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Synthesis of the bifunctional BINOL ligands and their applications in the asymmetric additions to carbonyl compounds

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Abstract—Efficient one-step syntheses of the bifunctional BINOL and H_8BINOL ligands (*S*)-**6** and (*S*)-**8** have been developed from the reaction of BINOL and H_8BINOL with morpholinomethanol, respectively. The X-ray analyses of these compounds have revealed their structural similarity and difference. The bifunctional H_8BINOL (*S*)-**8** is found to be highly enantioselective for the reaction of diphenylzinc with many aliphatic and aromatic aldehydes and especially is the most enantioselective catalyst for linear aliphatic aldehydes. Unlike other catalysts developed for the diphenylzinc addition which often require the addition of a significant amount of *diethylzinc* with cooling (or heating) the reaction mixture in order to achieve high enantioselectivity, using (*S*)-**8** needs no additive and gives excellent results at room temperature. (*S*)-**8** in combination with diethylzinc and $Ti(O^iPr)_4$ can catalyze the highly enantioselective phenylacetylene addition to aromatic aldehydes. It can also promote the phenylacetylene addition to acetophenone at room temperature though the enantioselectivity is not very high yet. Without using $Ti(O^iPr)_4$ and a Lewis base additive, (*S*)-**8** in combination with diethylzinc can catalyze the reaction of methyl propiolate with an aldehyde to form the highly functional γ-hydroxy-α,β-acetylenic esters except that the enantioselectivity is low at this stage. The bifunctional BINOL ligand (*S*)-**6** in combination with Me_2AlCl is found to be a highly enantioselective catalyst for the addition of TMSCN to both aromatic and aliphatic aldehydes.

1. Introduction

Development of catalysts containing both Lewis acidic sites and Lewis basic sites has attracted significant attention in the field of asymmetric catalysis.[1] Such bifunctional chiral catalysts can simultaneously activate both the electrophile and nucleophile in a chemical reaction and control the stereochemistry of the reaction course to provide efficient chiral induction. We are particularly interested in the study of the 1,1′-bi-2-naphthol (BINOL)-based bifunctional catalysts. The chiral Lewis acid catalysts prepared from the combination of BINOL with a metal complex have been used in many asymmetric organic reactions.[2] Recently, additional Lewis basic functional groups are also incorporated into BINOL to construct various bifunctional BINOL ligands for asymmetric catalysis.[3] Figure 1 gives a few examples of the bifunctional BINOL ligands. The aluminum complexes of the chiral ligands **1**[4] and **2**[5] have been used to catalyze the enantioselective reaction of aldehydes with trimethylsilylcyanide (TMSCN) to generate the synthetically useful chiral cyanohydrins. The zinc complexes of **3**[6] and **4**[7] were used to carry out the alkyne addition to aldehydes and the Simmons–Smith reaction, respectively. Ligand **5** catalyzed the aza-Morita–Baylis–Hillman reaction in the absence of a metal.[8] These ligands have exhibited high enantioselectivity in the corresponding reactions.

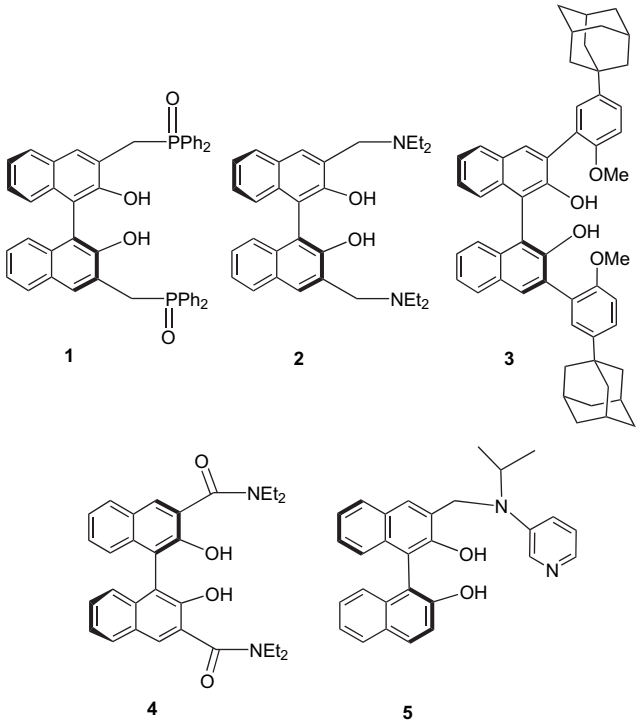

Figure 1. Examples of the bifunctional BINOL ligands.

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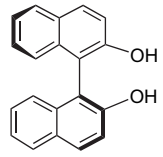
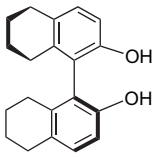
Since the bifunctional BINOL ligands often require a significant number of steps to prepare, we are interested in developing more efficient synthetic methods in order to make these ligands more practically applicable. We have conducted the one-step Mannich-type reaction of BINOL or its partially hydrogenated compound H_8BINOL to synthesize the 3,3′-amino methyl substituted BINOL derivatives.[9] Herein, we report our detailed study of the synthesis of these ligands and their use in the asymmetric organozinc and TMSCN additions to aldehydes and ketones.



(*S*)-BINOL

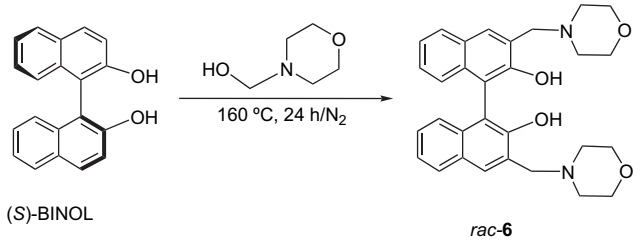


(*S*)-H_8BINOL

2. Results and discussion

2.1. One-step synthesis of the 3,3′-bismorpholinomethyl substituted BINOL and H_8BINOL compounds

2.1.1. Reaction of BINOL. Previously, Cram reported the reaction of racemic BINOL with α-alkoxyamines at 160 °C to prepare the 3,3′-bisaminomethyl substituted BINOLs.[10] We examined this reaction by using the optically pure (*S*)-BINOL to react with the in situ generated morpholinomethanol at 160 °C under nitrogen (Scheme 1). The resulting **6** was converted to its diacetate, and the subsequent analysis by using HPLC Chiralcel-OD column showed a racemic product. Thus, a complete racemization took place during this reaction.



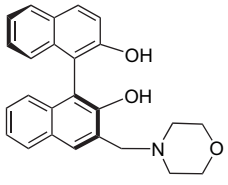
(*S*)-BINOL

rac-**6**

>90% yield, 0% ee

Scheme 1. Reaction of (*S*)-BINOL with morpholinomethanol at 160 °C.

When the reaction of (*S*)-BINOL with morpholinomethanol was conducted at 95–100 °C, the mono-morpholinomethyl substituted compound (*S*)-**7** was obtained in 3 d as the major product in 60% yield and >99% ee. The specific optical rotation of (*S*)-**7** was $[\alpha]_D$ −35.1 (*c* 1.0, CH_2Cl_2). The optically pure (*S*)-**6** was isolated only in 5% yield.



(*S*)-**7**

We further explored the reaction conditions and the results are summarized in Table 1. At 90 °C, various additives such as $NaBH_4$, P_2O_5, and Et_2Zn were used, but no product was obtained (entries 3–5). The best condition was at 110±2 °C, which gave (*S*)-**6** in 55% yield and 75% ee (entry 8). From this reaction, (*S*)-**7** was also isolated in 30% yield and >87% ee. We explored the addition of Lewis acid complexes such as $CeCl_3$, $Zn(OTf)_2$, $TbCl_3$, $InCl_3$, ZnI_2, LiCl, and $VO(acac)_2$, but no improvement was observed.

Table 1. Reaction of (*S*)-BINOL with morpholinomethanol under various conditions (under 30 psi nitrogen)

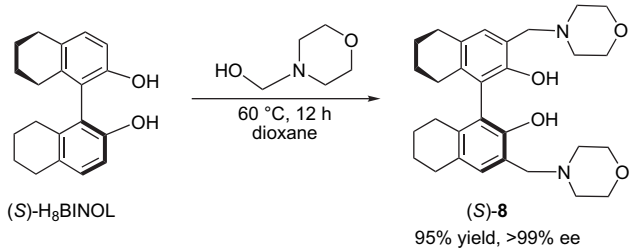
Entry	Temperature (°C)	Additive	Time (h)	Yield of (*S*)-**6** (%)	ee of (*S*)-**6** (%)
1	160	None	24	94	0
2	95–100	None	60	~5	>99
3	90	$NaBH_4$ (1 equiv)	24	~0	—
4	90	P_2O_5 (1 equiv)	24	~0	—
5	90	Et_2Zn (4–6 equiv)	24	~0	—
6	130	None	48	90	<30
7	120	None	72	63	<50
8	110	None	72	55	75

Compound (*S*)-**6** obtained in entry 8 of Table 1 was purified by recrystallization to give the optically pure product. It was first dissolved in a hot CH_2Cl_2/CH_3OH (3:1) mixture, which upon cooling gave white needle-like racemic crystals. After this process was repeated a couple of more times, the compound in the mother liquor was found to be the optically pure (*S*)-**6**. It was isolated as an off-white solid in 37% yield based on (*S*)-BINOL and the optical purity of this compound was over 99% ee. The specific optical rotation of (*S*)-**6** was $[\alpha]_D$ −152.1 (*c* 1.0, CH_2Cl_2). The side product (*S*)-**7** could be converted to (*S*)-**6** by further treatment with morpholinomethanol under the reaction conditions. We also obtained the optically pure (*R*)-**6** and (*R*)-**7** by starting from (*R*)-BINOL.

2.1.2. Reaction of H_8BINOL. Like BINOL, the partially hydrogenated derivative H_8BINOL is also very useful in asymmetric catalysis.[11,12] In a few reactions, the Lewis acid complexes based on H_8BINOL showed enhanced chiral induction over BINOL. This was attributed to the increased size of the partially hydrogenated rings in H_8BINOL. Although it should be very interesting to study the application of the bifunctional H_8BINOLs in asymmetric catalysis, very few functional H_8BINOL compounds have been prepared and studied.[12b–d]

We conducted the reaction of (*S*)-H_8BINOL with morpholinomethanol (Scheme 2). We expected that (*S*)-H_8BINOL should be more reactive in the Mannich-type reaction than (*S*)-BINOL because of its electron-donating alkyl groups on the phenol rings. Thus, the high-temperature condition employed in the reaction of BINOL that caused the partial racemization might not be necessary for H_8BINOL. In addition, it was previously reported that 2,2′-biphenol reacted with the in situ generated morpholinomethanol at 60 °C to give the 3,3′-bismorpholinomethyl substituted 2,2′-biphenol product in 50% yield.[13] Therefore, we treated the optically pure (*S*)-H_8BINOL with morpholinomethanol in dioxane at 60 °C. To our delight, the desired (*S*)-3,3′-bimorpholinomethyl H_8BINOL, (*S*)-**8**, was obtained in 95% yield and

over 99% ee. The specific optical rotation of (*S*)-**8** was $[\alpha]_D$ −35.4 (*c* 1.04, THF).



Scheme 2. Reaction of (*S*)-H_8BINOL with morpholinomethanol.

2.2. X-ray structures of (*S*)-6 and (*S*)-8

The bifunctional BINOL ligand (*S*)-**6** was crystallized by slow evaporation from a CH_2Cl_2/methanol (1:1) solution, whereas the X-ray quality crystals of the bifunctional H_8BINOL ligand (*S*)-**8** were obtained from its ethanol solution. The molecular structures of these compounds are shown in Figures 2 and 3. The most characteristic feature of these structures is the torsion angle C(2)–C(1)–C(1′)–C(2′) between the two binaphthyl moieties, which measures 113.7(2)° in (*S*)-**6** and 100.0(1)° in (*S*)-**8**. The 13.7° difference between the biaryl angles can be attributed to the increased steric interactions of the partially hydrogenated aryl rings, forcing the biaryl unit of (*S*)-**8** to move closer to the orthogonal (90°) conformation.

The molecules are stabilized by strong intramolecular hydrogen bonds O–H···N involving the alcohol groups and the morpholine ring N atoms. The O···N donor acceptor separations which are 2.681 and 2.732 Å in (*S*)-**6** become slightly shorter (2.650 and 2.671 Å) in (*S*)-**8.** The O–H···N angles in these bonds range from 147.3° to 157.4°.

2.3. Asymmetric diphenylzinc additions catalyzed by the bifunctional ligands[9c]

The asymmetric diphenylzinc addition to aldehydes can generate the synthetically useful chiral α-substituted benzyl alcohols. In 1999, we found that compound **9** showed high

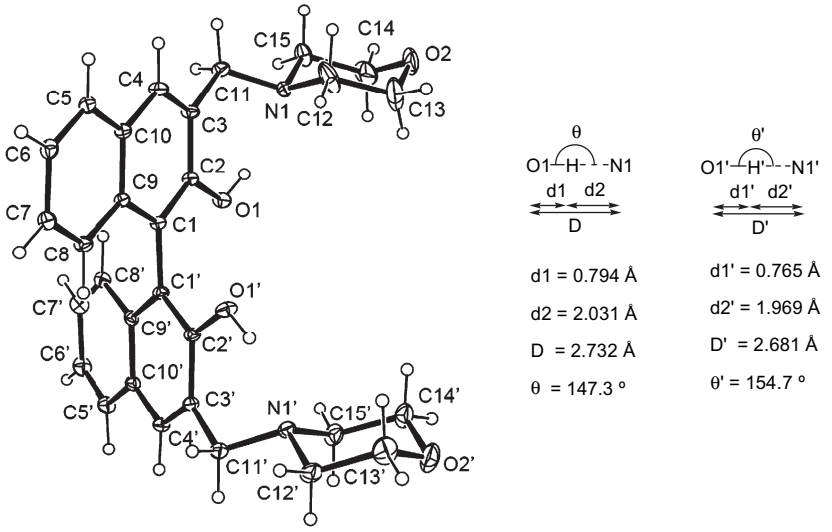


Figure 2. ORTEP drawing (30% probability ellipsoids) of (*S*)-**6**.

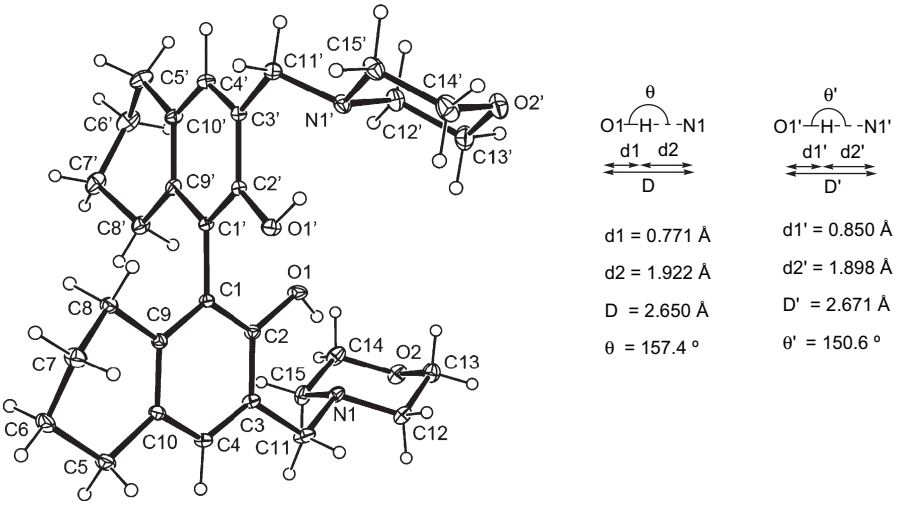
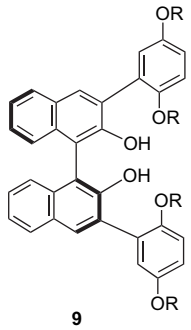
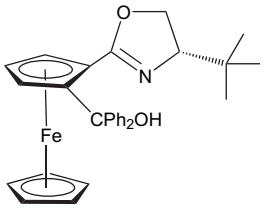


Figure 3. ORTEP drawing (30% probability ellipsoids) of (*S*)-**8**.

enantioselectivity for this reaction.[14] At a similar time, Bolm reported good results with the use of **10**.[15] Other chiral ligands were also developed for the asymmetric diphenylzinc addition.[14–20] A few of these compounds are able to catalyze the diphenylzinc addition to aromatic and α-branched aliphatic aldehydes with high enantioselectivity (>90% ee). However, the enantioselectivity for the reaction of linear aliphatic aldehydes is generally lower, and no catalyst has been reported to give over 90% ee for the reaction of diphenylzinc with a linear aliphatic aldehyde. In addition, the catalysts for the asymmetric diphenylzinc addition often require the use of a significant amount of the diethylzinc additive while cooling (or heating) the reaction mixtures.

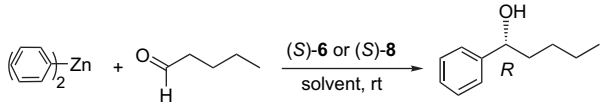


9



10

Since the bifunctional BINOL and H_8BINOL ligands (*S*)-**6** and (*S*)-**8** are structurally analogous to **9**, we have examined their catalytic properties for the asymmetric diphenylzinc addition to aldehydes. We first studied the reaction of diphenylzinc with valeraldehydes in the presence of (*S*)-**6** and (*S*)-**8** (Scheme 3). Table 2 summarizes the results of this reaction under various conditions. In solvents such as methylene chloride, toluene, and diethyl ether, (*S*)-**8** showed very low enantioselectivity (35–39% ee, entries 1–3). However, a dramatic increase in enantioselectivity was observed when the reaction was carried out in THF (92% ee, entry 4). The absolute configuration of the alcohol product was determined to be *R* by comparing its optical rotation with that in literature.[21,22] The enantioselectivity using the BINOL derivative (*S*)-**6** is lower than that using the H_8BINOL derivative (*S*)-**8** (entry 5). Slow addition of the aldehyde did not significantly change the ee (entry 6). Using diethylzinc and/or methanol as the additive slightly reduced the enantioselectivity (entries 7–9). Both decreasing and increasing the amount of the chiral ligand gave lower ee (entries 10 and 11).



Scheme 3. Asymmetric diphenylzinc addition to valeraldehyde.

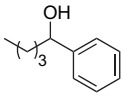
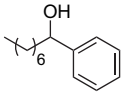
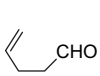
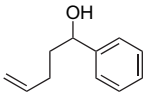
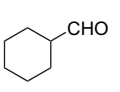
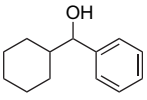
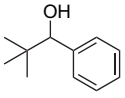
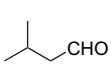
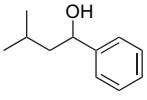
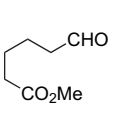
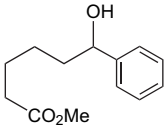
We then used (*S*)-**8** to catalyze the reaction of diphenylzinc with various aliphatic aldehydes by applying the conditions of entry 4 in Table 2. The results are summarized in Table 3. For the reactions of linear (entries 1–3), α-branched (entries 4 and 5) and β-branched (entry 6) aliphatic aldehydes, ee's were observed in the range of 92–98%. For the aldehyde containing an ester group (entry 7), 81% ee was observed. The yields for the reactions were in the range of 75–96%.

Table 2. Results for the diphenylzinc addition to valeraldehyde under various conditions catalyzed by (*S*)-**6** and (*S*)-**8**[a]

Entry	Ligand	Solvent	Ph_2Zn (equiv)	ee (%)[e,f]
1	(*S*)-**8** (10 mol %)	CH_2Cl_2	1.2	35
2	(*S*)-**8** (10 mol %)	Toluene	1.2	38
3	(*S*)-**8** (10 mol %)	Et_2O	1.2	39
4	(*S*)-**8** (10 mol %)	THF	1.2	92
5	(*S*)-**6** (10 mol %)	THF	1.2	87
6[b]	(*S*)-**8** (10 mol %)	THF	1.2	93
7[c]	(*S*)-**8** (10 mol %)	THF	1.0	91
8[d]	(*S*)-**8** (10 mol %)	THF	1.6	89
9[c,d]	(*S*)-**8** (10 mol %)	THF	1.6	91
10	(*S*)-**8** (5 mol %)	THF	1.2	84
11	(*S*)-**8** (20 mol %)	THF	1.4	87

[a] Unless indicated otherwise, the following procedure was used: Under nitrogen to a flask containing (*S*)-**8** (12.3 mg, 0.025 mmol) and diphenylzinc (66.0 mg, 0.3 mmol), a solvent (2 mL, dried) was added and the solution was stirred at room temperature for 1 h. Valeraldehyde (0.25 mmol) was then added and the resulting solution was stirred for 12 h. Aqueous work up and column chromatography on silica gel gave 1-phenyl-1-pentanol.
[b] Valeraldehyde was added dropwise over 2 h.
[c] (*S*)-**8** was pretreated with diethylzinc (20 mol %) for 1 h followed by the addition of diphenylzinc and aldehyde.
[d] MeOH (40 mol %) was added after (*S*)-**8** was treated with diphenylzinc or diethylzinc.
[e] Isolated yields of all these reactions were 82–89%.
[f] ee's were determined by HPLC-chiral OD column.

Table 3. Asymmetric diphenylzinc addition to aliphatic aldehydes catalyzed by (*S*)-**8**

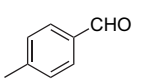
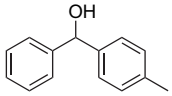
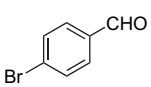
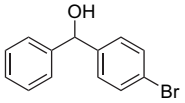
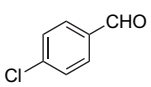
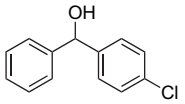
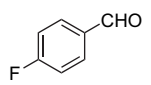
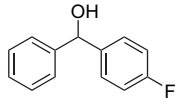
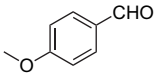
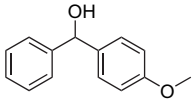
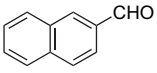
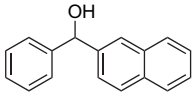
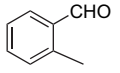
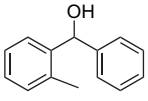
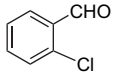
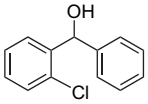
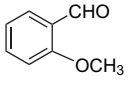
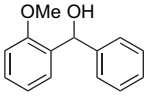
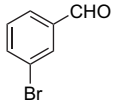
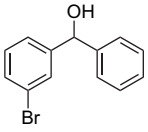
Entry	Aldehyde	Product	Time (h)	Yield (%)[a]	ee (%)[b,c]
1			12	87	92
2			12	78	93
3			12	75	92
4			8	96	98
5			6	93	98
6			16	82	92
7			12	80	81

[a] Isolated yield.
[b] Determined by HPLC-chiral column or GC-chiral column.
[c] All racemic compounds were prepared by mixing the aldehydes with diphenylzinc.

These results demonstrate that (*S*)-**8** is generally enantioselective for the reaction of diphenylzinc with both linear and branched aliphatic aldehydes. Optical rotation measurements showed that the absolute configurations of the alcohol products from the addition to the aliphatic aldehydes were *R* (entries 1 and 5).[21,22]

We also used (*S*)-**8** to catalyze the reaction of diphenylzinc with various aromatic aldehydes by applying the conditions of entry 4 in Table 2. The results are summarized in Table 4. High enantioselectivity was observed for the reaction of *para* substituted benzaldehydes (89–96% ee, entries 1–5).

Table 4. Diphenylzinc addition to various aromatic aldehydes catalyzed by (*S*)-**8**

Entry	Aldehyde	Product	Time (h)	Yield (%)[a]	ee (%)[b,c]
1			16	90	89
2			16	91	89
3			16	90	89
4			16	92	94
5			16	91	91
6			16	97	89
7			16	80	78
8			16	95	51
9			16	94	60
10			16	78	68

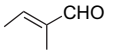
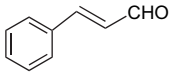
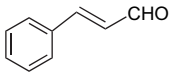
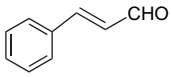
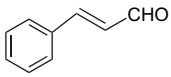
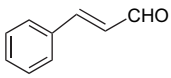
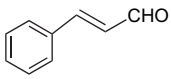
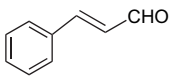
[a] Isolated yield.
[b] Determined by HPLC-chiral column or GC-chiral column.
[c] All racemic compounds were prepared by mixing the aldehydes with diphenylzinc.

The reaction of 2-naphthyl aldehyde gave 89% ee (entry 6). Moderate ee's were observed for the *ortho* and *meta* substituted benzaldehydes (51–78% ee, entries 7–10). The isolated yields for all the reactions were 75–97%. Optical rotation measurements showed that the addition to aromatic aldehydes gave (*S*)-alcohols (entries 3 and 4).[14a,23]

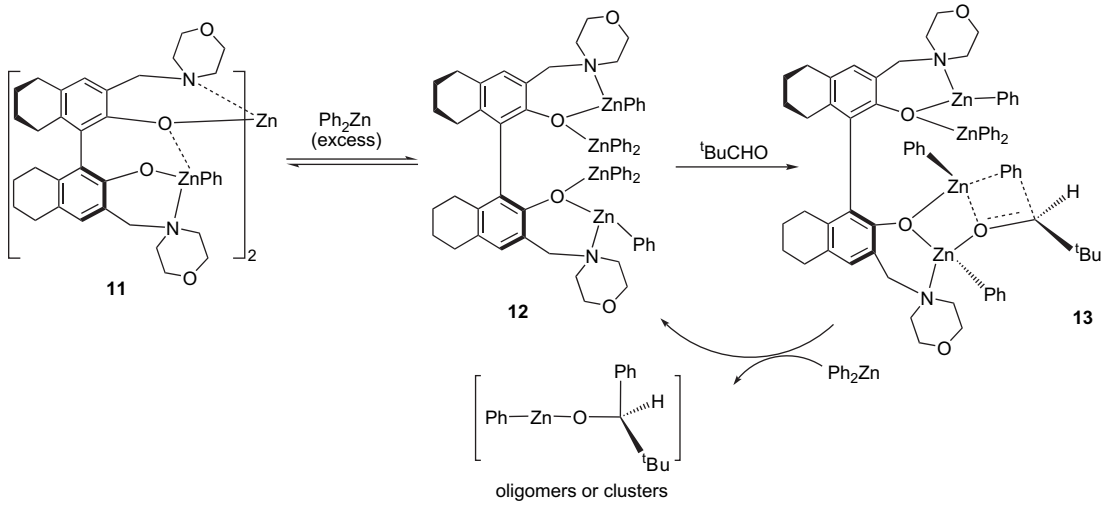
We further studied the reaction of α,β-unsaturated aldehydes with diphenylzinc in the presence of (*S*)-**8**. The results are summarized in Table 5. By using the conditions of entry 4 in Table 2, the reaction of 2-methyl-but-2-enal with diphenylzinc in the presence of (*S*)-**8** showed very high enantioselectivity and high yield (96% ee and 88% yield, entry 1). However, the reaction of cinnamaldehyde gave a significantly lower ee under the same conditions (77% ee, entry 2). Various reaction conditions were examined for the reaction of cinnamaldehyde, including lowering the reaction temperature (entry 3); increasing the amount of (*S*)-**8** and diphenylzinc (entry 4); using additives (entries 5 and 6); and changing the reaction concentration (entries 7 and 8), but no further improvement was observed. Apparently, an α-substituent is important for the high enantioselectivity in the reaction of the α,β-unsaturated aldehydes.

A linear relationship between the enantiomeric composition of the chiral ligand (*S*)-**8** and those of the diphenylzinc addition products was observed.[9c] This suggests that the catalysis for the diphenylzinc addition to either aliphatic or aromatic aldehydes might be catalyzed by a monomeric H_8BINOL catalyst. We also studied the mechanism of the diphenylzinc addition catalyzed by (*S*)-**8** by using NMR spectroscopy and

Table 5. Reaction of diphenylzinc with α,β-unsaturated aldehydes in the presence of (*S*)-**8**

Entry	Aldehyde	(*S*)-**8** (mol %)	Additive	*T*	THF (mL)	Ph_2Zn (equiv)	ee (%)
1		10	None	rt	2	1.2	96 (88)[a]
2		10	None	rt	2	1.2	77 (98)[a]
3		10	None	0 °C	2	1.2	70
4		20	None	rt	2	2.4	78
5		20	40 mol % MeOH	rt	2	2.4	73
6		10	20 mol % Et_2Zn	rt	2	1.2	78
7		10	None	rt	5	1.2	75
8		10	None	rt	1	1.0	78

[a] The isolated yield is given in the parentheses and the reaction time was 12 h.

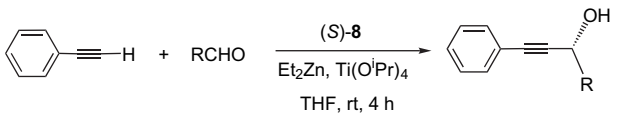


Scheme 4. A proposed mechanism for the catalytic diphenylzinc addition.

the detailed experiments were reported.[9c] The NMR study showed that 2 equiv of (*S*)-**8** reacted with 3 equiv of diphenylzinc to form a stable (2+3) complex with a proposed structure of **11** (Scheme 4). This complex then reacted with excess diphenylzinc to form a C_2-symmetric complex like **12**. Complex **12** might be the catalytically active species, which can activate an aldehyde and produce the phenyl addition product via the proposed transition state **13**.

2.4. Asymmetric alkyne addition to aldehydes catalyzed by (*S*)-8[9b]

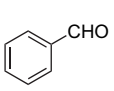
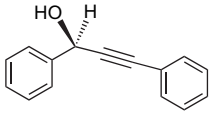
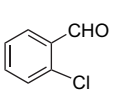
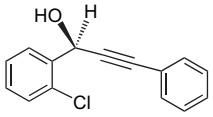
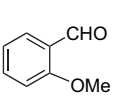
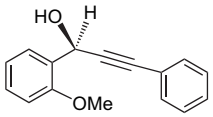
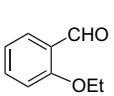
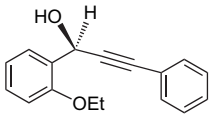
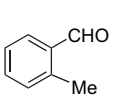
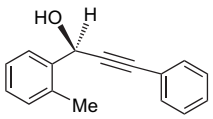
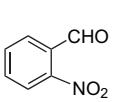
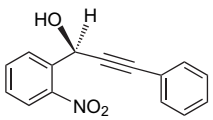
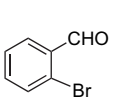
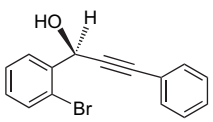
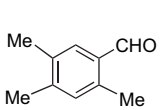
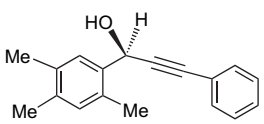
The bifunctional H_8BINOL ligand (*S*)-**8** was used to catalyze the asymmetric alkynylzinc addition to aldehydes to generate chiral propargylic alcohols that are of great utility in organic synthesis.[24–26] The results for the reactions of phenylacetylene with various aldehydes in the presence of (*S*)-**8** (Scheme 5) are summarized in Table 6. The reactions were completed in 4 h by mixing (*S*)-**8** (20 mol %), diethylzinc (4 equiv), $Ti(O^iPr)_4$ (100 mol %), 4 equiv of phenylacetylene (4 equiv), and benzaldehyde (1 equiv) at room temperature in THF. In the case of benzaldehyde, the product was (*R*)-1,3-diphenyl-prop-2-yn-1-ol obtained in 95% yield and 84% ee.



Scheme 5. Reaction of phenylacetylene with aldehydes catalyzed by (*S*)-**8**.

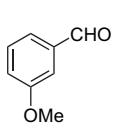
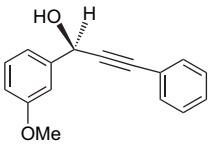
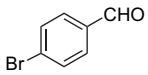
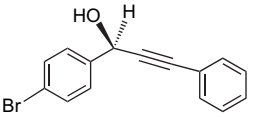
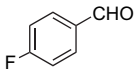
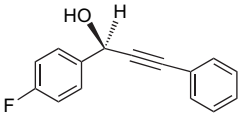
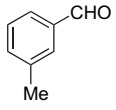
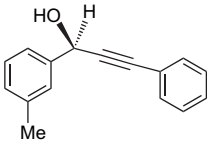
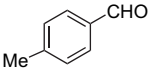
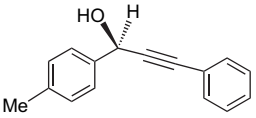
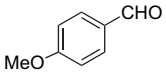
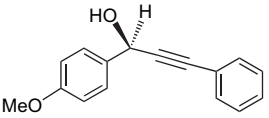
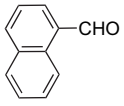
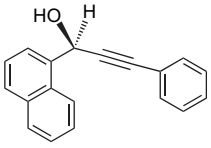
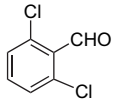
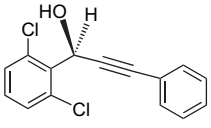
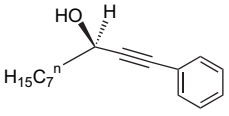
As shown in Table 6, (*S*)-**8** was highly enantioselective for the reaction of the alkyne with aromatic aldehydes. Earlier, Chan and co-workers found that H_8BINOL in combination with $Ti(O^iPr)_4$ and Me_2Zn catalyzed the reaction of phenylacetylene with certain aromatic aldehydes with high enantioselectivity at 0 °C.[27] Under these conditions, however, the reaction of an *ortho*-substituted benzaldehyde was not very good. Using H_8BINOL could give only 76% ee for the reaction of phenylacetylene with *o*-chlorobenzaldehyde. In contrast, the bifunctional H_8BINOL ligand (*S*)-**8** catalyzed the

Table 6. Asymmetric reactions of phenylacetylene with aromatic aldehydes in the presence of (*S*)-**8**, Et_2Zn, and $Ti(O^iPr)_4$[a]

Entry	Aldehyde	Product	Isolated yield (%)	ee (%)
1			93	83
2			88	97
3			76	93
4			83	92
5			88	89
6[b]			62	98
7			84	97
8			68	96

(*continued*)

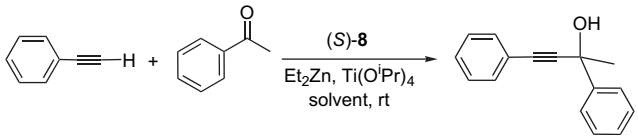
Table 6. (*continued*)

Entry	Aldehyde	Product	Isolated yield (%)	ee (%)
9			93	86
10			86	87
11			50	86
12			98	91
13			86	83
14			99	85
15			85	83
16[c]			62	86
17[d]	$CH_3(CH_2)_6CHO$		76	67

[a] Unless indicated otherwise, reactions were conducted by stirring (*S*)-**8**/Et_2Zn/PhCCH/$Ti(O^iPr)_4$/RCHO=0.1:4:4:1:1 at room temperature in THF for 4 h.
[b] 2 equiv of Et_2Zn and 2 equiv of PhCCH were used.
[c] The reaction time was 6 h.
[d] 20 mol % (*S*)-**8** was used.

same reaction with 97% ee (entry 2). This ligand was found to be good for the asymmetric reaction of a variety of *ortho*-substituted benzaldehydes with ee's in the range of 89–98% (entries 2–8). In addition, (*S*)-**8** was also generally good for other aromatic aldehydes (entries 9–16). The enantioselectivity for a linear aliphatic aldehyde was lower (67% ee, entry 17).

Although significant progress has been made on the asymmetric alkyne addition to aldehydes, not many good catalysts have been obtained for the asymmetric alkyne addition to ketones.[28] The lower reactivity of ketones requires more active catalysts than those for aldehydes. We also found that (*S*)-**8** was an active catalyst for the reaction of phenylacetylene with acetophenone at room temperature (Scheme 6). Table 7 summarizes the results under various reaction conditions. Generally, the reaction was conducted by mixing (*S*)-**8** (10 mol %), Et_2Zn (4 equiv), and phenylacetylene (4 equiv) at room temperature for 2 h in a solvent (1 mL) followed by the addition of $Ti(O^iPr)_4$ (100 mol %) and acetophenone. After 36 h, the reaction was quenched and the ee was determined by HPLC-chiral column. Less than 34% ee was observed for the reactions in toluene, methylene chloride, and diethyl ether (entries 1–3). A significant increase of the enantioselectivity was observed in THF (63% ee and 60% yield, entry 4). Reducing the amount of $Ti(O^iPr)_4$ or increasing the amount of THF decreased the enantioselectivity (entries 5 and 6). Changing the solvent from THF to 1,4-dioxane increased the ee to 69% (entry 7).



Scheme 6. Reaction of phenylacetylene with acetophenone catalyzed by (*S*)-**8**.

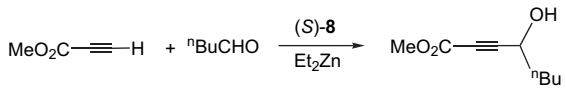
Table 7. Reaction of phenylacetylene with acetophenone in the presence of (*S*)-**8** under various conditions

Entry	(*S*)-**8** (mol %)	$Ti(O^iPr)_4$ (mol %)	Solvent	ee (%)
1	10	100	Toluene	0
2	10	100	CH_2Cl_2	34
3	10	100	Et_2O	19
4	10	100	THF	63 (60)[a]
5	10	40	THF	60
6	10	100	THF[b]	56
7	10	40	1,4-Dioxane	69

[a] Isolated yield in the parentheses.
[b] 3 mL THF was used.

We recently reported that the unfunctionalized BINOL in combination with Et_2Zn, $Ti(O^iPr)_4$, and HMPA can catalyze the highly enantioselective reaction of methyl propiolate with aldehydes to generate γ-hydroxy-α,β-acetylenic esters.[29] These compounds are used extensively in the synthesis of complex organic compounds.[30] We also studied the use of (*S*)-**8** to catalyze the reaction of methyl propiolate with valeraldehyde. It was found that (*S*)-**8** in combination with Et_2Zn was highly active at room temperature without the need for $Ti(O^iPr)_4$ and a Lewis base additive (Scheme 7). However, the enantioselectivity was low in various solvents such as Et_2O, CH_2Cl_2, and toluene. The highest enantioselectivity at room temperature was only 28% ee though the reaction was generally completed in 3–6 h (Table 8, entry 1). Other reaction conditions were examined and the results are shown in Table 8. In diethyl ether, decreasing the reaction temperature to −20 °C led to a significantly increased enantioselectivity (70% ee, entry 4). At −20 °C, all the reactions were completed in high yields in 16 h (entries 2–4). Further decreasing the temperature to −40 °C made the reaction sluggish and reduced both the yield and ee

(entry 5). Replacing diethylzinc with dimethylzinc decreased the enantioselectivity (entry 6). Increasing the amount of (*S*)-**8** and diethylzinc could not improve the reaction (entry 7). The ee of the product was determined by analyzing the ^{1}H NMR spectrum of the (*R*)-O–Ac mandelate derivative (Scheme 8).



Scheme 7. Asymmetric reaction of methyl propiolate with valeraldehyde.

Table 8. Results for the reaction of methyl propiolate with valeraldehyde in the presence of (*S*)-**8**

Entry	(*S*)-**8** (mol %)	Solvent	R_2Zn	*T* (°C)	ee (%)
1	10	Toluene	1.2 equiv Et_2Zn	25	28
2	10	Toluene	1.2 equiv Et_2Zn	−20	43
3	10	CH_2Cl_2	1.2 equiv Et_2Zn	−20	28
4	10	Et_2O	1.2 equiv Et_2Zn	−20	70
5	10	Et_2O	1.2 equiv Et_2Zn	−40	62
6	10	Et_2O	1.2 equiv Me_2Zn	−40	50
7	20	Et_2O	2.4 equiv Et_2Zn	−20	69

2.5. Asymmetric alkylzinc addition to aldehydes catalyzed by (*S*)-8

The use of (*S*)-**8** to catalyze the classical dimethylzinc and diethylzinc addition to aldehydes was tested.[25a,b] To our surprise, (*S*)-**8** could not give the desired product for the reaction of diethylzinc or dimethylzinc with valeraldehyde in THF at room temperature in spite of its high enantioselectivity for the diphenylzinc addition. For the reaction of diethylzinc with benzaldehyde in THF at room temperature, (*S*)-**8** produced 1-phenyl-propyl-1-ol in 78% yield and 73% ee.

2.6. Asymmetric TMSCN addition to aldehydes catalyzed by the bifunctional ligands

The asymmetric syntheses of cyanohydrins have attracted considerable research activity because these compounds are versatile starting materials for many functional organic molecules such as α-hydroxyacids, α-hydroxyketones, α-amino acids, and β-amino alcohols.[31] Previously, the aluminum complexes of the bifunctional ligands **1**[4] and **2**[5] have been used to catalyze the reaction of aldehydes with TMSCN to generate the chiral cyanohydrins with good enantioselectivity. These bifunctional ligands require either a six-step synthesis from the optically active BINOL[32] or an optical resolution in a multi-step synthesis from a naphthalene derivative.[5] This makes the use of the bifunctional BINOL and H_8BINOL ligands (*S*)-**6** and (*S*)-**8** very attractive because of their one-step synthesis.

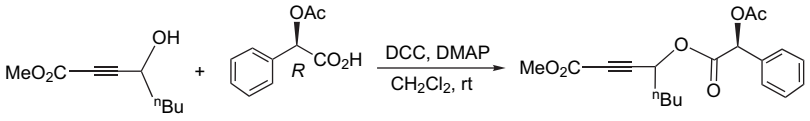
We studied the use of the ligands (*S*)-**6**, (*S*)-**7**, and (*S*)-**8** in combination with Me_2AlCl to catalyze the reaction of TMSCN with benzaldehyde (Scheme 9). The reaction conditions employed were similar to those using **1** and **2**. The catalyst was prepared by stirring Me_2AlCl (10 mol %) with ligand (10 mol %) in a solvent (1 mL) at room temperature for 1 h over 4 Å MS. Then Ph_3PO was added and the mixture was cooled down to −20 °C. Benzaldehyde and TMSCN were both added in one portion. After 48 h, the reaction was quenched with HCl (2 N), the product was converted to *O*-acetyl cyanohydrin. The ee of the acetate was analyzed by GC-chiral column. The results are summarized in Table 9.

As shown in Table 9, toluene was found to be the best solvent. The bifunctional BINOL ligand (*S*)-**6** was highly enantioselective for this reaction in toluene (96% ee, entry 2). The monosubstituted ligand (*S*)-**7** gave very low enantioselectivity (entries 5–7). The H_8BINOL ligand (*S*)-**8** showed significantly lower enantioselectivity than (*S*)-**6** (53% ee, entry 8).

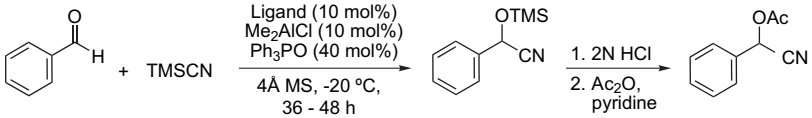
We also tested the use of $Ti(O^iPr)_4$ in place of Me_2AlCl in combination with the chiral ligands but only obtained moderate ee's. We found that switching the $Ph_3P{=}O$ additive to HMPA led to a shorter reaction time and a slightly higher yield. Thus the optimized conditions involved the use of (*S*)-**6** in combination with Me_2AlCl, HMPA, 4 Å MS in toluene at −20 °C. It gave 92% yield and 94% ee in 24 h for the TMSCN addition to benzaldehyde. The optimized conditions were applied for the reactions of TMSCN with various aromatic aldehydes and the results are summarized in Table 10. In general, good enantioselectivity was observed.

Table 9. Results for the TMSCN addition to benzaldehyde in the presence of the bifunctional ligands

Entry	Ligand	Solvent	ee (%)
1	(*S*)-**6**	THF	72
2	(*S*)-**6**	Toluene	96
3	(*S*)-**6**	Et_2O	73
4	(*S*)-**7**	THF	7
5	(*S*)-**7**	Toluene	20
6	(*S*)-**7**	Et_2O	11
7	(*S*)-**7**	CH_2Cl_2	7
8	(*S*)-**8**	Toluene	53

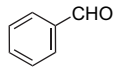
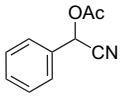
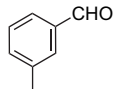
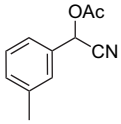
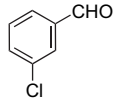
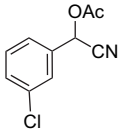
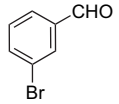
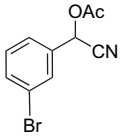
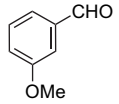
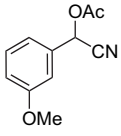
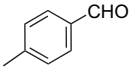
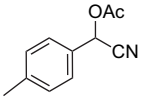
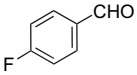
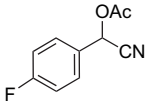
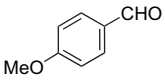
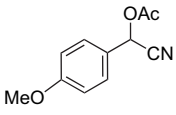
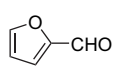
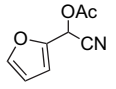
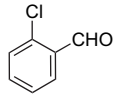
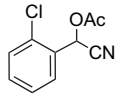


Scheme 8. Preparation of the O-Ac Mandelate derivative for NMR analysis.



Scheme 9. Catalytic reaction of benzaldehyde with TMSCN.

Table 10. Results of TMSCN addition to aromatic aldehydes

Entry	Aldehyde	Product	Yield (%)	ee (%)
1			92	94
2			90	93
3			77	94
4			88	82
5			82	80
6			86	75
7			85	90
8			80	80
9			70	74
10			94	80

Although ligand **2** was reported to be highly enantioselective for the reaction of aromatic aldehydes with TMSCN, it gave much lower ee's for the reaction of aliphatic aldehydes.[5] For example, even at −40 °C, (*S*)-**2** catalyzed the addition of TMSCN to heptaldehyde with only 66% ee. In general, very few catalysts could give consistently good results for the asymmetric reaction of aliphatic aldehydes with TMSCN in spite of a good number of highly enantioselective catalysts for the reaction of aromatic aldehydes.[31] Therefore, we explored the application of (*S*)-**6** for the asymmetric reaction of aliphatic aldehydes with TMSCN.

In Table 11, the results for the reaction of octyl aldehyde with TMSCN in the presence of (*S*)-**6** and Me_2AlCl under various conditions are summarized. In toluene solution, (*S*)-**6** showed up to 91% ee for this reaction (entry 1). Changing the solvent to THF reduced the ee (entry 2). In diethyl ether, however, a significant enhancement in ee was observed (97% ee, entry 3). Without the additive HMPA, a somewhat lower ee was observed (entry 4). Absence of molecular sieves led to a large reduction in enantioselectivity (entry 5). The room temperature reaction gave a lower but still significant ee (entry 6). Increasing the amount of molecular sieves at room temperature greatly decreased the enantioselectivity even with the increased amount of the chiral catalyst (entry 7). Changing the solvent to hexanes at room temperature diminished the enantioselectivity (entry 8).

Table 11. Asymmetric addition of TMSCN to octyl aldehyde in the presence of (*S*)-**6** and Me_2AlCl[a]

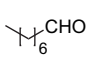
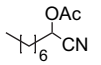
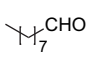
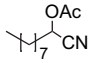
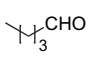
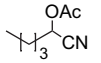
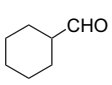
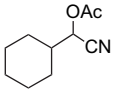
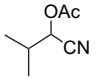
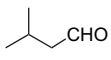
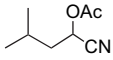
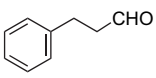
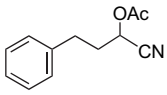
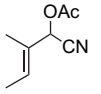
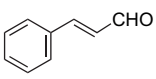
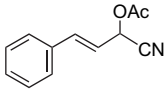
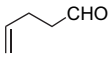
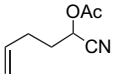
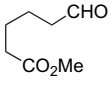
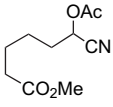
Entry	Solvent	4 Å MS (mg)	Time (h)	ee (%)
1	Toluene	5	24	91
2	THF	5	24	87
3	Et_2O	5	24	97
4[b]	Toluene	5	24	82
5	Toluene	None	24	46
6[c]	Et_2O	5	3	76
7[c,d]	Et_2O	15	4	31
8[c]	Hexane	5	24	6

[a] The following procedure was used unless otherwise indicated: (*S*)-**6** (0.025 mmol, 10 mol %), 4 Å molecular sieves, and Me_2AlCl (10 mol %, 1 M in hexanes) in a solvent (1 mL) were stirred under nitrogen at room temperature for 3 h. It was then combined with the additive HMPA (40 mol %) and cooled down to −20 °C. TMSCN (3.0 equiv) and an aldehyde were added.
[b] No additive.
[c] Reaction at rt.
[d] 20 mol % (*S*)-**6** and 20 mol % Me_2AlCl.

We applied the optimized conditions of entry 3 in Table 11 to the reaction of a variety of aliphatic aldehydes with TMSCN. As the results summarized in Table 12 show, in the presence of (*S*)-**6** (10 mol %) and Me_2AlCl (10 mol %), high enantioselectivities were achieved for the reactions of TMSCN with diverse aliphatic aldehydes including linear (entries 1–3), branched (entries 4–7), α,β-unsaturated (entries 8 and 9), and functionalized substrates (entries 10 and 11). The absolute configurations of the products from hydrocinnamaldehyde and cinnamaldehyde were determined to be *R* by comparing their optical rotations with those in the literature.

A large positive nonlinear effect was observed for the reaction of octyl aldehyde with TMSCN in the presence of (*S*)-**6** and Me_2AlCl.[9a] A chiral ligand of only 40% ee could generate the product of the same high ee as that by the ligand of high optical purity. The remarkable nonlinear effect indicates that the catalytic process may involve intermolecularly aggregated Al complexes. When (*S*)-**6** was treated with Me_2AlCl in toluene-d_8, the ^1H NMR spectrum showed a complete disappearance of all the signals of the ligand. A singlet at δ 0.16 appeared in the spectrum, which was attributed to methane generated from the protonation of Me_2AlCl by the chiral ligand. A white precipitate was produced in the toluene-d_8 solution, indicating the aggregation of the aluminum complexes. Octyl aldehyde and TMSCN were added to the NMR tube at room temperature. A triplet at δ 4.10

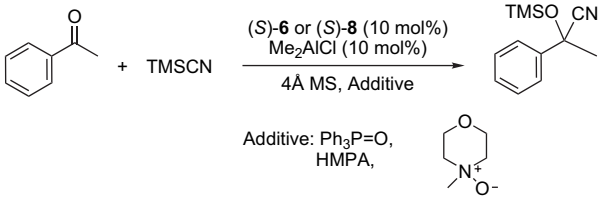
Table 12. Asymmetric addition of TMSCN to aliphatic aldehydes in the presence of (*S*)-**6** and Me_2AlCl

Entry	Aldehyde[a]	Product	Yield (%)	ee (%)
1			91	97
2			92	98
3			87	96
4			90	99
5			65	97
6			72	96
7			86	95
8			70	98
9			74	94
10			67	96
11			90	92

[a] Freshly distilled.

(J=6.4 Hz) appeared, which was attributed to –C*H*(CN)O-$Si(CH_3)_3$. Complicated aromatic signals were also observed, which were assigned to the aluminum complexes of the ligand. After the complete conversion of the aldehyde to the product, a C_2-symmetric complex might be generated because of the greatly simplified aromatic signals. However, the structure of this complex could not be determined yet.

We also used (*S*)-**6** and (*S*)-**8** to catalyze the cyanosilylation of acetophenone (Scheme 10).[33] The same amounts of ligands, Me_2AlCl, and 4 Å molecular sieves as used in the cyanosilylation of benzaldehyde were applied to this reaction. Various additives were examined. Using $Ph_3P{=}O$ (40 mol %) or HMPA (40 mol %) as the additive gave very low yield of the product with no enantioselectivity at −20 °C, 0 °C or room temperature. We also tested the use of *N*-methylmorpholine *N*-oxide (10, 20 or 40 mol %) as the additive at 0 °C or room temperature. Despite the high yield, only the racemic product was obtained.



Scheme 10. Reaction of acetophenone with TMSCN.

3. Summary

In summary, we have developed the efficient one-step synthesis of the bifunctional BINOL and H_8BINOL ligands (*S*)-**6** and (*S*)-**8** from the reaction of BINOL and H_8BINOL with morpholinomethanol, respectively. The X-ray analyses of these compounds have revealed their structural similarity and difference. The bifunctional H_8BINOL (*S*)-**8** is found to be highly enantioselective for the reaction of diphenylzinc with many aliphatic and aromatic aldehydes and especially is the most enantioselective catalyst for linear aliphatic aldehydes. Unlike other catalysts developed for the diphenylzinc addition which often require the addition of a significant amount of *diethylzinc* with cooling (or heating) the reaction mixtures in order to achieve high enantioselectivity, using (*S*)-**8** needs no additive and gives excellent results at room temperature. (*S*)-**8** in combination with diethylzinc and $Ti(O^iPr)_4$ can catalyze the highly enantioselective phenylactylene addition to aromatic aldehydes. It can also promote the phenylacetylene addition to acetophenone at room temperature though the enantioselectivity is not very high yet. Without using $Ti(O^iPr)_4$ and a Lewis base additive, (*S*)-**8** in combination with diethylzinc can catalyze the reaction of methyl propiolate with an aldehyde to form the highly functional γ-hydroxy-α,β-acetylenic esters except that the enantioselectivity is low at this stage. The bifunctional BINOL ligand (*S*)-**6** in combination with Me_2AlCl is found to be a highly enantioselective catalyst for the addition of TMSCN to both aromatic and aliphatic aldehydes.

4. Experimental

4.1. Preparation and characterization of (*S*)-3,3′-morpholinomethyl-1,1′-bi-2-naphthol, (*S*)-6

To a 250 mL round bottom flask containing paraformaldehyde (30.0 g, 1.0 mol), morpholine (88 mL, 1.0 mol) was added dropwise at 0 °C over 1 h with rigorous stirring. (Caution: this was a highly exothermic reaction.) The reaction mixture was allowed to warm up to room temperature. After 4 h, the mixture was slowly heated to 60 °C and maintained at the temperature for 10 h. This led to the formation of morpholinomethanol as a clear syrup-like liquid. Morpholinomethanol (60 mL) was combined with (*S*)-BINOL (3.0 g, 0.0106 mol) and degassed by bubbling with N_2. The mixture was placed in a Parr Non-Stirred Pressure Vessel (Series 4750 1.50 Inch Inside diameter, 125 mL) under 25–30 psi N_2 and heated at 110±2 °C for 72 h. Diethyl ether was then added after the reaction, and part of the product (*S*)-**6** precipitated out as a white solid. The white solid was washed twice with diethyl ether. The diethyl ether solutions were

combined with ethyl acetate (100 mL) and washed three times with 3% $NaHCO_3$. The organic phase was then concentrated under vacuum and the residue was purified by column chromatography on silica gel (size: 36 mm ID and 30 cm L) eluted with CH_2Cl_2/ethyl acetate (8:1) to give (*S*)-**6** and (*S*)-**7**. The combined yield of (*S*)-**6** was 55% (2.8 g). The optical purity of (*S*)-**6** was determined by HPLC analysis (vide infra) to be 75% ee. Yield of (*S*)-**7** was 30% (1.2 g). The optical purity of this (*S*)-**7** was determined by optical rotation measurement to be >87% ee [$[\alpha]_D$ −30.8 (*c* 1.0, CH_2Cl_2)]. For the preparation of the optically pure (*S*)-**7**, see below. The product (*S*)-**6** of 75% ee was dissolved in hot CH_2Cl_2/MeOH (3:1). The solution was cooled to room temperature and needle-shaped crystals appeared, which were found to be predominantly the racemic compound [$[\alpha]_D$ −1.9 to −4.5 (*c* 1.0, CH_2Cl_2)]. After separation of the racemic crystals, the solution was concentrated under vacuum and redissolved in hot CH_2Cl_2/MeOH (3:1). Cooling again allowed the separation of the racemic crystals. After this process was conducted for 3–4 times, removal of the solvent from the mother liquor gave the optically pure (*S*)-**6** (>99% ee, determined by HPLC vide infra). Sometimes, a simple column chromatography on silica gel (size: 36 mm ID and 30 cm L; eluent: 6:1 CH_2Cl_2/ethyl acetate) may be needed to remove impurities in the mother liquor after the crystallization. Mp 309–310 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.04 (s, 2H), 7.80 (m, 2H), 7.67 (s, 2H), 7.28 (m, 2H), 7.21 (m, 2H), 7.16 (m, 2H), 4.13 (m, 2H), 3.90 (m, 2H), 3.70 (m, 8H), 2.66 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.4, 134.0, 128.5, 127.9, 126.3, 125.0, 123.4, 123.3, 116.8, 66.8, 62.6, 53.1. $[\alpha]_D$ −152.1 (*c* 1.0, CH_2Cl_2). Anal. Calcd for $C_{30}H_{32}N_2O_4$: C, 74.36; H, 6.66; N, 5.78. Found: C, 74.60; H, 6.82; N, 6.05. High-resolution mass analysis: calcd for $C_{30}H_{32}N_2O_4$: 484.2362. Found: 484.2350.

The enantiomeric purity of (*S*)-**6** was determined by HPLC analysis of its acetate derivative: To a CH_2Cl_2 (5 mL) solution of (*S*)-**6** (13 mg) were added Ac_2O (250 μL) and pyridine (250 μL). After the solution was stirred at room temperature for 6 h, the volatiles were removed under vacuum. The resulting acetate of (*S*)-**6** as a white solid was purified by column chromatography on aluminum oxide (size: 12 mm ID and 10 cm L) eluted with petroleum ether/ethyl acetate (4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 2H), 7.88 (m, 2H), 7.44 (m, 2H), 7.24 (m, 2H), 7.14 (m, 2H), 3.52–3.76 (m, 12H), 2.50 (m, 8H), 1.80 (s, 6H). HPLC (CHIRALCEL AD) was used to measure the ee% of the acetate. Solvent: hexane/isopropanol (98:2). Flow rate: 1.0 mL/min. Retention times: t_R=31.0 min and t_S=35.5 min.

4.2. Preparation and characterization of (*S*)-3-morpholinomethyl-1,1′-bi-2-naphthol, (*S*)-7

A mixture of (*S*)-BINOL (3.0 g, 0.0106 mol) and morpholinomethanol (50 mL) in a Parr Non-Stirred Pressure Vessel (Series 4750 1.50 Inch Inside diameter, 125 mL) was degassed with nitrogen and then sealed under 30 psi nitrogen. After being heated at 95–100 °C for 48 h, the reaction mixture was diluted with ethyl acetate (150 mL) at room temperature, and washed with 3% sodium bicarbonate (2×60 mL) and water (100 mL). After rotoevaporation of the organic solution, the residue was purified by column chromatography on silica gel (size: 36 mm ID and 30 cm L) eluted with CH_2Cl_2/ethyl acetate (12:1) to give (*S*)-**7** in 52% yield (1.9 g) and (*S*)-**6** in 10% yield (0.46 g, >99% ee by HPLC). (*S*)-**7** as a white solid from this reaction was considered to be optically pure since the optical purity of (*S*)-**6** obtained from this reaction was found to be >99% ee by HPLC. In addition, the optical purity of (*S*)-**7** (>97% ee) was supported by the ^{1}H NMR studies of (*S*)-**7**, (*R*)-**7**, and racemic-**7** in the presence of 10 mol % chiral shift reagent Eu(hfc)$_3$ {Europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]} (vide infra). Mp 215.5–216.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74–7.93 (m, 4H), 7.10–7.39 (m, 7H), 4.015 (s, 2H), 3.71 (m, 4H), 2.66 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 151.6, 134.1, 133.8, 130.2, 129.7, 129.5, 128.7, 128.6, 128.0, 127.3, 126.7, 125.0, 124.8, 124.1, 123.7, 123.5, 117.8, 115.2, 113.1, 66.7, 62.5, 53.1. $[\alpha]_D$ −35.1 (*c* 1.0, CH_2Cl_2). Anal. Calcd for $C_{25}H_{23}NO_3$: C, 77.90; H, 6.01; N, 3.63. Found: C, 78.16; H, 5.99; N, 3.80. High-resolution mass analysis: calcd for $C_{25}H_{23}NO_3$: 385.1677. Found: 385.1662.

Determination of the optical purity of (*S*)-**7** and (*R*)-**7**. ^{1}H NMR spectrums of (*S*)-**7**, (*R*)-**7**, and racemic-**7** in the presence of 10 mol % chiral shift reagent Eu(hfc)$_3$ {Europium tris[3-(heptafluoropropylhydroxyl methylene)-(+)-camphorate]} were studied. Before the addition of the chiral shifting reagent, there was no signal at δ 7.39–7.73. After the samples were treated with Eu(hfc)$_3$ (10 mol %), new peaks appeared at δ 7.63 and/or 7.53 as summarized in Table 13. These data support the high optical purity of (*S*)-**7** and (*R*)-**7**.

Table 13. Resolution of the ^{1}H NMR signals of the enantiomers of **7** in the presence of the chiral shift reagent

Sample	^{1}H NMR signals	
	δ=7.63	δ=7.53
(*S*)- or (*R*)- or Rac-**7**	0H	0H
Rac-**7**+10 mol % Eu(hfc)$_3$	1H	1H
(*S*)-**7**+10 mol % Eu(hfc)$_3$	0H	1H
(*R*)-**7**+10 mol % Eu(hfc)$_3$	1H	0H

4.3. Preparation and characterization of (*S*)-3,3′-bismorpholinomethyl-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol, (*S*)-8

To a 250 mL round bottom flask containing 1,4-dioxane (30 mL) solution of (*S*)-H_8BINOL (5.0 g, 0.017 mol) was added morpholinomethanol (50 mL) at room temperature. After the mixture was heated at 60 °C for 12 h with stirring, it was cooled down to room temperature and combined with ethyl acetate (150 mL) in a separation funnel. The organic layer was then washed with saturated $NaHCO_3$ (3× 100 mL) and water (2×100 mL). Removal of ethyl acetate gave (*S*)-**8** as a white solid (8.0 g, 95% yield). Recrystallization of this compound from ethanol gave white needle crystals. ^{1}H NMR (500 MHz, toluene-d_8) δ 9.99 (s, 2H), 6.62 (s, 2H), 3.20–3.36 (m, 12H), 2.75 (m, 6H), 2.42 (m, 2H), 2.07 (m, 8H), 1.63–1.72 (m, 8H). ^{13}C NMR (125 MHz, toluene-d_8) δ 153.14, 136.44, 128.54, 127.19, 125.031, 118.26, 66.72, 62.19, 53.04, 29.91, 27.61, 24.04, 23.91. $[\alpha]_D^{25}$ −35.4 (*c* 1.04, THF). Anal. Calcd for $C_{30}H_{40}N_2O_4$: C,

73.14; H, 8.18; N, 5.69. Found: C, 73.22; H, 8.20; N, 5.66. High-resolution mass analysis: calcd for $C_{30}H_{40}N_2O_4$: 492.2988. Found. 492.2969.

4.4. A typical procedure for the asymmetric diphenylzinc addition to aldehydes

Under nitrogen to a 10 mL round bottom flask (flame dried under vacuum) were added diphenylzinc (66 mg, 0.3 mmol, 1.2 equiv), (*S*)-**6** or (*S*)-**8** (0.025 mmol, 0.1 equiv), and a solvent (2.0 mL, anhydrous) sequentially. After the resulting solution was stirred at room temperature for 1 h, an aldehyde (0.25 mmol) was added and the reaction was monitored by TLC. At the completion of the reaction, ammonium chloride (saturated, aq) was added to quench the reaction. The mixture was extracted with methylene chloride three times. After removal of the solvents, the residue was purified by column chromatography on silica gel (size: 12 mm ID and 15 cm L) eluted with hexanes/ethyl acetate (12:1) to give the product as either colorless oil or white solid in 75–97% yield.

4.5. General procedure for the phenylacetylene addition to aromatic aldehydes catalyzed by (*S*)-8

Under nitrogen to a 10 mL round bottom flask (flame dried under vacuum) were added phenylacetylene (1.0 mmol, 113 μL), THF (3 mL), Et_2Zn (1.0 mmol, 110 μL), $Ti(O^iPr)_4$ (74 μL, 0.25 mmol), (*S*)-**8** (12.3 mg, 0.025 mmol), and an aldehyde (0.25 mmol). After the resulting reaction mixture was stirred at room temperature for 4 h, a saturated ammonium chloride solution was added to quench the reaction. The mixture was extracted with methylene chloride (3×5 mL) and the organic solution was concentrated under vacuum. The residue was purified by passing through a short silica gel column (size: 12 mm ID and 10 cm L) eluted with methylene chloride/hexane (1:1), which afforded the pure propargylic alcohol product.

4.6. A typical procedure for the asymmetric methyl propiolate addition to aldehyde in the presence of (*S*)-8

(*S*)-**8** (12.3 mg, 0.025 mmol, 0.1 equiv) and 3 mL solvent were added into a 10 mL round bottom flask (flame dried under vacuum). Then diethylzinc (33 μL, 0.3 mmol, 1.2 equiv) and phenylacetylene (26 μL, 0.3 mmol, 1.2 equiv) were added sequentially. After the resulting solution was stirred at room temperature for 1 h, it was cooled down to −20 °C. Valeraldehyde (27 μL, 0.25 mmol) was added and the reaction was monitored by TLC at −20 °C. At the completion of the reaction in 6–12 h, ammonium chloride (saturated, aq) was added to quench the reaction. The mixture was extracted with methylene chloride three times. After removal of the solvents, the residue was purified by column chromatography on silica gel (size: 12 mm ID and 10 cm L) eluted with hexanes/ethyl acetate (12:1) to give the product as colorless oil.

4.7. A typical procedure for preparation of the derivative of 4-hydroxy-oct-2-ynoic acid methyl ester

To a solution of 4-hydroxy-oct-2-ynoic acid methyl ester (0.09 mmol) at room temperature was added 1,3-dicyclohexylcabodiimde (37 mg, 0.18 mmol), 4-(*N*,*N*-dimethylamino)pyridine (22 mg, 0.18 mmol), and (*R*)-acetoxyphenylacetic acid (30.0 mg, 0.18 mmol). The reaction was monitored by TLC and was judged to be completed after 15 min. The reaction mixture was concentrated and purified by flash column chromatography on silica gel (size: 36 mm ID and 30 cm L) eluted with 20% ether in hexane to give a clear oil. The NMR integrations of chemical shift at δ 5.96, 5.91, 3.78, and 3.75 were used to determine the enantiomeric excess.

4.8. A typical procedure for the catalytic cyanosilylation of aldehydes in the presence of (*S*)-6

Under nitrogen, a mixture of (*S*)-**6** (12.1 mg, 0.025 mmol), 4 Å molecular sieves (5 mg, activated at 180 °C 30 min under 0.09 mmHg vacuum), and diethyl ether (1 mL, dried) was stirred for 10 min and Me_2AlCl (25 μL, 0.025 mmol, 1 M hexane solution) was added. After stirred for 3 h, a white suspension formed to which HMPA (16 μL, 0.1 mmol) was added. The mixture was cooled down to −20 °C, and TMSCN (105 μL, 0.75 mmol) was added in one portion. In 5 min, an aldehyde (0.25 mmol, freshly distilled) was also added in one portion. After the reaction mixture was stirred at −20 °C for 24 h, water (1 mL) was added to quench the reaction at −20 °C. At room temperature, diethyl ether (2 mL) was added to dilute the reaction, and the diethyl ether solution was washed twice with water. (Removal of the solvent followed by column chromatography on silica gel (size: 12 mm ID and 10 cm L) eluted with hexanes/ethyl acetate (20:1) would give the pure cyanosilyl ether product.) In order to prepare the acetate derivative for ee determination, the diethyl ether solution of the crude silyl ether was treated with 2 N HCl (5 mL) and stirred for 2 h to remove the trimethylsilyl group. Then, CH_2Cl_2 (3×4 mL) was used for extraction. The organic layers were combined and then treated with acetic anhydride (0.2 mL) and pyridine (50 μL). After stirred for 1 h, the reaction mixture was concentrated by rotoevaporation and the residue was purified by column chromatography on silica gel (size: 12 mm ID and 10 cm L) eluted with hexanes/ethyl acetate (15:1) to give the cyano acetate product. The enantiomeric purity of *O*-acetyl cyanohydrin was determined by GC analysis. Conditions: HP 6890 series GC; Supelco Beta-Dex 120 Fused silica capillary column (30 m length×0.25 mm ID×0.25 μm film thickness); constant flow rate at 1.0 mL/min; inlet temperature 250 °C; FID detector temperature 280 °C.

4.9. Catalytic cyanosilylation of acetophenone in the presence of (*S*)-6 and (*S*)-8

Under nitrogen, a mixture of (*S*)-**6** or (*S*)-**8** (0.025 mmol), 4 Å molecular sieves (5 mg, activated at 180 °C for 30 min under 0.09 mmHg vacuum), and a solvent (1 mL, dried) was stirred for 10 min and Me_2AlCl (25 μL, 0.025 mmol, 1 M hexane solution) was added. After stirred for 3 h, a white suspension formed to which an additive was added. The mixture was cooled down to −20 °C (or kept at room temperature), and TMSCN (105 μL, 0.75 mmol) was added in one portion. In 5 min, acetophenone (30 μL, 0.25 mmol, freshly distilled) was also added in one portion. After the reaction mixture was stirred at −20 °C for 24–48 h, water (1 mL) was added to quench the reaction. At room temperature, diethyl ether (2 mL) was added to dilute the reaction, and the diethyl ether

solution was washed twice with water. Removal of the solvent followed by column chromatography on silica gel (size: 12 mm ID and 10 cm L) eluted with hexanes/ethyl acetate (20:1) would give the pure cyanosilyl ether product. The enantiomeric purity was determined by GC analysis. Conditions: HP 6890 series GC; Supelco Beta-Dex 120 Fused silica capillary column (30 m length×0.25 mm ID×0.25 μm film thickness); constant flow rate at 1.0 mL/min; inlet temperature 250 °C; FID detector temperature 280 °C.

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Supplementary data

Analytical data for the catalytic addition products. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.06.049.

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