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Salen-Derived Catalysts Containing Secondary Basic Groups in the Addition of Diethylzinc to Aldehydes

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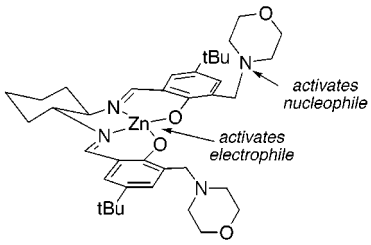
ABSTRACT



A set of modular bifunctional salen catalysts which contain Lewis acid and Lewis base activating groups is described. These groups can be altered independently to control nucleophilic and electrophilic activation of the reacting substrates. These salen-derived catalysts show enhanced reactivity in the addition of diethylzinc to aldehydes with respect to most other salen, amino alcohol, and diamine derived catalysts and reactivity comparable to that of Ti complexes of bis-sulfonamides and diols.

The use of bifunctional ligand systems in catalysis is an attractive method of emulating the reactivity of natural enzymes.[1] Over the past decade, catalysts containing chiral ligands with two or more reactive sites have proven successful in the asymmetric construction of C−C bonds.[2] In particular, complexes containing both a Lewis acid center and a Lewis basic moiety have recently emerged as powerful catalysts.[3]

The purpose of this work is to construct scaffolds in which these elements can be *independently* manipulated. In particular, new compounds can be envisioned with functional groups specifically tailored to activate the nucleophile and electrophile of a given reaction and with the optimal spacing and orientation between groups. The structurally well-defined and rigid salen architecture was chosen as a starting point, leading to general structure **1** (Figure 1). In a prior report,

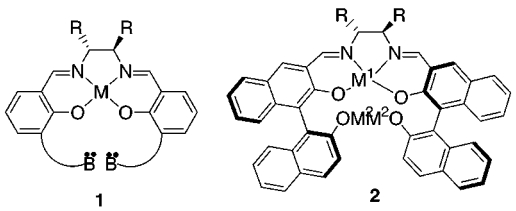


Figure 1.

the utility of the Lewis acid/Bronsted base BINOL-salen **2** in asymmetric Michael reactions has been outlined.[4] In this Letter, the potential of compounds such as **1** to act as bifunctional Lewis acid/Lewis base catalysts is examined.[5]

(1) (a) Murthy, N. N.; Mahroof-Tahir, M.; Karlin, K. D. *J. Am. Chem. Soc.* **1993**, *115*, 10404−10405. (b) Pessiki, P. J.; Dismukes, G. C. *J. Am. Chem. Soc.* **1994**, *116*, 898−903. (c) Gobel, M. W. *Angew. Chem., Int. Ed.* **1994**, *33*, 1141−1143. (d) Young, M. J.; Chin, J. *J. Am. Chem. Soc.* **1995**, *117*, 10577−10578. (e) Kodera, M.; Shimakoshi, H.; Kano, K. *Chem. Commun.* **1996**, 1737−1738.

(2) For reviews, see: (a) Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857−871. (b) Steinhagen, H.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2339−2342. (c) van den Beuken, E. K.; Ferringa, B. L. *Tetrahedron* **1998**, *54*, 12985−13011. (d) Rowlands, G. J. *Tetrahedron* **2001**, *57*, 1865−1882.

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To probe the bifunctional activity of these ligands, the addition of Et_2Zn to benzaldehyde was selected for initial study. When a β-aminoalkoxy zinc catalyst such as **3** is employed, this reaction proceeds by dual activation of the aldehyde electrophile and diethylzinc nucleophile (Figure 2).[3b,c,6] In applying framework **1** to this reaction, an apical

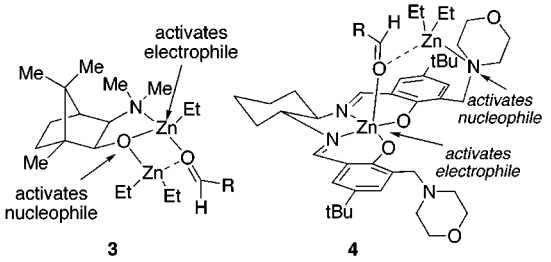


Figure 2.

coordination site on the salen metal center could act as a Lewis acid site to activate the aldehyde[7] while the tethered base could independently activate the Et_2Zn nucleophile (**4**, Figure 2).[8]

In the search for highly reactive Lewis acid catalysts for this reaction, titanium complexes of chiral diols and bis(sulfonamide) ligands have proven the most successful to date.[9] One drawback of these systems is the requirement for a stoichiometric amount of $Ti(OiPr)_4$. Although various chiral ligands (amino alcohols, diols, etc.) have been reported to catalyze the addition of Et_2Zn to aldehydes with excellent enantioselectivity, these catalysts are generally less reactive than the titanium-based systems.[6] Herein we report the discovery of a new class of catalysts that demonstrate excellent reactivity and good enantioselectivity in the absence of $Ti(OiPr)_4$.

As the first step toward development of this class of catalysts, the nature of the tether for the Lewis base was examined. The tether must be short and/or rigid enough to prevent internal complexation to the metal. A number of different tethers satisfy this criteria, leading to a variety of useful bifunctional salens, two of which are shown below (Figure 3).

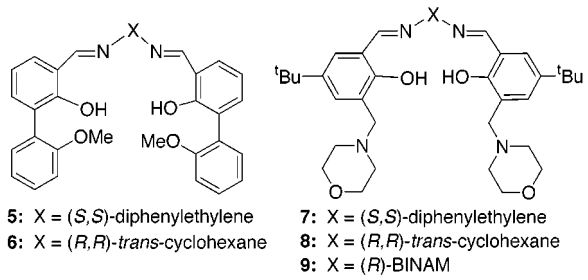
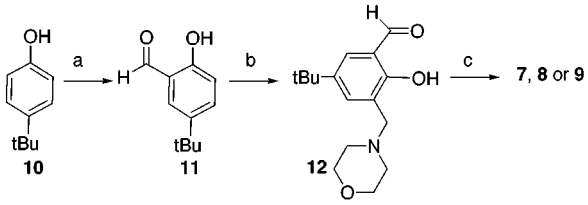


Figure 3.

The ease of preparation of the salen backbone lends itself to the rapid modular construction of a number of bifunctional ligands in which both the tether and diamine linker can be varied. Achiral and racemic compounds of type **1** have formerly been used as binucleating agents in the preparation of bimetallic complexes[10] and as ditopic ligands for salt extraction.[11] Salens **7**, **8**,[12] and **9** can be synthesized in three simple steps from phenol **10** (Scheme 1). The syntheses of **5** and **6** are somewhat longer, but similarly straightforward.[13]

Scheme 1[a]



[a] (a) $SnCl_4$, CH_2O, nBu_3N. (b) CH_2O, morpholine, HOAc. (c) diamine, EtOH.

The zinc complexes of ligands **5**−**9**[14] (eq 1) were examined as catalysts for the addition of Et_2Zn to benzaldehyde (Table 1, eq 2). A comparison of the reactivity of

(3) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551−5553. (b) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071−6072. (c) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49−69. (d) Kitajima, H.; Ito, K.; Aoki, Y.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 207−217. (e) Ooi, T.; Kondo, Y.; Maruoka, K. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1183−1184. (f) Sibi, M. P.; Cook, G. R.; Liu, P. *Tetrahedron Lett.* **1999**, *40*, 2477−2480. (g) Puigjaner, C.; Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **1999**, *64*, 7902−7911. (h) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Chem. Pharm. Bull.* **2000**, *48*, 1586−1592. (i) Hamashima, Y.; Sawada, D.; Nogami, H.; Kanai, M.; Shibasaki, M. *Tetrahedron*, **2001**, *57*, 805−814. (j) Gamble, M. P.; Smith, A. R. C.; Wills, M. *J. Org. Chem.* **1998**, *63*, 6068−6071.

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

(5) A few examples of chiral salens with secondary functional groups have been reported. Phosphines: (a) Quirmbach, M.; Kless, A.; Holz, J.; Tararov, B.; Börner, A. *Tetrahedron: Asymmetry* **1999**, *10*, 1803−1811. (b) Kless, A.; Kadyrov, R.; Börner, A.; Holz, J.; Kagan, H. B *Tetrahedron Lett.* **1995**, *36*, 4601−4602. Phenol ethers: (c) Keller, F.; Rippert, A. J. *Helv. Chim. Acta* **1999**, *82*, 125−137.

(6) For a recent review, see: (a) Pu, L.; Yu, H. *Chem. Rev.* **2001**, *101*, 757−824. (b) Soai, K.; Shibata, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; pp 911−922.

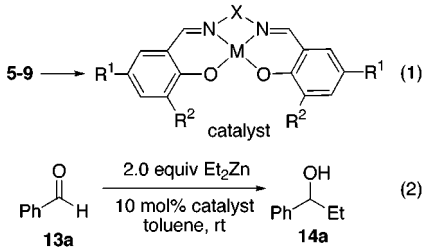
(7) For previous applications of salen ligands as catalysts in the Et_2Zn addition to aldehydes, see ref 5c and the following: Cozzi, P. G.; Papa, A.; Umani-Ronchi, A. *Tetrahedron Lett.* **1996**, *37*, 4613−4616.

(8) Bifunctional catalysts have been proposed in the Et_2Zn additions with binaphthyl-3, 3′-dicarboxamides. See ref 3d.

(9) (a) Schmidt, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1321−1323. (b) Seebach, D.; Beck, A. K.; Schmidt, B.; Wang, Y. M. *Tetrahedron* **1994**, *50*, 4363−4384. (c) Takahashi, H.; Kawakita, T.; Yoshioka, M.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1998**, *30*, 7095−7098. (d) Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1992**, *48*, 5691−5700. (e) Pritchett, S.; Woodmansee, D. H.; Gantzel, P.; Walsh, P. J. *J. Am. Chem. Soc.* **1998**, *120*, 6423−6424. (f) Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 92−138.

(10) (a) Liable-Sands, L. M.; Incarvito, C.; Rheingold, A. L.; Qin, C. J.; Gavrilova, A. L.; Bosnich, B. *Inorg. Chem.* **2001**, *40*, 2147−2155. (b) Adams, H.; Fenton, D. E.; Haque, S. R.; Heath, S. L.; Ohba, M. *J. Chem. Soc., Dalton Trans.* **2000**, 1849−1856. (c) De Angelis, S.; Solari, E.; Gallo, E.; Floriani; C.; Chiesi-Villa, A.; Rizzoli, C. *Inorg. Chem.* **1996**, *35*, 5995−6003. (d) Karunakaran, S.; Kandaswamy, M. *J. Chem. Soc., Dalton Trans.* **1995**, 1851−1855.

Table 1. Addition of Diethylzinc to Benzaldehyde Using Bifinctional Catalysts (eqs 1 and 2)



entry	ligand	M	t (h)	convn (%)[a,b]	ee (%)[a,c]
1	**5**	Zn	18	81 (3)	28 (*S*)
2	**6**	Zn	4	95 (1)	2 (*R*)
3	**7**	Zn	2	84	23 (*S*)
4	**8**	Zn	2	100	54 (*S*)
5	**9**	Zn	2	95	19 (*S*)
6	**8**	Ni	2	99 (2)	32 (*R*)
7	**8**	Cu	2	100	10 (*S*)
8	**8**	Mg	2	99	3 (*S*)
9	**8**	Ti(OPr)$_2$[d]	2	100	55 (*S*)

[a] Determined by chiral GC (CyclodexB column). [b] Values in parentheses refer to the amount of benzyl alcohol byproduct. [c] Absolute configuration assigned by comparison to the literature. [d] Reaction not homogeneous.

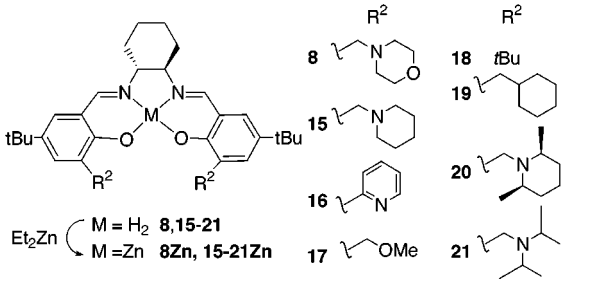
the different zinc complexes (entries 1−5) revealed that salens containing amine Lewis bases (**7**, **8**, and **9**) were much more efficient catalysts than the salens containing ethereal Lewis bases (**5** and **6**). This result is consistent with the supposition that superior activation of the nucleophilic Et_2Zn would be achieved with a more Lewis basic group.

Since the zinc complex of the *trans*-cyclohexanediamine-derived salen **8** displayed the best reactivity and selectivity (entry 4), complexes of **8** were investigated further. While the Ni,[15] Cu, Mg, and Ti(OiPr)$_2$ complexes[16] with **8** were also effective catalysts (entries 6−9), no increase in enantioselectivity was observed.

On the basis of the reactivity of the zinc complex of **8**, several further derivatives, **15**−**21**, were examined to directly probe the role of the Lewis base component (Table 2). An even more active catalyst was observed with the slightly more basic piperidyl salen **15**,[12] resulting in 90% conversion after 6 h at −30 °C (entry 1). Under the same conditions, the slightly less basic morpholine analogue **8** (entry 3) provided lower conversion (72%). However, after 12 h at −30 °C with the morpholine catalyst (entry 2), good conversion (98%) and enantioselectivity (80% ee) were observed. Surprisingly, the less basic pyridyl derivative **16**[17] provided the most reactive catalyst (entries 4 and 5). With the methyl ether derivative **17**, a much less reactive catalyst was formed which caused only 8% conversion after 6 h at −30 °C (entry 7).[15] Indeed, significant conversion was only observed at higher temperatures (i.e., rt, entry 6).

A similar loss in reactivity was observed with salens lacking secondary Lewis bases. For example, the catalyst derived from *tert*-butyl salen **18** provided only 2% conversion after 6 h at −30 °C (entry 8) along with significant amounts of the reduced byproduct benzyl alcohol (15%). Indeed, the catalyst derived from **18** requires 18 h at room temperature to achieve high conversion (90%).[18] To rule out any steric effect from the larger *tert*-butyl groups in **18**, an isosteric analogue (**19**) of **8** and **15** was synthesized. With the catalyst

Table 2. Addition of Diethylzinc to Benzaldehyde (eq 2) Using the Zinc Metal Complexes from Salens[a]



entry	ligand	T (°C)	t (h)	convn (%)[b,c]	ee (%)[c,d]	pK_a[e] HA$^+$
1	**15**	−30	6	90	76 (*S*)	9
2	**8**	−30	12	98	80 (*S*)	6
3	**8**	−30	6	72	77 (*S*)	6
4	**16**	−30	6	99	51 (*S*)	5
5	**16**	−50	20	97	78 (*S*)	5
6	**17**	rt	3	95	18 (*R*)	−3
7	**17**	−30	6	8 (3)	18 (*R*)	−3
8	**18**	−30	6	2 (15)	57 (*S*)	NA
9	**19**	−30	6	3 (7)	21 (*S*)	NA
10	**20**	−30	30	85	82 (*S*)	9
11	**20**	−30	6	33	73 (*S*)	9
12	**21**	rt	6	90 (5)	48 (*S*)	9
13	**21**	−30	6	5 (11)	52 (*S*)	9

[a] Reactions performed in $PhCH_3$ using 10 mol % of ligand and 2.1 equiv of Et_2Zn. [b] Determined by chiral GC (CyclodexB column). [c] Values in parentheses refer to the amount of benzyl alcohol byproduct. [d] Absolute configuration assigned by comparison to the literature. [e] Estimated from the pK_a(H_2O) values of *N*-methylmorpholine, *N*-methylpiperidine, benzylamine, methylamine, pyridine (Jencks, W. P.; Regenstein, J. Ionization Constants of Acids and Bases. In *Handbook of Biochemistry and Molecular Biology*, 3rd Ed.; CRC Press: Cleveland, 1975; Vol. 1), and dimethyl ether (Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry* 3rd Ed.; Harper & Row: New York, 1987).

(11) (a) Tasker, P. A.; White, D. J. Eur. Pat. WO0058225, 2000. (b) Miller, H. A.; Laing, N.; Parsons, S.; Parkin, A.; Tasker, P. A.; White, D. J. *J. Chem. Soc., Dalton Trans.* **2000**, 3773−3782. (c) White, D. J.; Laing, N.; Miller, H. A.; Parsons, S.; Coles, S.; Tasker, P. A. *Chem. Commun.* **1999**, 2077−2078.

(12) Ligands **8** and **15** have previously been synthesized in racemic form: see ref 11.

(13) See Supporting Information.

(14) Zinc complexes were prepared in situ by stirring the ligand with an equivalent amount of Et_2Zn for 1 h at room temperature prior to the addition of substrates.

(15) A reversal in facial selectivity was observed for this catalyst, which may indicate a different binding mode of the lignad or substrates for this case or an alternate mechanism.

(16) Ni and Cu complexes of **8** were prepared from the corresponding metal acetates (see Supporting Information) while the Mg and Ti(OiPr)$_2$ complexes were generated in situ by treatment of **8** with 1 equiv of $MgBu_2$ or Ti(OiPr)$_4$ for 1 h.

(17) For a previous synthesis of ligand **16**, see: Lam, F.; Xi Xu, J.; Shing Chan, K. *J. Org. Chem.* **1996**, *61*, 8414−8418.

derived from **19** (entry 9), again almost no conversion (3%) was observed after 6 h at −30 °C. Catalysts derived from salens **20** and **21**, containing α-branched amines, were less reactive (entries 10−13).

From these results, it appears that a good Lewis base is necessary to achieve a more active catalyst. Furthermore, the thermodynamic and kinetic basicity of this Lewis base can be correlated to catalyst reactivity. Figure 4 illustrates a

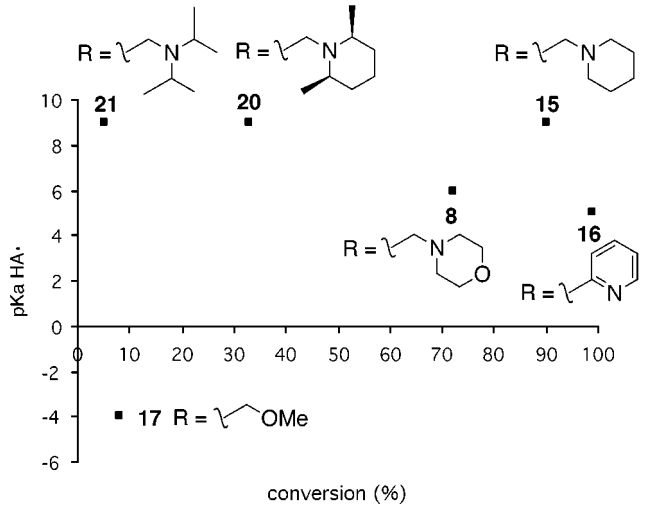


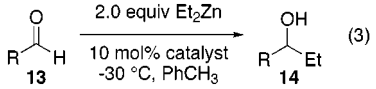
Figure 4. Conversion vs pK_a of the conjugate acid of the Lewis base in bifunctional salens for the reaction in eq 2 (6 h, −30 °C).

plot of the pK_a values of the conjugate acids of the Lewis base components for the salens described in Table 2 against conversion. For the derivatives in which the base is attached by a methylene group to the salen ring system, a similar steric environment is expected in the vicinity of the sp^3 base. As such, the observed linear correlation between the conjugate acid pK_a values and reactivity of **15**, **8**, and **17** most likely reflects a difference in reactivity due to the inherent basicity (thermodynamic). On the other hand, the departure from this trend with pyridyl derivative **16** indicates that the less hindered pyridine with softer Lewis base character possesses superior kinetic basicity in this catalyst structure. Departure from the trend is also observed with α-branched amine derivatives **20** and **21**, indicating decreased kinetic basicity as a result of steric hindrance.

The above data support a direct role for the Lewis base in the course of the reaction. In addition, the enantiomeric excess of the reaction in eq 2 with the Zn complex from **8** did not vary significantly as a function of conversion,[19] indicating that the composition of the catalytic species does not change over the course of the reaction. One model (**4**) consistent with this observation is illustrated in Figure 2. To provide further evidence for this model, the reaction in eq 2 was examined for a nonlinear effect using the Zn complex derived from **8**. A linear correlation was found between the product enantiomeric excess and the enantiomeric excess of **8**, consistent with monomeric catalyst model **4**.[20]

To demonstrate that the catalyst system developed can accept different substrates, a number of other aldehydes were examined in the Et_2Zn addition with **8** (eq 3, Table 3).

Table 3. Addition of Diethylzinc to Aldehydes (eq 3) Using **8Zn**[a]



entry	R	t (h)	convn (%)[b]	ee (%)[b]
1	Ph	12	98	80
2	*p*-MeO-C_6H_4	36	97	89
3	*p*-Cl-C_6H_4	10	92	83
4	*o*-Me-C_6H_4	36	99	69
5	cHx	24	78	75
6	$(CH_3CH_2)_2CH$	36	84	91

[a] Reactions performed in $PhCH_3$ using 10 mol % of ligand and 2.1 equiv of Et_2Zn. [b] Determined by chiral GC (CyclodexB column).

Similar levels of conversion and enantiomeric excess were obtained for aromatic aldehydes as well as aliphatic aldehydes.

A set of modular bifunctional salen catalysts has been described which contain Lewis acid and Lewis base activating groups. These groups can be altered independently to control nucleophilic and electrophilic activation of the reacting substrates. All of the salen ligands described are easily prepared crystalline solids that are stable to air and moisture. The morpholinyl, piperidyl, and pyridyl salen derived catalysts show enhanced reactivity with respect to most other salen, amino alcohol, and diamine derived catalysts[21] and reactivity comparable to that of Ti complexes of bis-sulfonamides and diols.[9] This promising class of ligands is currently being examined in related reactions.

Acknowledgment. Financial support was provided by the National Institutes of Health (GM59945), Merck Research Laboratories, and DuPont. We thank Prof. Patrick Walsh for helpful discussions and the use of GC instrumentation.

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

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(18) Cozzi et al. (ref 7) have reported that **18** provides up to 70% ee in the addition of Et_2Zn to PhCHO using a different set of conditions. To obtain good yields, reaction temperatures of 0 °C or room temperature were required.

(19) Using 10 mol % of catalyst at −35 °C over 15 h, the following data were collected: 9% conversion, 83% ee; 47% conversion, 85% ee; 81% conversion; 86% ee; 94% conversion, 87% ee.

(20) In reactions performed using the same conditions, the following selectivities were observed for PhCHO at 97% conversion: 100% ee **8**, 76% ee product; 50% ee **8**, 37% ee product.

(21) In a direct comparison (2 mol %, 0 °C), the Zn complex of **8** was found to be at least 3-fold more reactive than the DAIB (see ref 3b−c, 6) or MIB (Nugent, W. *Chem. Commun.* **1999**, 1369−1370) zinc complexes.