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Catalysis of the Michael Addition Reaction by Late Transition Metal Complexes of BINOL-Derived Salens

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Salen metal complexes incorporating two chiral BINOL moieties have been synthesized and characterized by X-ray crystallography. The X-ray structures show that this new class of Ni-BINOL-salen catalysts contains an unoccupied apical site for potential coordination of an electrophile and naphthoxides that are independent from the Lewis acid center. These characteristics allow independent alteration of the Lewis acidic and Brønsted basic sites. These unique complexes have been shown to catalyze the Michael reaction of dibenzyl malonate and cyclohexenone with good selectivity (up to 90% ee) and moderate yield (up to 79% yield). These catalysts are also effective in the Michael reaction between other enones and malonates. Kinetic data show that the reaction is first order in the Ni·Cs-BINOL-salen catalyst. Further experiments probed the reactivity of the individual Lewis acid and Brønsted base components of the catalyst and established that both moieties are essential for asymmetric catalysis. All told, the data support a bifunctional activation pathway in which the apical Ni site of the Ni·Cs-BINOL-salen activates the enone and the naphthoxide base activates the malonate.

Introduction

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 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 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**) developed by Shibasaki et al. (Figure 1).[1c,d] In these complexes, the central lanthanide metal is proposed to coordinate the electrophile while the hemilable BINOLate oxygens deprotonate the nucleophile.

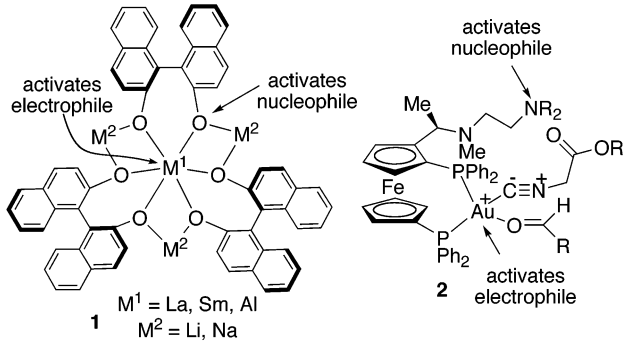

FIGURE 1. Bifunctional catalysts.

While several bifunctional ligands that operate along these lines have been discovered,[1,3] relatively few examples exist in which electronically decoupled sites are present for individual activation of the electrophilic and nucleophilic substrates.[4] One of the earliest examples of this latter motif can be found in complex **2** developed by Hayashi and Ito,[4a] which catalyzes the aldol reaction between isocyanoacetates and aldehydes. Complex **2** contains a gold metal site that coordinates both the

(1) (a) Corey, E. J.; Bakshi, 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.

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

(3) For other bimetallic catalysts, see: (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. (Zn·Zn) (f) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367−3368. (g) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466−2467.

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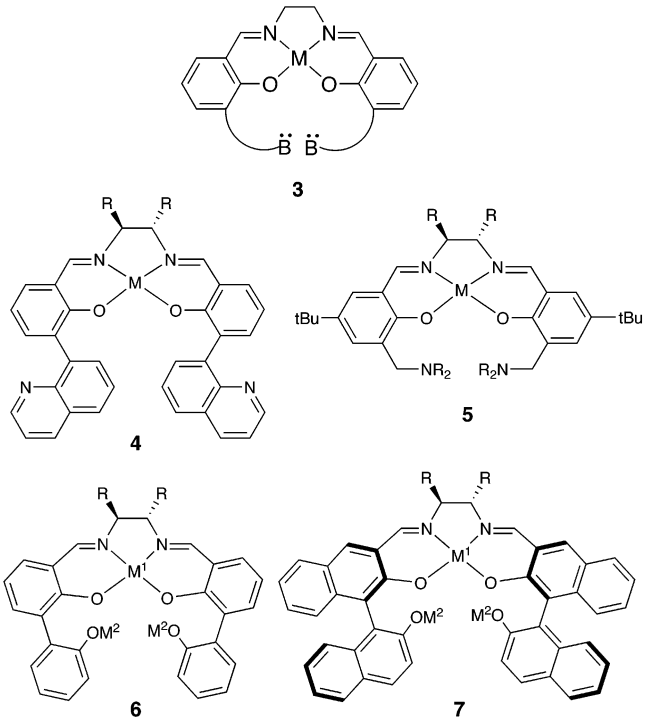


FIGURE 2. Bifunctional salen catalysts.

isocyanoacetate and the aldehyde while the pendant amine moiety effects the enolization of the isocyanoacetate. Even so, the potential for catalyst deactivation by coordination of the pendant amine to the gold center arises in such a system.

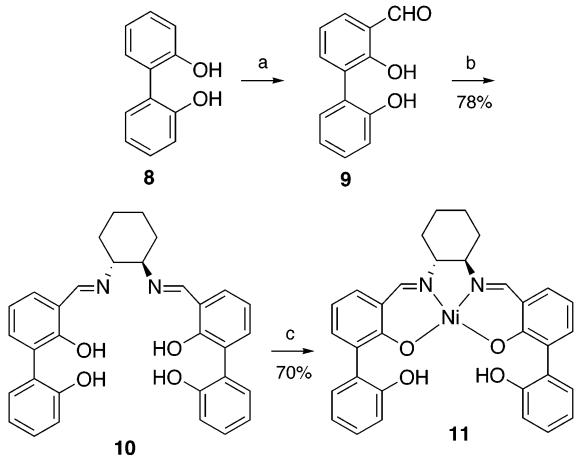
We directed our efforts to the construction of catalyst systems in which the Lewis acid and Brønsted base functional groups can be tailored independently. The catalyst design began from general structure **3** (Figure 2), which incorporates a basic moiety into a structurally well-defined and rigid salen complex. The salen scaffold was chosen because these salens (**4**−**7**) are easily made and their modular nature allows the rapid synthesis of several analogues. In addition, the functionalized salen complexes provide an accessible Lewis acid center for electrophile activation and a basic functional group for activation of the nucleophile. Finally, the acidic and basic sites are electronically decoupled and can be independently attenuated. In prior work, we found that structures **4** and **5** function as potent Lewis acid/Lewis base catalysts,[5] but were poor Lewis acid/Brønsted base catalysts.[6] Herein, we focus on the evaluation of structures **6** and **7** as Lewis acid/Brønsted base catalysts.

An important structural consideration in the design of these bifunctional scaffolds was the nature of the tether connecting the salen to the basic functional group. This tether must be sufficiently short and/or rigid to prevent internal complexation of the Brønsted base to the Lewis acid. Compounds **6** and **7** are inherently rigid by virtue of the biaryl bonds. We proposed that internal complexation is not feasible in these complexes; subsequent crystallographic characterization supports this assertion. In previous work, we have shown the utility of these BINOL-salen bifunctional catalysts in the Michael reaction of cyclohexenone and benzyl malonate.[7] In this report we explore the full structural and mechanistic details of these catalysts and their scope in the Michael addition of carbon nucleophiles to enones.

Results and Discussion

Synthesis of Biphenol- and BINOL-Salens. Biphenol ligand **10** was easily prepared from biphenol in a simple four-step procedure as shown in Scheme 1. After protection of biphenol (**8**) as the bis-MOM ether, monoformylation is accomplished via directed lithiation.[8] Subsequent deprotection yields aldehyde **9**, which is condensed with (*R*,*R*)-*trans*-cyclohexanediamine. The metalated catalyst **11** is prepared from **10** by heating with $Ni(OAc)_2$.

SCHEME 1[a]



[a] Reagents and conditions: (a) (i) NaH, MOMCl, 100%; (ii) nBuLi, DMF, TMEDA, 57%; (iii) HCl, THF, 0 °C, 90%. (b) EtOH, Δ, H_2N-X-NH_2 (c) $Ni(OAc)_2$, EtOH, Δ.

BINOL-salen ligands **13**−**18** and their corresponding Ni complexes were prepared in an analogous manner as shown in Scheme 2.[7] Alternatively, a more efficient preparation of the metallosalens could be accomplished by simultaneous condensation of the aldehyde with the corresponding amine and metalation (Scheme 2, reaction conditions c).

In a screening of azaphilic late transition metals, Ni(II) was identified as the optimal Lewis acid component.[7]

(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. (f) France, S.; Wack, H.; Hafez, A. M.; Taggi, A. E.; Witsil, D. R.; Lectka, T. *Org. Lett.* **2002**, *4*, 1603−1605. (g) Josephsohn, N. S.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 11594−11599.

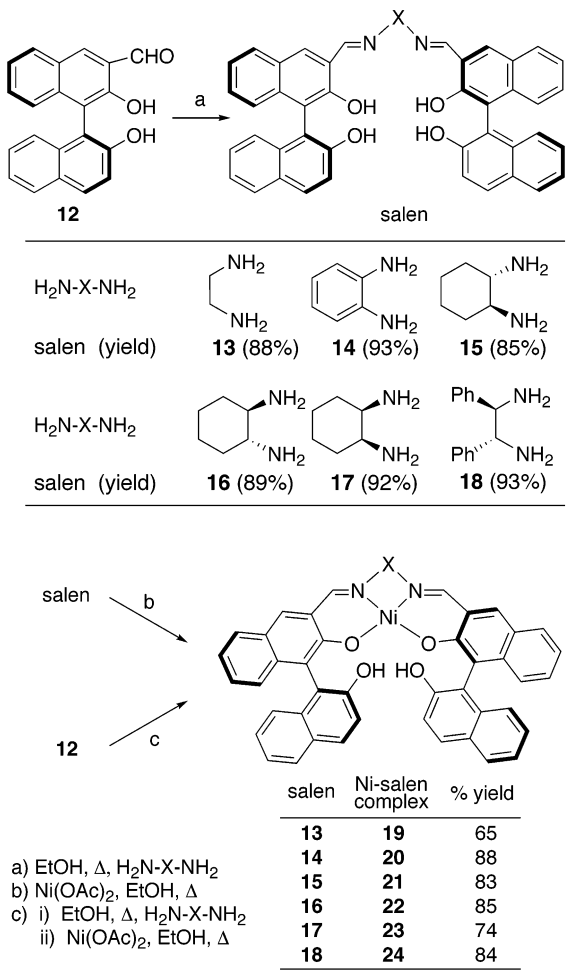
(5) (a) DiMauro, E. F.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*, 3053−3056. (b) DiMauro, E. F.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2002**, *124*, 12668−12669. (c) DiMauro, E. F.; Kozlowski, M. C. *Org. Lett.* **2002**, *4*, 3781−3784.

(6) DiMauro, E. F.; Mamai, A.; Kozlowski, M. C. *Organometallics* **2003**, *22*, 850−855.

(7) DiMauro, E. F.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*, 1641−1644.

(8) (a) For a related biphenol directed lithiation see: Rudkevich, D. M.; Verboom, W.; Brzozka, Z.; Palys, M. J.; Stauthamer, W. P. R. V.; van Hummel, G. J.; Franken, S. M.; Harkema, S.; Engbersen, J. F. J.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1994**, *116*, 4341−4351. (b) For directed lithiation of MOM-protected phenols see: Townsend, C. A.; Bloom, L. M. *Tetrahedron Lett.* **1981**, *22*, 3923−3924.

SCHEME 2



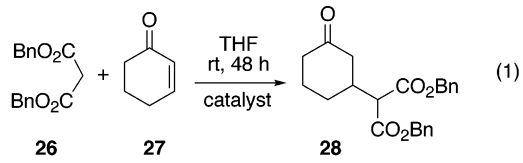
salen	Ni-salen complex	% yield
13	**19**	65
14	**20**	88
15	**21**	83
16	**22**	85
17	**23**	74
18	**24**	84

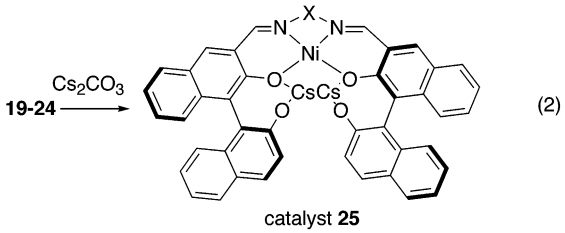
a) EtOH, Δ, H_2N-X-NH_2
b) $Ni(OAc)_2$, EtOH, Δ
c) i) EtOH, Δ, H_2N-X-NH_2
ii) $Ni(OAc)_2$, EtOH, Δ

The Ni(II) derivatives of salens **13**−**18** were therefore prepared from $Ni(OAc)_2$ as shown in Scheme 2. Consistent with formation of the illustrated complexes, a lower C═N stretch in the IR spectra of the complexes relative to that of the free salen was observed. Also, the C_2-symmetry element is indicated from the ^{13}C NMR spectra of the complexes.

Biphenol- and BINOL-Salen Catalysts in the Michael Reaction. Replacement of the two hydrogens in Ni-BINOL-salen complexes **19**−**24** with Li, Na, K, or Cs provides metal complexes containing Lewis acidic and Brønsted basic sites. From the trends observed in the crystal structure of the protonated form, interactions between the naphthoate counterion and the salen oxygens are likely to be weak.[9] As a result, it should be possible to modulate the reactivity of the salen Lewis acid and the naphthoate base independently.

The Ni-BINOL-salen complexes **19**−**24** were examined in the Michael reaction[10] of cyclohexenone with benzyl malonate (eq 1). The active catalysts were generated from the preformed Ni-BINOL-salen complexes **19**−**24** via treatment with a base in THF prior to addition of the reaction substrates (eq 2). Increased enantioselectivity is observed with increased atomic radius/polarizability of the naphthoxide counterion, with the Cs complexes yielding the best results.[7] It appears that more basic (less tightly coordinated) naphthoxides are necessary for optimal reactivity and selectivity.





Various solvents were examined with use of Ni·Cs BINOL-salen catalyst **25a** (Table 1). Although catalyst solubility was improved with increased solvent polarity (CH_2Cl_2, THF, DMF), strongly polar coordinating solvents (DMF) were detrimental to enantioselectivity. A solvent screen was also done with the more selective Ni·Cs BINOL-salen catalyst **25d** and various ethereal solvents. Catalyst solubility was worse in ether, DME, and methyltetrahydrofuran when compared to THF. This correlated to lower yields and selectivity.

TABLE 1. Solvent Screen of BINOL-Salen Catalysts 25a and 25d in the Michael Addition Reaction (Eqs 1 and 2)

catalyst	solvent	yield (%)[a]	ee (%)[b]
25a	DMF	77	5
25a	THF	80	31
25a	CH_3CN	66	4
25a	CH_2Cl_2	48	38
25a	toluene	81	0
25d	THF	79	71
25d	2-MeTHF	65	34
25d	Et_2O	43	27
25d	DME	66	21

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

TABLE 2. Ni·Cs-Salen Naphthoxide Complexes (Eq 2) in the Michael Addition Reaction (Eq 1)

entry	Ni salen	catalyst	yield (%)[a]	ee (%)[b]
1	**19**	**25a**	80	31 (*R*)
2	**20**	**25b**	49	31 (*R*)
3	**21**	**25c**	84	54 (*R*)
4	**22**	**25d**	79	71 (*R*)
5	**23**	**25e**	88	42 (*R*)
6	**24**	**25f**	83	21 (*R*)

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

The structural basis for stereoinduction was examined through variation of the configuration and the conformational mobility afforded by the salen diamine linker (Table 2). Exchanging the ethylenediamine linker in the Ni·Cs-BINOL-salen catalyst with a diaminobenzene or

(9) DiMauro, E. F.; Kozlowski, M. C. *Organometallics* **2002**, *21*, 1454−1461.

(10) 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.

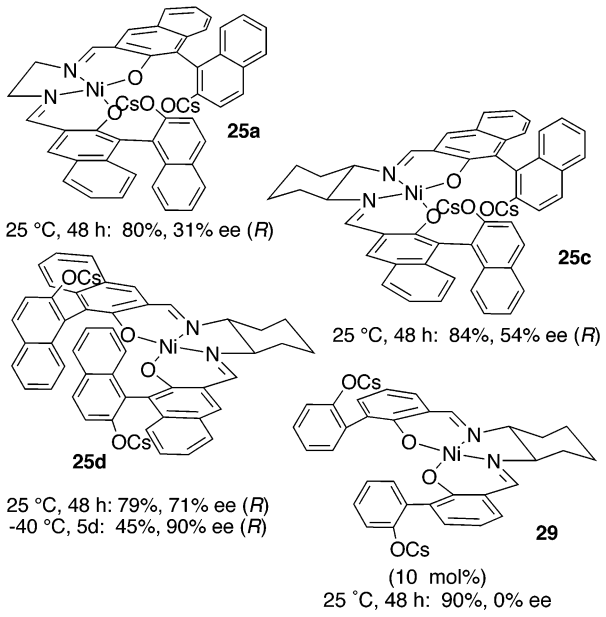
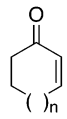
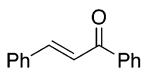
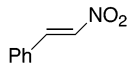


FIGURE 3. Results from the reaction of dibenzyl malonate with cyclohexenone (eq 1) employing 10 mol % of the indicated complexes (generated in situ, eq 2).

a diphenylethylene linker resulted in a less effective catalyst (entries 2 and 6 vs entry 1). Switching to a *cis*-diaminocyclohexane linker resulted in a more effective catalyst (entry 5 vs entry 1). The *trans*-diaminocyclohexane derivatives **25c** and **25d** (Figure 3) provided the largest degree of improvement (entries 3 and 4). The latter proved to be the matched catalyst system, providing the Michael adduct in 71% ee (entry 4). Upon cooling the reaction to −40 °C, the Michael adduct was obtained in up to 90% ee with 10 mol % **25d** (Figure 3).[11] Interestingly, both of the diaminocyclohexane derived Ni·Cs-BINOL-salen catalysts **25c** and **25d** catalyzed the Michael reaction with improved selectivity compared to the ethylenediamine analogue **25a** (Figure 3). This phenomenon may result from the stereochemical influence and conformational restriction imposed by the cyclohexyl backbone. Since catalysts **25c** and **25d**, which differ in the configuration of the bisimine linker, afford the same prevailing enantiomer in the product, the biaryl chirality appears to be the dominant control element responsible for facial selectivity. This conclusion is supported by the results from the biphenol-derived complex **29** (Figure 3). While complex **29** was an efficient catalyst for the Michael reaction (90% yield), the product was obtained in 0% ee. Thus, a rigid biaryl axis is necessary for asymmetric induction.

The substrate scope of the matched Ni·Cs-BINOL-salen catalyst **25d** in the Michael addition reaction was next investigated (Table 3). The highest yield and enantioselectivity were observed for the reaction between cyclohexenone and dibenzyl malonate (entries 1−4, Table 3). When the reaction temperature is lowered enantioselection is improved at the expense of reactivity. With dimethyl malonate as the nucleophile, catalyst reactivity and selectivity are significantly lower (entry 5 vs entry 1, Table 3). Similar enantioselectivity was observed in the addition of dibenzyl malonate to cycloheptenone (73% ee, entry 6) compared to cyclohexenone, but much lower selectivity was observed with cyclopentenone (38−50% ee, entries 7 and 8). Moderate selectivity could also be obtained with acyclic enones such as chalcone (72% ee, entry 10), but catalyst turnover was compromised.

TABLE 3. Matched Salen Naphthoxide Catalyst 25d in the Michael Addition Reaction[a]

entry	enone	malonate $CH_2(CO_2R)_2$	T (°C)	%yield[b]	%ee[c]
1		n = 1 R = Bn	rt	79	70
2		n = 1 R = Bn	0	75	82
3		n = 1 R = Bn	-20	47	87
4		n = 1 R = Bn	-40	45	90
5		n = 1 R = Me	rt	48	17
6		n = 2 R = Bn	rt	45	73[d]
7		n = 0 R = Bn	rt	79	38[d]
8		n = 0 R = Bn	-20	54	50[d]
9		R = Me	rt	61	20
10		R = Me	-20	19	72
11		R = Me	rt	60	5

[a] 10 mol % catalyst. [b] Isolated yields. [c] Enantiomeric excess determined by HPLC. Absolute configuration based on optical rotation values. [d] Enantiomeric excess determined from the ^{1}H NMR spectra of the (*S*,*S*)-2,3-pentanediol ketals.

Crystallographic Structures of the BINOL-Salen Ni Complexes. Crystal structures of the nickel complexes **19** and **22** provided definitive evidence that the proposed salen metal complexes were formed. The structures of **19** and **22** are remarkably similar (Figures 4 and 5, Table 4), including similar conformational forms in the unit cells for the two different compounds (**19a** vs **22a** and **19b** vs **22b**).

Despite their apparent structural similarities, bimetallic catalysts derived from complexes **19** and **22** cause significantly different levels of enantioselection (31% vs 71% ee) in the Michael addition reaction. Although solid-state crystallographic structures may not be representative of the solution structures due to crystal packing forces, several points encouraged us that comparison of **19a** and **22a** would be informative. First, the NMR spectra of **19** and **22** were consistent with C_2-symmetric structures as found in **19a** and **22a**. Second, the core structures of the two conformational forms found in the crystal structure of **19** are similar, as are the two conformational forms of **22**, indicating that these core structures likely persist in different conformational forms such as those found in solution. Finally, prior reports indicate that solid-state Ni(II) salen geometries (square planar, square pyramidal, or octahedral) are retained in solution.[12]

In the pseudo-C_2-symmetric complexes **19a** and **22a**, the binaphthyl dihedral angles are compressed to 68.1° and 63.2° (for the C2−C17 biaryl) and 65.4° and 64.7° (for the C15−C27 biaryl), respectively. The binaphthyl dihedral angle in uncoordinated BINOL is 78.3°. Even

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

(12) For example: Mockler, G. M.; Chaffey, G. W.; Sinn, E.; Wong, H. *Inorg. Chem.* **1972**, *11*, 1308−1314.

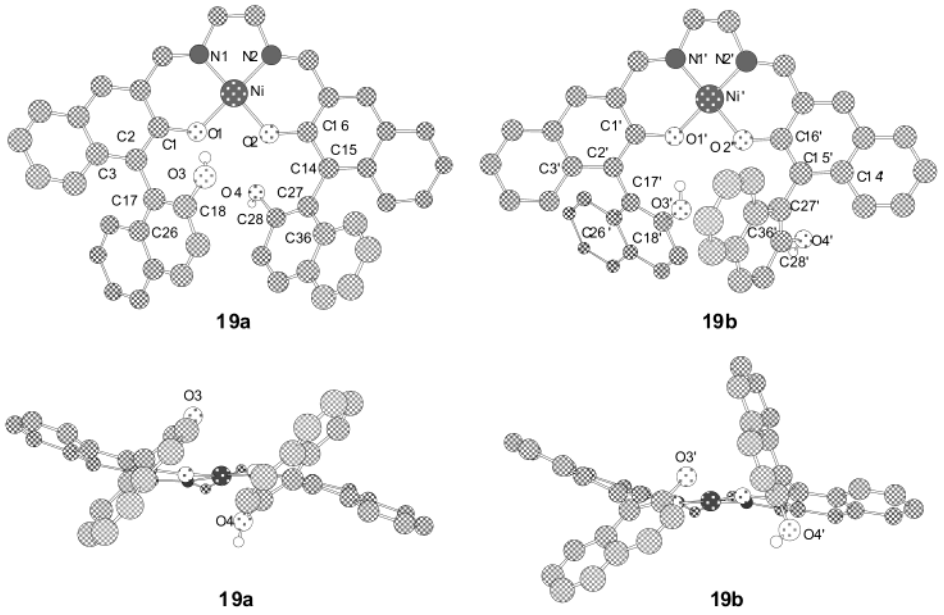


FIGURE 4. Top and side views for both unit cell structures of Ni-BINOL-salen **19** X-ray structure.

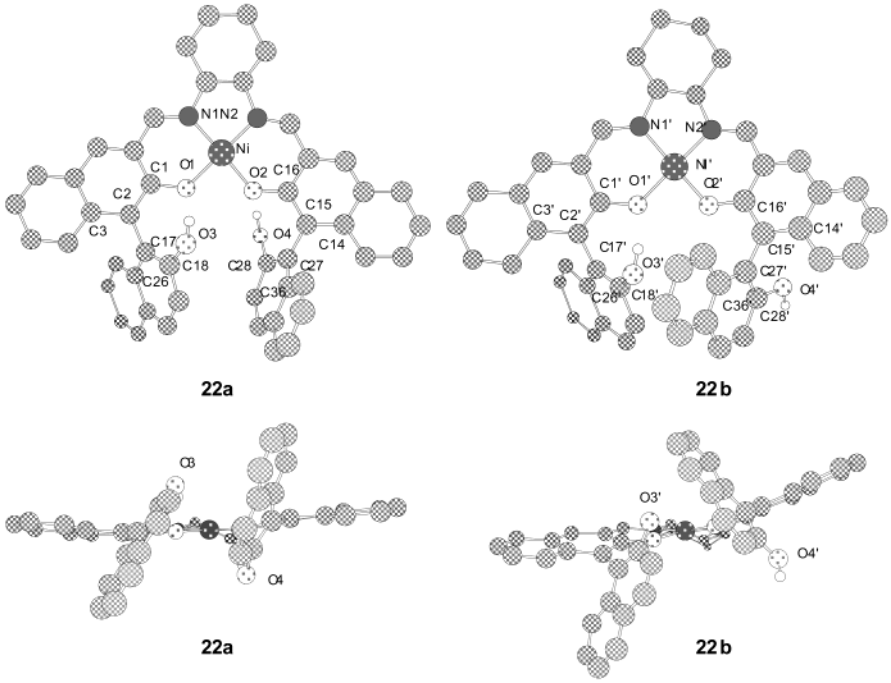


FIGURE 5. Top and side views of both unit cell structures for Ni-BINOL-salen **22** X-ray structure.

so, the naphthoate oxygens simply cannot reach a position to bind to the Ni. Rather these naphthoates are in the proper orientation for delivery of a stabilized anion to an electrophile bound to the salen metal center.[13] An overlay (Figure 6) shows that complexes **19a** and **22a** differ in the positioning of this putatively important naphthoate with respect to the salen core.

In the case of **19**, the ethylenediamine linker responds to the helical twist imposed by the BINOL portions which causes the ethylene to cant from lower left to upper right in the orientation shown in Figure 6b. In the (*R*,*R*)-cyclohexanediamine case, such an orientation would require the amines of the *trans*-cyclohexanediamine to be axial, which is not possible in this structure. When the amine groups are equatorial, the cant of the diamine linking portion is reversed (upper left to lower right).

(13) Examination of nickel salen complexes in the Cambridge Structural Database (The United Kingdom Chemical Database Service: Fletcher, D. A.; McMeeking, R. F.; Parkin, D. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 746) revealed square-pyramidal or octahedral adducts upon coordination of further ligands. In general, the salen ligand coordinates in a square-planar array. Square pyramidal: (a) Elerman, Y.; Kabak, M.; Atakol, O. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1993**, *49*, 1905−1906. (b) Clarke, N.; Cunningham, D.; Higgins, T.; McArdle, P.; McGinley, J.; O'Gara, M. *J. Organomet. Chem.* **1994**, *469*, 33−40. Octahedral: (c) Gomes, L.; Sousa, C.; Freire, C.; de Castro, B. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **2000**, *56*, 1201−1203.

TABLE 4. Selected Bond Distances (Å), Bond Angles (deg), and Dihedral Angles (deg) for 19 and 22

	19a	19b	22a	22b
Ni−N1	1.832(7)	1.821(7)	1.858(8)	1.876(8)
Ni−N2	1.823(6)	1.847(6)	1.843(8)	1.842(8)
Ni−O1	1.855(5)	1.849(4)	1.831(6)	1.855(7)
Ni−O2	1.846(5)	1.835(5)	1.877(7)	1.848(6)
O1−C1	1.342(9)	1.332(9)	1.327(11)	1.324(11)
O3−C18	1.377(8)	1.374(8)	1.382(11)	1.307(13)
O2−C16	1.345(9)	1.333(9)	1.329(10)	1.345(10)
O4−C28	1.393(9)	1.356(7)	1.375(12)	1.355(11)
N1−Ni−N2	86.1(3)	86.0(3)	86.9(3)	85.0(3)
N1−Ni−O1	94.9(3)	94.0(2)	95.2(3)	94.8(3)
N2−Ni−O2	94.9(2)	94.4(2)	93.9(3)	94.3(3)
O1−Ni−O2	84.2(2)	85.9(2)	84.0(3)	86.9(3)
N1−Ni−O2	176.8(3)	175.4(3)	177.8(3)	173.3(3)
N2−Ni−O1	178.0(3)	176.0(3)	177.3(3)	171.0(3)
C3−C2−C17−C18	−117.09(0.76)	−128.09(0.62)	−119.1(1.0)	−119.02(1.09)
C3−C2−C17−C26	61.98(0.93)	53.42(0.75)	64.1(1.2)	59.9(1.3)
C1−C2−C17−C18	59.63(0.94)	54.33(0.85)	53.0(1.2)	60.7(1.3)
C1−C2−C17−C26	−121.37(0.77)	−124.16(0.60)	−123.9(1.0)	−120.4(1.0)
C14−C15−C27−C28	−116.15(0.73)	−73.99(0.70)	−120.8(0.9)	−76.7(1.1)
C14−C15−C27−C36	59.44(0.85)	106.83(0.63)	55.2(1.1)	97.6(1.0)
C16−C15−C27−C28	57.69(0.87)	112.99(0.66)	56.3(1.1)	103.2(1.0)
C16−C15−C27−C3	−126.72(0.66)	−66.19(0.74)	−127.7(0.9)	−82.5(1.1)

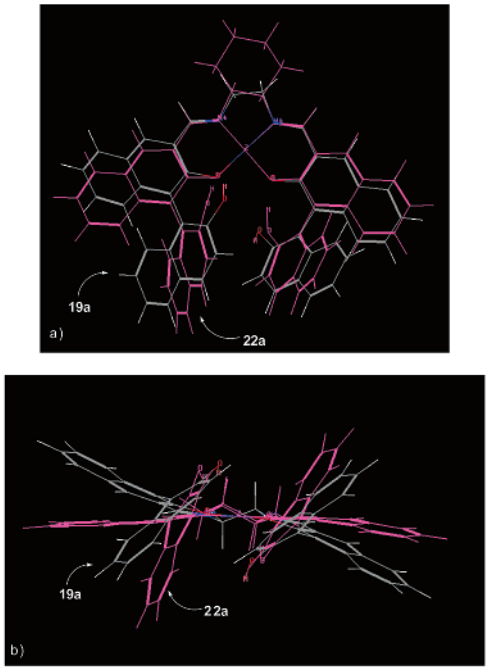


FIGURE 6. Overlay of **19a** and **22a** (superposition of Ni, N1, N2, O1, O2). Half-bond structure = ethylenediamine Ni complex **19a**; purple structure = (*R,R*)-cyclohexanediamine Ni complex **22a**. (a) Top view (b) Edge view.

Thus, the (*R,R*)-cyclohexanediamine counters the twist imposed by the BINOL portions. The net result is that the dihedral angle between the core salen plane (Ni−N1−N2−O1−O2) and the ancillary naphthols is more perpendicular for the (*R,R*)-cyclohexanediamine derivative [70.1(1), 57.8(1)°] compared to the ethylenediamine derivative [45.4(1), 40.7(2)°]. This angle governs the position of the naphthoxide Brønsted base with respect to an electrophile bound in the salen apical position[12,13] and is correlated to the higher selectivity of **22** compared to **19** (Table 2). If an electrophile binds perpendicular to the core salen plane, then the more perpendicular naphthoate oxygens are closer to the bound electrophile (Figure 6). Since the proposed mechanism involves coordination of the nucleophile to the deprotonated naphthoate oxygen, such an arrangement may lead to higher selectivity. This hypothesis is also consistent with the lower selectivity of the catalyst derived from **21** (54% ee) vs **22** (71% ee). In **21**, the (*S,S*)-cyclohexanediamine would be able to better accommodate the helical twist caused by the BINOL portions and the type of change observed from **19** to **22** (shift of the diamine cant) would not occur.

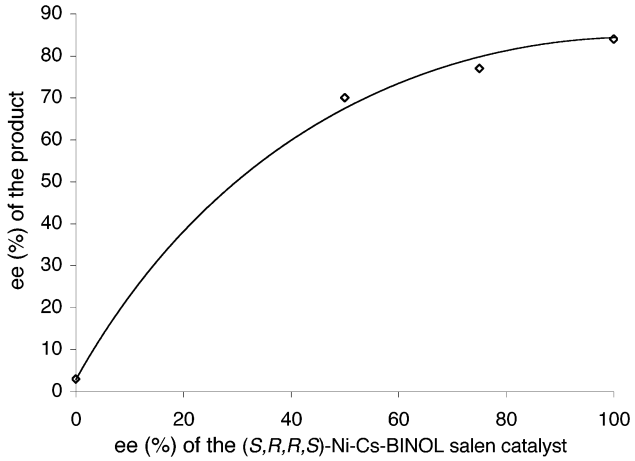


FIGURE 7. Nonlinear effects study with matched Ni·Cs-BINOL-salen **25d** and its enantiomer *ent*-**25d** for the reaction in eq 1 (THF, 5 d, −20 °C, 10 mol % catalyst).

Reaction Mechanism. To probe the reaction mechanism, several studies were undertaken. In the first, nonlinear effects were measured (Figure 7). A positive nonlinear effect was observed; however, the formation of a visible precipitate with the lower enantiomeric excess catalysts along with their much lower reactivity indicates the formation of nonreactive aggregates. These results are consistent with a reservoir effect[14] rather than the intervention of two catalyst molecules in the enantioselectivity-determining step.

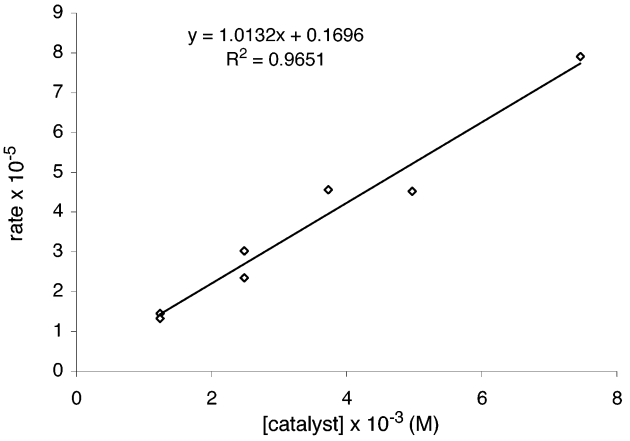
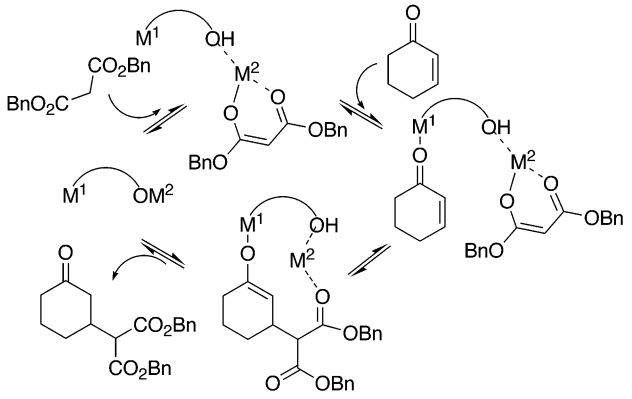


FIGURE 8. Kinetic analysis of the catalyst order for salen naphthoxide catalyst **25d** in the Michael addition reaction.

SCHEME 3. Possible Catalytic Cycle for the Catalyzed Michael Reaction



The reaction mechanism for the Michael addition of dibenzyl malonate to cyclohexanone with **25d** was further studied by measuring pseudo-first-order rates over a range of catalyst concentrations (Figure 8). A plot of rate vs [catalyst] indicates that the reaction is first order in **25d**. On this basis, it appears that only one molecule of the salen catalyst is involved in the rate-determining step.

Using this information a potential catalytic cycle for the Michael reaction is depicted in Scheme 3. 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 transfer from the naphthol to the enolate intermediate would then allow product release and catalyst regeneration.

However, several other mechanisms are also possible, including the following: (1) the Lewis acid of the salen complex acts alone to catalyze the addition, (2) the Brønsted base of the salen complex acts alone to catalyze the addition, (3) the Lewis acid of the salen complex acts in concert with a base arising from a separate source (not an intramolecular base), or (4) the Brønsted base of the salen complex acts in concert with an acid arising from a separate source (not an intramolecular Lewis acid). To determine which of these pathways is most likely, several additional experiments were performed (Figure 9).

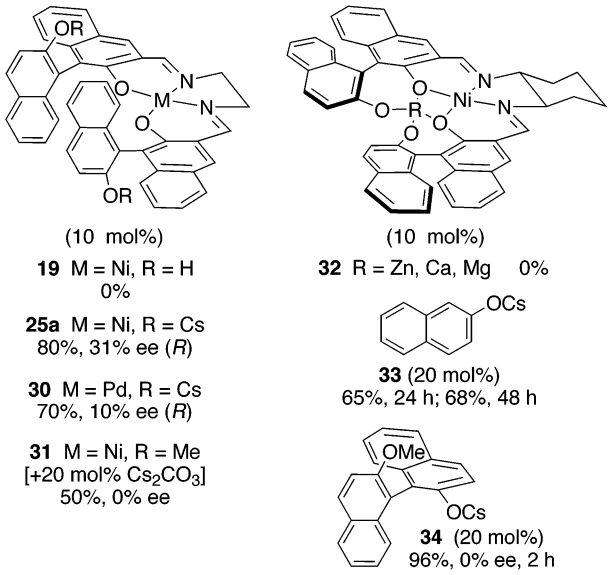


FIGURE 9. Additional catalysts used in the Michael reaction of benzyl malonate and cyclohexenone (eq 1) to probe the mechanism (48 h reaction time unless otherwise noted).

If the active portion of the catalyst was simply the salen Lewis acid, then the protonated form of the complex **25a** should give rise to similar enantioselectivity and reactivity. When this form (**19**) was employed, no reaction was observed (Figure 9). Further evidence for the necessity of a Brønsted base can be found in the lack of reactivity observed upon replacement of both phenolic protons with a divalent metal such as Zn, Mg, or Ca leading to general structure **32** (Figure 9). Presumably a stable tetrahedral complex forms between the four BINOL oxygens, rendering the naphthoates ineffective as bases. These results indicate that a component is needed in addition to the Lewis acid or that the Lewis acid of the salen does not play any role. To rule out the latter possibility, a reaction was performed employing the Pd·Cs-BINOL-salen catalyst **30**. We anticipated that the Pd(II) derivative, which is less Lewis acidic than the isosteric Ni(II) derivative, would give rise to lower reactivity/selectivity if the salen metal acted as a Lewis acid. Since reaction with the Pd derivative **30** was slower in a side-by-side trial and the selectivity was lower compared with that of Ni·Cs-BINOL-salen **25a**, we conclude that the salen metal does play a role as a Lewis acid. Thus, it appears that the salen Lewis acid is a critical component and that it acts in concert with a second moiety.

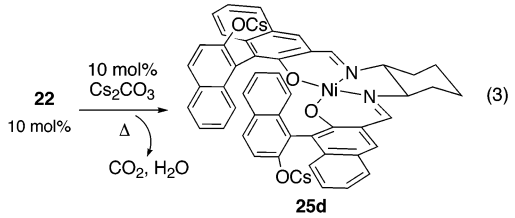
Further experiments were directed at determining if the Brønsted base in the Ni·Cs-BINOL-salen complexes **25a**−**d** was solely responsible for the catalytic activity. The high rates obtained with Cs-naphthoxide **33** indicate that a reaction in which the naphthoxide portion of the catalyst acts alone as a Brønsted base is feasible. However, a BINOL-derived chiral Cs-naphthoxide base,

(14) For reviews on nonlinear effects, see: (a) Blackmond, D. G. *J. Am. Chem. Soc.* **1997**, *119*, 12934−12939. (b) Guillaneux, D.; Zhao, S.; Samuel, O.; Rainford, D.; Kagan, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 9430−9439. (c) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922−2959.

such as **34**, alone is not a sufficient determinant for good enantioselectivity. Rather, the entire Ni·Cs-BINOL-salen assembly is required for selectivity in line with a bifunctional catalyst comprised of a Lewis acid salen metal acting in concert with a naphthoxide Brønsted base.

The third possibility, that the salen metal acts as a Lewis acid and a separate Brønsted base such as Cs_2CO_3 or $CsHCO_3$ (see below)[15] is involved, was tested by employing the methylated Ni-BINOL-salen **31** in the presence of Cs_2CO_3. This complex displays reduced reactivity compared to **25a**−**d** and the absence of any selectivity points away from the salen Lewis acid acting in concert with a separate Brønsted base.

The fourth possibility, that the salen complex acts as a Brønsted base while a separate species acts as a Lewis acid, seems unlikely in light of the correlation between the Lewis acidity of the salen metal and the selectivity (see above). In addition, the only other species present that could act as a Lewis acid is the Cs counterion. To rule out the direct involvement of the Cs_2CO_3 or $CsHCO_3$ present in the in situ catalyst preparations obtained by treatment of 10 mol % **22** with 20 mol % Cs_2CO_3 (see below), we undertook a preparation of Ni·Cs-BINOL-salen **25d** in pure form (eq 3). A solution containing 10



(3)

mol % Ni-BINOL-salen **22** was treated with 10 mol % Cs_2CO_3 and was then heated to reflux to promote formation of Ni·Cs-BINOL-salen **25d** by evolution of H_2CO_3 as H_2O and CO_2. When **25d** prepared in this manner was employed in the reaction of dibenzyl malonate with cyclohexenone, the results were very similar (58% conv, 72% ee) relative to the form of **25d** prepared in situ from 20 mol % Cs_2CO_3 (79% conv, 71% ee). Thus, the involvement of a Cs Lewis acid from the Cs_2CO_3 or $CsHCO_3$ in the enantioselective reaction pathway is unlikely. Overall, both the Lewis acid and the Brønsted base were determined to be essential for catalysis and the preceding sets of experiments are all consistent with the bifunctional mechanism outlined in Scheme 3.

Background Reactions and Synergistic Effects. Additional experiments were conducted to gain insight into potential competitive catalytic pathways (Figure 10). When **25d** was prepared as described in eq 3 (no residual Cs_2CO_3 and $CsHCO_3$), the same level of enantioselection was observed as when **25d** was prepared in situ with 2 equiv of Cs_2CO_3 (Figure 10). From this result, it is likely that the same chiral catalyst is responsible for the enantioselective reaction in each preparation. However, other species ($CsHCO_3$ and/or Cs_2CO_3) will also be present in the in situ preparation of **25d** by treatment of **22** with 2 equiv of Cs_2CO_3 (eq 3 vs Figure 10). Assuming that naphthol is approximately one pK_a unit

(15) Present from preparation of the catalyst.

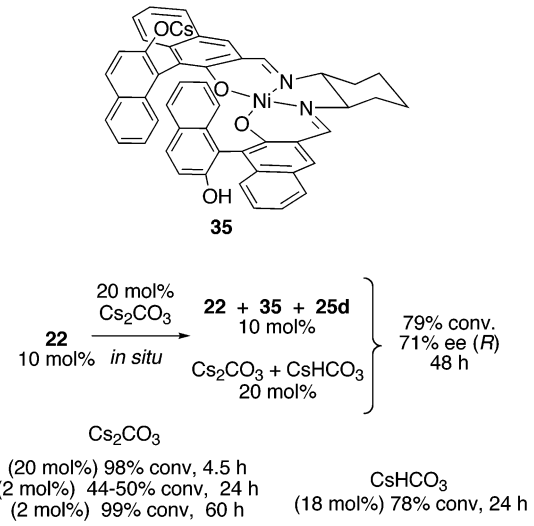


FIGURE 10. Experiments for studying competing pathways in the Michael addition reaction (eq 1, room temperature).

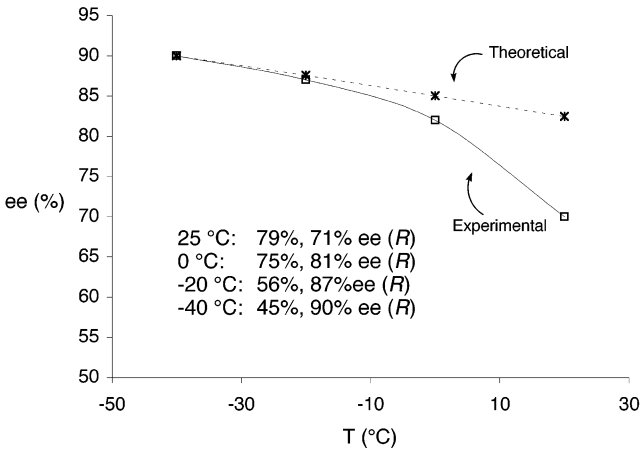


FIGURE 11. Non-Arrhenius behavior of the salen naphthoxide catalyst **25d** in the Michael addition reaction (eq 1).

more basic than bicarbonate,[16] 8 mol % of Ni·Cs-BINOL-salen **25d**, 1 mol % of the monodeprotonated **35**,[17] 1 mol % of Ni-BINOL-salen **22**, 2 mol % of Cs_2CO_3, and 18 mol % of $CsHCO_3$ are estimated to be present at the time the reaction is initiated (Figure 10). Regardless of the precise breakdown, there will be 20 mol % total of $CsHCO_3$ + Cs_2CO_3 present. On the basis of the results collected in Figure 10, both of these species alone are very effective catalysts for the Michael reaction and give rise to nonselective processes. Paradoxically, the rate of reaction with the Ni·Cs-BINOL-salen catalyst **25d** is slower than these nonselective reactions, yet the enantioselectivity

(16) The distribution of species indicated in Figure 10 upon the treatment of **22** with Cs_2CO_3 is roughly estimated from the relative pK_a values of $CsHCO_3$ and naphthol ($\Delta pK_a \sim 0.5-2$). While the absolute pK_a values change substanially with solvent, the ΔpK_a values of these delocalized oxygen acids are about the same in water, DMSO, and THF (see: Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463 and references therein). If $\Delta pK_a = 1$, the values in Figure 10 are obtained. This analysis is not quantitative, but clearly indicates that a small amount of Cs_2CO_3 (<**25d**) and a large amount of $CsHCO_3$ (>**25d**) would be present in the catalyst mix.

(17) Since the nondeprotonated adduct (**22**) is not a catalyst, it seems reasonable that only the half of **35** containing the naphthoate portion can act as a catalyst.

is good with **25d** from the in situ preparation. In other words, the nonselective background reactions are suppressed in the presence of **25d**, but it is not clear how this suppression occurs. On the basis of the non-Arrhenius behavior (Figure 11) of **22d** in the Michael reaction of dibenzyl malonate and cyclohexenone, these nonselective background reactions appear to account for a greater portion of the reaction at higher temperatures.

Concluding Remarks

In conclusion, several novel salen complexes have been synthesized and characterized. These complexes are effective in catalyzing the Michael reaction between various enones and malonates. The preponderance of evidence from mechanistic studies of the Ni·Cs-BINOL-salen catalysts supports a bifunctional activation mechanism in the Michael reaction. There is sufficient spatial and electronic separation between the Lewis acid and Brønsted basic sites such that these catalyst elements can be independently altered. The major elements influencing stereoselection in this family of catalysts are the chiral diamine linker and the chiral biaryl, with the latter playing a larger role. The activity of nonselective competitive catalyst species appears to be attenuated in the presence of these chiral catalysts. While the mechanism of this attenuation is unclear, the implication is that the rates of catalyzed reactions do not necessarily need to be more rapid than those of the background reactions (i.e., in the absence of catalyst). This family of compounds has promise in reactions requiring Lewis acid/Brønsted base catalysts.

Acknowledgment. Financial support was provided by the National Institutes of Health (GM-59945) and Merck Research Laboratories. E.F.D. thanks the University of Pennsylvania for an SAS Dissertation Fellowship.

Supporting Information Available: Experimental details, characterization of all new compounds, and X-ray data for **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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