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Asymmetric Functional Organozinc Additions to Aldehydes Catalyzed by 1,1′-Bi-2-naphthols (BINOLs)†

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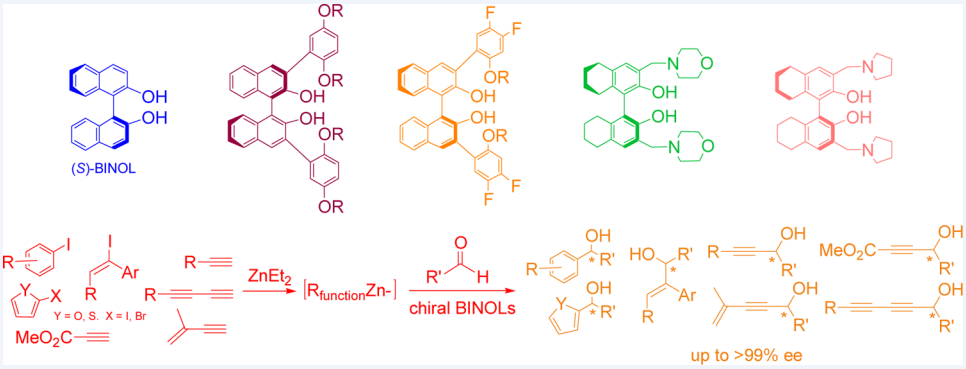

CONSPECTUS: Chiral alcohols are ubiquitous in organic structures. One efficient method to generate chiral alcohols is the catalytic asymmetric addition of a carbon nucleophile to a carbonyl compound since this process produces a C−C bond and a chiral center simultaneously. In comparison with the carbon nucleophiles such as an organolithium or a Grignard reagent, an organozinc reagent possesses the advantages of functional group tolerance and more mild reaction conditions. Catalytic asymmetric reactions of aldehydes with arylzincs, vinylzincs, and alkynylzincs to generate functional chiral alcohols are discussed in this Account. Our laboratory has developed a series of 1,1′-bi-2-naphthol (BINOL)-based chiral catalysts for the asymmetric organozinc addition to aldehydes. It is found that the 3,3′-dianisyl-substituted BINOLs are not only highly enantioselective for the alkylzinc addition to aldehydes, but also highly enantioselective for the diphenylzinc addition to aldehydes. A one-step synthesis has been achieved to incorporate Lewis basic amine groups into the 3,3′-positions of the partially hydrogenated H_8BINOL. These H_8BINOL−amine compounds have become more generally enantioselective and efficient catalysts for the diphenylzinc addition to aldehydes to produce various types of chiral benzylic alcohols. The application of the H_8BINOL−amine catalysts is expanded by using *in situ* generated diarylzinc reagents from the reaction of aryl iodides with $ZnEt_2$, which still gives high enantioselectivity and good catalytic activity. Such a H_8BINOL−amine compound is further found to catalyze the highly enantioselective addition of vinylzincs, *in situ* generated from the treatment of vinyl iodides with $ZnEt_2$, to aldehydes to give the synthetically very useful chiral allylic alcohols.

We have discovered that the unfunctionalized BINOL in combination with $ZnEt_2$ and $Ti(O^iPr)_4$ can catalyze the terminal alkyne addition to aldehydes to produce chiral propargylic alcohols of high synthetic utility. The reaction was conducted by first heating an alkyne with $ZnEt_2$ in refluxing toluene to generate an alkynylzinc reagent, which can then add to a broad range of aldehydes at room temperature in the presence of BINOL and $Ti(O^iPr)_4$ with high enantioselectivity. It was then found that the addition of a catalytic amount of dicyclohexylamine (Cy_2NH) allows the entire process to be conducted at room temperature without the need to generate the alkynylzincs at elevated temperature. This BINOL−$ZnEt_2$−$Ti(O^iPr)_4$−Cy_2NH catalyst system can be used to catalyze the reaction of structurally diverse alkynes with a broad range of aldehydes at room temperature with high enantioselectivity and good catalytic activity.

The work described in this Account demonstrates that BINOL and its derivatives can be used to develop highly enantioselective catalysts for the asymmetric organozinc addition to aldehydes. These processes have allowed the efficient synthesis of many functional chiral alcohols that are useful in organic synthesis.

1. INTRODUCTION

Since Oguni and Omi reported that an amino alcohol, (*S*)-leucinol, catalyzed the reaction of $ZnEt_2$ with benzaldehyde to give the corresponding chiral alcohol with 49% ee in 1984,[1] a tremendous amount of research has been conducted in the area of catalytic asymmetric organozinc additions to carbonyl compounds, and many highly enantioselective catalysts have been obtained.[2−4] Besides the extensive work on the catalytic asymmetric $ZnEt_2$ addition to aldehydes, recent years have seen rapid growth in the study of the addition of functional organozincs such as arylzincs,[5−7] vinylzincs,[8−11] and alkynylzincs[12−15] to carbonyl compounds. These reactions can produce a variety of functional chiral alcohols that are important in organic syntheses.

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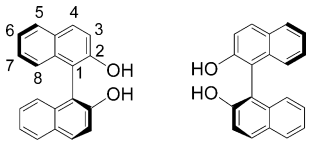
1,1′-Bi-2-naphthol (BINOL) is an easily available chiral molecule whose chirality is derived from the restricted rotation around its 1,1′-bond. The two enantiomers of BINOL can be readily resolved and have exhibited high configurational stability. In the past four decades, the optically active BINOL has served as an important chirality source for the research fields of molecular recognition and asymmetric synthesis.[16−19] In our laboratory, we have studied the use of BINOL to build novel chiral materials for diverse applications.[20] We have also explored the application of chiral Lewis acid complexes of BINOL and its derivatives to catalyze the asymmetric functional organozinc additions to aldehydes. Highly enantioselective catalysts for the reaction of aldehydes with arylzincs, vinylzincs, and alkynylzincs have been obtained. These studies are discussed in this Account.

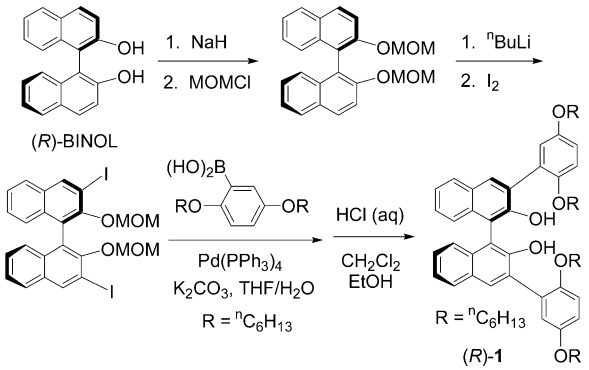


2. CATALYTIC ASYMMETRIC ARYLZINC ADDITION TO ALDEHYDES

2.1. Using the Commercially Available Diphenylzinc

In 1999, we prepared the 3,3′-dianisyl-substituted BINOL compound (*R*)-**1** from (*R*)-BINOL according to Scheme 1.[21]

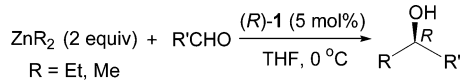
Scheme 1. Synthesis of the 3,3′-Dianisyl BINOL, (*R*)-1

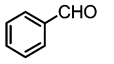
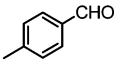
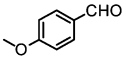
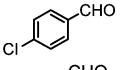
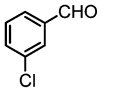
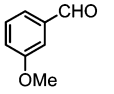
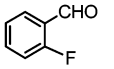
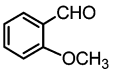
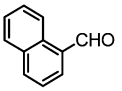
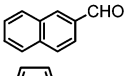
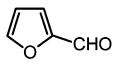
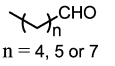
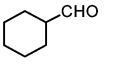
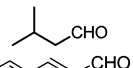
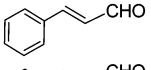
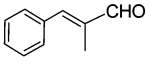
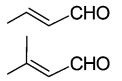
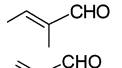
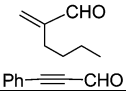
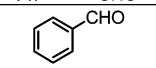
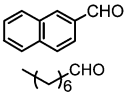
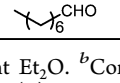


This compound showed high enantioselectivity for the asymmetric reaction of alkylzincs with aldehydes. In the presence of 5 mol % of (*R*)-**1**, the reaction of an alkylzinc with aliphatic, aromatic, and *α*,*β*-unsaturated aldehydes proceeded at 0 °C with 90% to >99% ee's (Table 1). It represents the most generally enantioselective catalysts for the asymmetric alkylzinc addition to aldehydes.

In 1997, Fu reported a catalytic asymmetric diphenylzinc addition to an aldehyde but with only 57% ee.[6a] We found that (*R*)-**1** was the first highly enantioselective catalyst for the diphenylzinc addition to aldehydes with up to 94% ee.[22a] This reaction generates chiral *α*-substituted benzylic alcohols that exist in many organic structures. As shown in Table 2, in the presence of 10−20 mol % of (*R*)-**1**, high enantioselectivities (83−94% ee) were observed for the reaction of the commercially available diphenylzinc with aliphatic, aromatic,

Table 1. Asymmetric Alkylzinc Addition to Aldehydes Catalyzed by (*R*)-1



Aldehyde	Alkylzinc	Isolated Yield (%)	*ee* (%)
	$ZnEt_2$	95	99
		91	98
		92	97
		96	>99
		97	98
		95	99
		93	94
		90	94
		92	>99
		94	99
		90	91
 n = 4, 5 or 7		86-91	98
		90	98
		73	98
		91	92
		86	98
		66	91[a]
		62	93[a,b]
		64	97
		90	98
		90	93[c]
	$ZnMe_2$	90	90
		86	92
		62	88

[a]Solvent Et_2O. [b]Conditions: −40 °C, 0.3 equiv of (*R*)-**1**. [c]With 0.2 equiv of (*R*)-**1**. Solvent THF; −10 °C; distilled aldehyde.

and vinyl aldeyhdes in 10−96 h. The reaction conditions were found to be substrate dependent. For different aldehydes, the

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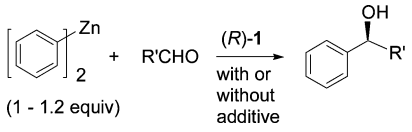
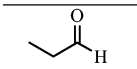
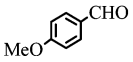
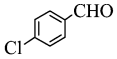
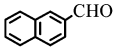
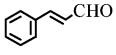
Table 2. Asymmetric Diphenylzinc Addition to Aldehydes Catalyzed by (*R*)-1



Aldehyde	(*R*)-**1** or +Additive (mol%)	Aldehyde Conc. (mM)	Solv	T (°C)	Time (h)	Isolated Yield (%)	ee (%)
	10	100	Tol	0	20	90	87
	20 + 40 $ZnEt_2$	50	Tol	-30	24	84	93
	20 + 40 $ZnEt_2$	5	Et_2O	r.t.	10	86	94
	20 + 40 $ZnEt_2$	5	THF	-10	96	66	87
	20 + 80 $ZnEt_2$ + 40 MeOH	5	CH_2Cl_2	reflux	10	94	83

solvent, temperature, concentration, and additive needed to be varied in order to achieve the high enantioselectivity.

For the asymmetric diphenylzinc addition to aldehydes, one of the main challenges is the uncatalyzed reaction often in competition with the chiral catalyst-controlled reaction, which leads to reduced enantioselectivity. In order to increase the catalytic activity of (*R*)-**1**, electron-withdrawing groups are introduced to the 3,3′-anisyl substituents. This strategy could increase the Lewis acidity of the corresponding zinc complex and thus increase the catalytic activity. As shown in Scheme 2, we prepared a series of 3,3′-bisanisyl BINOL ligands (*S*)-**2a** through (*S*)-**2e** (Scheme 2).[22b] These compounds were tested for the reaction of diphenylzinc with cinnamaldehyde without using methanol as an additive, and the results are compared in Table 3. In these experiments, the BINOL compounds were

Scheme 2. Synthesis of Ligands (*S*)-2a through (*S*)-2e

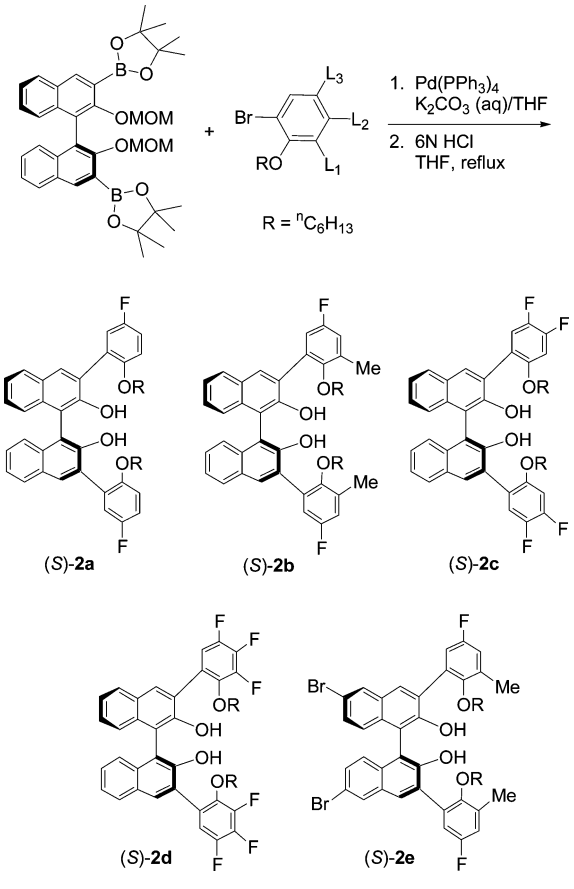


Table 3. Reaction of Cinnamaldehyde with Diphenylzinc in the Presence of the Chiral Ligands[a]

Ligand	Isolated yield (%)	ee (%)	Config.
(*R*)-**1**	88	50	S
(*S*)-**2a**	90	73	R
(*S*)-**2b**	88	81	R
(*S*)-**2c**	92	87	R
(*S*)-**2d**	90	81	R
(*S*)-**2e**	88	70	R

[a]The reaction was carried out under nitrogen at room temperature in CH_2Cl_2 in the presence of 20 mol % of the chiral ligand and 40 mol % of $ZnEt_2$. The concentration of aldehyde was 5 mM. The reaction was quenched in 5 h.

first treated with 2 equiv of $ZnEt_2$ in methylene chloride to generate the corresponding zinc complexes. The zinc complex (20 mol %) was then used to catalyze the diphenylzinc addition to cinnamaldehyde. As shown in Table 3, all these electronically and sterically modified ligands exhibited improved enantioselectivity over (*R*)-**1**. Among these, ligand (*S*)-**2c** gave the best result with up to 87% ee. Addition of methanol could not further increase the enantioselectivity of (*S*)-**2c**.

Compound (*S*)-**2c** was used to catalyze the reaction of diphenylzinc with several aromatic aldehydes and showed high enantioselectivity (Table 4). It possesses better catalytic properties than (*R*)-**1**. When (*R*)-**1** was used to catalyze the reaction of diphenylzinc with aldehydes, it often required longer reaction time, lower or higher temperature, and very different conditions for different substrates. However, when (*S*)-**2c** (20 mol %) in combination with $ZnEt_2$ (40 mol %) was used, it catalyzed the diphenylzinc addition to various aldehydes in methylene chloride at room temperature with high enantioselectivity in 5 h.

Scheme 3 shows a proposed mechanism for the diphenylzinc addition catalyzed by (*S*)-**2c**. Treatment of (*S*)-**2c** with 2 equiv

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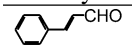
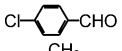
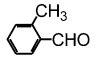
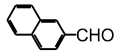
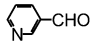
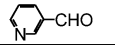
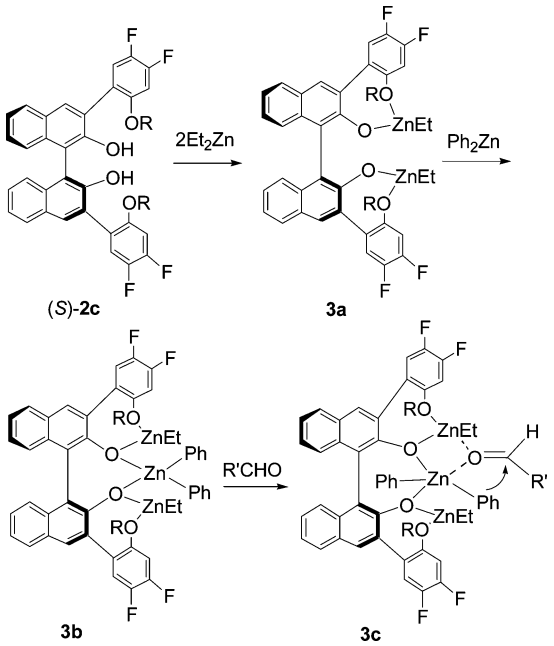
Table 4. Synthesis of Chiral Diarylcarbinols by the Diphenylzinc Addition to Aryl Aldehydes Catalyzed by (*S*)-2c[a]

Aldehyde	Isolated Yield (%)	ee (%)	Config.
	92	87	R
	92	95	S
	87	91	S
	90	88	S
	86	80	(+)
	89	86[b]	(+)

[a]The reaction was carried out under nitrogen at room temperature in CH_2Cl_2 in the presence of 20 mol % (*S*)-**2c** and 40 mol % Et_2Zn. The concentration of aldehyde was 5 mM. The reaction was quenched in 5 h. [b]Et_3B-pretreated aldehyde was used.

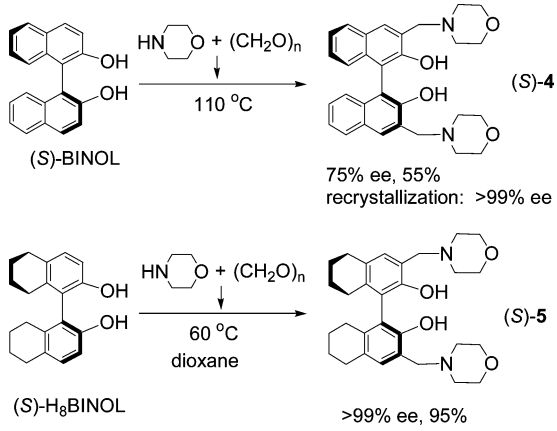
Scheme 3. A Proposed Mechanism for the Catalytic Asymmetric Diphenylzinc Addition by (*S*)-2c



of $ZnEt_2$ could form **3a**, which upon coordination of diphenylzinc could generate the zinc complex **3b**. An aldehyde molecule can coordinate to the zinc centers to generate **3c**. In **3c**, the electron-withdrawing fluorine atoms on the anisyl substituent can increase the Lewis acidity of the Zn center of the [ZnEt] unit. This should provide more catalyst control for the diphenylzinc addition to aldehydes, leading to the much higher enantioselectivity of (*S*)-**2c** than (*R*)-**1**. However, the additional fluorine atoms in (*S*)-**2d** did not further increase the enantioselectivity. The fluorine atom adjacent to the alkoxyl group may have an unfavorable interaction with the [ZnEt] unit to reduce the enantioselectivity. The significantly lower enantioselectivity of (*S*)-**2e** than (*S*)-**2b** shows that the electron-withdrawing bromine atoms on the BINOL unit are not favorable for the diphenylzinc addition. As shown in intermediate **3b**, coordination of $ZnPh_2$ with the Lewis basic central oxygen atoms of the BINOL unit should have activated the subsequent phenyl addition to the aldehyde. When the bromine atoms are introduced to the 6,6′-positions of the BINOL unit as in ligand (*S*)-**2e**, it should reduce the Lewis basicity of the central two oxygen atoms. This should reduce the activation effect for the coordinated $ZnPh_2$ unit and decrease the catalyst-controlled diphenylzinc addition. The lower catalyst control means more of the uncatalyzed diphenylzinc addition. This could explain the lower enantioselectivity of (*S*)-**2e** than (*S*)-**2c**.

In order to further improve the asymmetric diphenylzinc addition, we have examined the introduction of amine substituents to the 3,3′-positions of BINOL to modify the catalyst structure. We have developed a one-step synthesis of the 3,3′-dimorpholinomethyl BINOL (*S*)-**4** from the Mannich-type reaction of (*S*)-BINOL with morpholine and paraformaldehyde (Scheme 4).[23] At 110 °C, partial racemization was

Scheme 4. Preparation of the BINOL−Amine (*S*)-4 and the H_8BINOL−Amine (*S*)-5



observed, which gave (*S*)-**4** with 75% ee and 55% yield. Recrystallization gave the optically pure (*S*)-**4**. When the partially hydrogenated BINOL, (*S*)-H_8BINOL, was used to react with morpholine and paraformaldehyde, the reaction could be conducted at a much lower temperature of 60 °C, and the (*S*)-H_8BINOL−amine product (*S*)-**5** was obtained with >99% ee and 95% yield.[24] Upon treatment with ZnR_2, these 3,3′-dimorpholinomethyl compounds could form a zinc complex similar to **3a** generated from (*S*)-**2c**. In such an intermediate, the cyclic amine groups of (*S*)-**4** and (*S*)-**5** could provide a better defined steric environment around the catalytically active zinc center than the MeO group of (*S*)-**2c**, which could potentially be translated into an increased steric control. In addition, it is also possible to systematically vary the alkyl groups on the nitrogen atoms to tune the catalytic properties of (*S*)-**4** and (*S*)-**5**.

Both (*S*)-**4** and (*S*)-**5** were tested for the diphenylzinc addition to aldehydes.[25,26] It was found that the H_8BINOL−amine (*S*)-**5** gave higher enantioselectivity than the BINOL−amine (*S*)-**4** for the reaction of diphenylzinc with valeraldehyde (92% ee versus 87% ee). Unlike the 3,3′-anisyl-substituted BINOL compounds (*R*)-**1** and (*S*)-**2c** that require the addition of $ZnEt_2$ to generate the enantioselective catalysts, the 3,3′-morpholinomethyl-substituted BINOL compounds (*S*)-**4** and (*S*)-**5** did not need $ZnEt_2$ to achieve the observed high enantioselectivity. We used (*S*)-**5** to catalyze the reaction of diphenylzinc with a variety of aldehydes, and the results are

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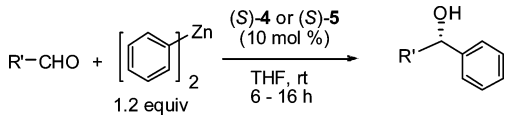
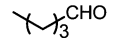
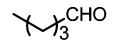
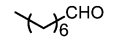
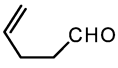
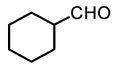
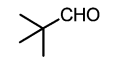
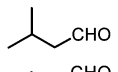
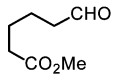
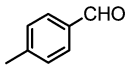
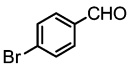
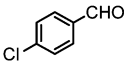
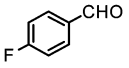
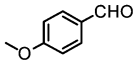
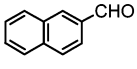
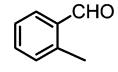
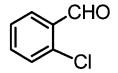
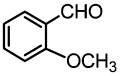
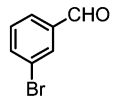
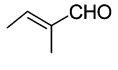
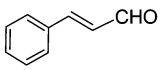
summarized in Table 5. In the presence of 10 mol % (*S*)-**5** and 1.2 equiv of Ph_2Zn at room temperature in THF in 6−16 h, highly enantioselective (81−98% ee) additions to linear and branched aliphatic aldehydes, *p*-substituted aromatic aldehydes, and an α-substituted vinyl aldehyde were observed. The enantioselectivities for the reactions of *ortho*-substituted aromatic aldehydes, a *meta*-substituted aromatic aldehyde, and cinnamaldehyde were lower (51−78% ee).

Table 5. Asymmetric Diphenylzinc Addition to Aliphatic Aldehydes Catalyzed by (*S*)-4 and (*S*)-5



Catalyst	Aldehyde	Isolated Yield (%)	ee (%)
(*S*)-**4**		>82	87
(*S*)-**5**		87	92
		78	93
		75	92
		96	98
		93	98
		82	92
		80	81
		90	89
		91	89
		90	89
		92	94
		91	91
		97	89
		80	78
		95	51
		94	60
		78	68
		88	96
		98	77

We found that the ee of (*S*)-**5** exhibited a linear relationship with those of the diphenylzinc addition products. This indicates that the catalytically active species may contain only one H_8BINOL unit. A detailed NMR spectroscopic study was conducted that allowed us to propose a mechanism for this reaction as shown in Scheme 5. When (*S*)-**5** was treated with 1 equiv of $ZnPh_2$, the resulting complex such as **6** could not react with 2,2-dimethylpropanal to give the addition product. When (*S*)-**5** was treated with 1.5 equiv of $ZnPh_2$, a two-ligand−three-Zn (2 + 3) complex **7a** might be generated. This complex was also unreactive with the aldehyde. The interaction of **7a** with excess $ZnPh_2$ gave a symmetric intermediate with a possible structure of **7b**, which was found to be catalytically active for the $ZnPh_2$ addition to the aldehyde. A transition state **7c** might be involved for the migration of Ph from the coordinated $ZnPh_2$ unit to the coordinated aldehyde. After the consumption of the aldehyde, **7b** was regenerated.

2.2. Using the *in Situ* Generated Diarylzincs[27,28]

In order to expand the application of catalyst (*S*)-**5**, we investigated its catalytic properties for the *in situ* generated diarylzincs. We adopted Knochel's method[29] to prepare diarylzincs such as **8** from the reaction of an aryl iodide with $ZnEt_2$ (Scheme 6). These *in situ* generated diarylzincs were of low reactivity for the addition to aldehydes as shown in the reaction with cyclohexanecarboxaldehyde in Scheme 6. However, when (*S*)-**5** (10 mol %) was introduced to this reaction, the desired addition product was obtained with both high yield (93%) and high enantioselectivity (>99% ee). Thus, (*S*)-**5** not only enhanced the reactivity of the diarylzinc but also provided excellent stereocontrol. Catalyst (*S*)-**5** was used to catalyze the addition of the *in situ* generated diarylzinc to various aldehydes, and the results are summarized in Table 6. These reactions were conducted in three steps. In the first step, the aryl iodide was mixed with $ZnEt_2$ in the presence of Li(acac) and NMP at 0 °C for 12 h. Here, the Lewis basic Li(acac) facilitated the transmetalation of $ZnEt_2$ with the aryl iodide. Then the THF solution of (*S*)-**5** was added, and the resulting solution was stirred at 0 °C for 1 h. In the third step, the solution was warmed to room temperature, and the aldehyde was added. As shown in Table 6, high enantioselectivities (83% to >99% ee) were obtained for the reaction of both aromatic and aliphatic aldehydes.

We also tested the use of methyl *p*-iodobenzoate for the diarylzinc addition catalyzed by (*S*)-**5**. It was found that for this substrate the conditions of Table 6 could not give high enantioselectivity. However, when the solvent in the second step was changed to CH_2Cl_2 and the amount of (*S*)-**5** was increased to 20 mol %, the entire process could be conducted at 0 °C to give the aryl addition products with high enantioselectivity (88−96% ee) for the aromatic, aliphatic, and α,β-unsaturated aldehydes (Table 7).

In Tables 6 and 7, (*S*)-**5** exhibited high enantioselectivity for the reaction of the *in situ* generated diarylzincs with the aromatic aldehydes containing *p*- or *m*-substituents. However, for the reaction of *o*-substituted aromatic aldehydes such as *o*-anisylaldehyde, the enantioselectivity was much lower (79% ee). In order to improve the enantioselectivity of this reaction, we prepared a variety of analogues of (*S*)-**5**, such as (*S*)-**9** to (*S*)-**17**

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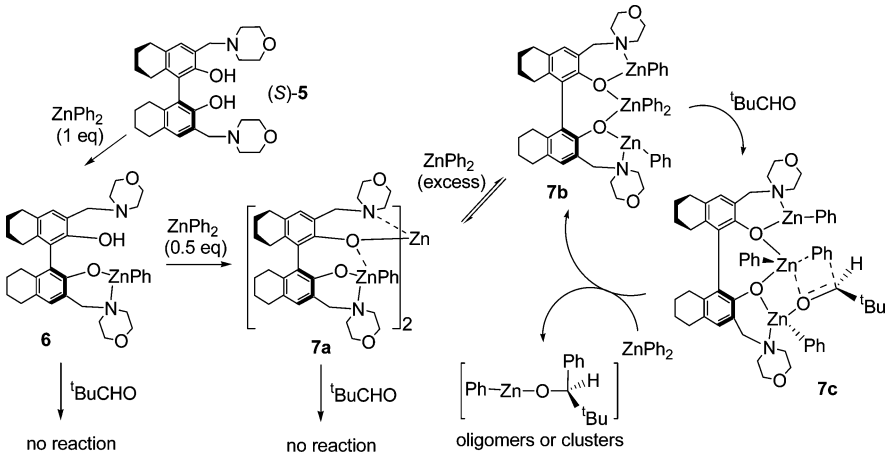
Scheme 5. A Proposed Mechanism for the Diphenylzinc Addition Catalyzed by (*S*)-5



Scheme 6. Preparation of a Substituted Arylzinc and Its Addition to an Aldehyde

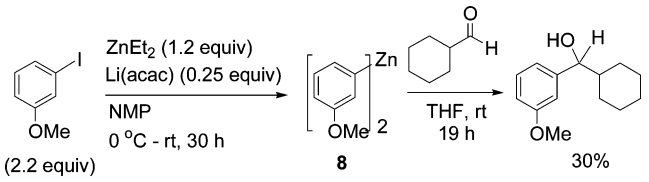
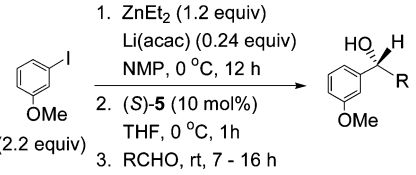
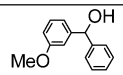
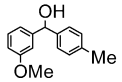
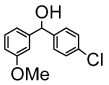
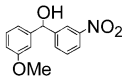
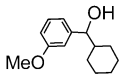
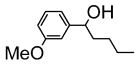
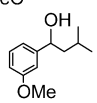


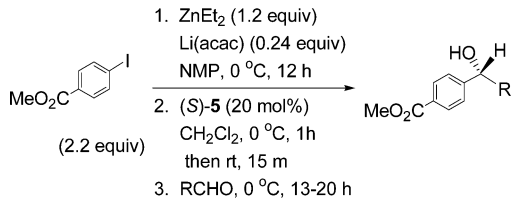
Table 6. Addition of the Arylzinc Generated from *m*-Iodoanisole to Aldehydes in the Presence of (*S*)-5

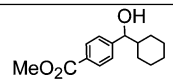
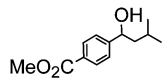
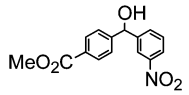
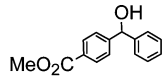
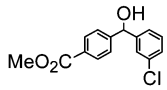
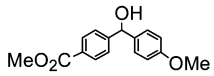
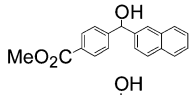
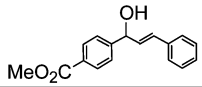


Product	Yield (%)	ee (%)
	93	91
	95	91
	85	90
	93	83
	93	>99
	85	96
	85	93
	90[a]	>99; 99

[a]Combined yield of both diastereomers.

Table 7. Addition of the Arylzinc Generated from Methyl *p*-Iodobenzoate to Aldehydes in the Presence of (*S*)-5



Product	Yield (%)	ee (%)
	86	96
	91	94
	84	92
	97	94
	93	88
	52	89
	89	92
	90	87

(Table 8), by using the same one-step reaction shown in Scheme 4. These compounds were used to catalyze the reaction of methyl *p*-iodobenzoate with *o*-anisylaldehyde, and the results are summarized in Table 8.[28] As shown in entry 7, (*S*)-**14** containing 3,3′-bis(pyrrolidinylmethyl) groups gave excellent enantioselectivity for the reaction (93% ee). The additional sulfur atoms in (*S*)-**15** did not change the enantioselectivity (entry 8). Other H_8BINOL–amine derivatives gave lower enantioselectivity. No enantioselectivity was observed when the dicyclohexylamine-based compound (*S*)-**10** was used (entry 3).

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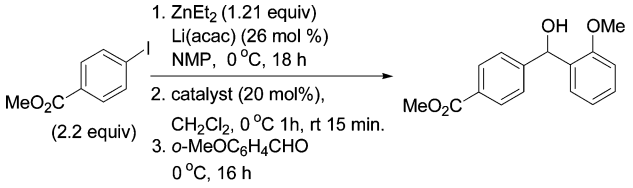
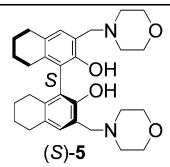
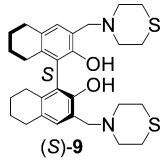
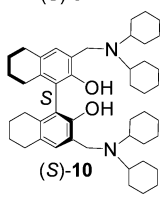
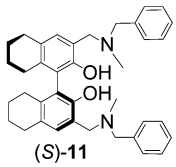
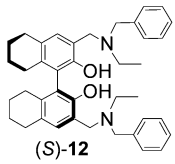
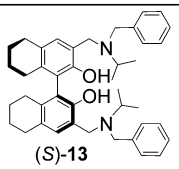
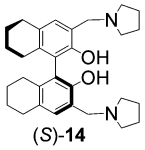
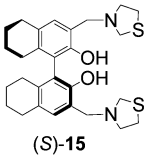
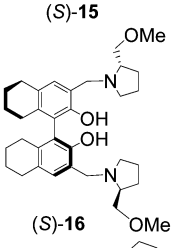
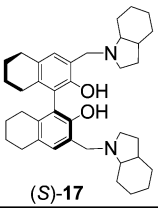
Table 8. Reaction of Methyl *p*-Iodobenzoate with *o*-Methoxybenzaldehyde in the Presence of a Variety of H_8BINOL−Amines



Entry	Catalyst	Isolated Yield (%)	ee (%)
1	 (*S*)-**5**	83	79
2	 (*S*)-**9**	98	79
3	 (*S*)-**10**	80	0
4	 (*S*)-**11**	95	81
5	 (*S*)-**12**	75	74
6	 (*S*)-**13**	65	48
7	 (*S*)-**14**	**90**	**93**
8	 (*S*)-**15**	**98**	**92**
9	 (*S*)-**16**	60	46
10	 (*S*)-**17**	80	83

Thus, the very bulky amine groups of this compound might have prevented the reaction from taking place around the central chiral H_8BINOL unit, giving no chiral induction for the arylzinc addition reaction. We have further found that (*S*)-**14** is generally more enantioselective than (*S*)-**5** for the reaction of methyl *p*-iodobenzoate and 2-halothiophene with other aldehydes. The smaller ring size of (*S*)-**14** might provide a less sterically hindered catalytic site than that by (*S*)-**5** or the other H_8BINOL−amine derivatives, which could be responsible for the improved enantioselectivity.

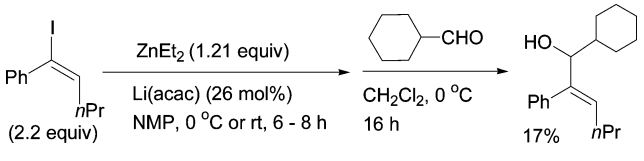
Using iodobenzene allowed us to replace the commercial diphenylzinc for the asymmetric diphenylzinc addition. In the presence of (*S*)-**14** (10 mol %), the reaction of iodobenzene (2.2 equiv) with *p*-anisaldehyde in the presence of Li(acac) (26 mol %), $ZnEt_2$ (1.21 equiv), and NMP (1.5 mL) at room temperature gave the alcohol product with 98% yield and 93% ee.

3. CATALYTIC ASYMMETRIC VINYLZINC ADDITION TO ALDEHYDES[30]

Previously, several highly enantioselective catalysts were reported for the asymmetric vinylzinc addition to carbonyls to generate the synthetically very useful chiral allylic alcohols.[8−11] Those vinylzincs were prepared by using methods such as the hydrozirconation[8] or hydroboration[9,10] of alkynes followed by transmetalation, the use of vinyl boronic acids or esters,[11a] and the Ni-catalyzed $ZnMe_2$ addition to alkynes.[11b] One limitation for the use of the hydrozirconation and hydroboration of terminal alkynes is that they cannot be applied to make normal cycloalkenylzincs.

We tested the treatment of vinyl iodides with $ZnEt_2$ to generate vinylzincs for the catalytic asymmetric vinylzinc addition to aldehydes to generate chiral allylic alcohols. Scheme 7

Scheme 7. Reaction of Vinyl Iodides with Aldehydes in the Presence of $ZnEt_2$



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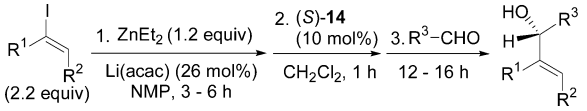
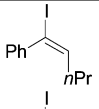
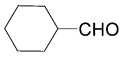
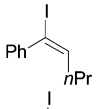
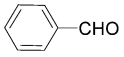
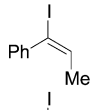
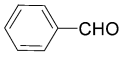
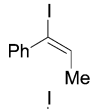
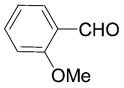
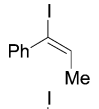
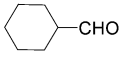
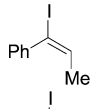
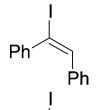
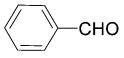
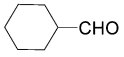
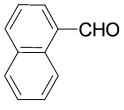
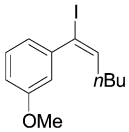
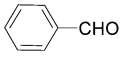
shows the reaction of a vinyl iodide, *E*-1-iodo-1-phenyl-1-pentene, with *c*-$C_6H_{11}CHO$ in the presence of $ZnEt_2$, which gave the corresponding allylic alcohol in only 17% yield. The reactions of other vinyl iodides with aldehydes also did not give good yield except in a few cases. Thus, the vinylzincs prepared directly from the vinyl iodides generally have low reactivity for the addition to aldehydes. However, when the H_8BINOL−amine (*S*)-**14** (10 mol %) was added to this reaction, good yield and high enantioselectivity were achieved. Table 9 shows that the reaction of vinyl iodides with aromatic, aliphatic, and vinyl aldehydes proceeded with 90−98% ee and 60−90% yields at room temperature or 0 °C in the presence of (*S*)-**14** and $ZnEt_2$. These reactions can tolerate functional groups such as ester, chlorine, ether, and silyl ether on the substrates.

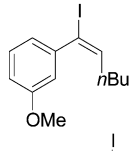
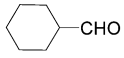
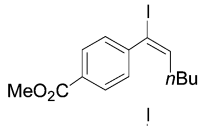
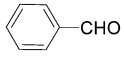
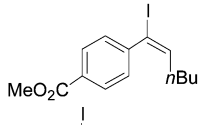
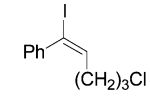
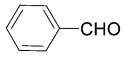
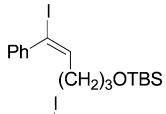
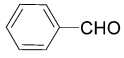
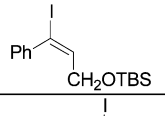
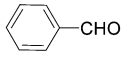
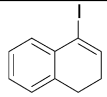
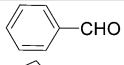
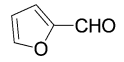
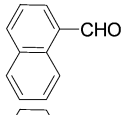
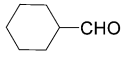
4. CATALYTIC ASYMMETRIC ALKYNYLZINC ADDITION TO ALDEHYDES

Asymmetric alkyne addition to aldehydes is an efficient way to generate chiral propargylic alcohols that are versatile precursors to many organic compounds.[12−15] In 2000, Carreria reported the highly enantioselective reaction of alkynes with aldehydes in the presence of $Zn(OTf)_2$, Et_3N, and an amino alcohol *N*-methyl ephedrine.[13] In this process, a terminal alkyne reacted with $Zn(OTf)_2$ first in the presence of Et_3N to give an alkynylzinc reagent. At room temperature, the alkynylzinc addition to aldehydes required 1.2 equiv of the amino alcohol. Later, they found that when the temperature was increased to 60 °C, the reaction could proceed with a catalytic amount of both $Zn(OTf)_2$ and *N*-methyl ephedrine. This catalytic process was good for α-substituted aliphatic aldehydes but not good for linear aliphatic, vinyl, and aromatic aldehydes.

Table 9. Reaction of Vinyl Iodides with Aldehydes in the Presence of (*S*)-14[a]



Vinyl iodide	Aldehyde	Yield (%)	ee (%)
		82	90
		68	97
		79	97
		60	90
		84	97
	n-$C_7H_{15}CHO$	68	90
		90	97
		75	94
		90	97
		73	98

Vinyl iodide	Aldehyde	Yield (%)	ee (%)
		60	97
		81	97
	Me_2CHCH_2CHO	74	96
		86	98
		84	94
		72	98
		88	93
		79	96
		90	91
		84	96
	Me_2CHCH_2CHO	61	91

[a]Reagents for entries 1−16: vinyl iodide (2.2 equiv), Zn Et_2 (1.2 equiv), Li(acac) (26 mol %), NMP (1.0 mL in entries 1−6 and 10−16; 450 μL in entries 7−9), (*S*)-**14** (10 mol %), aldehyde (1.0 equiv). Reagents for entries 17−21: vinyl iodide (8.0 equiv), $ZnEt_2$ (4.0 equiv), Li(acac) (50 mol %), NMP (1.0 mL), (*S*)-**14** (10 mol %), aldehyde (1.0 equiv). At 0 °C except at room temperature for entries 7−9.

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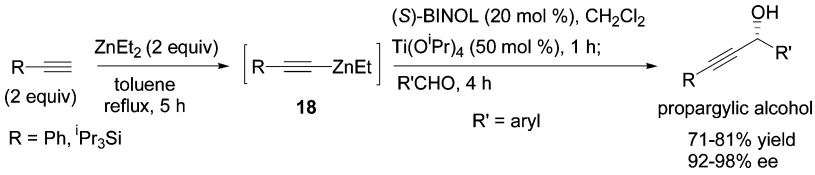
Scheme 8. Enantioselective Addition of Phenylacetylene to Aromatic Aldehydes Catalyzed by BINOL−$ZnEt_2$−$Ti(O^iPr)_4$



In order to develop generally useful catalysts for the asymmetric alkyne addition to aldehydes, we have studied the use of BINOL and its derivatives to catalyze these reactions in the presence of dialkylzincs. Highly enantioselective catalysts for structurally diverse substrates have been obtained. In this section, our methods by using the commercially available unfunctionalized BINOL are discussed. References 14 and 15 give some selected reports and reviews for other work on the catalytic asymmetric alkyne addition to aldehydes including a review of our work on the use of BINOL derivatives.[15f]

4.1. Catalysis Using the BINOL−$ZnEt_2$−$Ti(O^iPr)_4$ System

In 2002, our laboratory reported that BINOL in combination with $ZnEt_2$ and $Ti(O^iPr)_4$ can catalyze the highly enantioselective reaction of phenylacetylene with aromatic aldehydes.[31a] At about the same time, Chan reported the use of BINOL in combination with $ZnMe_2$ and $Ti(O^iPr)_4$ to catalyze the alkyne addition to aldehydes.[14a] A two step procedure for the BINOL-catalyzed alkyne addition to aldehydes was developed (Scheme 8): (1) treatment of a terminal alkyne with $ZnEt_2$ in refluxing toluene; (2) addition of (*S*)-BINOL, $Ti(O^iPr)_4$, an aldehyde, and CH_2Cl_2. The first step probably generated the alkynylzinc intermediate **18**, which then underwent nucleophilic addition to benzaldehyde in the presence of BINOL and $Ti(O^iPr)_4$ to form the chiral propargylic alcohol product. Table 10 gives the results obtained for the reactions of phenylacetylene and triisopropylsilylacetylene with aromatic aldehydes by using the conditions of Scheme 8. It shows that the reactions of alkynes with a variety of aromatic aldehydes gave excellent enantioselectivity (92−97% ee).

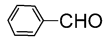
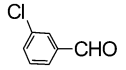
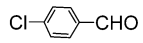
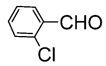
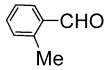
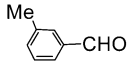
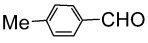
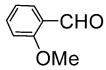
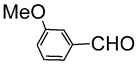
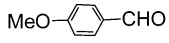
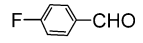
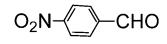
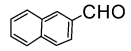
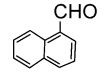
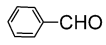
For the reaction of phenylacetylene with aliphatic aldehydes, the reaction conditions of Scheme 8 were modified.[31b] As summarized in Table 11, highly enantioselective alkyne additions to various aliphatic aldehydes were achieved in Et_2O by using the BINOL−$ZnEt_2$−$Ti(O^iPr)_4$ catalyst system (91−95% ee). The reactions of various α,β-unsaturated aldehydes also gave very high enantioselectivity (96−99% ee). Besides the aryl alkyne, this catalyst system was also effective for alkyl alkynes, as demonstrated by the addition of 4-phenyl-1-butyne to linear aliphatic aldehydes (90−95% ee).[32]

We studied the effect of the ee of BINOL on the ee of the propargylic alcohol product for the reaction of phenylacetylene with benzaldehyde in the presence of BINOL−$ZnEt_2$−$Ti(O^iPr)_4$, which gave a small negative nonlinear relationship. This indicates that this catalytic process might not simply contain a monomeric BINOL unit and catalysts containing multiple BINOL or Ti units are possible.[33] Structure **19** only gives a working model for an intermediate with a monomeric BINOL unit. The migration of the alkynyl group in **19** to the coordinated carbonyl group would generate the chiral propargylic center.

4.2. Catalysis Using the BINOL−$ZnEt_2$−$Ti(O^iPr)_4$−Hexamethylphosphoramide (HMPA) System

The BINOL−$ZnEt_2$−$Ti(O^iPr)_4$ system described above has shown a broad substrate scope with respect to the aldehydes in the catalytic asymmetric alkyne addition. However, because the first step of this process requires heating an alkyne with $ZnEt_2$ in refluxing toluene, a number of functional alkynes showed side reactions or underwent decomposition under these conditions. It was previously reported that deprotonation of terminal alkynes by $ZnEt_2$ could take place rapidly at room temperature in highly polar solvents such as DMSO, DMF, and HMPA.[34] However, these highly polar solvents were found to

Table 10. BINOL−$ZnEt_2$−$Ti(O^iPr)_4$ Catalyzed Alkyne Addition to Aromatic Aldehydes[a]

Alkyne	Aldehyde	Isolated Yield (%)	ee (%)
		77	96
		79	92
		81	92
		95	92[b]
		81	96
		77	94
		93	97[b]
		73	93
		78	93
		97	94[b]
		74	96
		79	97
		72	92[b]
		77	98
		71	92
		75	92

[a]Conditions of Scheme 8 were used unless otherwise noted. [b]Alkyne/$ZnEt_2$/$Ti(O^iPr)_4$/BINOL/aldehyde = 4:4:1:0.4:1.[32]

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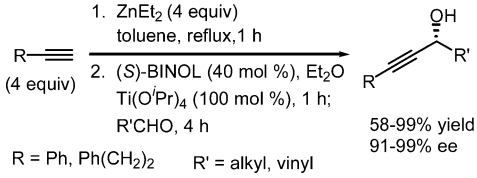
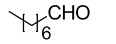
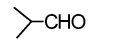
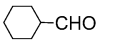
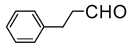
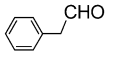
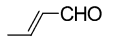
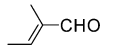
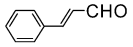
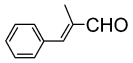
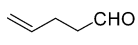
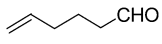
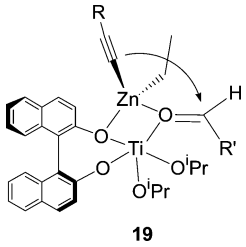
Table 11. BINOL−$ZnEt_2$−$Ti(O^iPr)_4$ Catalyzed Alkyne Addition to Aliphatic and α,β-Unsaturated Aldehydes



Alkyne	Aldehyde	Isolated Yield (%)	ee (%)
		70	93
		84	97
		58	95
		99	93
		93	91
		92	96
		93	96
		89	97
		96	99
		95	95
		83	90

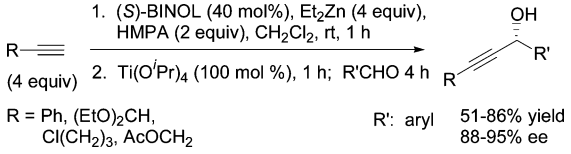


19

be unsuitable for the asymmetric alkyne addition to aldehydes. We then tested the use of these molecules as additive and found that HMPA showed better catalytic properties than the other compounds. Addition of 2 equiv of HMPA facilitated the deprotonation of terminal alkynes by $ZnEt_2$ and allowed the BINOL−$ZnEt_2$−$Ti(O^iPr)_4$ catalyzed alkyne addition to aldehydes to be conducted entirely at room temperature. Using the BINOL−$ZnEt_2$−$Ti(O^iPr)_4$−HMPA system at room temperature gave high enantioselectivity not only for the phenylacetylene addition to aromatic aldehydes but also for the functional alkyne addition to aromatic aldehydes (Scheme 9).[35]

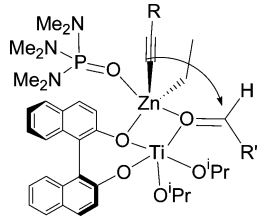
In these reactions, it is proposed that HMPA should act as a Lewis base to coordinate to $ZnEt_2$ to increase the basicity of its Et group and accelerate the subsequent deprotonation of the alkynes. Using HMPA led to a slight reduction of the enantioselectivity from 97% to 93% ee for the reaction of phenylacetylene with benzaldehyde. This indicates that the coordination of HMPA with the zinc center might also influence the

Scheme 9. BINOL−$ZnEt_2$−$Ti(O^iPr)_4$−HMPA Catalyzed Alkyne Addition to Aromatic Aldehydes



alkyne addition step. Compound **20** is a proposed intermediate for the HMPA promoted alkyne addition to an aldehyde.

The BINOL−$ZnEt_2$−$Ti(O^iPr)_4$−HMPA system was applied to the addition of methyl propiolate to aldehydes to generate γ-hydroxy-α,β-acetylenic esters, a class of synthetically very useful functional propargylic alcohols.[36] As shown in Table 12, high enantioselectivities were obtained for the addition of methyl propiolate to a range of aromatic, aliphatic, and α,β-unsaturated aldehydes (81−95% ee).[37]



20

4.3. Catalysis Using the BINOL−$ZnEt_2$−$Ti(O^iPr)_4$−Dicyclohexylamine (Cy_2NH) System

Through a further screening of a broad range of nitrogen-based Lewis bases, we found that a bulky secondary amine additive, dicyclohexylamine (Cy_2NH), showed remarkable improvement of the catalytic process. Using only a catalytic amount (5 mol %) of Cy_2NH in place of the 2 equiv of HMPA in the BINOL−$ZnEt_2$−$Ti(O^iPr)_4$−HMPA system allowed the catalytic alkyne addition to aldehydes to be conducted at room temperature with high enantioselectivity.[38] For example, the BINOL−$ZnEt_2$−$Ti(O^iPr)_4$−Cy_2NH system was found to be good for the reaction of 1,3-diynes with aldehydes.[39,14d] As shown in Table 13, the reaction of 6-phenylhexa-1,3-diyne with aromatic aldehydes in the presence of BINOL−$ZnEt_2$−$Ti(O^iPr)_4$−Cy_2NH gave the corresponding addition products with 56−98% yield and 85−94% ee. Table 14 gives the conditions and results for the reaction of aliphatic and α,β-unsaturated aldehydes with 6-phenylhexa-1,3-diyne, which shows high enantioselectivity (87−92% ee) and yields (80−99%). High enantioselectivities have also been achieved for the addition of aryl, alkyl, and silyl substituted 1,3-diynes to a variety of aldehydes.[39]

Besides 1,3-diynes, a broad range of functional alkynes containing vinyl, aryl, alkyl, or silyl substituents could also be added to many aldehydes in the presence of the BINOL−$ZnEt_2$−$Ti(O^iPr)_4$−Cy_2NH catalyst system to give structurally diverse functional propargylic alcohols with high enantioselectivity.[40] These propargylic alcohols were used to construct multicyclic organic compounds of potential biological and pharmaceutical applications.[41] For most of the substrates, the BINOL−$ZnEt_2$−$Ti(O^iPr)_4$−Cy_2NH catalyst system could be used to replace the other BINOL-based catalyst systems for the asymmetric alkyne addition to aldehydes.

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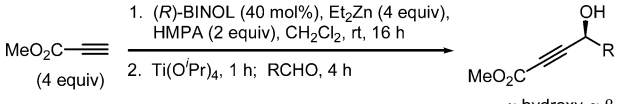
Table 12. Reaction of Methyl Propiolate with Aldehydes in the Presence of BINOL−$ZnEt_2$−$Ti(O^iPr)_4$−HMPA



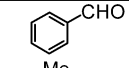
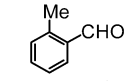
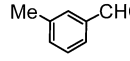
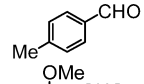
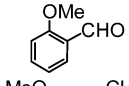
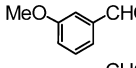
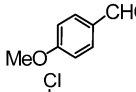
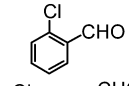
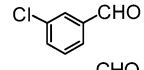
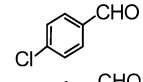
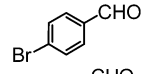
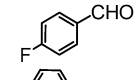
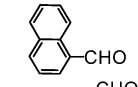
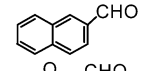
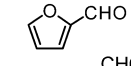
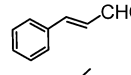
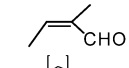
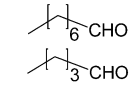
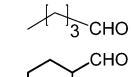
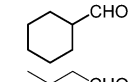
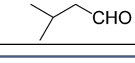
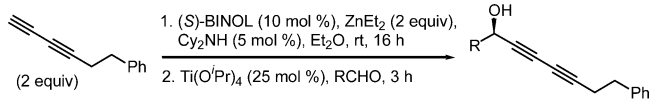
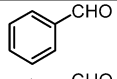
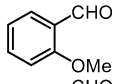
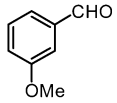
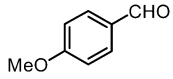
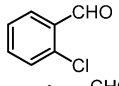
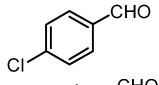
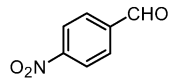
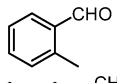
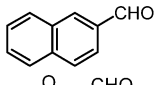
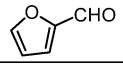
RCHO	Isolated Yield (%)	ee (%)
	69	91
	96	91
	91	93
	81	93
	91	90
	52	90
	82	91
	94	91
	90	93
	84	95
	82	93
	76	85
	87	95
	84	93
	55[c]	87
	65	91
	38	90
	72	81
	76	89
	60	81
	73	83

Table 13. BINOL-$ZnEt_2$-$Ti(O^iPr)_4$−Cy_2NH Catalyzed 1,3-Diyne Addition to Aromatic Aldehydes



RCHO	Isolated Yield (%)	ee (%)
	95	94
	81	91
	96	90
	94	94
	92	89[a]
	94	92
	56	90
	98	92[a]
	98	93
	89	85

[a] (S)-BINOL/$ZnEt_2$/$Ti(O^iPr)_4$/Cy_2NH/diyne/aldehyde = 0.2:2:0.5:0.05:2:1.

5. SUMMARY

In this Account, we have shown that efficient catalysts based on BINOL and its derivatives have been developed for the asymmetric reaction of organozincs with aldehydes. The 3,3′-dianisyl BINOL (*R*)-**1** and (*S*)-**2c** were found to be highly enantioselective for the asymmetric dialkylzinc and diphenylzinc addition to aldehydes. A one-step method was developed for the synthesis of the 3,3′-bismorpholinomethyl H_8BINOL (*S*)-**5** and the 3,3′-bispyrrolidinylmethyl H_8BINOL (*S*)-**14**. These compounds have exhibited high enantioselectivity and good catalytic activity for the arylzinc and vinylzinc additions to aldehydes to generate the synthetically useful chiral benzylic alcohols and allylic alcohols, respectively. In these reactions, aryl iodides and vinyl iodides are converted to the corresponding organozinc reagents *in situ* by treatment with $ZnEt_2$, which in the presence of the chiral catalysts undergo efficient addition to a broad range of aldehydes with high stereocontrol. We have demonstrated that the commercially available unfunctionalized BINOL in combination with $ZnEt_2$, $Ti(O^iPr)_4$, and Cy_2NH can be used to catalyze the reaction of structurally diverse alkynes with a broad range of aldehydes at room temperature with high enantioselectivity and good catalytic activity. These processes generate many types of chiral propargylic alcohols that are important precursors to diverse organic compounds.

Despite the progress described in this Account, as well as in other reports in this area, there are still many challenges in this research such as reducing the catalyst and reagent loading and shortening the reaction time. We are continuously working on developing new, more efficient, and more broadly applicable

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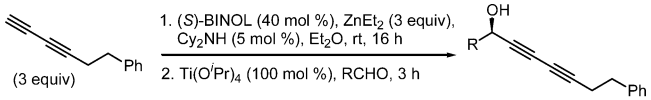
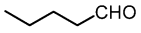
Table 14. BINOL−$ZnEt_2$−$Ti(O^iPr)_4$−Cy_2NH Catalyzed 1,3-diyne Addition to Aliphatic Aldehydes



R = alkyl 80-95% yield 87-92% ee

RCHO	Isolated Yield (%)	ee (%)
	92	92
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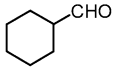
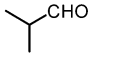
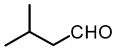
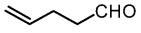
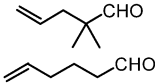
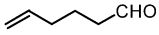
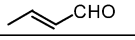
	91	91
	95	90
	90	87
	80	92
	82	89
	86	90
	99	92

catalysts for the asymmetric addition of functional organozincs to carbonyl compounds aiming at providing the synthetic community with practically useful methods to access structurally diverse chiral alcohols.

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Notes

The authors declare no competing financial interest.

Biography

Lin Pu was born in 1965 in Xuyong, Sichuan Province, China. He received his B.S. degree in chemistry from Sichuan University in 1984. He then obtained the Doering Fellowship (CGP) to undertake graduate study in the department of chemistry at University of California, San Diego, in 1985 and received his Ph. D. degree in 1990 under the supervision of Professor Joseph M. O'Connor. As a postdoctoral fellow, he worked with Professor Henry Taube at Stanford University from January 1991 to November 1992 and with Professor Robert Grubbs at California Institute of Technology from November 1992 to August 1994. In the fall of 1994, he was appointed as an assistant professor at North Dakota State University. He then moved to University of Virginia as an associate professor in 1997 and as a professor in 2003. The research projects in his laboratory focus on the design and synthesis of novel chiral molecules and macromolecules for applications in areas such as asymmetric catalysis, enantioselective fluorescent sensors, and electrical and optical materials.

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DEDICATION

†Dedicated to Professor Joseph M. O'Connor at University of California San Diego on the occasion of his 60th birthday.

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