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)

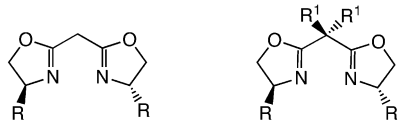

Figure 1. Bisoxazoline (BOX) ligands.

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 one-point 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] 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 ferrocenyl 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 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 *n*BuLi, whereas ferrocenyloxazolines required *n*BuLi/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

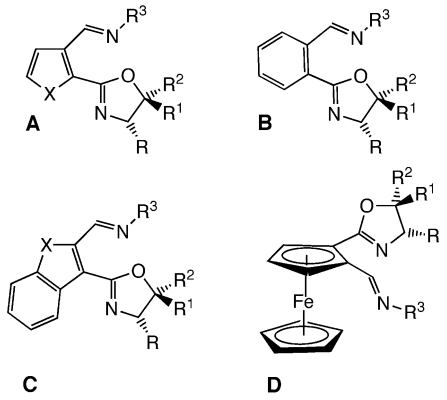

Figure 2. Readily available oxazoline frameworks.

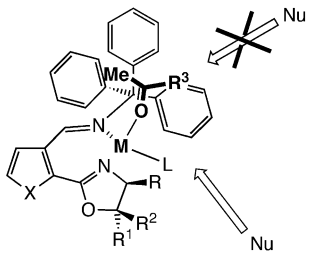

Figure 3. Blocking one face of the chiral complex with a bulky group.

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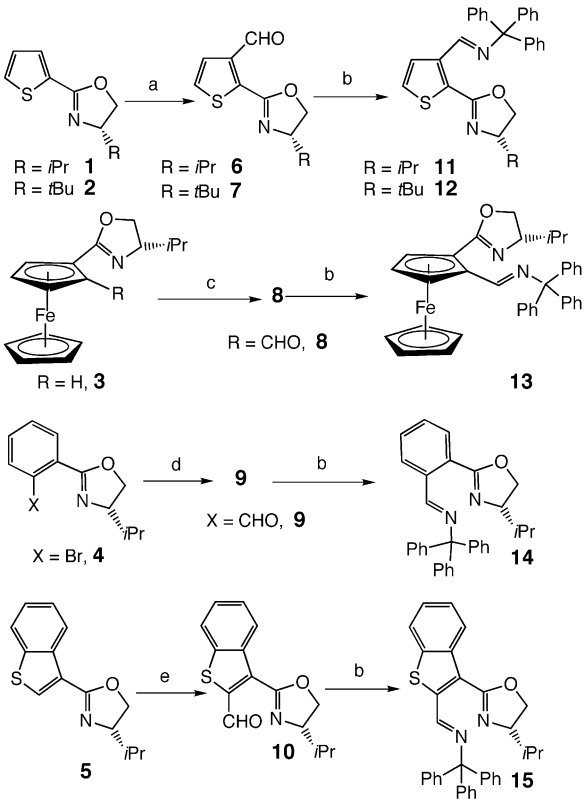


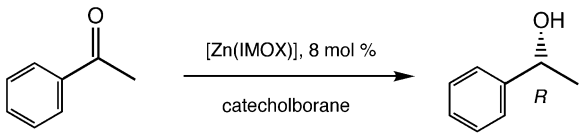
Scheme 1. Preparation of the IMOX ligands: a) *n*BuLi, Et_2O, −78 °C 30 min, 0 °C 30 min, then DMF, −78 °C; b) TritylNH$_2$, $MgSO_4$, CH_2Cl_2, RT; c) *n*BuLi, TMEDA, −78 °C, DMF, −78 °C; d) *n*BuLi, −78 °C, THF, then DMF, −78 °C; e) *n*BuLi, Et_2O, −78 °C, then DMF, −78 °C. TMEDA = *N*,*N*,*N*′*N*′-tetramethyethylenediamine.

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 CH_2Cl_2 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 Et_2O. [f] The reaction was performed in toluene.



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

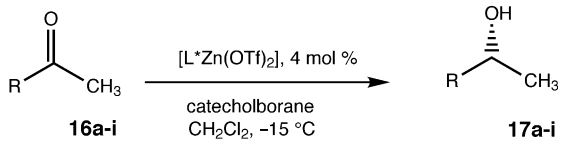
IMOX ligands gave high enantioselectivities with this non-chelating substrate. The reaction conditions were further optimized with the most readily available ligand **11**, by varying the number of equivalents of reducing agent, temperature, and catalyst loading. A reaction temperature of −15 °C with 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**	**16b**	80	89 (*R*)
5	**15**	**16b**	57	93 (*R*)
3	**11**	**16c**	84	88 (*R*)
4	**12**	**16d**	83	87 (*R*)
8	**12**	**16e**	81	86 (*R*)
2	**11**	**16f**	62	87 (*R*)
3	**15**	**16f**	70	91 (R)
9	**11**	**16g**	85	86 (*R*)
10	**11**	**16h**	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



16a R = Ph,
16b R = *p*-F-Ph,
16c R = *p*-Cl-Ph,
16d R = *p*-Br-Ph,
16e R = *p*-CF_3-Ph,
16f R = *p*-Me-Ph,
16g R = α-Naphtyl,
16h R = CH=CHPh,
16i R = CH_2CH_2Ph,

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

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.[13] 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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[1] H.-U. Blaser, *Chem. Commun.* **2003**, 293–296.
[2] A. Pfaltz, *Synlett* **1999**, 835–843.
[3] T. P. Yoon, E. N. Jacobsen, *Science* **2003**, *299*, 1691–1693.
[4] For recent examples of C_2 bisoxazoline–Lewis acid complexes as catalysts, see a) J. S. Johnson, D. A. Evans, *Acc. Chem. Res.* **2000**, *33*, 325–335; b) N. Gathergood, W. Zhuang, K. A. Jørgensen, *J. Am. Chem. Soc.* **2000**, *122*, 12517–12522; c) K. B. Jensen, J. Thorhauge, R. G. Hazell, K. A. Jørgensen, *Angew. Chem.* **2001**, *113*, 164–167; *Angew. Chem. Int. Ed.* **2001**, *40*, 160–163; d) H. Audrain, K. A. Jørgensen, *J. Am. Chem. Soc.* **2000**, *122*, 11543–11544; e) K. Juhl, N. Gathergood, K. A. Jørgensen, *Angew. Chem.* **2001**, *113*, 3083–3085; *Angew. Chem. Int. Ed.* **2001**, *40*, 2995–2997; f) K. R. Knudsen, T. Risgaard, N. Nishiwaki, K. V. Gothelf, K. A. Jørgensen, *J. Am. Chem. Soc.* **2001**, *123*, 5843–5844; g) N. Nishiwaki, K. R. Knudsen, K. V. Gothelf, K. A. Jørgensen, *Angew. Chem.* **2001**, *113*, 3080–3083; *Angew. Chem. Int. Ed.* **2001**, *40*, 2992–2995; h) K. Juhl, K. A. Jørgensen, *J. Am. Chem. Soc.* **2002**, *124*, 2420–2421; i) J. Thorhauge, M. Roberson, R. G. Hazell, K. A. Jørgensen, *Chem. Eur. J.* **2002**, *8*, 1888–1898; j) D. A. Evans, M. C. Kozlowski, J. A. Murry, C. S. Burgey, K. R. Campos, B. T. Connell, R. J. Staples, *J. Am. Chem. Soc.* **1999**, *121*, 669–685; k) D. A. Evans, C. S. Burgey, M. C. Kozlowski, S. W. Tregay, *J. Am. Chem. Soc.* **1999**, *121*, 686–699; l) D. A. Evans, K. A. Scheidt, J. N. Johnston, M. C. Willis, *J. Am. Chem. Soc.* **2001**, *123*, 4480–4491; m) D. A. Evans, D. M. Barnes, J. S. Johnson, T. Lectka, P. von Matt, S. J. Miller, J. A. Murry, R. D. Norcross, E. A. Shaughnessy, K. R. Campos, *J. Am. Chem. Soc.* **1999**, *121*, 7582–7594; n) D. A. Evans, S. J. Miller, T. Lectka, P. von Matt, *J. Am. Chem. Soc.* **1999**, *121*, 7559–7573; o) D. A. Evans, T. Rovis, M. C. Kozlowski, J. S. Tedrow, *J. Am. Chem. Soc.* **1999**, *121*, 1994–1995.
[5] Copper–PyBOX complexes promote enantioselective Diels–Alder reactions of monodentate dienophiles.[4m]
[6] M. Bandini, P. G. Cozzi, M. DeAngelis, A. Umani-Ronchi, *Tetrahedron Lett.* **2000**, *41*, 1601–1605.
[7] For efficient modular ligands, see a) H. Deng, M. P. Isler, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **2002**, *114*, 1051–1054; *Angew. Chem. Int. Ed.* **2002**, *41*, 1009–1012; b) C. A. Luchaco-Cullis, H. Mizutani, K. E. Murphy, A. H. Hoveyda, *Angew. Chem.* **2001**, *113*, 1504–1508; *Angew. Chem. Int. Ed.* **2001**, *40*, 1456–1460; c) K. D. Shimizu, B. M. Cole, C. A. Krueger, K. W. Kuntz, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **1996**, *108*, 1776–1779; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1668–1674; d) I. Chataigner, C. Gennari, U. Piarulli, S. Ceccarelli, *Angew. Chem.* **2000**, *112*, 953–956; *Angew. Chem. Int. Ed.* **2000**, *39*, 916–918; e) J. Blankenstein, A. Pfaltz, *Angew. Chem.* **2001**, *113*, 4577–4579; *Angew. Chem. Int. Ed.* **2001**, *40*, 4445–4447.
[8] Oxazoline **3:** M. Peer, J. C. de Jong, M. Kiefer, T. Langer, H. Rieck, H. Schell, P. Sennhenn, J. Sprinz, H. Steinhagen, B. Wiese, G. Helmchen, *Tetrahedron* **1996**, *52*, 7547–7583. Oxazoline **4:** C. J. Richards, A. W. Mulvaney, *Tetrahedron: Asymmetry* **1996**, *7*, 1419–1430. Oxazolines **1, 2**, and **5**: a) P. G. Cozzi, F. Menges, S. Kaiser, *Synlett* **2003**, 833–836; b) L. F. Tietze, J. K. Lohmann, *Synlett* **2002**, 2083–2085.
[9] Modular ligands described by Hoveyda, Snapper, et al. were prepared by condensation between aldehydes bearing a coordinating group and chiral amines.[7] See also a) N. S. Josephsohn, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2003**, *125*, 4018–4019; b) K. E. Murphy, A. H. Hoveyda, *J. Am. Chem. Soc.* **2003**, *125*, 4690–4691.
[10] We have obtained a preliminary crystal structure for IMOX ligand **13**. The absolute planar chiral configuration was assigned on the basis of the crystal structure (P. G. Cozzi, M. Monari, S. Selva, unpublished results).
[11] Other reducing agents (silanes, BH_3, poly(methylhydroxysiloxane) (PMSH)) were also studied. However, racemic products or low enantiomeric excesses were obtained in the reduction of acetophenone. For enantioselective reduction of ketones by metal complexes and catecholborane, see a) W.-S. Huang, Q.-S. Hu, L. Pu, *J. Org. Chem.* **1999**, *64*, 7940–7956; b) A. J. Blake, A. Cunningham, A. Ford, A. J. Teat, S. Woodward, *Chem. Eur. J.* **2000**, *6*, 3586–3594; c) I. Sarvary, F. Almqvist, T. Frejd, *Chem. Eur. J.* **2001**, *7*, 2158–2166.
[12] The following aromatic ketones were reduced under the optimized reaction conditions: phenyl isopropyl ketone (60% yield, 49% *ee*), isovalerophenone (82% yield, 78% *ee*), α-bromoacetophenone (76% yield, 76% *ee*), and butyrophenone (84% yield, 85% *ee*).
[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).

