Enantioselective Alcohol Synthesis

Effective Modular Iminooxazoline (IMOX) Ligands for Asymmetric Catalysis: [Zn(IMOX)]-Promoted Enantioselective Reduction of Ketones by Catecholborane^{**}

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Chiral catalysts based on readily available chiral ligands are widely used in academia and industry for the synthesis of enantioenriched precursors of materials, sensors, and drugs.^[1] The C_2 -symmetric bisoxazoline (BOX) ligands (Figure 1)



Figure 1. Bisoxazoline (BOX) ligands.

were introduced into asymmetric catalysis by Pfaltz et al.^[2] in their seminal work on semicorrins, and have since been applied to a wide variety of asymmetric transformations.^[3] Indeed, Diels–Alder, aldol, ene, amination, Friedel–Crafts, and other Lewis acid catalyzed reactions are all effectively promoted by chiral metal BOX complexes.^[4] The underlying feature of the aforementioned reactions is substrate activation by two-point binding to the chiral metal BOX complex. Chiral information seems to be poorly transmitted when the two-point binding criterion is not met (i.e., one-point binding).^[5] Hence, the development of a new family of chiral N,N ligands capable of general substrate activation by onepoint binding would be a significant advance in the field of Lewis acid/BOX-mediated reactions.

Earlier we showed that a new catalyst system capable of reducing α -alkoxyketones with up to 82% *ee* is obtained by combining BOX ligands and Zn(OTf)₂ in the presence of catecholborane.^[6] Unfortunately, the reduction of nonchelating ketones led to racemic products, a typical symptom of BOX-mediated processes with two-point binding. We tackled this problem by designing a new family of novel modular^[7]

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author. oxazoline/imine ligands that simulate BOX-type N,N coordination. We first focused on the commercial availability of the necessary chiral building blocks **A–D** containing the oxazoline framework (Figure 2). Aromatic, heterocyclic, and ferro-



Figure 2. Readily available oxazoline frameworks.

cenyl oxazolines are readily available and can be further functionalized without difficulty. We reasoned that introduction of a bulky group near the imino moiety would be the key to efficiently blocking one face of the chiral metal complexes (Figure 3). In addition, free coordination sites on the complex



Figure 3. Blocking one face of the chiral complex with a bulky group.

could be controlled by subtle conformational changes of the bulky group. Hence, we employed a hindered amine bearing aromatic rings, namely, tritylamine, as a bulky group in the synthesis of a variety of iminooxazoline (IMOX) ligands. Oxazolines 1-5 were prepared without difficulty by known procedures.^[8] The aldehyde moiety near the oxazoline ring was introduced by reaction of the corresponding lithium derivatives with DMF (Scheme 1). Facile metalation of benzothienyl- and thienyloxazolines occured with nBuLi, whereas ferrocenyloxazolines required nBuLi/TMEDA. Metalation was achieved by lithium/bromine exchange in the case of the oxazoline obtained from 2-bromobenzonitrile. Aldehydes 6-10 were thus obtained in fair to good yields. To the best of our knowledge, syntheses of 6-10 have not been reported in the literature. This was quite surprising, given the potential utility of aldehyde oxazolines for the preparation of a variety of chiral ligands.^[9] The IMOX ligands 11-15 were obtained by adding tritylamine to a solution of aldehydes 6-10 in CH_2Cl_2 in the presence of magnesium sulfate as a



Scheme 1. Preparation of the IMOX ligands: a) *n*BuLi, Et₂O, -78 °C 30 min, 0 °C 30 min, then DMF, -78 °C; b) TrityINH₂, MgSO₄, CH₂Cl₂, RT; c) *n*BuLi, TMEDA, -78 °C, DMF, -78 °C; d) *n*BuLi, -78 °C, THF, then DMF, -78 °C; e) *n*BuLi, Et₂O, -78 °C, then DMF, -78 °C. TMEDA = *N*,*N*/*N*'-tetramethyethylenediamine.

dehydrating agent (Scheme 1).^[10] The IMOX ligands were isolated after purification by chromatography on triethylamine-deactivated silica gel. However, even under these mild isolation conditions, purification of **14** was complicated by ligand decomposition. Our preliminary studies with the novel IMOX ligands were carried out on the reduction of acetophenone as model substrate with modification of the solvent and the reaction temperature (Table 1, Scheme 2). The

Table 1: Enantioselective reduction of acetophenone promoted by [Zn(IMOX)] complexes.^[a]

Entry	IMOX	Yield [%] ^[b]	T [°C]	ee [%] ^[c]
1	11	86	0	84
2	12	88	0	84
3	11	77	-15	89
4	12	75	-15	90
5	14	_[d]	-15	86
6	13	_[d]	-15	20
7	11	60 ^[e]	0	56
8	11	76 ^[f]	0	77

[a] All the reactions were carried out in anhydrous CH₂Cl₂ at the indicated temperature for 48 h. [b] Yield of isolated product after chromatographic purification. [c] Determined by chiral GC analysis (see Supporting Information for details). The absolute configurations of the products were determined by comparison with analytical data reported in the literature. [d] Not determined. [e] The reaction was performed in Et₂O. [f] The reaction was performed in toluene.



Scheme 2. Asymmetric reduction of acetophenone with catecholborane with promotion by chiral [Zn(IMOX)] complexes.

IMOX ligands gave high enantioselectivities with this nonchelating substrate. The reaction conditions were further optimized with the most readily available ligand **11**, by varying the number of equivalents of reducing agent, temperature, and catalyst loading. A reaction temperature of -15 °C with 1.4 equiv of catecholborane^[11] and 4 mol% [Zn-(IMOX)](OTf)₂ catalyst were found to be optimal. The generality of these optimal conditions is shown in Table 2 and

 Table 2:
 Enantioselective reduction of methylketones catalyzed by
 [Zn(IMOX)] complexes.

Entry ^[a]	Ligand	Ketone	Yield [%] ^[b]	ee of 17 [%] ^[c]
1	15	16a	76	92 (R)
2	12	16 b	80	89 (R)
5	15	16 b	57	93 (R)
3	11	16 c	84	88 (R)
4	12	16 d	83	87 (R)
8	12	16 e	81	86 (R)
2	11	16 f	62	87 (R)
3	15	16 f	70	91 (R)
9	11	16 g	85	86 (R)
10	11	16 h	54	92 (R) ^[d]
11	11	16i	92	53 (R) ^[d]

[a] All reactions were performed at -15 °C in a freezer without stirring. [b] Yield of isolated product after flash chromatography. [c] Determined by chiral GC analysis (see Supporting Information for details). [d] Determined by chiral HPLC analysis (Chiralcel OD column).

Scheme 3. Various aromatic methylketones were reduced in good-to-excellent yields and with excellent enantiomeric excesses. Other aromatic alkyl ketones were also reduced in good yield, although the results were inferior in terms of enantioselectivity.^[12] High *ee* values (86–93 %) were obtained with *p*-substituted aromatic acetyl ketones. Electron-withdrawing groups accelerate the reactions considerably, while



Scheme 3. Asymmetric reduction of methyl ketones promoted by IMOX ligands 11, 12, and 15.

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electron-donating groups decrease the reaction rates. It is noteworthy that IMOX ligands 11 and 12 give virtually identical enantiomeric excesses in the reduction of acetophenone. Hence, these ligands were used interchangeably throughout our work. Benzo[b]thiophene-derived ligand 15 appeared to give slightly better results, but its synthesis is more laborious than those of 11 and 12. Unsaturated ketones are chemoselectively and enantioselectively reduced by this system (Table 2, entry 10). We believe that the new IMOX ligands create a suitable chiral pocket in which the methylketones are coordinated such that nonbonding interactions are minimized (Figure 3, $R^3 = aryl$). The trityl group serves to control the size of the pocket and hinder the approach of the reducing agent to one face of the substrate $\bar{[^{\bar{1}3]}}$ Our work suggests that hindered aromatic amines can be effectively used as elements of stereocontrol in the design of effective, novel catalysts.

In summary we have synthesized, in a modular fashion, a novel class of chiral iminooxazoline (IMOX) ligands capable of effectively promoting enantioselective reductions of aromatic methyl ketones with good enantioselectivity (86–93% *ee*). This facile synthetic approach to IMOX ligands may lend itself to the creation of large libraries of these compounds. The application of IMOX ligands to other asymmetric transformations is currently under investigation in our laboratories.

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- [13] To stress the importance of the hindered trityl group next to the imino moiety, IMOX ligands prepared from different aromatic and aliphatic amines were studied in the enantioselective reduction of acetophenone under the optimized reaction conditions. However, only racemic products or low enantiomeric excesses were obtained (see Supporting Information).