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Optimization of Catalyst Enantioselectivity and Activity Using Achiral and Meso Ligands

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Abstract: The optimization of asymmetric catalysts for enantioselective synthesis has conventionally revolved around the synthesis and screening of enantiopure ligands. In contrast, we have optimized an asymmetric reaction by modification of a series of *achiral ligands*. Thus, employing (S)-3,3'-diphenyl BINOL [(S)-Ph₂-BINOL] and a series of achiral diimine and diamine activators in the asymmetric addition of alkyl groups to benzaldehyde, we have observed enantiomeric excesses between 96% (*R*) and 75% (*S*) of 1-phenyl-1-propanol. Some of the ligands examined have low-energy chiral conformations that can contribute to the chiral environment of the catalyst. These include achiral diimine ligands with meso backbones that adopt chiral conformations, achiral diimine ligands with backbones that become axially chiral on coordination to metal centers, achiral diamine ligands that form stereocenters on coordination to metal centers, and achiral diamine ligands with pendant groups that have axially chiral conformations. Additionally, we have structurally characterized (Ph₂-BINOLate)Zn(diimine) and (Ph₂-BINOLate)Zn(diamine) complexes and studied their solution behavior.

Introduction

The ever-increasing demand for chiral intermediates of high enantiopurity has driven the enormous effort to develop new and improved catalytic asymmetric reactions.^{1,2} While optimization of the vast majority of catalysts for these reactions has traditionally relied on the synthesis and screening of resolved chiral ligands,^{2–4} promising alternative approaches that have the potential to streamline the optimization process have been advanced. These include the following: (1) chiral poisoning,^{5–12} (2) chiral activation,¹³ (3) use of large, flexible achiral ligands with chiral conformations,^{14–19} and (4) optimization of asym-

metric catalysts by screening of achiral ligands,^{18–20} as well as other techniques.^{21–23}

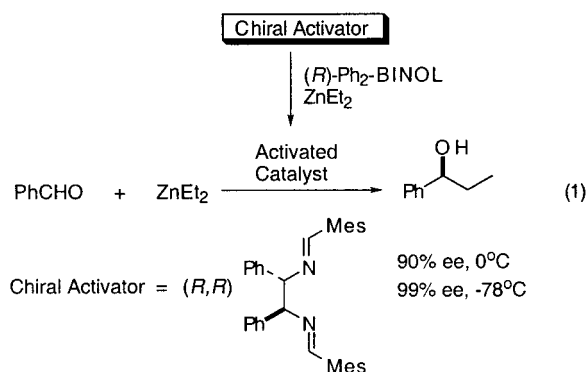
A strategy that has been used successfully to activate one enantiomer of a racemic catalyst, or to activate an enantiopure catalyst, is “asymmetric activation”.¹³ Asymmetric activation was introduced by Mikami and co-workers and applied with impressive results to several asymmetric reactions including the carbonyl–ene reaction,²⁴ hydrogenation reaction,²⁵ Diels–Alder reaction,²⁶ and addition of alkyl groups to aldehydes.²⁷ In one application, a racemic (BINOLate)Ti-based catalyst is combined with enantiopure BINOL activator, which preferentially activates one of the enantiomers of the racemic catalyst.²⁴ The resulting combination of racemic catalyst and resolved activator exhibited 90% ee in the asymmetric carbonyl–ene reaction. A similar methodology was employed with racemic ruthenium BINAP derivatives and enantiopure chiral diamines in the asymmetric reduction of ketones.²⁵ Addition of the enantiopure diamine to the racemic ruthenium–phosphine precursor gave rise to the two expected diastereomeric catalysts. Employing this mixture

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of diastereomeric catalysts in the asymmetric reduction of ketones resulted in generation of the alcohol product with very high enantioselectivity.²⁵ It is important to note that when mixtures of diastereomeric catalysts are used in asymmetric reactions, the ee of the product is determined by the enantioselectivity of each diastereomeric catalyst and their relative rates. Both of these characteristics are dependent on the substrate. Thus, the faster diastereomeric catalyst for reduction of 9-acetyl-anthracene is the slower diastereomer for reduction of the closely related 1'-acetonaphthone.²⁵ It is clear from this example that the asymmetric activation of racemic catalysts is more complex than the use of single catalyst systems.

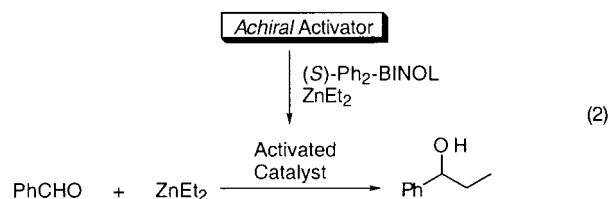
Asymmetric activation has also been successfully performed by activation of an enantiopure catalyst with an enantiopure activator in the asymmetric carbonyl-ene reaction²⁸ and the asymmetric addition of alkyl groups to aldehydes.^{29,30} Mikami and co-workers have prepared highly enantioselective catalysts using resolved 3,3'-diphenyl BINOL ($\text{Ph}_2\text{-BINOL}$)^{31,32} and resolved diimines as the asymmetric activators (eq 1).^{27,30} The



catalyst generated from only (*R*)- $\text{Ph}_2\text{-BINOL}$ and diethylzinc is sluggish and only moderately enantioselective (eq 1). However, combining (*R*)- $\text{Ph}_2\text{-BINOL}$, diethylzinc, and enantiopure diimine activators, substantial ligand acceleration³³ was observed and the resulting catalysts were quite efficient. These workers then screened a series of enantiopure diimine activators with (*R*)- $\text{Ph}_2\text{-BINOL}$ in eq 1 and were able to optimize the enantioselectivity of the asymmetric addition reaction. The catalyst prepared from a resolved stilbene diimine derivative (eq 1) with (*R*)- $\text{Ph}_2\text{-BINOL}$ generated (*R*)-1-phenyl-1-propanol with 90% ee at 0 °C and 99% ee at -78 °C.²⁷ This example demonstrates the utility of asymmetric activation. The only shortcoming of this novel and useful approach to asymmetric catalysis is that two different types of chiral ligands must be resolved. The resolution of chiral ligands is often the rate-limiting step in the optimization of asymmetric processes.³⁴

A better approach to asymmetric catalysis than activation of racemic or enantiopure catalysts with enantiopure activators would be achiral activation whereby an achiral ligand would

be used to activate an enantiopure catalyst and the resulting catalyst would exhibit enhanced efficiency and enantioselectivity (eq 2).²³ Using this strategy, many catalysts could be prepared



from each enantiopure ligand through combination with a series of achiral and meso ligands. The advantage of this method is that many more achiral and meso ligands, and ligand precursors, are commercially available than related enantiopure ligands or building blocks. Furthermore, the cost of achiral ligands is usually a fraction of that of enantiopure ligands.

In the present work, we demonstrate the dramatic impact that achiral ligands can have on catalyst efficiency and enantioselectivity. Using one configuration of a single resolved ligand and carefully chosen classes of achiral and *meso*-nitrogen-based ligands,^{35,36} we observed a remarkable range of enantioselectivities of 1-phenyl-1-propanol [76% (*S*) to 96% (*R*)] in the asymmetric addition of alkyl groups to aldehydes. Additionally, we present studies that provide insight into the structure and reactivity of these highly enantioselective and efficient Lewis acid catalysts.

Results and Discussion

The present study was inspired by the work of Ding, Ishii, and Mikami,^{27,30} who reported that enantiopure ($\text{Ph}_2\text{-BINOLate}$)-Zn species could be activated with enantiopure diimine ligands to form very efficient and enantioselective catalysts for the asymmetric addition of alkyl groups to aldehydes (eq 1). We rationalized that the enantioselectivities and the activities of resolved catalysts could be increased by adding achiral and meso ligands (eq 2) rather than enantiopure ligands. We are particularly interested in the application of achiral and meso ligands that have chiral conformations and can extend and amplify the chiral environment of the catalyst.^{18,19}

Classification of Achiral Ligands. The achiral and meso ligands that we have selected for our study fall into six distinct classes: (1) achiral diimine ligands that do not generate additional chirality on binding to tetrahedral metals, (2) diimine ligands with meso backbones that have chiral conformations, (3) achiral diimine ligands with backbones that become axially chiral on coordination to metal centers, (4) achiral diamine ligands that do not form stereocenters on coordination to metal centers, (5) achiral diamine ligands that form stereocenters on coordination to metal centers, and (6) achiral diamine ligands with pendant groups that have axially chiral conformations.

Use of Simple Achiral Diimine Ligands. Based on the work of Mikami and co-workers (eq 1),^{27,30} achiral diimines from the first class were initially examined in combination with (*S*)- $\text{Ph}_2\text{-BINOL}$ (eq 2, Table 1). Under our conditions, (*S*)- $\text{Ph}_2\text{-BINOL}$ (10 mol %) with no added achiral ligand resulted in the production of (*S*)-1-phenyl-1-propanol with low ee and poor

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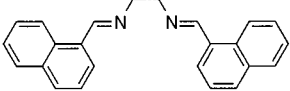
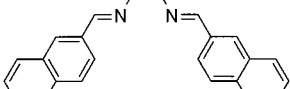
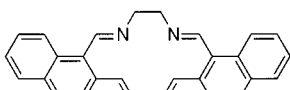
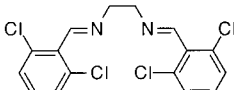
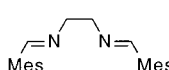
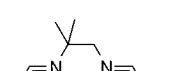
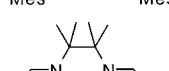
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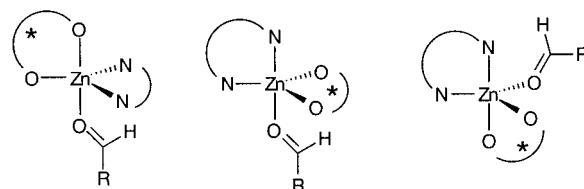
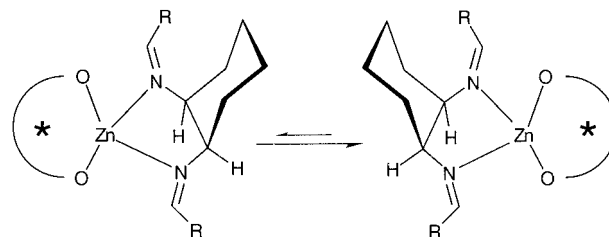
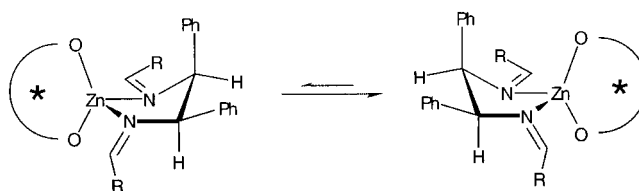
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Table 1. Results of Screening Achiral Diimine Activators **1a–1g** with (S)-Ph₂-BINOL in Eq 2^a

entry	ligand	ee at 0°C (config)	ee at -45°C (config)
1	No achiral activator	44 (S)	–
2	1a 	52 (S)	–
3	1b 	49 (S)	–
4	1c 	30 (R)	–
5	1d 	66 (R)	74 (R)
6	1e 	75 (R)	87 (R)
7	1f 	76 (R)	78 (R)
8	1g 	74 (R)	77 (R)

^a Reactions employed 10 mol % Ph₂-BINOL, 10 mol % diimine ligand, and 300 mol % diethylzinc. Conversion data and alcohol ee's were obtained as outlined in the Supporting Information.

efficiency in eq 2 (Table 1, entry 1, 44% ee and 83% conversion after 28 h). Asymmetric addition reactions in this study were conducted with 10 mol % (S)-Ph₂-BINOL and 10 mol % achiral ligand unless otherwise stated. Diimines derived from aromatic aldehydes and 1,2-diaminoethane, 1,2-diamino-2-methylpropane, and 2,3-diamino-2,3-dimethylbutane were employed as achiral ligands (Table 1). With diimines derived from smaller aldehydes (**1a** and **1b**), catalysts were significantly faster than the catalyst formed solely from (S)-Ph₂-BINOL and ZnEt₂. However, enantioselectivities were moderate with the (S) enantiomer of the product predominating (entries 2 and 3). Surprisingly, with ligands derived from bulkier aromatic aldehydes (**1c–1e**), the opposite enantiomer of the product formed with moderate to good enantioselectivity (Table 1, entries 4–6). Employing diimines derived from 2,4,6-trimethylbenzaldehyde enantioselectivities were 74–76% at 0 °C and as high as 87% at –45 °C (entry 6). Thus, in examination of these readily accessible diimines, a range of product ee's was observed spanning 52% ee (S) with **1a** to 87% ee (R) with **1e** employing a single resolved ligand (Table 1). As we have previously emphasized, simple achiral ligands can bind in an asymmetric binding mode in certain metal geometries.¹⁹ Shown in Figure 1 are three diastereomeric trigonal bipyramidal aldehyde adducts that differ only in the positions of the coordinated ligands (other isomers are also possible). One conceivable explanation for the different sense of enantioselectivity of the catalyst incorporating ligands

**Figure 1.** Diastereomeric coordination geometries of (Ph₂-BINOLate)Zn(diimine) bonded to the substrate aldehyde.**Figure 2.** Diastereomeric conformations of (Ph₂-BINOLate)Zn(diimine) derived from *meso*-1,2-diaminocyclohexane.**Figure 3.** Diastereomeric conformations of (Ph₂-BINOLate)Zn(diimine) derived from ligand **2g**.

1a [52% ee, (S)] and **1e** [87% ee, (R)] is that the ligands could be bonded to different positions on the trigonal bipyramidal zinc center. In this case, we anticipate that simple achiral ligands could greatly change the enantioselectivity of catalysts.¹⁹

Achiral diimine ligands can also augment catalyst efficiency. When diimine **1e** was used as the achiral ligand, the reaction at 0 °C was complete in less than 30 min (as compared to 83% conversion after 28 h with no achiral ligand, entry 1). This substantial increase in TOF on addition of the achiral diimine ligand is related to ligand-accelerated catalysis and is described in detail below.³³

Use of Diimine Ligands with Meso Backbones. The second class of diimine ligands examined were those based on *meso*-diamine backbones such as *cis*-1,2-diaminocyclohexane and (*1R,2S*)-1,2-diamino-1,2-diphenylethane (Table 2). These diamines are distinct from those reported in Table 1 because they possess stereocenters. In the case of *cis*-1,2-diaminocyclohexane, the two static chair conformations are enantiomers that interconvert by cyclohexane ring inversion. When diimines derived from *cis*-1,2-diaminocyclohexane bind to the (Ph₂-BINOLate)-Zn moiety, the enantiomeric conformations of the free ligand become diastereomeric (Figure 2). If the diimine in (Ph₂-BINOLate)Zn(diimine) preferentially adopts one of the diastereomeric conformations, the *meso*-diimine can extend the chiral environment of the catalyst. We previously demonstrated that chiral conformations of achiral ligands can be used to control the relay of chiral information to a substrate in an asymmetric transformation.¹⁸ A similar situation arises when diimines derived from (*1R,2S*)-1,2-diamino-1,2-diphenylethane bind to the (Ph₂-BINOLate)Zn moiety (Figure 3). The resulting diaza-metallacyclopentane will pucker to avoid eclipsing the phenyl groups, giving rise to diastereomeric conformations.

Table 2. Results of Screening *meso*-Diimines **2a–g** with (*S*)-Ph₂-BINOL in eq 2^a

entry	ligand	ee at 0°C (config)	ee at -45°C (config)
1	2a	20 (<i>S</i>)	--
2	2b	3 (<i>R</i>)	--
3	2c	66 (<i>R</i>)	--
4	2d	74 (<i>R</i>)	71 (<i>R</i>)
5	2e	75 (<i>R</i>)	60 (<i>R</i>)
6	2f	39 (<i>R</i>)	--
7	2g	73 (<i>R</i>)	86 (<i>R</i>)

^a Reactions employed 10 mol % Ph₂-BINOL, 10 mol % diimine ligand, and 300 mol % diethylzinc. Conversion data and alcohol ee's were obtained as outlined in the Supporting Information.

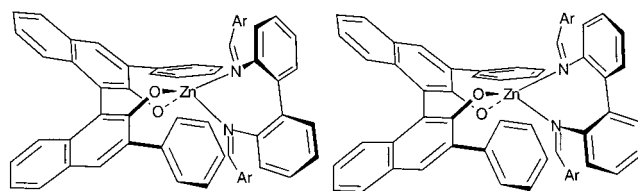
The catalysts derived from diimines in Table 2 showed trends in enantioselectivity similar to those in Table 1. The larger the aryl groups of the diimines, the higher the enantioselectivity of the resulting catalysts. Catalysts incorporating diimines derived from 2,4,6-trimethylbenzaldehyde and 1,2-diamines were the most enantioselective regardless of the structure of the ligand backbone. Thus, unlike our previous studies,¹⁸ ligands containing *meso* backbones (Table 2) had essentially no additional impact on the enantioselectivity of the resultant catalyst when compared to their simple ethylene diimine counterparts (Table 1).

Achiral Diimines with Biphenyl Backbones. The third class of achiral diimine ligands was based on the 2,2'-diaminobiphenyl backbone (Table 3). These ligands become axially chiral on binding to metal centers (Figure 4). They were chosen because we believed that the chiral environment of the (Ph₂-BINOLate)-Zn could be amplified by the chiral conformations of these achiral ligands. Similar biphenyl phosphine derivatives have been used successfully in the asymmetric reduction of ketones.¹⁷ In that work, the slow interconversion of the enantiomeric conformations of the biphenyl diphosphine led to formation of

Table 3. Results of Screening Achiral Diimine Activators Derived from 2,2'-Diamino-biphenyl **3a–3f** with (*S*)-Ph₂-BINOL in Eq 2^a

entry	ligand	ee at 0°C (config)	ee at -45°C (config)
1	3a	38 (<i>S</i>)	--
2	3b	27 (<i>S</i>)	--
3	3c	38 (<i>S</i>)	--
4	3d	25 (<i>R</i>)	--
5	3e	54 (<i>R</i>)	--
6	3f	89 (<i>R</i>)	96 ^b (<i>R</i>)

^a Reactions employed 10 mol % Ph₂-BINOL, 10 mol % diimine ligand, and 300 mol % diethylzinc. Conversion data and alcohol ee's were obtained as outlined in the Supporting Information. ^bThe catalyst formed from ligand **3f** was not completely soluble at -45 °C.

**Figure 4.** Diastereomeric conformations of (Ph₂-BINOLate)Zn(diimine) derived from ligands **3a–3f**.

diastereomeric catalysts that exhibited a large difference in relative rates. In contrast, an interesting study by Gagné and co-workers recently appeared in which they prepared a biphenyl phosphine with a high barrier to atropisomerization when bound to the metal center. Once locked into a chiral conformation, the diastereomeric platinum complexes were separated, the chiral-resolved ligand removed from the metal center, and the platinum bearing the atropisomeric ligand locked in the chiral conformation was used in two catalytic asymmetric reactions with excellent results.³⁷ Atropisomerization of chelating phosphines has been studied in platinum³⁸ and ruthenium sys-

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tems.^{39,40} In related work, the structure and racemization of the biphenyldiamine in $[(\eta^6\text{-C}_6\text{H}_6)\text{Ru}(2,2'\text{-diaminobiphenyl})\text{Cl}]^+$ was studied by Ashby and co-workers using X-ray crystallography and 2D EXSY NMR spectroscopy.⁴¹ Although the angle between the biphenyl rings in the ruthenium complex was 60.4° in the solid state, atropisomerization occurred with $\Delta G^\ddagger_{283\text{K}} = 66.8 \text{ kJ mol}^{-1}$. On the basis of their studies, they proposed a mechanism in which the isomerization of the biphenyldiamine takes place without breaking either of the Ru–N bonds.

It can be seen that combination of (*S*)-Ph₂-BINOL with achiral ligands **3a–f** (eq 2) resulted in a wide range of enantioselectivities [38% ee (*S*) to 89% ee (*R*) at 0 °C]. Further extending the trends observed in Tables 1 and 2, ligands derived from 1-naphthaldehyde and 2-naphthylaldehyde resulted in formation of predominantly the (*S*) enantiomer. In contrast, use of ligands derived from 9-anthraldehyde, 2,6-dichlorobenzaldehyde, and 2,4,6-trimethylbenzaldehyde generated the (*R*) enantiomer as the major product. The use of ligand **3f** resulted in the formation of the most enantioselective catalysts of our study, generating the product in 89% ee at 0 °C and 96% ee at –45 °C. At –45 °C, not all the catalyst was soluble (Table 3).

It is interesting to note that in each series of diimine ligands examined, regardless of the backbone, it was the ligands derived from 2,4,6-trimethylbenzaldehyde that formed the most enantioselective catalysts (Tables 1–3). It is also quite surprising that catalysts incorporating ligands **1e–1g** (Table 1) and meso ligands **2e** and **2g** (Table 2) generated product in the narrow range of enantioselectivities between 73 and 76% ee at 0 °C. The results in Tables 1–3 indicate that the aromatic groups on the imine ligands are very important in determining the enantioselectivity of the catalyst in this system. It is possible that the (Ph₂-BINOLate)Zn moiety dictates the position of the mesityl groups, and therefore, minor changes in the diimine backbone have little influence in the enantioselectivity-determining step.

Use of Simple Achiral Diamines. Employing the achiral diimine activators in Tables 1–3 in eq 2 we observed product ee's from 96% (*R*) to 52% (*S*). Our goal was then to optimize the catalyst by screening achiral ligands such that the (*S*) enantiomer of the product could be generated with higher enantioselectivity. We therefore examined the use of diamines as achiral ligands in eq 2 (Table 4). All of these ligands were available from commercial sources. These diamines do not generate additional stereocenters on binding to tetrahedral metal centers. Employing simple diamines such as ethylenediamine and *N*-alkylated derivatives **4b** and **4c** again resulted in generation of alcohol product with a wide range of ee's (Table 4). The product ee was found to be very sensitive to the size of the *N*-alkyl groups and the number of methylene units in the diamine backbone. Ethylenediamine resulted in a slight increase in the ee of the product over Ph₂-BINOL alone (Table 4, entry 1). TMEDA (entry 2) resulted in a further increase in the ee of the (*S*) product to 64% ee without a significant increase in the catalyst activity (as described below). *N,N,N',N'*-Tetraethyleth-

Table 4. Results of Screening Diamines **4a–4d** with (*S*)-Ph₂-BINOL in Eq 2^a

entry	ligand		ee at 0 °C (config)	ee at –45 °C (config)
1	4a		47 (<i>S</i>)	--
2	4b		64 (<i>S</i>)	--
3	4c		36 (<i>R</i>)	72 (<i>R</i>)
4	4d		4 (<i>S</i>)	75 (<i>R</i>)

^a Reactions employed 10 mol % Ph₂-BINOL, 10 mol % diimine ligand, and 300 mol % diethylzinc. Conversion data and alcohol ee's were obtained as outlined in the Supporting Information.

ylenediamine, however, gave the opposite enantiomer with 36% ee of the (*R*) product at 0 °C and 72% ee at –45 °C. Similarly, *N,N,N',N'*-tetramethyl-1,3-propanediamine gave 4% of the (*S*) enantiomer at 0 °C and 75% ee of the (*R*) enantiomer at –45 °C. A possible cause for this dramatic difference in enantioselectivity generated with **4b** and **4d** could be that the ligands bind to different coordination sites on the metal (Figure 1). It is not clear why some catalysts show large changes in enantioselectivity with decreasing temperature and others do not. It is possible that at lower temperatures certain ligand conformations or catalyst geometries are less accessible. If the most active form of the catalyst involves a higher energy conformation of the ligand, the product ee might show more complex behavior with changes in temperature (Curtin–Hammett principle).

Achiral Diamines That Form Stereogenic Centers on Binding to Metals. The next class of achiral diamines employed were those that form stereocenters on coordination to metals. Coordination of the nitrogen lone pairs of these ligands to zinc suspends nitrogen inversion, rendering the nitrogens stereogenic centers.^{42,43} It is likely, however, that inversion of the configuration at nitrogen can still occur by a mechanism that involves dissociation of one of the amine nitrogens to generate a 3-coordinate zinc intermediate.^{44–46} This is followed by inversion of the nitrogen lone pair and recoordination. We envisioned that the *C*₂-symmetric (Ph₂-BINOLate)Zn moiety would induce the diamine to bind in one of the enantiomeric *C*₂-symmetric modes. The chiral nitrogens would then be in close proximity to the C–C bond-forming processes and influence the enantiofacial selectivity of the catalyst. A similar biasing of the nitrogens in a chiral diamine ligand bound to zinc has been characterized by X-ray crystallography.⁴⁷

Use of ligands **5a–5d** (Table 5) in the asymmetric addition reaction (eq 2) with (Ph₂-BINOLate)Zn led to a range of product ee's [30% (*R*) to 76% (*S*)]. Higher enantioselectivity was observed with bulkier diamines, such as *N,N'*-di-*tert*-butylethylenediamine (**5b**), which gave the highest ee for the (*S*) product in this study (73% ee at 0 °C and 76% ee at –20 °C). Use of

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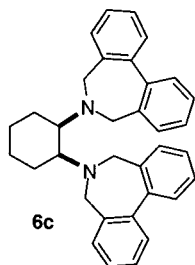
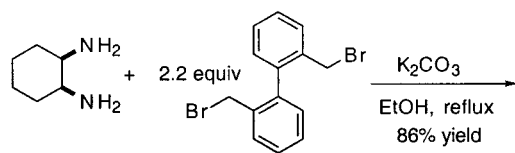
Table 5. Results of Screening Diamines **5a–d** with (S)-Ph₂-BINOL in Eq 2

entry	ligand	ee at 0°C (config)	ee at -20°C (config)
1	5a	47 (S)	--
2	5b	73 (S)	76 (S)
3	5c	30 (R)	--
4	5d	48 (S)	--

^a Reactions employed 10 mol % Ph₂-BINOL, 10 mol % diimine ligand, and 300 mol % diethylzinc. Conversion data and alcohol ee's were obtained as outlined in the Supporting Information.

the bulkier *N*-alkyl groups derived from tritylamine (**5c**) resulted in a reversal of the configuration of the product [30% ee (*R*)]. It is possible that the *N*-alkyl groups are sufficiently large to disfavor simultaneous coordination of both amine nitrogens to the Ph₂-BINOLate)Zn moiety.

Diamines with Axially Chiral Substituents. Diamines with flexible pendant biphenyl groups listed in Table 6 were also examined in eq 2. Ligands **6a–6d** were synthesized as shown for **6c** in eq 3. These ligands were prepared because the



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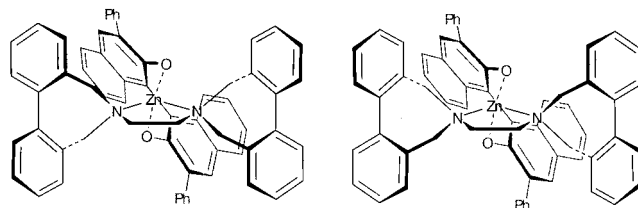
atropisomerization about the biphenyl unit should be facile.^{22,41,42,48,49} Interaction of the rapidly racemizing biphenyl groups with the (Ph₂-BINOLate)Zn moiety could be envisioned to bias the configuration of the atropisomers and extend the chiral environment of the resulting (Ph₂-BINOLate)Zn(diamine) Lewis acids (Figure 5). Phosphite ligands with atropisomeric groups have been successfully employed in asymmetric hydroformylation^{50,51} and hydrogenation reactions.²² Reetz and Neugebauer found that the atropisomeric group had a significant impact on the enantioselectivity of the catalysts in some cases.²²

The results from our study with achiral atropisomeric ligands are shown in Table 6. Catalysts of the type (Ph₂-BINOLate)-Zn(diamine) incorporating ligands **6a** and **6b** behaved very differently from the catalyst generated with TMEDA in the

Table 6. Results of Screening Achiral Diamines **6a–6d** with (S)-Ph₂-BINOL in Eq 2

entry	ligand	ee at 0°C, -45°C, -78°C (config)		
1	6a	71 (R)	87	90
2	6b	75 (R)	87	92
3	6c	83 (R)	92	94
4	6d	45 (S)	--	--

^a Reactions employed 10 mol % Ph₂-BINOL, 10 mol % diimine ligand, and 300 mol % diethylzinc. Conversion data and alcohol ee's were obtained as outlined in the Supporting Information.

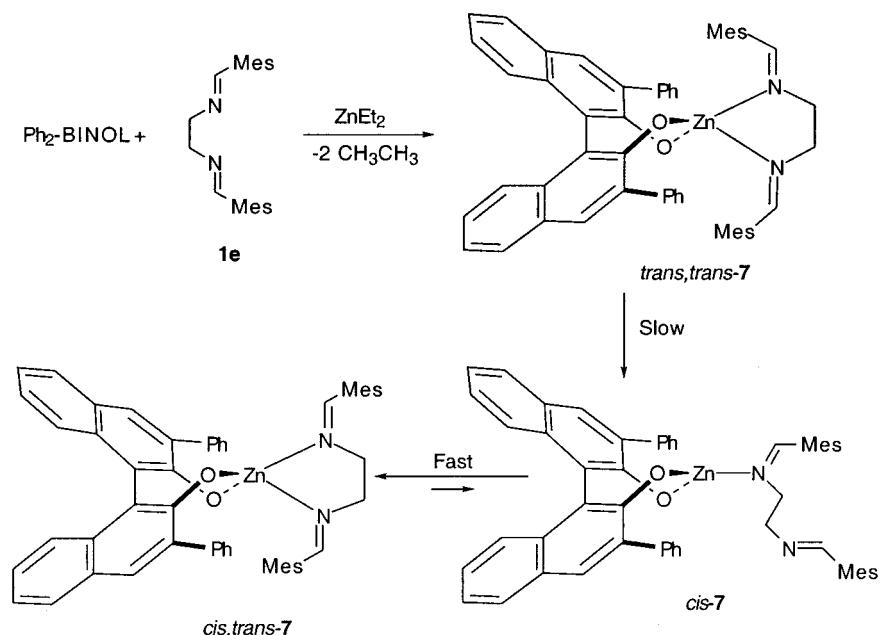
**Figure 5.** Diastereomeric conformations of (Ph₂-BINOLate)Zn(diimine) derived from ligand **6a**.

asymmetric addition reaction (eq 2). Catalysts derived from **6a** and **6b** were more enantioselective, forming product of the (*R*) configuration in 71% ee and 75% ee, respectively, at 0 °C (Table 6, entries 1 and 2) while the TMEDA-based catalyst generated the opposite enantiomer in 63% ee. Catalysts derived from **6a** and **6b** both gave 87% ee at -45 °C. Additionally, catalysts formed with ligands **6a** and **6b** were much faster than the TMEDA complex as discussed below. Ligand **6c**, with the *cis*-1,2-diaminocyclohexane backbone, generated one of the most enantioselective catalysts in this study. At 0, -45, and -78 °C, (*R*)-1-phenyl-1-propanol was generated in 83, 92, and 94% ee.

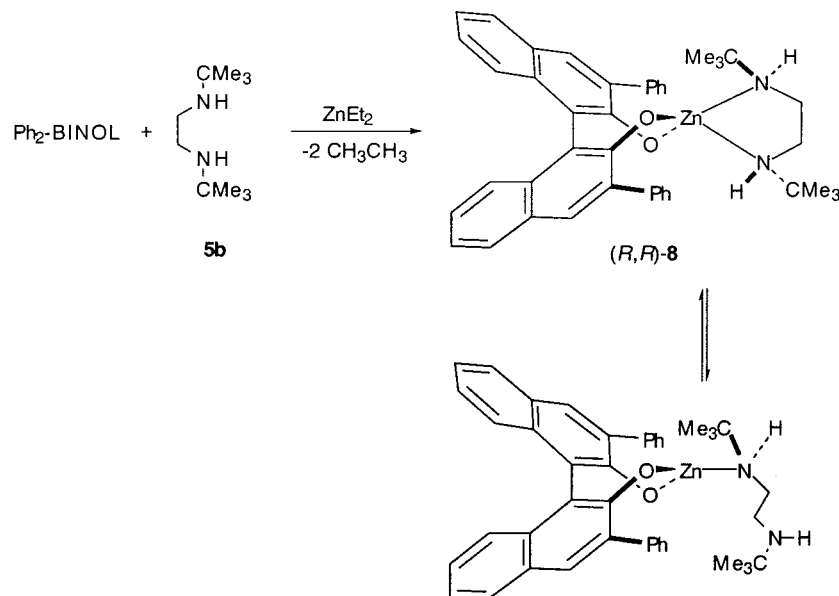
Synthesis of (Ph₂-BINOLate)Zn(diimine) and (Ph₂-BINOLate)Zn(diamine). Our working hypothesis is that the active Lewis acid catalysts in the asymmetric addition process are the 4-coordinate zinc complexes (Ph₂-BINOLate)Zn(diimine) and (Ph₂-BINOLate)Zn(diamine). We therefore decided to synthesize these complexes and examine their solid-state and solution structures. The syntheses were performed by dissolving the diimine **1e** (Scheme 1) or the diamine **5b** (Scheme 2) and 1

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Scheme 1



Scheme 2



equiv of $\text{Ph}_2\text{-BINOL}$ in dichloromethane at room temperature followed by addition of 1 equiv of diethylzinc. A small amount of gas, presumed to be ethane, was evolved upon combining the diethylzinc with the solution of the ligands. The resulting compounds, **7** and **8**, were characterized as outlined below.

Molecular Structure of $(\text{Ph}_2\text{-BINOLate})\text{Zn}(\text{diimine})$, **7.** A search of the Cambridge Data Base found no structurally characterized zinc(BINOLate) complexes. A single-crystal X-ray diffraction study of **7** was undertaken for the purpose of characterization and for comparison with $(\text{Ph}_2\text{-BINOLate})\text{Zn}(\text{diamine})$. Crystals of **7** were grown by slow diffusion of diethyl ether into a dichloromethane solution of the compound at room temperature. A thermal ellipsoid plot of the structure of **7** is illustrated in Figure 6 along with selected bond distances and bond angles. The structure consists of zinc bonded to the $\text{Ph}_2\text{-BINOLate}$ and the diimine ligands with a pseudotetrahedral geometry. Interestingly, the diimine ligand has one *cis* and one

trans imine linkage in the solid-state structure (denoted *cis,trans-7*). The $\text{Zn}-\text{O}(1)$ and $\text{Zn}-\text{O}(2)$ distances of 1.881(2) and 1.918(2) Å, respectively, are similar to other $\text{Zn}-\text{O}$ bonds with phenoxide ligands.^{44,45} The $\text{Zn}-\text{N}(1)$ and $\text{Zn}-\text{N}(2)$ distances of 2.080(2) and 2.058(3) Å, respectively, are slightly shorter than typical $\text{Zn}-\text{N}$ distances when zinc is bonded to other electronegative atoms.^{52–54} The $\text{O}(1)-\text{Zn}-\text{O}(2)$ bond angle is $101.32(10)^\circ$ while the $\text{N}(1)-\text{Zn}-\text{N}(2)$ is more acute at $82.37(11)^\circ$. The torsional angle between the naphthyl rings is 59.5° .

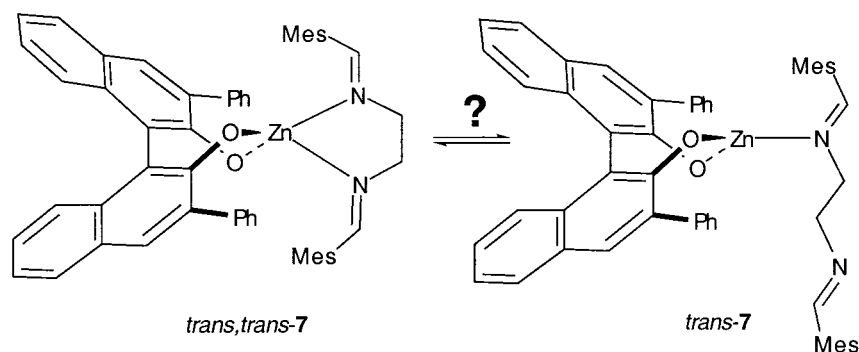
Solution Behavior of **7.** The solution properties of *cis,trans-7* were investigated by dissolving recrystallized *cis,trans-7* in CDCl_3 and collecting NMR data. The ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra were not consistent with the solid-state structure. The

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Scheme 3



downfield region of the ^1H NMR spectrum contained five slightly broadened singlets in a ratio of 2:2:2:1:1 attributed to the aromatic and imine protons rather than six singlets in a ratio of 2:2:1:1:1:1 expected based on the solid-state structure of *cis,trans*-7. Also informative was the observation of a doublet at 7.79 (4H) ppm, a triplet at 7.24 (4H) ppm, and a triplet at 7.16 (2H) ppm that belong to the *equivalent* 3,3'-diphenyl groups (assigned by analysis of the COSY spectrum). These results indicate that the $\text{Ph}_2\text{-BINOLate}$ ligand is in a C_2 -symmetric environment on the NMR time scale. In the upfield region, there are singlets at 1.79 and 1.92 ppm (6H each) and singlets at 2.07 and 2.18 ppm (3H each). Four multiplets integrating to one H each were found between 3.0 and 3.5 ppm representing the four methylene hydrogens of the diimine backbone. These data suggest that the diimine is not symmetrically coordinated to the zinc. A possible explanation for the data above is that only one diimine nitrogen is bound to a C_2 -symmetric ($\text{Ph}_2\text{-BINOLate}$)Zn moiety (*cis*-7, Scheme 1).^{55,56} However, the $^{13}\text{C}\{^1\text{H}\}$ NMR and IR data are inconsistent with this explanation. The $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum supports the C_2 symmetry of the $\text{Ph}_2\text{-BINOLate}$ ligand. The imine carbons resonate at 172 and 176 ppm while in the free ligand **1e** they are found at 162 ppm.⁵⁷ The downfield shifts of the imine carbons indicate that both nitrogens are bound to zinc. The IR of the ligand **1e** has a strong stretch at 1634 cm^{-1} for the imine groups. In solution, the ($\text{Ph}_2\text{-BINOLate}$)Zn(diimine) complex has $\text{C}=\text{N}$ stretching frequencies at 1421 cm^{-1} with a shoulder at slightly higher frequency. The absence of an imine stretch around 1630 cm^{-1} indicates that both imine nitrogens are bound to zinc. The IR and NMR data are consistent with *cis,trans*-7 that readily dissociates the *trans*-imine to give a transient *cis*-7 followed by rapid recoordination of the *trans*-imine to the zinc.

The unexpected solution behavior of crystallized *cis,trans*-7 prompted us to examine its formation. Combination of diimine **1e**, $\text{Ph}_2\text{-BINOL}$, and ZnEt_2 in a 1:1:1 ratio in CDCl_3 followed immediately by collection and analysis of the NMR data from this sample indicated that the complex formed was the C_2 -symmetric *trans,trans*-7 (Scheme 1). Singlets in a ratio of 4:2:2 for the aromatic mesityl hydrogens, the 4,4'-hydrogens of the BINOL backbone, and the imine hydrogens were observed. Additionally, only one type of mesityl group was present and two doublets were observed for the diimine backbone at 3.24

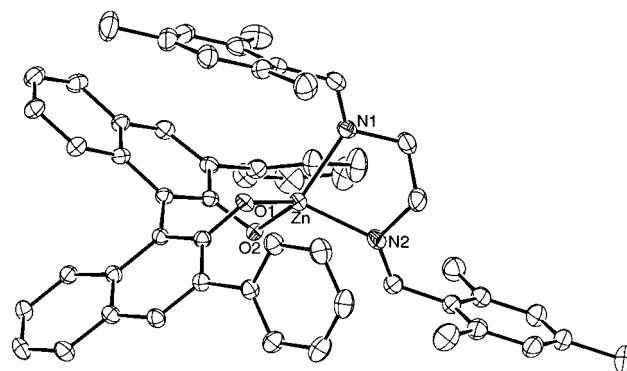


Figure 6. Thermal ellipsoid plot of **7**. Ellipsoids are at the 30% probability level. Selected bond distances (Å) and angles (deg): Zn–O(1) 1.881(2), Zn–O(2) 1.918(2), Zn–N(1) 2.080(2), Zn–N(2) 2.058(3), O(1)–Zn–O(2) 101.32(10), and N(1)–Zn–N(2) 82.37(11).

and 3.47 ppm. Over several days *trans,trans*-7 isomerized to the same compound formed on dissolving *cis,trans*-7 (NMR spectrometry). The chemistry of these compounds is outlined in Scheme 1. Isomerization of free imines,⁵⁸ and those coordinated to metal complexes,^{57,59,60} have been reported to occur slowly at room temperature. Consistent with the observed behavior of *cis,trans*-7, use of crystalline *cis,trans*-7 in place of $\text{Ph}_2\text{-BINOL}$ and **1e** in eq 2 exhibited significantly lower enantioselectivity and overall rate than the in situ prepared catalyst. After 10 min at 0°C , *cis,trans*-7 exhibited 18% ee and 22% conversion in the asymmetric addition compared to the in situ preparation of *trans,trans*-7 which gave 75% ee and 98% conversion under the same conditions.

Because the spectroscopic data of *cis,trans*-7 raise the possibility of the formation of the 3-coordinate intermediate *cis*-7 on dissolving crystals of *cis,trans*-7, we were curious as to whether *trans,trans*-7 might dissociate one imine nitrogen to give the 3-coordinate *trans*-7 (Scheme 3). If this were occurring it might be possible that *trans*-7 would catalyze the asymmetric addition reaction (eq 2). To examine this possibility, we modeled the monodentate diimine in *trans*-7 with a simple monodentate imine. As a model imine we chose the *n*-butyl derivative **9** and examined its use at 10 and 20 mol % (Scheme 4). We found that use of 10 and 20 mol % of the *n*-butylimine **9** and 10 mol % (*S*)- $\text{Ph}_2\text{-BINOL}$ gave identical ee's and overall rates. While use of **1e** and (*S*)- $\text{Ph}_2\text{-BINOL}$ gave 75% ee of the (*R*) enantiomer, **9** and (*S*)- $\text{Ph}_2\text{-BINOL}$ gave the opposite enantiomer

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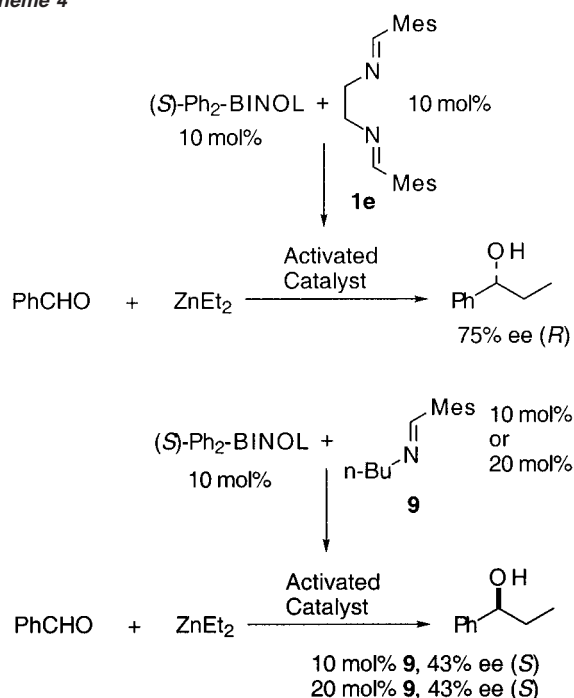
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Scheme 4



in 43% ee. Additionally, the catalyst formed from **1e** promoted the asymmetric addition rapidly, with completion at 0 °C in 10 min. However, both 10 and 20 mol % **9** showed only 30% completion after 1 h under the same conditions. These results suggest that the active form of the catalyst generated from **1e** and $\text{Ph}_2\text{-BINOL}$ is not the 3-coordinate *trans*-**7**.

Molecular Structure of $(\text{Ph}_2\text{-BINOLate})\text{Zn}(\text{diamine})$, **8.** Crystals of **8** were grown by diffusing hexanes vapor into a solution of the complex in dichloromethane. X-ray diffraction data were collected at low temperature, and the structure was solved by direct methods. The asymmetric unit contains two independent molecules that have slightly different conformations. A thermal ellipsoid plot of molecule 1 of $(\text{Ph}_2\text{-BINOLate})\text{-Zn}(\text{diamine})$ is shown in Figure 7 with relevant bond distances and bond angles. Molecule 2 is shown in the Supporting Information. The zinc center in **8** is also 4-coordinate and pseudotetrahedral, bound to the $\text{Ph}_2\text{-BINOLate}$ and the diamine. The diamine is coordinated to zinc in a C_2 -symmetric fashion, and the diamine nitrogens are chiral with the (*R*) configuration. This compound will be referred to as (*R,R*)-**8**. The Zn–O(1) and Zn–O(2) distances of 1.900(4) and 1.940(2) Å and the Zn–N(1) and Zn–N(2) distances of 2.057(4) and 2.086(4) Å, respectively, are very close to those found in *cis,trans*-**7**. The O(1)–Zn–O(2) bond angle of 101.30(14)° is virtually identical to that found in *cis,trans*-**7** while the N(1)–Zn–N(2) of 86.5-(2)° is slightly more open. The torsional angles between the naphthyl rings in molecule 1 and molecule 2 are 63.0° and 64.6°, respectively.

Solution Behavior of **8.** Crystals of (*R,R*)-**8** were dissolved in CDCl_3 , and ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR data were obtained. The ^1H NMR spectrum was more complicated than expected with three *tert*-butyl resonances (between 0.6 and 0.8 ppm) rather than the expected singlet based on the solid-state structure of (*R,R*)-**8**. Also, between 1 and 2.5 ppm, eight resonances were observed instead of the expected three (diamine backbone and N–H's) based on the solid-state structure of (*R,R*)-**8**. The

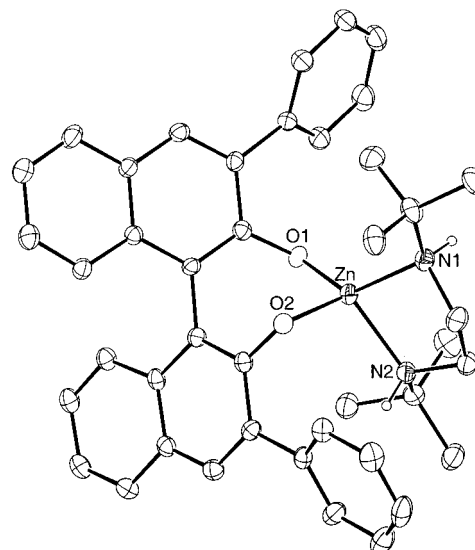


Figure 7. Thermal ellipsoid plot of **8**. Ellipsoids are at the 30% probability level. Selected bond distances (Å) and angles (deg): Zn–O(1) 1.900(4), Zn–O(2) 1.940(2), Zn–N(1) 2.057(4), Zn–N(2) 2.086(4), O(1)–Zn–O(2) 101.30(14), and N(1)–Zn–N(2) 86.5(2).

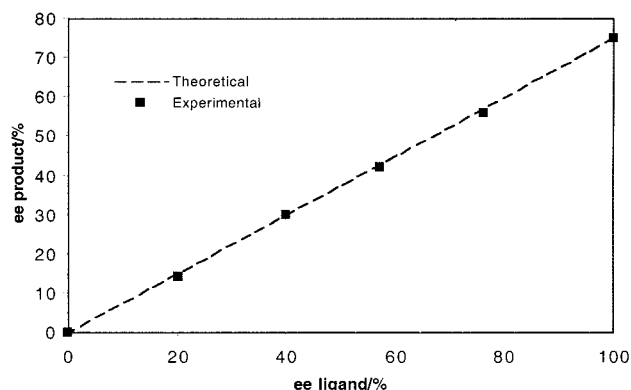


Figure 8. NLE with $\text{Ph}_2\text{-BINOL}$ of various ee's and ligand **1e** at 0 °C.

aromatic region of the ^1H NMR spectrum is very complex. However, the $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum exhibits three resonances for each expected resonance of (*R,R*)-**8**. Thus, in solution it appears that (*R,R*)-**8** is in equilibrium with either the 3-coordinate species or the tetrahedral complex with the (*R,S*) configuration of the nitrogens. Use of crystals of this compound in eq 2 at –20 °C gave 75% ee while generation of the catalyst in the reaction mixture resulted in product of 74% ee.

Nonlinear Studies. To address the nuclearity of the catalysts under the reaction conditions, the ee of the $\text{Ph}_2\text{-BINOL}$ was varied and the ee of the product was determined. Using a representative achiral diimine (**1e**) and diamine (**4b**) in separate sets of experiments with $\text{Ph}_2\text{-BINOL}$ of varying ee's, we observed no nonlinear effects in the asymmetric addition in eq 2 (Figures 8 and 9, respectively). These results suggest that the catalysts for the asymmetric addition reactions are likely to be monomeric⁶¹ unlike the amino alcohol-based catalysts of Oguni,⁶² Noyori,^{63–65} Nugent,^{66,67} and others.²⁹

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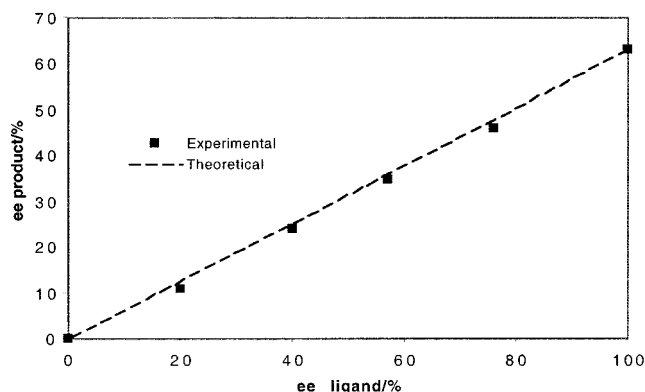


Figure 9. NLE with Ph₂-BINOL of various ee's and ligand **4b** at 0 °C.

Ligand-Accelerated Catalysis. We have performed several experiments designed to provide insight into the nature of the catalysts in this efficient asymmetric process. Dialkylzinc reagents react very slowly with aldehydes in the absence of Lewis acids. However, asymmetric addition reactions involving Lewis acid catalysts formed from chiral amino alcohol ligands have been shown to exhibit strong ligand acceleration.³³ The catalysts in these reactions can form 3-coordinate zinc species that dimerize.^{63,65,68–70} The dimers are the resting state of the catalyst and are believed to be in equilibrium with the 3-coordinate monomers that enter the catalytic cycle.

Mikami proposed that the catalyst formed from Ph₂-BINOL, a chiral diimine, and diethylzinc is the 4-coordinate (Ph₂-BINOLate)Zn(diimine). This is reasonable based on the propensity of zinc to form tetrahedral complexes and our structural and solution investigations of **7** and **8**.⁷¹ Because there is a large excess of zinc (300 mol %) relative to Ph₂-BINOL (10 mol %) and the diimine or diamine (10 mol %), several different zinc complexes can be envisioned to form. These include (Ph₂-BINOLate)Zn, which is likely to be aggregated in solution due to the instability of bent 2-coordinate zinc complexes.⁷¹ It is also possible that (diimine)ZnEt₂ is formed, as related compounds have been characterized.⁷² Species such as [(Ph₂-BINOLate)Zn]_n, (diimine)ZnEt₂, and (diamine)ZnEt₂ may promote the addition reaction with different efficiencies and reduce the ee of the product. To investigate these possibilities, three diamines and two diimines were examined in the asymmetric addition reaction in the absence and presence of (*S*)-Ph₂-BINOL. Under our standard conditions, the reaction of diethylzinc with benzaldehyde in the absence of other ligands is 1% complete after 8 h at 0 °C. Addition of Ph₂-BINOL to this system results in a significant increase in the rate of the reaction with just under 25% conversion after 2 h (Figures 8 and 9). Addition of a diamine (10 mol %) to the diethylzinc and benzaldehyde solution also resulted in an increase in the rate of the addition reaction. Using ligand **4b**, diethylzinc, and aldehyde, less than

3% conversion was realized after 2 h, while diamine **5b** gave 54% conversion in this period. Ligand **6c** gave 51% conversion after 2 h. When the diamine **4b** was combined with Ph₂-BINOL, the reaction was 46% complete after 2 h, which was only slightly faster than Ph₂-BINOL alone. Similar results were observed with **5b** and Ph₂-BINOL (57% after 2 h). Thus, achiral diamines such as **4b** or **5b** and Ph₂-BINOL must be weighed carefully to ensure a 1:1 ratio of the ligands to maximize enantioselectivities. In contrast, combination of Ph₂-BINOL with **6c** resulted in a huge increase in the rate of the reaction. In this case, the reaction was complete in 5 min at 0 °C (Figure 10) and the product was generated with high enantioselectivity (Table 6).

Use of diimines and Ph₂-BINOL also resulted in significant ligand acceleration. Like the diamines of Figure 10, diimine ligands alone were not efficient promoters of the asymmetric addition reaction (Figure 11). However, combination of diimines and Ph₂-BINOL resulted in the formation of highly efficient catalysts for the asymmetric addition reaction. In experiments with ligands **3f** and BINOL, 5 mol % of each ligand was employed. The most efficient (Ph₂-BINOLate)Zn(diamine) and (Ph₂-BINOLate)Zn(diimine) catalysts studied in this work are markedly faster than catalysts formed from amino alcohol ligands. This may be due to the fact that the amino alcohol-based catalysts have a dimeric resting state, and therefore, the concentration of the active, 3-coordinate zinc catalyst is low. Similar ligand acceleration has also been observed with bifunctional zinc–salen complexes.⁷³

Ligand acceleration is easily detected but difficult to understand because it is often not clear which step in the catalytic cycle is rate determining. In the asymmetric addition reaction, important steps include coordination of the aldehyde to the zinc catalyst, formation of the C–C bond, and removal of the product alkoxide or regeneration of the catalyst.⁷⁰ If the rate-determining step were removal of the product alkoxide from the catalyst, we would expect that use of aldehyde substrates substituted with electron-withdrawing and -donating groups in the para position would show similar reactivity. The influence of the substituent on the basicity of the zinc-bound alkoxide should be small due to the inductive effect. However, if the rate-determining step involves the addition of the alkyl group to the carbonyl carbon, the electronic properties of the aldehyde will have a substantial impact. Experiments were carried out using benzaldehyde and *p*-trifluoromethylbenzaldehyde with ligand **1e** under the conditions in eq 2. Reactions with these two substrates were conducted side by side and repeated twice. In both cases, after 1 h, *p*-trifluoromethylbenzaldehyde was 90% complete (75% ee) while benzaldehyde was 58% complete (87% ee). These results indicate that with catalyst formed from ligand **1e**, the rate-determining step is *not* removal of the alkoxide from the catalyst. It is conceivable that variation of the achiral or meso ligands may change the rate-determining step and it is, therefore, not possible to generalize that all the ligands will behave similarly to **1e**. Ligand acceleration could also arise if a catalyst that is only partially soluble becomes soluble on binding the ligand. We have taken care to check the solubility of the reactions outlined here and have noted when reactions were not visually soluble. From the data presented, it appears that the ligand acceleration is not simply a function of the Lewis acidity of the zinc catalyst. Catalysts formed from diamine **6c** or

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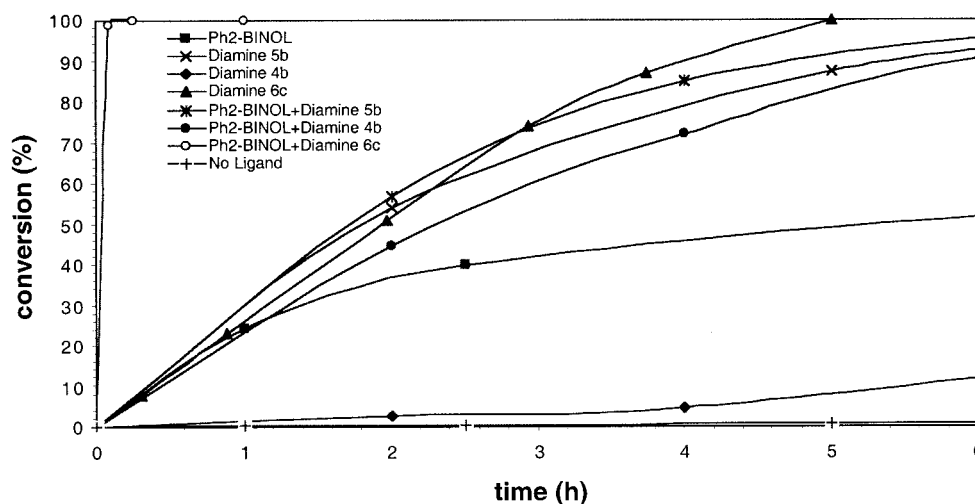


Figure 10. Conversion vs time for ligands **4b**, **5b**, and **6c** with and without Ph₂-BINOL (eq 2).

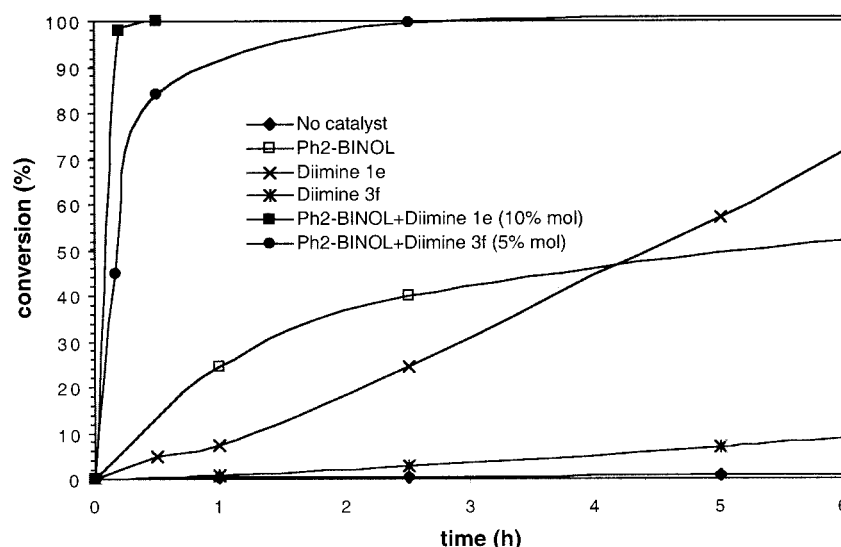


Figure 11. Conversion vs time for ligands **1e** and **3f** with and without Ph₂-BINOL (eq 2).

diimines **1e** and **3f** exhibit similar efficiencies, even though amines are significantly more basic than imines. Furthermore, catalysts bearing diamine ligands such as TMEDA, **6a**, **6b**, and **6c** are expected to have similar Lewis acidity. Yet, as seen for TMEDA and **6c** in Figure 10, the resultant catalysts have very different TOFs. Even in the case of ligands that are very similar in structure, such as **6a**–**6c**, significant differences in TOFs were seen at $-78\text{ }^{\circ}\text{C}$. These three ligands form efficient and enantioselective catalysts in the asymmetric addition reaction (eq 2) giving between 90 and 94% ee. Nonetheless, the TOFs were different. After 3 h at $-78\text{ }^{\circ}\text{C}$, the conversions were as follows: **6a** 12%, **6b** 90%, and **6c** 11%. Thus, simply extending the diamine backbone by a single methylene unit causes a significant increase in the TOF. In this example, the difference in ligand acceleration is likely due to the increased bite angle of the six-membered chelate with **6b** over the five-membered chelate formed with **6a** and **6c**.^{74–77}

Summary

Optimization of asymmetric catalysts has traditionally been performed by the synthesis and screening of chiral ligands.⁴ The resolution of such chiral ligands, or their components, can be an arduous and time-consuming task that severely limits the production of new catalysts. The purpose of this research was to demonstrate that catalyst enantioselectivity and activity could be optimized by modification of achiral and meso ligands. Several of the achiral and meso ligands developed here have chiral conformations and can amplify or extend the chiral environment of the catalyst. Interestingly, these ligands were found to form *the most enantioselective catalysts in this study*. Thus, using a single configuration of a resolved ligand and a series of carefully chosen achiral and meso ligands, we have observed a remarkable range of catalysts enantioselectivities [76% (*S*) to 96% (*R*)]. These results, along with our previous work,^{18,19} clearly indicate that catalysts can be optimized by modification of achiral ligands. Because these catalysts are modular, they lend themselves to combinatorial methods.

We have also examined the structures of the proposed catalysts and the impact of the achiral and meso ligand on catalyst efficiency. On the basis of reactivity studies and crystal

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structure data, the catalysts for the asymmetric addition reactions are proposed to have a pseudotetrahedral zinc that can coordinate the aldehyde to give a 5-coordinate zinc center. Investigation into ligand acceleration shows that achiral diamines with larger bite angles show greater ligand acceleration. Additionally, larger diamines show increased catalyst efficiency than smaller diamines such as TMEDA.

We are currently applying the strategy of optimizing asymmetric catalysts by modification of achiral ligands to a variety of reactions.

Experimental Section

General Methods. Details concerning handling of air-sensitive compounds and purification of solvents have been previously reported.⁷⁸ All Et₂Zn additions were carried out under a nitrogen atmosphere using standard Schlenk techniques. Proton and carbon-13 NMR spectra were recorded on either a Bruker 360-MHz or a 500-MHz Fourier transform NMR spectrometer at the University of Pennsylvania NMR facility. Proton NMR spectra were recorded relative to tetramethylsilane. Chemical shifts are reported in units of parts per million downfield from tetramethylsilane and all coupling constants are reported in hertz. Carbon-13 NMR spectra were obtained at either 90 or 125 MHz on the 360- or 500-MHz instrument, respectively, and chemical shifts were recorded relative to the solvent resonance. Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. High-resolution mass spectra were measured at the University of Pennsylvania Mass Spectrometry Service Center on either a VG Micromass 70/70H or a VG ZAB-E spectrometer. Microanalyses were performed at the University of Pennsylvania. Single-crystal X-ray structures were determined at the University of Pennsylvania with an Enraf Nonius CAD-4 automated diffractometer. IR spectra were either obtained from solid samples in KBr disks or in solution with a Perkin-Elmer 1600 Series FT-IR spectrometer. Enantiomeric excesses were determined by chiral capillary gas chromatography on a Hewlett-Packard 6890 gas chromatograph.

Materials. Unless otherwise specified, all reagents were purchased from Aldrich Chemical Co. and used without further purification. 1,2-Ethylenediamine, *N,N,N',N'*-tetramethylethylenediamine (TMEDA), *N,N,N',N'*-tetraethylethylenediamine, and *N,N,N',N'*-tetramethylpropylenediamine were purified by distillation from CaH₂ prior to use. Solutions of diethylzinc in toluene (1.0 M) were made from neat Et₂Zn (Aldrich) and stored in Schlenk storage tubes under nitrogen. Benzaldehyde was distilled and stored in a Schlenk tube under nitrogen. The following intermediates and ligands were prepared by following literature procedures or are commercially available: 2,3-diamino-2,3-dimethylbutane,⁷⁹ 2,2'-diaminobiphenyl,⁸⁰ 2,2'-bis(bromomethyl)-1,1'-biphenyl,⁸¹ 3,3'-diphenyl-2,2'-dihydroxy-1,1'-dinaphthyl (Ph₂-BINOL),³¹ *N,N'*-bis(1-naphthylidene)ethylenediamine (**1a**),⁸² *N,N'*-bis(2-naphthylidene)ethylenediamine (**1b**),⁸³ *N,N'*-bis(2,6-dichlorobenzylidene)ethylenediamine (**1d**),^{84,85} *N,N'*-bis(2,4,6-trimethylbenzylidene)-1,2-diphenylethylenediamine (**2g**),⁸⁶ *N,N'*-bis(1-benzylidene)biphenyl-2,2'-diamine (**3a**), *N,N'*-bis(2-naphthylidene)biphenyl-2,2'-diamine (**3c**),

N,N'-bis(mesitylmethyl)ethylenediamine (**5a**),⁸⁷ *N,N'*-di-*tert*-butyldiamine (**5b**), *N,N'*-bis(triphenylmethyl)ethylenediamine (**5c**),⁸⁸ and *N,N'*-bis(diphenylmethyl)ethylenediamine (**5d**).⁸⁹ Synthesis and characterization of new achiral imines and amine ligands (**1c**, **1e**, **1f**, **1g**, **2a–2f**, **3b**, **3d–3f**, **6a–6d**, and **9**) are outlined in the Supporting Information.

Synthesis and Characterization of (Ph₂-BINOLate)Zn(diimine) *cis,trans*-7. Under a nitrogen atmosphere, (S)-Ph₂-BINOL (134 mg, 0.30 mmol) and *N,N'*-bis(2,4,6-trimethylbenzylidene)ethylenediamine (**1e**, 97.0 mg, 0.30 mmol) were dissolved in dichloromethane (2 mL). Et₂Zn (38.4 mg, 0.31 mmol) in dichloromethane (1 mL) was then added dropwise to this solution, and the mixture was stirred at room temperature for 30 min. Crystals were grown from this solution over several days by diffusion of hexanes. The crystals were washed with hexanes and dried in vacuo (197 mg of *cis,trans*-7, 0.24 mmol, 78%). *cis,trans*-7: ¹H NMR (CDCl₃, 500 MHz) δ 8.48 (s, 1H), 7.87 (s, 1H), 7.79 (d, *J* = 6.9 Hz, 4H), 7.71 (s, 2H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.24 (t, *J* = 7.5 Hz, 4H), 7.16 (t, *J* = 7.5 Hz, 2H), 6.96 (p, *J* = 4.0 Hz, 2H), 6.87 (d, *J* = 3.7 Hz, 4H), 6.73 (s, 2H), 6.47 (s, 2H), 3.49 (m, 1H), 3.29 (m, 1H), 3.12 (m, 1H), 3.00 (m, 1H), 2.18 (s, 3H), 2.07 (s, 3H), 1.93 (s, 6H), 1.79 (s, 6H) ppm; ¹³C{¹H} NMR (CDCl₃, 125 MHz) δ 175.6, 171.8, 161.2, 141.8, 141.2, 140.1, 136.4, 136.0, 135.0, 134.1, 130.3, 129.8, 129.4, 128.9, 128.6, 128.3, 127.8, 127.4, 127.3, 127.0, 126.2, 125.6, 124.5, 120.4, 58.8, 50.7, 21.2, 21.0, 19.5, 19.1 ppm; IR (CH₂Cl₂): 3054, 2986, 1421, 1264, 896, 746 cm⁻¹. Anal. Calcd for C₅₄H₄₈N₂O₂Zn: C, 78.87; H, 5.88; N, 3.89. Found: C, 78.53; H, 5.91; N, 3.39.

Synthesis of *trans,trans*-7. (S)-Ph₂-BINOL, **1e**, and Et₂Zn were combined in a 1:1:1 ratio in CDCl₃, and a ¹H NMR spectrum was acquired after 30 min at room temperature. ¹H NMR (CDCl₃, 360 MHz) δ 8.44 (s, 2H), 7.73 (d, *J* = 7.3 Hz, 4H), 7.58 (s, 2H), 7.54 (d, *J* = 7.9 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 4H), 7.20 (m, 2H), 6.88 (t, *J* = 7.2 Hz, 2H), 6.72 (m, 2H), 6.46 (d, *J* = 8.4 Hz, 2H), 6.30 (s, 4H), 3.48 (br d, *J* = 8.2 Hz, 2H), 3.25 (br d, *J* = 8.3 Hz, 2H), 1.95 (s, 6H), 1.86 (s, 12 H) ppm.

Synthesis and Characterization of (Ph₂-BINOLate)Zn(diamine) **8.** (S)-Ph₂-BINOL (51.5 mg, 0.12 mmol) and *N,N'*-di-*tert*-butyldiamine (**5b**; 21.2 mg, 0.12 mmol) were dissolved, under a nitrogen atmosphere, in dichloromethane (2 mL). Then, Et₂Zn (15.0 mg, 0.12 mmol) in dichloromethane (1 mL) was added to the solution, which was stirred for 30 min at room temperature. Red crystals of **8** were grown by vapor-phase diffusion of hexanes into the reaction mixture. The crystals were then washed with Et₂O and dried in vacuo (76 mg of **8**·CH₂Cl₂, 0.10 mmol, 85%). In solution, **8** is a mixture of two isomers: ¹H NMR (CDCl₃, 500 MHz) δ 7.91–7.85 (m, 7H), 7.81 (s, 2H), 7.70–7.66 (m, 3H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.28 (t, *J* = 7.7 Hz, 2H), 7.22 (t, *J* = 7.7 Hz, 2H), 7.20–6.94 (m, 12H), 2.45 (m, 1H), 2.37 (m, 2H), 2.17 (m, 1H), 2.01 (m, 1H), 1.88 (t, *J* = 6.7 Hz, 1H), 1.72 (m, 1H), 1.45 (t, *J* = 6.3 Hz, 1H), 1.11 (m, 1H), 0.78 (s, 9H), 0.78 (s, 9H), 0.64 (s, 9H) ppm (the spectrum of **8** is shown in the Supporting Information); ¹³C{¹H} NMR (CDCl₃, 125 MHz) δ 160.6, 160.3, 160.1, 141.8, 141.6, 141.1, 136.1, 135.9, 135.8, 135.2, 134.7, 133.9, 130.9, 130.9, 130.8, 128.1, 127.7, 127.7, 127.6, 127.4, 127.3, 127.1, 127.0, 126.4, 126.3, 126.2, 126.2, 125.8, 125.7, 125.0, 124.7, 124.5, 122.8, 122.4, 121.6, 120.8, 120.7, 120.5, 54.0, 53.8, 53.7, 42.0, 41.4, 41.4, 28.0, 27.8, 27.5 ppm (three aromatic signals could not be located due to overlapping resonances); IR (KBr): 3053, 2986, 1558, 1540, 1506, 1419 cm⁻¹. Anal. Calcd for C₄₂H₄₄N₂O₂Zn·CH₂Cl₂: C, 68.03; H, 6.11; N, 3.69. Found: C, 68.26; H, 6.18; N, 3.68.

Representative Procedure for the Diethylzinc Addition to Benzaldehyde. Ph₂-BINOL (21.6 mg, 0.05 mmol) and the corresponding achiral ligand (0.05 mmol) were introduced in a dry Schlenk flask,

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and the system was purged with nitrogen. To this flask were added dichloromethane (0.5 mL) and Et₂Zn (1.0 mL of a 1.0 M solution in toluene). After the reaction mixture was stirred for 20 min at room temperature, the reaction flask was placed in a bath at 0 °C and benzaldehyde (51 mL, 52 mg, 0.5 mmol) was added dropwise. Aliquots were taken from the reaction at given times, quenched in a saturated ammonium chloride solution, diluted with pentane, and stirred for 5 min. The organic layer was analyzed by GC.

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Supporting Information Available: Detailed information on the crystal structure determinations of **7** and **8**, including tables of data collection parameters, final atomic positional and thermal parameters, and interatomic distances and angles as well as ORTEP diagrams. Synthesis and characterization of new achiral imines and amine ligands (**1c**, **1e**, **1f**, **1g**, **2a–2f**, **3b**, **3d–3f**, **6a–6d**, **9**). NMR data for ligands **1a**, **1b**, **1d**, **2g**, **5a**, **5c**, and **5d**, plots of nonlinear studies, and ¹H NMR spectra of **7** and **8** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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