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BINOL–Salen Metal Catalysts Incorporating a Bifunctional Design

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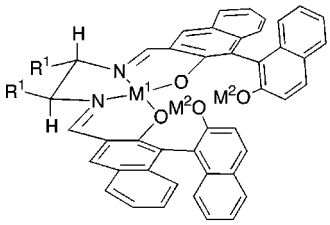
ABSTRACT



Salen metal complexes incorporating two chiral BINOL moieties have been synthesized and characterized crystallographically. The corresponding bisnaphthoxide complexes have been found to catalyze the asymmetric addition of benzyl malonate to cyclohexenone in up to 90% ee. With these modular catalysts, the Lewis acid and Bronsted base portions can be independently altered.

A number of recent studies have shown that multifunctional ligands possess useful characteristics for catalysis and asymmetric synthesis.[1] For example, ligands have been reported in which one portion engages a Lewis acid moiety that coordinates an electrophilic substrate while another portion of the ligand coordinates to the nucleophilic substrate partner. The positioning by such a catalyst assembly of the two reactant partners in close proximity and with the correct relative geometry facilitates a reaction in a manner similar to that of some enzyme catalysts (i.e., ligases). Dual coordination by such catalyst assemblies further enables the reaction by simultaneously enhancing the electrophilic character of one partner and the nucleophilic character of the other partner.[2]

An example of this motif can be found in the heterobimetallic complexes (**1**, Figure 1) developed by Shibasaki and co-workers.[1c,d] In these complexes, the central lanthanide metal is proposed to coordinate the electrophile while the hemilable BINOLate oxygens deprotonate the nucleophile.

While several bifunctional ligands that operate along these lines have been discovered,[1,3] relatively few examples exist in which separate and distinct sites are present for individual activation of the electrophilic and nucleophilic portions.[4] One of the earliest examples of this latter motif can be found in

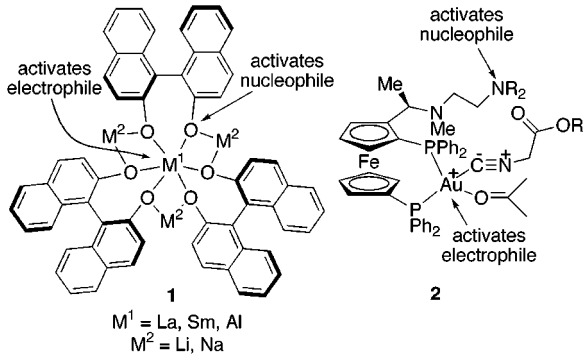


Figure 1.

(1) (a) Corey, E. J.; R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551−5553. (b) Kitamura, M.; Suga, S.; Niwa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 4832−4842. (c) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236−1256. (d) Kim, Y. S.; Matsunaga, S.; Das, J.; Sekine, A.; Oshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6506−6507 and references therein. (e) Gample, M. P.; Smith, A. R. C.; Wills, M. *J. Org. Chem.* **1998**, *63*, 6068−6071. (f) Yamakawa, M.; Ito, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 1466−1478 and references therein. (g) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003−12004. (h) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573−575 and references cited herein.

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complex **2** developed by Hayashi and Ito,[4a] which catalyzes the aldol reaction of isocyanoacetates and aldehydes.

The goal of the present work is to construct scaffolds in which the Lewis acid and base elements can be independently manipulated. In particular, new compounds can be envisioned with functional groups specifically tailored to the nucleophile and electrophile of a given reaction *and* with the optimal spacing and orientation between groups. The structurally well-defined and rigid salen scaffold was chosen as a starting point, leading to general structure **3** (Figure 2). An apical

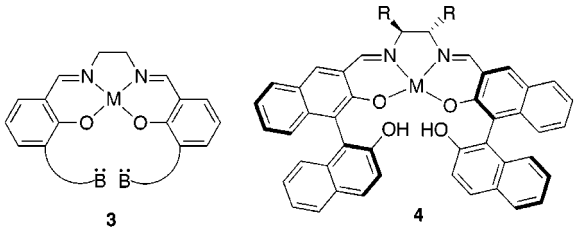


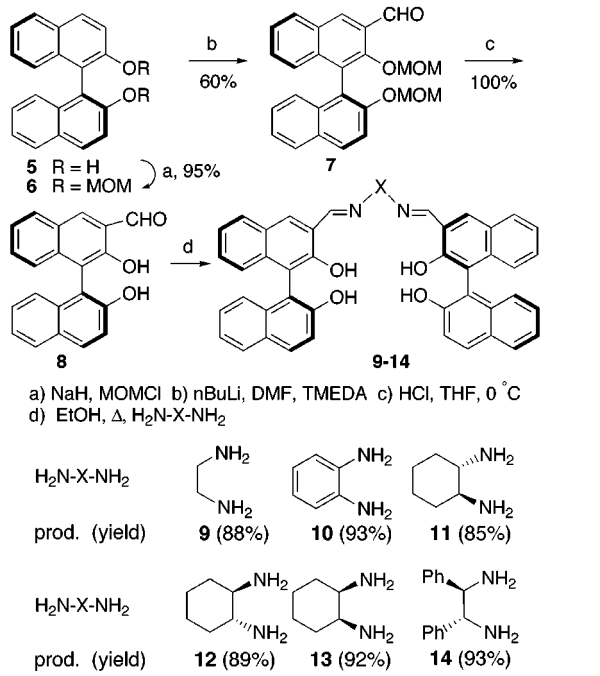
Figure 2.

coordination sight at the salen metal center could act as the docking site for a Lewis basic substrate. In addition, the ease of preparation and derivatization of the salen backbone is ideal for the rapid construction of many ligands.

The tether connecting the salen to the basic functional group must be short and/or rigid enough to prevent internal complexation to the metal. In this Letter, the synthesis and utility of salen **4** incorporating a BINOL structure is presented. For **4**, the biaryl bond provides the requisite tether which prevents complexation of the free naphthols to the metal center but positions them close to substrates bound to the salen metal.

BINOL−salen ligands **9**−**14** were prepared in four steps as shown in Scheme 1. Aldehyde **7**[5] was readily generated from (*S*)-BINOL by lithiation and acylation of the bisprotected derivative **6**. Cleavage of the MOM ethers then provided the requisite aldehyde **8** which underwent ready condensation with various diamines to provide salens **9**−**14**. The three diastereomeric salen compounds **11**, **12**, and **13**,[6] derived from diaminocyclohexane, were prepared in order

Scheme 1



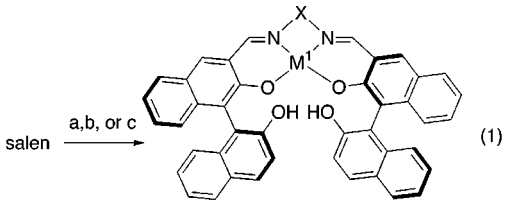
a) NaH, MOMCl b) nBuLi, DMF, TMEDA c) HCl, THF, 0 °C
d) EtOH, Δ, H_2N-X-NH_2

H_2N-X-NH_2			
prod. (yield)	**9** (88%)	**10** (93%)	**11** (85%)
H_2N-X-NH_2			
prod. (yield)	**12** (89%)	**13** (92%)	**14** (93%)

to determine whether the diamine or BINOL portion of the catalyst is the key feature controlling the transfer of asymmetry.

The M[1]−BINOL−salen complexes (**15**−**25**) incorporating Ni(II), Cu(II), Zn(II), or Pd(II) were prepared from the corresponding metal salts as shown in Table 1. Nickel, copper, zinc, and palladium were chosen on the basis of their affinity for nitrogen, to promote the salen binding mode over

Table 1. Formation of M[1]−BINOL−Salen Complexes (eq 1)



a) $Ni(OAc)_2$, EtOH, Δ b) $Cu(OAc)_2$, EtOH/H_2O, Δ
c) Et_2Zn, THF/toluene d) $Pd(OAc)_2$, MeONa, MeOH

salen	conditions	M[1]	M[1]−salen complex	% yield
9	a	Ni	**15**	65
9	b	Cu	**16**	92
9	c	Zn	**17**	in situ
9	d	Pd	**18**	87
10	a	Ni	**19**	88
11	a	Ni	**20**	83
11	b	Cu	**21**	86
12	a	Ni	**22**	85
12	b	Cu	**23**	85
13	a	Ni	**24**	74
14	a	Ni	**25**	84

(2) For reviews on bifunctional catalysis, see: Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857−871. van den Beuken, E. K.; Feringa, B. L. *Tetrahedron* **1998**, *54*, 12985−13011. Rowlands, G. J. *Tetrahedron* **2001**, *57*, 1865−1882.

(3) For other heterobimetallic catalysts, see the following. Al·Li: (a) Keller, E.; Veldman, N.; Spek, A. L.; Feringa, B. L. *Tetrahedron: Asymmetry* **1997**, *8*, 3403−3413. (b) Arai, T.; Hu, Q.; Zheng, X.; Pu, L.; Sasai, H. *Org. Lett.* **2000**, *2*, 4261−4263. (c) Manickam, G.; Sundarajan, G. *Tetrahedron* **1999**, *55*, 2721−2736. (d) Sundararajan, G.; Prabagaran, N. *Org. Lett.* **2001**, *3*, 389−392. Zn·Li: (e) Nina, S.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2717−2720.

(4) (a) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405−6406. (b) Kitajima, H.; Ito, K.; Aoki, Y.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 207−217. (c) Sibi, M. P.; Cook, G. R.; Liu, P. *Tetrahedron Lett.* **1999**, *40*, 2477−2480. (d) Hamashima, Y.; Sawada, D.; Nogami, H.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2001**, *57*, 805−814 and references therein. (e) Ooi, T.; Kondo, Y.; Maruoka, K. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1183−1185.

an undesired mode involving coordination to only the BINOL components. Consistent with formation of the desired complexes, a lower C═N stretch in the IR spectra of the complexes relative to that of the free salen was observed. Also, a C_2-symmetry element is indicated from the ^{13}C NMR spectrum of the Ni− and Pd−BINOL−salen complexes.

An X-ray crystal structure of the nickel complex **22** provided further evidence for the structure of the salen metal complex. Two conformational forms of the salen were observed in the unit cell, one of which is illustrated in Figure 3. In this structure, the ancilliary naphthols adopt a parallel

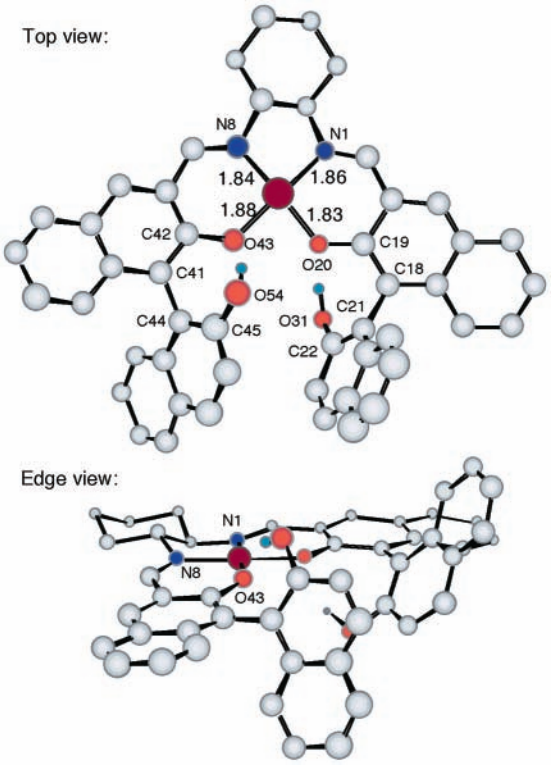


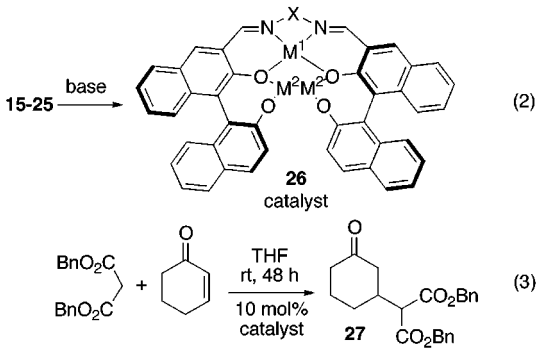
Figure 3. X-ray crystal structure of **22**. Non-heteroatom hydrogens and solvent molecules omitted for clarity. Selected distances and angles: O20−O31 2.65 Å, O43−O54 2.60 Å, C45−O54−O43 92.1°, C22−O31−O20 89.6°, C42−C41−C44−C45 56.3(1)°, C19−C18−C21−C22 53.0(1)°.

arrangement with one naphthoate oxygen above and one below the plane of the salen. The hydrogens on these naphthols hydrogen bond with the metal-bound oxygen of each BINOL fragment.

Formation of the Li, Na, K, or Cs naphthoxides of M^1−BINOL−salen complexes **15**−**25** would provide heterobimetallic metal complexes **26**. From the trends observed in the crystal structure of the protonated form, interactions between the naphthoate anion and the salen oxygens are likely to be weak.[7] As a result, it should be possible to modulate the reactivity of the salen Lewis acid and the naphthoate base independently.

The BINOL−salen−metal complexes were examined in the Michael reaction[8] of cyclohexenone with benzyl malonate (Table 2). The active catalysts, **26a**−**26l** were generated from

Table 2. Salen Naphthoxide Complexes (eq 2) in the Michael Addition Reaction (eq 3)



entry	catalyst	M^1	M^2	base	% yield[a]	% ee[b]
1	**15**	Ni	H		0	
2	**26a**	Ni	Li	NaOtBu	20	2 (*S*)
3	**26b**	Ni	Na	LiOtBu	55	7 (*R*)
4	**26c**	Ni	K	KOtBu	75	15 (*R*)
5	**26d**	Ni	Cs	Cs_2CO_3	80	31 (*R*)
6	**26e**	Cu	Cs	Cs_2CO_3	73	31 (*R*)
7	**26f**	Zn	Cs	Cs_2CO_3	57	8 (*R*)
8	**26g**	Pd	Cs	Cs_2CO_3	70	10 (*R*)
9	**26h**	Ni	Cs	Cs_2CO_3	49	31 (*R*)
10	**26i**	Ni	Cs	Cs_2CO_3	84	54 (*R*)
11	**26j**	Ni	Cs	Cs_2CO_3	79	71 (*R*)
12	**26k**	Ni	Cs	Cs_2CO_3	88	42 (*R*)
13	**26l**	Ni	Cs	Cs_2CO_3	83	21 (*R*)

[a] Isolated yields. [b] Enantiomeric excess determined by HPLC. Absolute configuration based on optical rotation values.

the preformed M^1−BINOL−salen complexes **15**−**25** via treatment with the indicated base in THF[9] prior to addition of the reaction substrates. Beginning with Ni(II)−salen complex **15**, the effects of M^2 were examined (entries 1−5, Table 2).[10] Replacement of both phenolic protons with a

(5) Matsunaga, S.; Das, J.; Roels, J.; Vogl, E. M.; Yamamoto, N.; Iida, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2000** *122*, 2252−2260.

(6) The BINOL portion of salen **13** is anticipated to create a chiral conformation in the achiral diamine portion. See: Balsells, J.; Walsh, P. J. *J. Am. Chem. Soc.* **2000**, *122*, 1802−1803.

(7) In the second structure in the unit cell, the ancilliary naphthols adopt a nonparallel arrangement while most of the other features are the same as the first structure. Once again, one naphthoate oxygen is above the plane and one below the plane of the salen; however, only one of the naphthols forms an intramolecular hydrogen bond with the salen nucleus. The second naphthol participates in an intermolecular hydrogen bond with a naphthoate oxygen from the other complex in the unit cell. See Supporting Information for full details.

(8) For recent reviews, see: (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Chapter 31. (b) Leonard, J.; Ciez-Barra, E.; Merino, S. *Eur. J. Org. Chem.* **1998**, 2051−2061.

(9) Of the solvents examined with the Ni•Cs−BINOL−salen catalyst **26d** (toluene, THF, CH_2Cl_2, CH_3CN, DMF), THF gave the best results.

(10) The role of anion of the base used to provide M^2 in the catalyst is not clear (KOtBu vs Cs_2CO_3).

divalent metal (M^1:M^2 = 1:1) such as Zn, Mg, and Ca was ineffective. Presumably, a stable tetrahedral complex forms between the four BINOL oxygens, rendering the naphthoates ineffective as bases.

Next, the effects of M^1 were examined with M^2 = Cs held constant (entries 5−8). Among the various metal combinations examined, the Ni·Cs−BINOL−salen catalyst **26d** gave the best result (entry 5).

Exchanging the ethylenediamine linker in the Ni·Cs−BINOL−salen catalyst with a diaminobenzene or a diphenyl ethylene linker resulted in a less effective catalyst (entries 9 and 13 vs entry 5). Switching to a *cis*-diaminocyclohexane linker resulted in a more effective catalyst (entry 12 vs entry 5). Finally, the *trans*-diaminocyclohexane derivatives **26i** and **26j** (Figure 4) were examined (entries 10 and 11, Table 2).

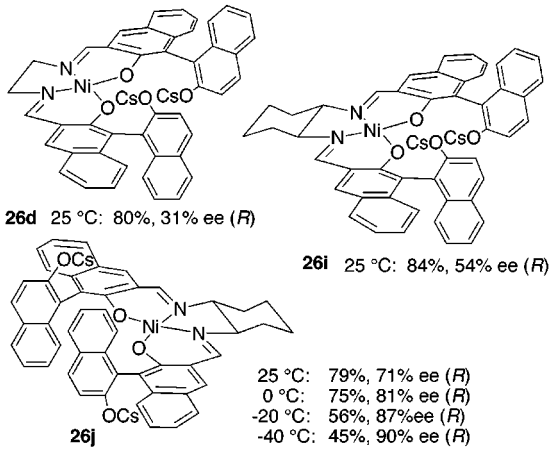


Figure 4.

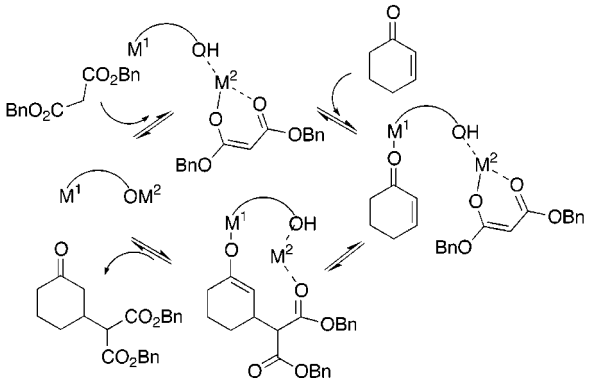
The latter proved to be the matched catalyst system, providing the Michael adduct in 71% ee (entry 11). Upon cooling the reaction to −40 °C, the Michael adduct is obtained in up to 90% ee with 10 mol % of **26j** (Figure 4).[11]

Contrary to expectations, catalysts differing in the configuration of the bisimine backbone afforded the same prevailing enantiomer in the product (Figure 4). Furthermore, all of the Ni·Cs−BINOL−salen catalysts containing a diaminocyclohexane backbone catalyzed the reaction with improved selectivity over that of Ni·Cs−BINOL−salen catalyst **26d** containing an ethylenediamine backbone. As such, the chirality in the biaryl axis appears to be the dominant control element responsible for facial selectivity.

A possible catalytic cycle for the Michael reaction is depicted in Scheme 2. Deprotonation of the dibenzyl malonate by the naphthoate anion would yield a malonate anion held in proximity to the salen via coordination through the naphthoate counterion (i.e., Cs). Coordination of the cyclohexenone to an apical site of the Ni−salen complex would activate the electrophile in close proximity to this nucleophile, allowing the Michael addition to occur. Proton

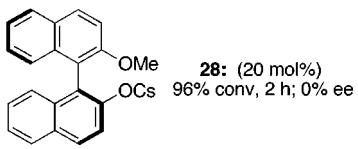
(11) Reaction time was 48 h at 20 and 0 °C and 5 d at −20 and −40 °C.

Scheme 2. Possible Catalytic Cycle for the Catalyzed Michael Reaction



transfer from the naphthol to the enolate intermediate would then allow product release and catalyst regeneration.

Several control reactions were conducted in order to determine whether the mechanism outlined in Scheme 2 is reasonable for these reactions. First, the Lewis acid center alone is not sufficient to ensure reactivity, since Ni−BINOL−salen **15** is completely ineffective as a catalyst (Table 2, entry 1). While a rapid reaction was obtained with BINOL-derived Cs-naphthoxide **28**, the lack of selectivity



with **28** suggests that a Cs-naphthoxide base alone is not a sufficient determinant for good enantioselectivity. Rather, the entire Ni·Cs−BINOL−salen assembly is required for selectivity. Finally, a decrease in yield and enantioselectivity is observed upon switching from the Ni·Cs−BINOL−salen catalyst **26d** to the Pd·Cs−BINOL−salen catalyst **26g** (Table 2, entry 8 vs entry 5). This result is consistent with the proposed catalytic cycle since Pd(II) is less Lewis acidic than Ni(II).

In conclusion, several novel salen complexes have been synthesized and characterized. These complexes were effective catalysts for the Michael reaction. Significant enantioselective cooperative effects between different components of these modular ligands have been observed. The Ni·Cs−BINOL−salen complexes show promise as chiral catalysts for asymmetric synthesis.

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Supporting Information Available: Experimental details and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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