lewis acids shows pronounced counter ion[15a–c] as well as solvent dependence in context of yield, enantioselectivity, rate, and success of reaction. The selectivity observed is due to the fact that the bisoxazoline ligands form six membered metal chelates which are conformationally constrained and the chiral centers in these ligands are located in close proximity to donor nitrogen, thereby imposing a strong directing effect on the catalytic sites.[16]

Preparation of the catalyst

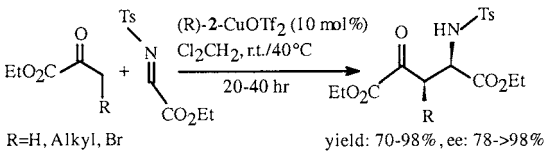
A wide variety of chiral bisoxazoline ligands are commercially available or can be synthesised.[1a,3,14,17]



1: R=*t*Bu, R'=H, R"=Me
2: R=Ph, R'=Ph, R"=H
3: R=Ph, R'=H, R"=Me
4: R=Ph, R'=Ph, R"=Me
5: R=CH_2Ph, R'=H, R"=Me
6: R=*i*Pr, R'=H, R"=Me
7: R=CH_2OH, R'=H, R"=Me

Abstracts

(A) BOX [(*R*)-**2**]-metal complex has been used in highly enantioselective, Mannich reactions[18] of a variety of carbonyl compounds with an *N*-tosyl-α-imino ester to efficiently produce a range of highly functionalized 4-oxo-glutamic acid ester derivatives, which were further used to prepare optically active α-amino-γ-lactones.



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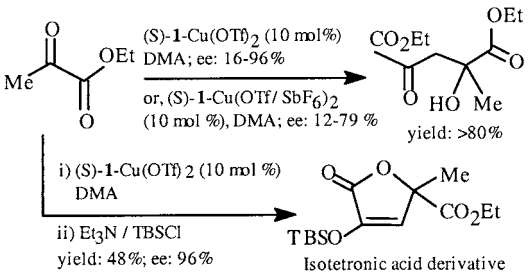
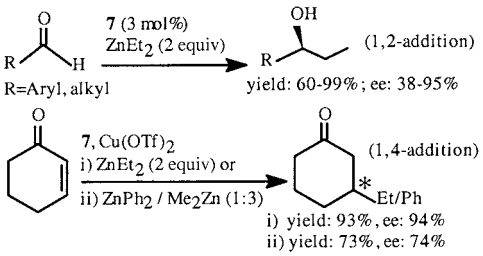
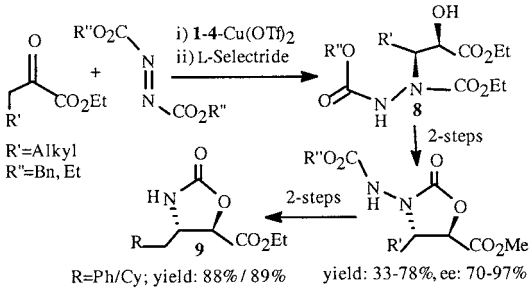
(B) Chiral Lewis acid-BOX [(*S*)-**1**]-metal complex catalyzes a highly enantioselective homo-aldol reaction[19] to give diethyl-2-hydroxy-2-methyl-4-oxo-glutarate in up to 96% enantiomeric excess. This reaction, which mimics the pyruvate dependent aldolase enzymes, was used for the preparation of an optically active, bioactive isotetronic acid derivative.



(C) Enantioselective 1,2-addition of $ZnEt_2$ to aldehydes and 1,4-addition to cyclic enones were accomplished using BOX (**7**)-metal complex as chiral catalyst.[20] In the case of aliphatic aldehydes, both yield and enantioselectivity were increased by the addition of catalytic amounts of butyllithium.



(D) Direct asymmetric catalytic α-amination reaction of 2-keto esters with azodicarboxylates using BOX (**1**–**4**)-metal complexes provides an easy entry to optically active *syn*-β-amino-α-hydroxy esters which form the chiral fragments of many biologically active compounds such as Bestatin, Valinoctin A and the side chain of Taxol analogs.[21] Because of the loss of enantioselectivity of the keto analogue during purification, the keto functionality was stereoselectively reduced by L-Selectride prior to removal of copper catalyst to give **8**, which was then further converted to *syn*-β-amino-α-hydroxy esters masked as oxazolidinones (**9**).



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