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Facile Synthesis of a Family of H_8BINOL-Amine Compounds and Catalytic Asymmetric Arylzinc Addition to Aldehydes

Albert M. DeBerardinis, Mark Turlington, Jason Ko, Laura Sole, and Lin Pu*

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22904

lp6n@virginia.edu

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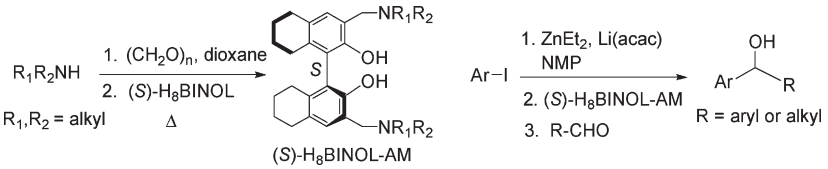
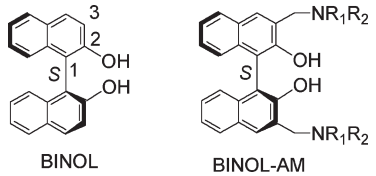


A family of optically active H_8BINOL-AM compounds containing 3,3′-bis-tertiary amine substituents are synthesized by using a one-step reaction of H_8BINOL with amino methanols that were *in situ* generated from various cyclic or acyclic secondary amines and paraformaldehyde. The H_8BINOL-AM compounds are used to catalyze the reaction of functional arylzincs, *in situ* prepared from the reaction of aryliodides with $ZnEt_2$, with aldehydes to produce chiral diaryl carbinols and a few arylalkyl carbinols. Through this study, highly enantioselective catalysts were identified. It was found that the H_8BINOL-AM compounds with sterically less congested cyclic or acyclic amino methyl substituents were more enantioselective than those with more bulky substituents. The pyrrolidinyl derivative (*S*)-**12** in most cases showed greater enantioselectivity than other H_8BINOL-AM compounds, especially for the challenging *ortho*-substituted aromatic aldehydes. A H_8BINOL-AM with 3,3′-bis-*sec*-amine substituents, prepared by a multistep method, was also used to catalyze the arylzinc addition to aldehydes, but it showed enantioselectivity lower than that of the compounds with tertiary amine groups. It was found for the first time that an aryl bromide, 2-bromothiophene, could be used to prepare an arylzinc reagent by reaction with $ZnEt_2$. The addition of this heteroarylzinc reagent to an aldehyde in the presence of (*S*)-**12** proceeded with good enantioselectivity.

Introduction

1,1′-Bi-2-naphthol (BINOL) and its 3,3′-substituted derivatives have been extensively used in asymmetric catalysis.[1] The two hydroxyl groups of BINOL allow easy incorporation of Lewis acidic metal centers such as Ti(IV), Zn(II), and Al(III) to prepare chiral Lewis acid complexes for asymmetric catalysis. Substituents at the 3,3′-positions of BINOL can modify both the steric and electronic properties of the Lewis acid complexes and in many cases lead to more efficient chiral catalysts for diverse organic reactions.[1] Among the 3,3′-substituted BINOL derivatives, compounds containing amino methyl substituents, that is BINOL-AMs, have received special attention in recent years.[2] It is found that the Lewis basic amine atoms in the BINOL-AMs can cooperate with the Lewis acidic metals introduced at the central BINOL unit to enhance the catalytic activity and enantioselectivity when used in asymmetric catalysis.



A number of synthetic methods have been developed for the preparation of the optically active BINOL-AMs.[2] Although the most direct method should be the one-step Mannich reaction of BINOL with morpholinomethanol to

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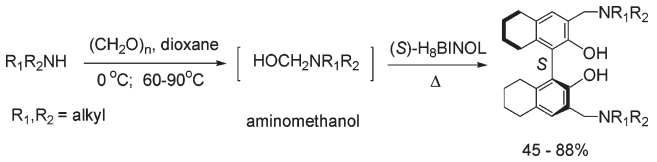
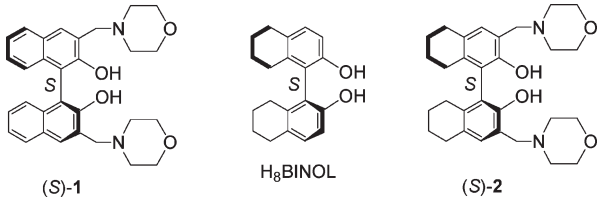
SCHEME 1. Synthesis of the H_8BINOL-AM Compounds



generate the BINOL-AM compound (*S*)-**1**,[3] this reaction required an elevated temperature of 110 °C, which led to partial racemization of the BINOL unit. Recrystallization was needed in order to obtain the enantiomerically pure (*S*)-**1**. However, when the partially hydrogenated BINOL, H_8BINOL,[4] was used, the Mannich reaction with morpholinomethanol could be conducted at a much lower temperature of 60 °C to produce the optically active H_8BINOL-AM compound (*S*)-**2** with excellent enantiomeric purity and high yield.[5] We have explored the use of (*S*)-**2** to catalyze the asymmetric reactions of arylzinc and alkynylzinc with aldehydes to generate the synthetically useful chiral alcohols, and high enantioselectivity has been achieved.[5,6] We have further expanded the synthesis of (*S*)-**2** by introducing structurally diverse 3,3′-bis-aminomethyl groups and studied the use of this family of compounds to catalyze the asymmetric arylzinc addition to aldehydes. Herein, the synthesis of the new H_8BINOL-AM compounds and their catalytic properties are reported.



Results and Discussion

1. Synthesis of a Family of H_8BINOL-AM Compounds from the One-Step Mannich Reaction of H_8BINOL. Scheme 1 shows the general scheme used to prepare the H_8BINOL-AM compounds. In the first step, a secondary aliphatic amine was mixed with paraformaldehyde in dioxane at 0 °C and then heated at 60−90 °C depending on the amine used. This led to the formation of an aminomethanol intermediate that was then heated with the optically pure (*S*)-H_8BINOL at varying temperatures depending on the amine used. This one-pot Mannich reaction quickly produced a family of H_8BINOL-AM compounds as listed in Figure 1. Among these H_8BINOL-AMs, compounds (*S*)-**3**−(*S*)-**6** are made of acyclic aliphatic amines, (*S*)-**7**−(*S*)-**9** are made of benzylic amines, and (*S*)-**10**−(*S*)-**17** are made of cyclic

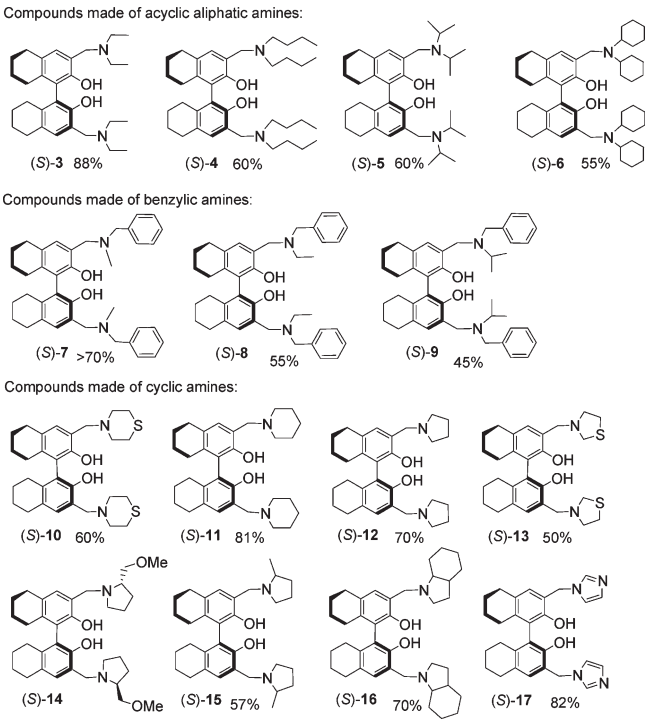


FIGURE 1. Structures of the newly prepared structurally diverse H_8BINOL-AM compounds.

amines. It was found that in general the less sterically hindered amines react more readily in the preparation of both the aminomethanol intermediate and the H_8BINOL-AM products. For example, lower temperature and less time were required for the synthesis of compounds (*S*)-**4** and (*S*)-**12**, but higher temperature (up to refluxing in dioxane) and longer reaction time were needed to prepare (*S*)-**6** and (*S*)-**9**. While imidazole reacted with paraformaldehyde under the normal conditions, the resulting imidazole methanol failed to react with H_8BINOL in dioxane at elevated temperature. In order to prepare the H_8BINOL-imidazole compound, (*S*)-H_8BINOL was heated with imidazole methanol in a sealed tube at 135 °C, which produced the desired product (*S*)-**17** without racemization. This demonstrates that H_8BINOL has a much more stable chiral configuration than BINOL, which underwent partial racemization in the preparation of (*S*)-**1** at 110 °C. Compounds (*S*)-**10**, (*S*)-**11**, (*S*)-**12**, (*S*)-**13**, and (*S*)-**15** containing cyclic amines similar to the previously reported (*S*)-**2** were purified by recrystallization. Compounds (*S*)-**3**, (*S*)-**4**, (*S*)-**5**, (*S*)-**6**, (*S*)-**7**, (*S*)-**8** ,and (*S*)-**9** containing acyclic amines proved to be more difficult to purify. After workup of their synthesis, the resulting oily residues could not form crystals. Column chromatography on alumina or silica gel was necessary to remove a sufficient amount of the excess amino alcohols before recrystallization. Compound (*S*)-**14** was made from the corresponding enantiomerically pure amine, but compounds (*S*)-**15** and (*S*)-**16** were made from the corresponding racemic amines and contained a mixture of diastereomers. The preparation of (*S*)-**2** was also scaled up with the use of 5 g of (*S*)-H_8BINOL, which gave (*S*)-**2** in 90% yield, >99% ee, and 99% purity.[5d]

2. Application of H_8BINOL-AM Compounds in the Asymmetric Arylzinc Addition to Aldehydes. Asymmetric arylzinc additions to aldehydes can generate chiral diaryl and arylalkyl

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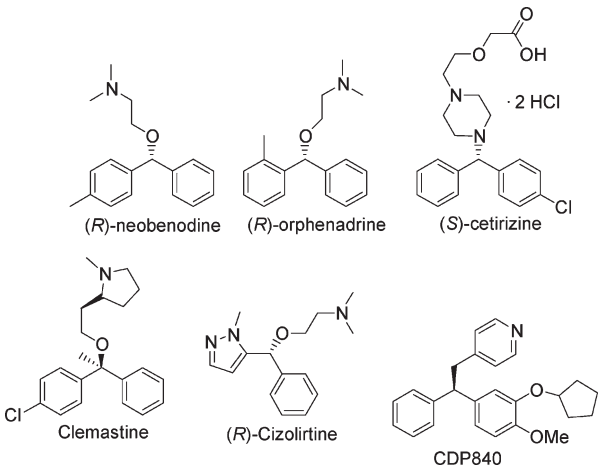

FIGURE 2. Drug molecules made from diaryl carbinols.

carbinols that are ubiquitous in organic molecules including those of biological significance. For example, the diaryl carbinol derivatives shown in Figure 2 are found to be useful drug molecules with antihistamine, anticholergenic, analgesic, and other properties.[7] Although significant progress has been made on the asymmetric Ph_2Zn addition to aldehydes,[8] the study on the asymmetric reaction of other functional arylzincs with aldehydes is still very limited.[9] Since 2005, Walsh has studied the *in situ* conversion of aryl bromide to arylzincs by treatment with ^{n}BuLi and $ZnCl_2$ or EtZnCl and the subsequent asymmetric arylzinc addition to aldehydes.[9a,b] High enantioselectivity was achieved for a number of substrates. The catalytic asymmetric additions of other nucleophilic aryl reagents to carbonyl compounds have also been reported.[10]

Earlier, we reported that the H_8BINOL-AM compound (*S*)-**2** can not only activate the arylzincs, *in situ* prepared with a modification of Knochel's method from aryliodides and $ZnEt_2$,[11] to react with aromatic and aliphatic aldehydes but also provide high enantioselectivity for a number of substrates.[6] In order to further expand the scope of this asymmetric reaction we have examined the use of the newly prepared and structurally diverse H_8BINOL-AM compounds and compared their catalytic properties with those of (*S*)-**2**.

a. Asymmetric Reaction of Arylzinc Reagent Derived from Methyl *p*-Iodobenzoate Catalyzed by the Chiral H_8BINOL-AM Compounds. As shown in Scheme 2, an arylzinc species was generated *in situ* from the reaction of methyl *p*-iodobenzoate with $ZnEt_2$ in the presence of Li(acac) and NMP.[11] This reaction needed to be conducted at 0 °C since dimerization of the aryliodide was observed at room temperature. After the formation of the arylzinc, the H_8BINOL-AM compounds (20 mol %) were added to catalyze the arylzinc addition to aldehydes in CH_2Cl_2 at 0 °C. We have chosen to screen the H_8BINOL-AM compounds for the addition to *o*-methoxybenzaldehyde to generate the chiral diaryl carbinol **18**, since the *ortho*-substituted benzaldehydes were found to be challenging substrates for the asymmetric arylzinc addition.[5c] The results for the formation of **18** in the presence of the H_8BINOL-AM compounds are summarized in Table 1.

As shown in entry 1 of Table 1, (*S*)-**2** catalyzed the arylzinc addition to *o*-methoxybenzaldehyde with 79% ee. This enantioselectivity is significantly lower than those we previously reported for the reactions of *p*- or *m*-substituted aromatic aldehydes and aliphatic aldehydes catalyzed by (*S*)-**2**.[6] Compound (*S*)-**10** in which the oxygen atom in the morpholinyl groups of (*S*)-**2** was replaced with a sulfur atom was then tested and showed the same enantioselectivity as (*S*)-**2** (entry 2). That is, the oxygen and sulfur atoms in the cyclic amine substituents of (*S*)-**2** and (*S*)-**10** did not interfere with the catalysis and probably were not involved in the coordination with the Lewis acidic catalyst center. Using compound (*S*)-**6**, in which the sterically much more bulky dicyclohexylamine was used in place of the morpholinyl groups of (*S*)-**2**, gave only the racemic product (entry 3). The cyclohexyl rings in (*S*)-**6** might have generated an overly crowded environment around the central chiral H_8BINOL unit and prevent the reaction from taking place there. Thus, no chiral induction could be provided by the H_8BINOL unit of (*S*)-**6**. When the less sterically crowded benzylmethylamine-based compound (*S*)-**7** was used, good enantioselectivity was observed (entry 4). As the steric congestion increased from (*S*)-**7** to (*S*)-**8** and (*S*)-**9**, the enantioselectivity decreased accordingly (entries 5 and 6). When the six-membered ring of the amine group of (*S*)-**2** was replaced with the

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SCHEME 2. Asymmetric Reaction of Methyl *p*-Iodobenzoate with *o*-Methoxybenzaldehyde Catalyzed by H_8BINOL-AM Compounds

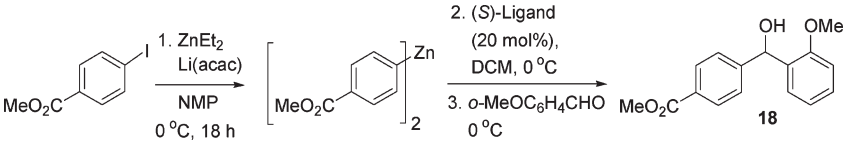


TABLE 1. Reaction of Methyl *p*-Iodobenzoate and *o*-Methoxybenzaldehyde in the Presence of $ZnEt_2$ and H_8BINOL-AM Compounds to Form 18[a]

entry	chiral ligand	isolated yield (%)	ee (%)[b]
1	(*S*)-**2**: NR_1R_2 = $N(CH_2CH_2)_2O$	83	79
2	(*S*)-**10**: NR_1R_2 = $N(CH_2CH_2)_2S$	98	79
3	(*S*)-**6**: NR_1R_2 = $N(^cC_6H_{11})_2$	80	0
4	(*S*)-**7**: NR_1R_2 = NMeBn	95	81
5	(*S*)-**8**: NR_1R_2 = NEtBn	75	74
6	(*S*)-**9**: NR_1R_2 = N^iPrBn	65	48
7	(*S*)-**12**: NR_1R_2 = $N(CH_2)_4$	**90**	**93**
8	(*S*)-**13**: NR_1R_2 = $N(CH_2CH_2SCH_2)$	**98**	**92**
9	(*S*)-**14**: NR_1R_2 = $N(CH_2CH_2CH_2CHCH_2OMe)$	60	46
10	(*S*)-**16**: NR_1R_2 = octahydroindenyl	80	83

[a]Conditions: methyl *p*-iodobenzoate (2.2 equiv), Li(acac) (26 mol %), Et_2Zn (1.21 equiv), NMP (1.5 mL), chiral ligand (20 mol %), CH_2Cl_2 (20 mL), aldehyde (1.0 equiv). Step 1: 18 h, 0 °C. Step 2: 1 h, 0 °C; 15 min, rt. Step 3: 16 h, 0 °C. [b]Determined by using HPLC-chiral column.

five-membered ring of the pyrrolidinyl-based compound (*S*)-**12**, excellent enantioselectivity was achieved (entry 7). Thus, the reduced ring size of the amine substituent greatly enhanced the enantioselectivity. Incorporation of a sulfur atom into the five-membered ring of (*S*)-**12** gave compound (*S*)-**13**, which maintained the high enantioselectivity (entry 8). That is, the additional heteroatom in the aminocycle had no influence on the enantioselectivity, similar to that observed for (*S*)-**2** and (*S*)-**10**. Additional substituents on the five-membered rings of (*S*)-**12** decreased the enantioselectivity as shown by the use of compounds (*S*)-**14** and (*S*)-**16** (entries 9 and 10). Although (*S*)-**16** contained a mixture of diastereomers, its enantioselectivity was still greater than that of (*S*)-**14**, which contained only one stereoisomer. The extra MeO groups of (*S*)-**14** might lead to chelate coordination to the Lewis acidic metal centers outside the chiral cavity of the H_8BINOL unit, causing the dramatic reduction of the enantioselectivity versus the use of (*S*)-**12**.

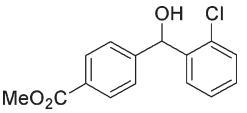
The use of the H_8BINOL-AM compounds to catalyze the addition of the methyl *p*-iodobenzoate-derived arylzinc reagent to *o*-cholorobenzaldehyde to generate the chiral diarylcarbinol **19** was also investigated, and the results are summarized in Table 2. Compounds (*S*)-**2**, (*S*)-**10**, and (*S*)-**11** containing six-membered cyclic amine groups showed similarly low enantioselectivity (entries 1−3). The oxygen and sulfur atoms in the six-membered rings had little effect on the reaction. Changing the cyclic amines of (*S*)-**2**, (*S*)-**10**, and (*S*)-**11** to the acyclic dialkyl amines (*S*)-**3** and (*S*)-**4** increased the enantioselectivity (entries 4 and 5). However, increasing the size of the alkyl groups from the primary alkyls of (*S*)-**3** and (*S*)-**4** to the secondary alkyl groups of (*S*)-**5** diminished the enantioselectivity (entry 6). This is similar to what was observed in the reaction of *o*-methoxybenzaldehyde shown in Table 1. The use of the benzylmethylamine-based compound (*S*)-**7** could not improve the enantioselectivity (entry 7). When the pyrrolidinyl-based compound (*S*)-**12** was used, it again exhibited significantly improved enantioselectivity over the other compounds (entry 8). Addition of another Lewis

TABLE 2. Reaction of Methyl *p*-Iodobenzoate and *o*-Chlorobenzaldehyde in the Presence of $ZnEt_2$ and H_8BINOL-AM Compounds to Form 19[a]

entry	ligand	isolated yield (%)	ee (%)[b]
1	(*S*)-**2**: NR_1R_2 = $N(CH_2CH_2)_2O$	92	55
2	(*S*)-**10**: NR_1R_2 = $N(CH_2CH_2)_2S$	98	57
3	(*S*)-**11**: NR_1R_2 = $N(CH_2)_5$	96	59
4	(*S*)-**3**: NR_1R_2 = NEt_2	90	64
5	(*S*)-**4**: NR_1R_2 = NBu_2	90	67
6	(*S*)-**5**: NR_1R_2 = N^iPr_2	98	33
7	(*S*)-**7**: NR_1R_2 = NMeBn	95	55
8	(*S*)-**12**: NR_1R_2 = $N(CH_2)_4$	98	79
9[c]	(*S*)-**12**: NR_1R_2 = $N(CH_2)_4$	87	61
10	(*S*)-**15**: NR_1R_2 = $N(CH_2CH_2CH_2CHMe)$	96	48
11	(*S*)-**17**: NR_1R_2 = imidazole	55	35

[a]The following conditions were used unless otherwise noted: methyl *p*-iodobenzoate (2.2 equiv), Li(acac) (26 mol %), Et_2Zn (1.21 equiv), NMP (1.5 mL), chiral ligand (20 mol %), CH_2Cl_2 (20 mL), aldehyde (1.0 equiv), 0 °C. Step 1: 18 h. Step 2: 1 h. Step 3: 12 h. [b]Determined by using HPLC-chiral column. [c]$Ti(O^iPr)_4$ (1.0 equiv) was added after step 2 and was stirred from 1 h prior to the addition of the aldehyde.

acid, $Ti(O^iPr)_4$, reduced the enantioselectivity (entry 9). Using the substituted pyrrolidinyl compound (*S*)-**15** also reduced the enantioselectivity (entry 10).



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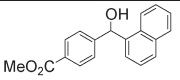
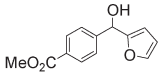
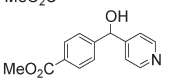
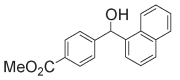
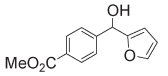
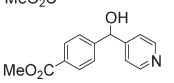
When the imidazole-based compound (*S*)-**17** was used, very low enantioselectivity was observed (entry 11). The ^1H NMR spectrum of (*S*)-**17** shows the OH proton signal at δ 3.48, which is much more upfield in comparison with those (δ 10−12) of all the other H_8BINOL-AMs we have prepared. This dramatic difference in the proton signals of the OH groups can be attributed to the lack of intramolecular hydrogen bonding between the OH groups of (*S*)-**17** and its imidazole nitrogens. In each of the imidazole rings, the nitrogen connected to the 3-methylene group is not basic, and the more basic nitrogen atom in the ring is pointing away from the chiral H_8BINOL unit of (*S*)-**17**, which makes it sterically incapable of forming an intramolecular hydrogen bond. Participation of this more basic nitrogen atom in the catalysis might have allowed the reaction to take place outside the chiral H_8BINOL cavity, leading to the diminished enantioselectivity. The results in Table 2 show that *o*-chlorobenzaldehyde is still a quite challenging substrate for this asymmetric arylzinc addition reaction.

The results in Tables 1 and 2 demonstrate that the pyrrodinyl-based compound (*S*)-**12** forms a more enantioselective catalyst than (*S*)-**2** and the other H_8BINOL-AM compounds in the asymmetric arylzinc addition to the *ortho*-substituted benzaldehydes. We used (*S*)-**12** to catalyze the reaction of additional aldehyde substrates with the arylzinc derived from methyl *p*-iodobenzoate by using the conditions of entry 7 in

TABLE 3. Comparison of (*S*)-2 and (*S*)-12 for the Asymmetric Reaction of Methyl *p*-Iodobenzoate with Additional Aldehydes[a]

entry	ligand	aldehyde	product	isolated yield (%)	ee (%)[b]
1	(*S*)-**2**: $NR_1R_2 = N(CH_2CH_2)_2O$			95	92
2	(*S*)-**2**: $NR_1R_2 = N(CH_2CH_2)_2O$			95	87
3	(*S*)-**2**: $NR_1R_2 = N(CH_2CH_2)_2O$			73	50
4	(*S*)-**12**: $NR_1R_2 = N(CH_2)_4$			88	97
5	(*S*)-**12**: $NR_1R_2 = N(CH_2)_4$			90	97
6	(*S*)-**12**: $NR_1R_2 = N(CH_2)_4$			75	76

[a]Conditions: methyl *p*-iodobenzoate (2.2 equiv), Li(acac) (26 mol %), Et_2Zn (1.21 equiv), NMP (1.5 mL), chiral ligand (20 mol %), CH_2Cl_2 (20 mL), aldehyde (1.0 equiv), 0 °C. Step 1: 18 h. Step 2: 1 h. Step 3: 6−12 h. [b]Determined by using HPLC-chiral column.

Table 1. The use of (*S*)-**2** in these reactions is also compared with the use of (*S*)-**12**, and the results are summarized in Table 3. For all of the reactions, (*S*)-**12** exhibited enantioselectivity significantly higher than that of (*S*)-**2**. The enantioselectivity for the addition to 4-pyridinyl aldehyde is low for both (*S*)-**2** and (*S*)-**12**, which indicates a possible coordination of the pyridine nitrogen to the Lewis acidic catalyst to disturb the catalytic process (entries 3 and 6).

b. Asymmetric Reaction of the Arylzinc Reagent Derived from *m*-Iodoanisole Catalyzed by the Chiral H_8BINOL-AM Compounds. Similar to methyl *p*-iodobenzoate, *m*-iodoanisole can be converted to an arylzinc reagent by using a modified Knochel's method in the presence of $ZnEt_2$ and Li(acac) in NMP at 0 °C.[11] We investigated the asymmetric addition of this arylzinc reagent to *o*-methoxybenzaldehyde in the presence of the H_8BINOL-AM compounds (10 mol %) to generate the chiral diaryl carbinol **20** (Scheme 3). As the results summarized in Table 4 show, increasing the steric bulkiness of the amine substituents from (*S*)-**2** to (*S*)-**6** led to a significant reduction of the enantioselectivity (entries 1 and 2). A small improvement was observed with the use of the benzylmethylamine-based compound (*S*)-**7** (entry 3). As the steric congestion increased from (*S*)-**7** to (*S*)-**8** and (*S*)-**9**, the enantioselectivity diminished (entries 4 and 5). The pyrrolidinyl compound (*S*)-**12** exhibited enhanced enantioselectivity over the other compounds (entry 6). Decreasing the step 2 and step 3 temperature to 0 °C (entry 7) or increasing the amount of (*S*)-**12** to 20 mol % (entry 8) could not significantly improve the enantioselectivity. Incorporation of a sulfur atom into the pyrrolidinyl ring of (*S*)-**12** led to a small reduction in enantioselectivity (entry 9). Compounds (*S*)-**14** and (*S*)-**16** containing additional substituents on the pyrrolidinyl rings gave reduced enantioselectivity (entries 10 and 11). The dramatic reduction of enantioselectivity from (*S*)-**12** to (*S*)-**14** is similar to that observed in entry 9 of Table 1. This could be attributed to the undesired participation of the MeO groups of (*S*)-**14** in the coordination to the Lewis acidic metal centers.

The three H_8BINOL-AM compounds (*S*)-**2**, (*S*)-**7**, and (*S*)-**12** that showed better enantioselectivity in the above reaction were used to catalyze the addition of the *m*-iodoanisole-derived arylzinc to other *ortho*-substituted benzaldehydes, and the results are summarized in Table 5. Among these three compounds, (*S*)-**12** gave better enantioselectivity for the reaction of *o*-chlorobenzaldehyde (entry 6); (*S*)-**7** gave better enantioselectivity for the reaction of *o*-methylbenzaldehyde (entry 3) and *o*-bromobenzaldehyde (entry 9). Increasing the amount of (*S*)-**7** from 10 to 20 mol % and decreasing the step 2 and 3 temperature to 0 °C could not improve the enantioselectivity (entry 4). These results demonstrate that the asymmetric arylzinc addition to *ortho*-substituted benzaldehydes still remains a challenging task, and further exploration in this area is needed.

SCHEME 3. Asymmetric Reaction of *m*-Iodoanisole with *o*-Methoxybenzaldehyde Catalyzed by H_8BINOL-AM Compounds

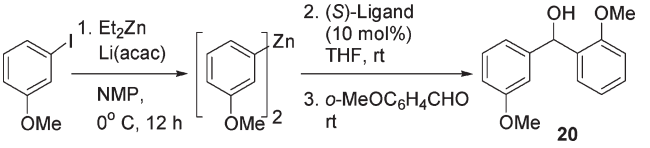
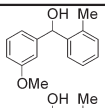
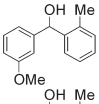
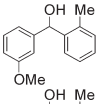
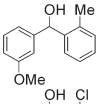
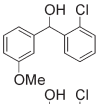
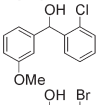
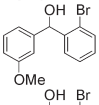
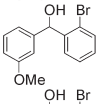


TABLE 4. Reaction of *m*-Iodoanisole and *o*-Methoxybenzaldehyde in the Presence of $ZnEt_2$ and the H_8BINOL-AM Compounds to Form 20[a]

entry	ligand	isolated yield (%)	ee (%)[b]
1	(*S*)-**2**: $NR_1R_2 = N(CH_2CH_2)_2O$	98	74
2	(*S*)-**6**: $NR_1R_2 = N(^cC_6H_{11})_2$	91	13
3	(*S*)-**7**: NR_1R_2 = NMeBn	98	78
4	(*S*)-**8**: NR_1R_2 = NEtBn	98	72
5	(*S*)-**9**: $NR_1R_2 = N^iPrBn$	70	16
6	(*S*)-**12**: $NR_1R_2 = N(CH_2)_4$	98	80
7[c]	(*S*)-**12**: $NR_1R_2 = N(CH_2)_4$	98	82
8[d]	(*S*)-**12**: $NR_1R_2 = N(CH_2)_4$	86	80
9	(*S*)-**13**: $NR_1R_2 = N(CH_2CH_2SCH_2)$	91	72
10	(*S*)-**14**: $NR_1R_2 = N(CH_2CH_2CH_2CHCH_2OMe)$	98	31
11	(*S*)-**16**: NR_1R_2 = octahydroindenyl	98	74

[a]Following conditions were used unless otherwise noted: *m*-iodoanisole (2.2 equiv), Li(acac) (26 mol %), Et_2Zn (1.21 equiv), NMP (1.5 mL), chiral ligand (10 mol %), THF (5 mL), aldehyde (1.0 equiv). Step 1: 12 h, 0 °C. Step 2: 1 h, 0 °C. Step 3: 12 h, rt. [b]Determined by using HPLC-chiral column. [c]Step 3: 20 h, 0 °C. [d]20 mol % (*S*)-**12**. Step 3: 20 h, 0 °C.

TABLE 5. Reaction of *m*-Iodoanisole and Additional *ortho*-Substituted Benzaldehydes in the Presence of $ZnEt_2$ and H_8BINOL-AMs[a]

entry	ligand	aldehyde	product	isolated yield (%)	ee (%)[b]
1	(*S*)-**2**: $NR_1R_2 = N(CH_2CH_2)_2O$			95	69
2	(*S*)-**12**: $NR_1R_2 = N(CH_2)_4$			99	67
3	(*S*)-**7**: NR_1R_2 = NMeBn			95	73
4[c]	(*S*)-**7**: NR_1R_2 = NMeBn			95	73
5	(*S*)-**2**: $NR_1R_2 = N(CH_2CH_2)_2O$			93	55
6	(*S*)-**12**: $NR_1R_2 = N(CH_2)_4$			91	74
7	(*S*)-**2**: $NR_1R_2 = N(CH_2CH_2)_2O$			87	44
8	(*S*)-**12**: $NR_1R_2 = N(CH_2)_4$			97	51
9	(*S*)-**7**: NR_1R_2 = NMeBn			92	54

[a]Following conditions were used unless otherwise noted: *m*-iodoanisole (2.2 equiv), Li(acac) (26 mol %), Et_2Zn (1.21 equiv), NMP (1.5 mL), chiral ligand (10 mol %), THF (5 mL), aldehyde (1.0 equiv). Step 1: 12 h, 0 °C. Step 2: 1 h, 0 °C. Step 3: 12−16 h, rt. [b]Determined by using HPLC-chiral column. [c]20 mol % (*S*)-**7**. Step 3: 20 h, 0 °C.

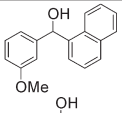
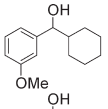
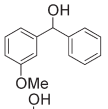
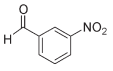
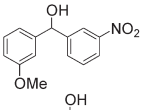
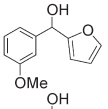
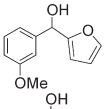
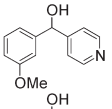
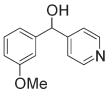
Compound (*S*)-**12** was further used to catalyze the reaction of the *m*-iodoanisole-derived arylzinc with other aldehydes, and the results are summarized in Table 6. Despite the lower enantioselectivity for the addition to *ortho*-substituted benzaldehydes, (*S*)-**12** is highly enantioselective for the reaction of other aromatic and aliphatic aldehydes as shown in entries 1−4. For these substrates, the enantioselectivity of (*S*)-**12** is comparable with that of (*S*)-**2** previously reported.[6a] The reaction of the *m*-iodoanisole derived arylzinc with cyclohexanecarboxaldehyde in the presence of compound (*S*)-**2** was scaled up with the use of 29 mmol of the aldehyde. This gave the corresponding alcohol product in 92% yield, >99% ee, and >99% purity.[6b]

Compounds (*S*)-**2** and (*S*)-**12** were also used to catalyze the addition to heteroaromatic aldehydes. For the reaction of 2-furaldehyde, both showed high enantioselectivity (entries 5 and 6). However, lower ee's were observed for the reaction of 4-pyridinecarboxaldehyde catalyzed by (*S*)-**2** and (*S*)-**12** (entries 7 and 8), similar to that observed in entries 3 and 6 of Table 3. The pyridine nitrogen atom of this aldehyde could interfere with the catalysis probably through coordination to the Lewis acidic metal center.

c. Asymmetric Reaction of the Arylzinc Reagent Derived from *m*-Iodobenzonitrile Catalyzed by the Chiral H_8BINOL-AM Compounds. The experiments for the asymmetric arylzinc addition to aldehydes in the above sections show that (*S*)-**2**, (*S*)-**4**, (*S*)-**7**, and (*S*)-**12** have enantioselectivity higher than that of all other H_8BINOL-AM compounds. We have thus tested the use of these four compounds to catalyze the reaction of *p*-methoxybenzaldehyde with the arylzinc reagent derived from *m*-iodobenzonitrile to give the chiral diaryl carbinol **21** (Scheme 4). As the results summarized in Table 7 show, compounds (*S*)-**4**, (*S*)-**7**, and (*S*)-**12** improved the enantioselectivity previously reported for (*S*)-**2**.[6a] The highest enantioselectivity was obtained with the use of (*S*)-**7** (entry 3). In these reactions, 40 mol % of the ligands was needed.

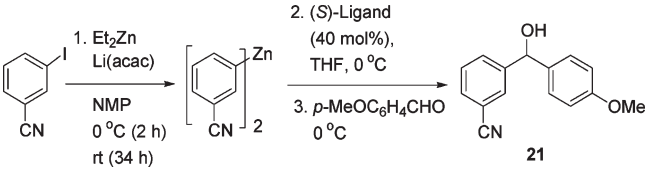
d. Asymmetric Reaction of the Arylzinc Reagents Derived from 2-Iodothiophene and 2-Bromothiophene Catalyzed by the Chiral H_8BINOL-AMs. We also explored the use of the H_8BINOL-AMs to promote the asymmetric reaction of thiophenyl halides with aldehydes. Scheme 5 shows the conversion of 2-iodothiophene to a thiophenylzinc reagent using $ZnEt_2$, Li(acac), and NMP and its subsequent asymmetric addition to aldehydes in THF in the presence of 10 mol % of a chiral H_8BINOL-AM. The entire process was conducted at room temperature. The results are summarized in Table 8. Entry 1 shows that (*S*)-**2** is a good catalyst for the thiophenyl addition to benzaldehyde. When the thiophenylzinc formation time in step 1 was shortened from 12 h in entry 1 to 6 h, the same result was obtained (entry 2). Entry 2 used the dried and distilled 2-iodothiophene, and entry 1 used the reagent as received, which did not affect the outcome of the experiment. Using the dibutylamine derivative (*S*)-**14** gave a slightly increased ee (entry 3). Compounds (*S*)-**5** and (*S*)-**6** with increased size of the alkyl groups on the nitrogen atoms gave diminished ee's (entries 4 and 5).

TABLE 6. Reaction of *m*-Iodoanisole and Other Aldehydes in the Presence of $ZnEt_2$ and (*S*)-2 and (*S*)-12[a]

entry	ligand	aldehyde	product	isolated yield (%)	ee (%)[b]
1	(*S*)-**12**: $NR_1R_2 = N(CH_2)_4$			85	92
2	(*S*)-**12**: $NR_1R_2 = N(CH_2)_4$			94	>99
3	(*S*)-**12**: $NR_1R_2 = N(CH_2)_4$			96	92
4	(*S*)-**12**: $NR_1R_2 = N(CH_2)_4$			85	84
5	(*S*)-**2**: $NR_1R_2 = N(CH_2CH_2)_2O$			96	90
6	(*S*)-**12**: $NR_1R_2 = N(CH_2)_4$			94	91
7	(*S*)-**2**: $NR_1R_2 = N(CH_2CH_2)_2O$			82	62
8	(*S*)-**12**: $NR_1R_2 = N(CH_2)_4$			86	70

[a]Conditions: *m*-iodoanisole (2.2 equiv), Li(acac) (26 mol %), Et_2Zn (1.21 equiv), NMP (1.5 mL), chiral ligand (10 mol %), THF (5 mL), aldehyde (1.0 equiv). Step 1: 12 h, 0 °C. Step 2: 1 h, 0 °C. Step 3: 6−12 h, rt. [b]Determined by using HPLC-chiral column.

SCHEME 4. Asymmetric Reaction of *m*-Iodobenzonitrile with *p*-Methoxybenzaldehyde Catalyzed by the H_8BINOL-AM Compounds



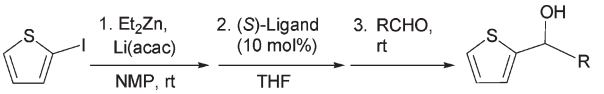
The benzylmethylamine derivative (*S*)-**7** gave enhanced enantioselectivity over both (*S*)-**2** and (*S*)-**4** (entry 6). Increasing the size of the methyl group of (*S*)-**7** to the ethyl of (*S*)-**8** and the isopropyl of (*S*)-**9** reduced the enantioselectivity (entries 7 and 8). When the pyrrolidinyl compound (*S*)-**12** was used, the highest enantioselectivity was achieved (entry 9). Reducing the amount of NMP used in step 1 did not cause significant change in the reaction (entry 10). The imidazole-based compound (*S*)-**17** could not carry out this reaction enantioselectively (entry 11). The high enantioselectivity of (*S*)-**12** for the reaction with benzaldehyde prompted us to examine its use for the reaction of aliphatic aldehydes. Good enantioselectivity was observed for the reaction of cyclohexanecarboxaldehyde and octyl aldehyde (entries 12 and 13). The four chiral compounds (*S*)-**2**, (*S*)-**4**, (*S*)-**7**, and (*S*)-**12** were used to catalyze the thiophenylzinc addition to *o*-methoxybenzaldehyde. As the results in entries 14−17 show, the *ortho*-substituted benzaldehyde remains a challenging substrate for this reaction. The highest ee was 73%, obtained by using either (*S*)-**7** or (*S*)-**12** (entries 15 and 16).

TABLE 7. Reaction of *m*-Iodobenzonitrile and *p*-Methoxybenzaldehyde in the Presence of $ZnEt_2$ and the H_8BINOL-AM Compounds to Form 21[a]

entry	ligand	isolated yield (%)	ee (%)[b]
1	(*S*)-**2**: $NR_1R_2 = N(CH_2CH_2)_2O$	74	79
2	(*S*)-**4**: $NR_1R_2 = NBu_2$	60	85
3	(*S*)-**7**: $NR_1R_2 = NMeBn$	80	91
4	(*S*)-**12**: $NR_1R_2 = N(CH_2)_4$	97	88

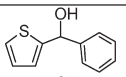
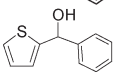
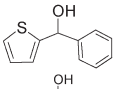
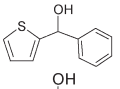
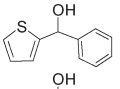
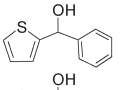
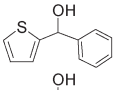
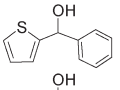
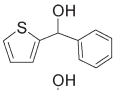
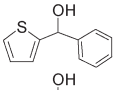
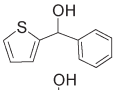
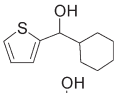
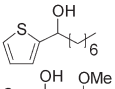
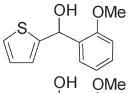
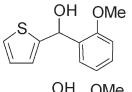
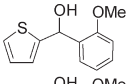
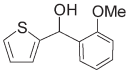
[a]Conditions: *m*-iodobenzonitrile (3.2 equiv), Li(acac) (37 mol %), Et_2Zn (1.6 equiv), NMP (1.5 mL), chiral ligand (40 mol %), THF (25 mL), *p*-methoxybenzaldehyde (1.0 equiv). Step 1: 2 h at 0 °C, then 34 h at rt. Step 2: 1 h, 0 °C. Step 3: 48 h, 0 °C. [b]Determined by ^{1}H NMR spectroscopic analysis of the mandelic ester of **21** prepared from the reaction with (*R*)-(-)-(O-acetoxy)mandelic acid in the presence of DCC and DMAP in CH_2Cl_2.

SCHEME 5. Asymmetric Reaction of 2-Iodothiophene with Aldehydes Catalyzed by the H_8BINOL-AM Compounds



The conditions for the reaction of 2-iodothiophene with benzaldehyde in the presence of (*S*)-**12** were further explored in order to determine the effect of the solvent and additive on this reaction. These experiments are summarized in Table 9. As shown in entries 1−5, when the solvent was changed from THF to others, the enantioselectivity was significantly reduced. When the additive Li(acac) was replaced with 1,3-bis(diphenylphosphine)propane, a small reduction in

TABLE 8. Reaction of 2-Iodothiophene with Aldehydes in the Presence of $ZnEt_2$ and H_8BINOL-AM Compounds[a]

entry	ligand	aldehyde	step 3 (h)	product	isolated yield (%)	*ee* (%)[b]
1[c]	(*S*)-**2**: $NR_1R_2 = N(CH_2CH_2)_2O$		11		95	84
2	(*S*)-**2**: $NR_1R_2 = N(CH_2CH_2)_2O$		16		95	84
3	(*S*)-**4**: $NR_1R_2 = NBu_2$		16		84	86
4	(*S*)-**5**: $NR_1R_2 = N^iPr_2$		16		57	5
5	(*S*)-**6**: $NR_1R_2 = N(^cC_6H_{11})_2$		16		66	9
6	(*S*)-**7**: NR_1R_2 = NMeBn		12		91	89
7	(*S*)-**8**: NR_1R_2 = NEtBn		16		95	82
8	(*S*)-**9**: $NR_1R_2 = N^iPrBn$		16		98	58
9	(*S*)-**12**: $NR_1R_2 = N(CH_2)_4$		**16**		**90**	**92**
10[d]	(*S*)-**12**: $NR_1R_2 = N(CH_2)_4$		**16**		**96**	**90**
11	(*S*)-**17**: NR_1R_2 = imidazole		16		81	2
12	(*S*)-**12**: $NR_1R_2 = N(CH_2)_4$		**14**		**90**	**94**
13	(*S*)-**12**: $NR_1R_2 = N(CH_2)_4$		14		75	85
14	(*S*)-**2**: $NR_1R_2 = N(CH_2CH_2)_2O$		16		98	64
15	(*S*)-**4**: $NR_1R_2 = NBu_2$		16		98	66
16	(*S*)-**7**: NR_1R_2 = NMeBn		16		98	73
17	(*S*)-**12**: $NR_1R_2 = N(CH_2)_4$		16		92	73

[a]Following reaction conditions were used unless otherwise noted: 2-iodothiophene (2.2 equiv, dried, distilled), Li(acac) (26 mol %), Et_2Zn (1.21 equiv), NMP (1.5 mL), chiral ligand (10 mol %), 5 mL THF (5 mL), benzaldehyde (1.0 equiv), rt. Step 1: 6 h. Step 2: 1 h. Step 3. 12−16 h. [b]Determined by using HPLC-chiral column. [c]Undistilled 2-iodothiophene was used. [d]0.75 mL of NMP was used in step 1.

enantioselectivity was observed (entry 6). Removing both Li(acac) and NMP led to no thiophenyl addition product, only the $ZnEt_2$ addition product (entry 7). This indicates that the thiophenylzinc was not generated under these conditions. In the presence of NMP but without Li(acac), high enantioselectivity and excellent yield were obtained (entry 8). That is, the additive Li(acac) that is necessary for the formation of other arylzinc reagents[11] is not needed for the reaction of 2-iodothiophene. This gives a simplified reaction procedure.

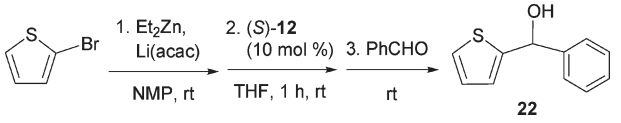
Previously, we found that aryl bromides could not be used in place of aryl iodides for the asymmetric arylzinc addition to aldehydes. For example, *m*-bromoanisole and methyl *p*-bromobenzoate did not react with $ZnEt_2$ under the conditions used for the reaction of the aryl iodides even with extended reaction time and under refluxing. The excellent reactivity of 2-iodothiophene described here encouraged us to test the use of 2-bromothiophene for the reaction with benzaldehyde in the presence of (*S*)-**12** and $ZnEt_2$ to give the diaryl carbinol **22** (Scheme 6). We were pleased to find that the thiophenylzinc could be generated from 2-bromothiophene to react with benzaldehyde in the presence of (*S*)-**12** with good enantioselectivity. The results are summarized in Table 10. The use of distilled 2-bromothiophene in entry 4 showed enantioselectivity higher than that obtained using undistilled 2-bromothiophene (entries 1−3). This is the first example that an arylbromide can be used to react with $ZnEt_2$ to form a diarylzinc reagent. The product was obtained with slightly reduced enantioselectivity relative to that using 2-iodothiophene. Unlike that found for 2-iodothiophene shown

TABLE 9. Varying the Conditions for the Reaction of 2-Iodothiophene and Benzaldehyde in the Presence of $ZnEt_2$ and (*S*)-12[a]

entry	solvent	additive	NMP (mL)	isolated yield (%)	ee (%)[b]
1	THF	Li(acac) (26%)	1.5	95	90
2	CH_2Cl_2	Li(acac) (26%)	1.5	95	84
3	toluene	Li(acac) (26%)	1.5	91	82
4	ether	Li(acac) (26%)	1.5	92	78
5	hexanes	Li(acac) (26%)	1.5	91	75
6[c]	THF	$(Ph_2PCH_2)_2CH_2$ (20%)	1.5	92	86
7[d]	THF	none	none	none	n/a
8[e]	**THF**	**none**	**1.5**	**98**	**91**
9[f]	**THF**	**none**	**1.5**	**98**	**91**

[a]Following reaction conditions were used unless otherwise noted: 2-iodothiophene (2.2 equiv), an additive, Et_2Zn (1.21 equiv), chiral ligand (10 mol %), NMP (1.5 mL), THF (5 mL), benzaldehyde (1.0 equiv), rt. Step 1: 6 h. Step 2: 1 h. Step 3: 8 h. [b]Determined by using HPLC-chiral column. [c]Step 1: 16 h. [d]Step 1: THF (5 mL), no NMP, 16 h. Step 3: 16 h. The ethyl addition product was obtained in 90% yield. [e]Step 1: 12 h. [f]Step 1: 6 h.

SCHEME 6. Use of 2-Bromothiophene for the Asymmetric Arylzinc Addition in the Presence of (*S*)-12 and $ZnEt_2$



in entry 8 of Table 9, without Li(acac) the thiophenylzinc could not be generated from 2-bromothiophene and only ethyl addition product was observed in the presence of (*S*)-**12**. 2-Chlorothiophene did not react with $ZnEt_2$ to form the arylzinc.

e. Asymmetric Reaction of the in situ Generated Diphenylzinc from Iodobenzene Catalyzed by the Chiral H_8BINOL-AM Compounds. We previously reported the use of (*S*)-**2** to catalyze the reaction of the commercially available Ph_2Zn with aldehydes.[5b,c] In order to utilize iodobenzene for this reaction, we examined the reaction of the *in situ* generated Ph_2Zn from iodobenzene with *p*-methoxybenzaldehyde in the presence of (*S*)-**2** and (*S*)-**12** to form the diaryl carbinol **23** (Scheme 7). The results are summarized in Table 11. Using distilled iodobenzene led to significant enhancement of the enantioselectivity from entry 1 to entry 2 in the presence of (*S*)-**2**. The time for the *in situ* formation of Ph_2Zn in the first step was found to strongly influence both the yield and ee of the reaction. Increasing the time in the first step from entry 2 to entry 3 reduced both the yield and ee, indicating a degradation of Ph_2Zn over time. Changing the solvent from THF to CH_2Cl_2 diminished both the yield and ee (entry 4). The optimal reaction time for the first step was 3 h, which led to the formation of **23** with good enantioselectivity and yield (entry 6). Under these conditions, replacing (*S*)-**2** with (*S*)-**12** enhanced both the yield and ee (entry 7). This demonstrates that in the presence of (*S*)-**12**, iodobenzene could be used to replace Ph_2Zn for the asymmetric Ph_2Zn addition to aldehydes. When the commercially pure Ph_2Zn was used for the addition to *p*-methoxybenzaldehyde in the presence of (*S*)-**2**, the product was obtained with 91% ee and 91% yield.[5b]

f. Correlation between the Enantiomeric Purity of the Chiral Ligand and That of the Addition Product, Absolute Configuration Assignment, and NMR Study. In order to gain more information about the asymmetric arylzinc addition to aldehydes in the presence of the H_8BINOL-AM compounds, we studied the relationship between the enantiomeric purity of (*S*)-**2** and

TABLE 10. Asymmetric Reaction of 2-Bromothiophene and Benzaldehyde in the Presence of (*S*)-12 and $ZnEt_2$ to Form 22[a]

entry	2-bromothiophene	step 1 (h)	step 3 (h)	Isolated Yield (%)	ee (%)[b]
1	undistilled	12	24	80	82
2	undistilled	24	16	90	79
3	undistilled	6	10.5	87	83
4	distilled	6	10	98	86

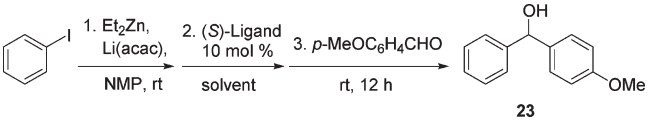
[a]Conditions: 2-bromothiophene (2.2 equiv), Li(acac) (26 mol %), $ZnEt_2$ (1.21 equiv), (*S*)-**12** (10 mol %), NMP (1.5 mL), THF (5 mL), benzaldehyde (1.0 equiv), rt. Step 2: 1 h. [b]Determined by using HPLC-chiral column.

TABLE 11. Asymmetric Reaction Using Iodobenzene and *p*-Methoxybenzaldehyde in the Presence of H_8BINOL-AMs to Form 23[a]

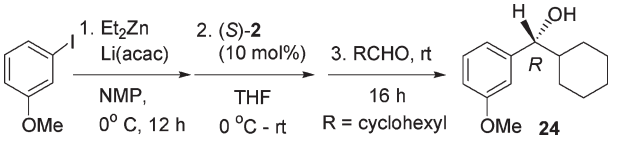
entry	ligand	step 1 (h)	isolated yield (%)	ee (%)[(b)]
1[(c)]	(*S*)-**2**: $NR_1R_2 = N(CH_2CH_2)_2O$	13	64	62
2	(*S*)-**2**: $NR_1R_2 = N(CH_2CH_2)_2O$	13	77	85
3	(*S*)-**2**: $NR_1R_2 = N(CH_2CH_2)_2O$	24	50	64
4[(d)]	(*S*)-**2**: $NR_1R_2 = N(CH_2CH_2)_2O$	24	12	40
5	(*S*)-**2**: $NR_1R_2 = N(CH_2CH_2)_2O$	6	56	82
6	(*S*)-**2**: $NR_1R_2 = N(CH_2CH_2)_2O$	3	85	88
7	(*S*)-**12**: $NR_1R_2 = N(CH_2)_4$	**3**	**98**	**93**

[a]Following conditions were used unless otherwise noted: iodobenzene (2.2 equiv, freshly distilled), Li(acac) (26 mol %), Et_2Zn (1.21 equiv), NMP (1.5 mL), chiral ligand (10 mol %), THF (5 mL), *p*-anisaldehyde (1.0 equiv, treated with $NaHCO_3$, passed through alumina, degassed), rt, under nitrogen. Step 2: 1 h. Step 3: 12 h. [(b)]Determined by using HPLC-chiral column. [(c)]Undistilled iodobenzene was used. [(d)]CH_2Cl_2 was used in place of THF.

SCHEME 7. Use of Iodobenzene for the Asymmetric Arylzinc Addition in the Presence of the H_8BINOL-AMs



SCHEME 8. Asymmetric Reaction of *m*-Iodoanisole with Cyclohexanecarboxaldehyde Catalyzed by (*S*)-2



that of the product **24** from the reaction of *m*-iodoanisole with cyclohexanecarboxaldehyde (Scheme 8). As shown in Figure 3, a linear relationship was obtained between the ee of (*S*)-**2** and the ee of **24**. This indicates that the monomeric complex of (*S*)-**2** rather than its intermolecular aggregates is responsible for the catalysis. The observed linear relationship between the ee of (*S*)-**2** and that of the arylzinc addition product is similar to what we previously reported for the reaction of the commercially available pure Ph_2Zn with aldehydes catalyzed by (*S*)-**2**.[5b,c]

We have prepared the (*R*)- and (*S*)-α-methoxy-α-phenylacetic (MPA) ester derivatives of **24** in order to determine its absolute configuration.[12] The ^1H NMR analysis showed that in

(12) (a) Trost, B. M.; Belletire, J. L.; Goldleski, P. G.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370. (b) Seco, J.; Quinoa, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17–117.

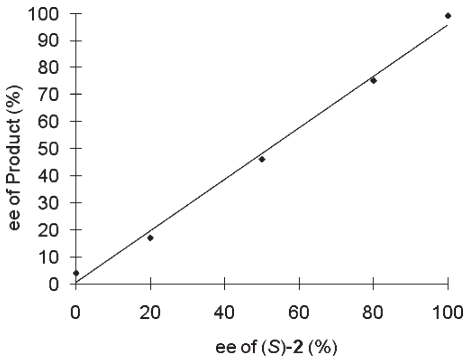
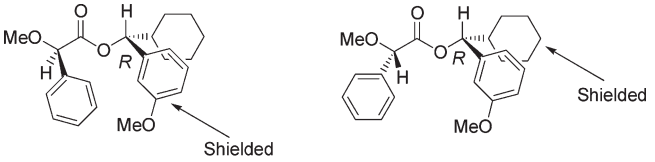
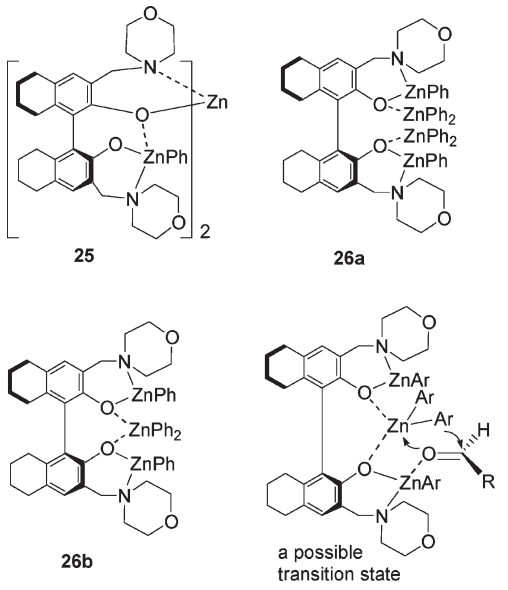


FIGURE 3. Relationship of the enantiomeric purity of (*S*)-**2** with that of the corresponding product **24**.

the (*R*)-MPA derivative of **24**, the anisyl aromatic signals of **24** shifted upfield in comparison with those in the (*S*)-MPA derivative of **24**.[12] This supports a *R* configuration for **24** prepared by using (*S*)-**2**. Thus, the nucleophilic arylzinc should add to the *si* face of the aldehyde during the asymmetric arylation.



We also conducted a NMR spectroscopic investigation for the reaction of the *in situ* generated arylzinc catalyzed by (*S*)-**2**. Under nitrogen, a portion of the reaction solution (prepared at 0 °C for 18 h) of methyl *p*-iodobenzoate (0.067 mmol) with $ZnEt_2$ (0.037 mmol) in NMP (0.05 mL, 0.52 mmol) and Li(acac) (0.008 mmol) was added to C_6D_6, and the ^1H NMR spectrum of the solution showed signals at δ 8.34 (d, J = 8.1 Hz, 4H), 8.24 (d, J = 7.8 Hz, 4H), 3.56 (s, 6H) corresponding to the desired diarylzinc (p-$MeO_2CC_6H_4)_2Zn$. The conversion of methyl *p*-iodobenzoate to (p-$MeO_2CC_6H_4)_2Zn$ was almost complete. When 1 equiv of the diarylzinc solution was added to a C_6D_6 solution of (*S*)-**2**, methyl benzoate was produced with a similar amount of unreacted (*S*)-**2** but no free (p-$MeO_2CC_6H_4)_2Zn$ was observed. This indicates that one molecule of (*S*)-**2** probably consumed more than one molecule of (p-$MeO_2CC_6H_4)_2Zn$. When 1.8 equiv of (p-$MeO_2CC_6H_4)_2Zn$ was added, (*S*)-**2** was completely consumed, but the structure of the resulting complex could not be established because of the complicated NMR signals. This is quite different from the reaction of (*S*)-**2** with the commercially pure Ph_2Zn, which gave much better defined NMR signals.[5b] When (*S*)-**2** was treated with 1.5 equiv of Ph_2Zn, the NMR spectrum showed the formation of a 2 + 3 complex **25**. This complex collapsed upon reaction with excess Ph_2Zn to form a C_2-symmetric complex that might have the structure of either **26a** or **26b**. This complex was found to be the catalytically active species for the arylzinc addition involving a possible transition state as shown. The much more complicated NMR spectrum obtained for the reaction of (*S*)-**2** with the *in situ* generated (p-$MeO_2CC_6H_4)_2Zn$ could be partly attributed to the additional components such as NMP, Li(acac), and EtI present in this reaction system. When up to 5 equiv of the (p-$MeO_2CC_6H_4)_2Zn$ solution was added to (*S*)-**2**, the NMR spectrum still showed complicated signals for the ligand-zinc complex with no free (p-$MeO_2CC_6H_4)_2Zn$ present.



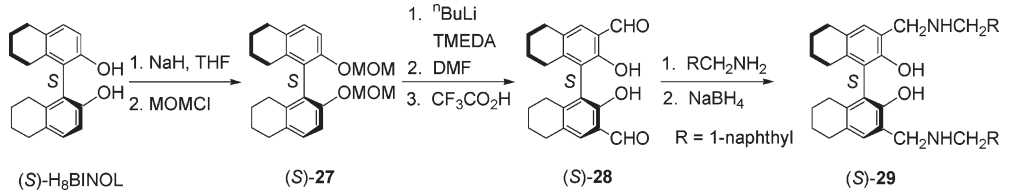
When the H_8BINOL-AM compounds are used for the arylzinc addition to aldehydes, the active catalysts are the zinc complexes generated from the reaction of the arylzincs with the chiral compounds. That is, for each arylzinc addition reaction, the catalyst is different because different arylzincs are used. On the basis of the reaction time described earlier, the following order was found for the relative activity of the reactions studied: (methyl *p*-benzoate)$_2$zinc > (2-thiophenyl)$_2$zinc > (phenyl)$_2$zinc > (*m*-anisyl)$_2$zinc ≫ (*m*-benzonitrile)$_2$zinc.

3. Synthesis of a H_8BINOL-AM Compound Containing Secondary Amine Substituents and Their Use in the Asymmetric Arylzinc Addition. The results in Tables 1, 2, 4, and 8 show that the H_8BINOL-AM compounds containing more sterically crowded tertiary amine substituents are generally less enantioselective than those containing sterically less crowded tertiary amine substituents. It would be interesting to compare the catalytic properties of these compounds with those containing the sterically less crowded secondary amines. We found that the use of a primary amine in combination with paraformaldehyde could not undergo the Mannich-type reaction with H_8BINOL like that shown in Scheme 1 to generate the corresponding secondary amine-substituted H_8BINOL-AM. Therefore, a multistep synthesis was conducted to prepare such a compound. As shown in Scheme 9, (*S*)-H_8BINOL was first protected with methoxymethyl groups to give (*S*)-**27**. Treatment of (*S*)-**27** with ^{n}BuLi and TMEDA followed by reaction with DMF and acidic deprotection gave the 3,3′-diformylH_8BINOL (*S*)-**28**.[13] Reaction of (*S*)-**28** with 1-naphthylmethylamine followed by reduction with $NaBH_4$ gave the H_8BINOL-AM derivative (*S*)-**29** that contains 3,3′-secondary amine substituents.

Compound (*S*)-**29** (10 mol %) was used to catalyze the reactions of *m*-iodoanisole with *o*-methoxybenzaldehyde and *o*-chlorobenzaldehyde under the same conditions as entry 1 in Table 4 (see Scheme 3). For the reaction of *o*-methoxybenzaldehyde, it gave 96% yield and 68% ee. For the reaction of

(13) (a) Zhang, H. -C.; Huang, W. -S.; Pu, L. *J. Org. Chem.* **2001**, *66*, 481–487. (b) Cox, P. J.; Wang, W.; Snieckus, V. *Tetrahedron Lett.* **1992**, *33*, 2253–2256.

SCHEME 9. Synthesis of the Secondary Amine-Substituted H_8BINOL-AM Compound (*S*)-29



o-cholorobenzaldehyde, it gave 80% yield and 40% ee. These enantioselectivities are lower than those of (*S*)-**2**, (*S*)-**7**, and (*S*)-**12** shown in Tables 4 and 5. Thus, using the H_8BINOL-AM containing secondary amine substituents did not improve the enantioselectivity over those with tertiary amine substituents.

4. Conclusion

In summary, we have prepared a family of optically active H_8BINOL-AM compounds containing 3,3′-tertiary amine substituents by using a one-step reaction of H_8BINOL with amino methanols. These H_8BINOL-AM compounds were used to catalyze the reaction of the *in situ* generated functional arylzincs from aryliodides and $ZnEt_2$ with a variety of aldehydes to produce chiral diaryl carbinols and a few arylalkyl carbinols. This study shows that the H_8BINOL-AM compounds with less sterically congested cyclic or acyclic tertiary amine substituents are more enantioselective than those with more bulky tertiary amine substituents. A linear correlation was observed between the enantiomeric excess of the chiral ligand and that of the arylzinc addition product, suggesting a monomeric active catalytic species.

Previously, we found that compound (*S*)-**2** was highly enantioselective for the asymmetric arylzinc addition to *p*- and *m*-substituted aromatic aldehydes and aliphatic aldehydes. In the study described in this report, the newly prepared pyrrolidinyl derivative (*S*)-**12** was found in most cases to give enhanced enantioselectivity over (*S*)-**2** and the other H_8BINOL-AM compounds, especially for the challenging *ortho*-substituted aromatic aldehydes. The benzylmethylamine-based compound (*S*)-**7** also gave better enantioselectivity in several cases. A H_8BINOL-AM containing 3,3′-bis-*sec*-amine substituents, prepared by a multistep method, was used to catalyze the arylzinc addition to aldehydes but showed lower enantioselectivity than that using the tertiary amine derivatives (*S*)-**2**, (*S*)-**7** ,and (*S*)-**12**. It was found for the first time that an aryl bromide, 2-bromothiophene, could be used to prepare a heteroarylzinc reagent by reaction with $ZnEt_2$. The addition of this heteroarylzinc reagent to an aldehyde in the presence of (*S*)-**12** proceeded with good enantioselectivity.

Experimental Section

Synthesis and Characterization of (*S*)-3. Paraformaldehyde (3.4 mmol, 102.1 mg, 5 equiv) was added to a 2-neck round-bottom flask fitted with condenser under nitrogen. The flask was then charged with dioxane (5 mL, degassed), and the mixture was cooled to 0 °C. Diethylamine (3.4 mmol, 353 μL, 5 equiv) was added dropwise into the mixture cautiously over 15−20 min. After the addition was complete, the ice bath was removed, and the mixture was warmed to room temperature for 30 min. It was then heated at 50 °C for about 20 h during which a slightly colored solution formed. After the solution was cooled to room temperature, (*S*)-H_8BINOL (200 mg, 0.68 mmol) was added, and the resulting solution was reheated to 60 °C for 12 h. Upon completion of the reaction, CH_2Cl_2 (50 mL) was added to the reaction mixture. The organic fraction was washed with $NaHCO_3$ (saturated, aq) (3 × 35 mL) and H_2O (3 × 50 mL). The organic layer was then dried over Na_2SO_4, filtered, and concentrated. The residual oil was dissolved in a minimal amount of ethyl acetate and passed through an alumina column eluted with hexanes/ethyl acetate (3−5%) to give pure (*S*)-**3** as a white powder in 88% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.13 (bs, 2H), 6.70 (s, 2H), 3.86 (d, J = 14.1 Hz, 2H), 3.64 (d, J = 14.1 Hz, 2H), 2.73 (m, 4H), 2.59 (m, 8H), 2.44 (m, 2H), 2.18 (m, 2H), 1.71 (m, 8H), 1.07 (t, J = 7.2 Hz, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 135.3, 128.1, 126.7, 124.0, 119.1, 57.0, 46.0, 29.2, 26.8, 23.2, 14.0. $[\alpha]^{25}_D$ −55.6 (*c* 0.995, THF). Mp 95−100 °C. HRMS calcd for $C_{30}H_{44}N_2O_2$ + H: 465.3476. Found for MH^+: 465.3481.

Synthesis and Characterization of (*S*)-4. Paraformaldehyde (301 mg, 10.0 mmol, 5 equiv) was added to a 2-neck round-bottom flask fitted with a condenser under nitrogen. The flask was then charged with dioxane (6 mL, degassed), and the mixture was cooled to 0 °C. Dibutylamine (1.7 mL, 10.0 mmol, 5 equiv) was added dropwise into the mixture cautiously over 15−20 min. In order to prevent the complete freezing of the reaction mixture, the addition was conducted in the following fashion. The ice bath was removed followed by the addition of a few drops of amine and was then replaced. After the addition was complete, the mixture was warmed to room temperature for 30 min and then heated at 75 °C for 22 h. An amber-colored, viscous solution formed, which was cooled to room temperature, and (*S*)-H_8BINOL (590 mg, 2.01 mmol) was added. The solution was reheated to 75 °C for 41 h. Upon completion of the reaction, CH_2Cl_2 (50 mL) was added, and the organic fraction was washed with $NaHCO_3$ (saturated, aq) (3 × 35 mL) and H_2O (2 × 35 mL). The organic layer was then dried over Na_2SO_4, filtered, and concentrated. The residual oil was dissolved in a minimal amount of ethyl acetate and passed through an alumina column eluted with hexanes/ethyl acetate (5%). This column chromatography separation was repeated to give (*S*)-**4** as a white powder in 60% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.89 (s, 2H), 6.56 (s, 2H), 3.92 (d, J = 13.8 Hz, 2H), 3.47 (d, J = 13.9 Hz, 2H), 2.73 (m, 4H), 2.54 (m, 4H), 2.37 (m, 6H), 2.11 (m, 2H), 1.69 (m, 8H), 1.46 (m, 8H), 1.25 (m, 8H), 0.85 (t, J = 8.3 Hz, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 135.2, 128.1, 126.6, 123.9, 119.2, 58.4, 53.1, 29.2, 28.7, 26.8, 23.2, 20.6, 14.0. $[\alpha]^{25}_D$ −13.5 (*c* 0.955, THF). Mp 88−93 °C. Anal. Calcd for $C_{38}H_{60}N_2O_2$: C, 79.11; H, 10.48; N, 4.86. Found: C, 79.17; H, 10.68; N, 4.79. HRMS calcd for $C_{38}H_{60}N_2O_2$ + H: 577.4733. Found for MH^+: 577.4735.

Synthesis and Characterization of (*S*)-5. Paraformaldehyde (50 mmol) was added to a 2-neck round-bottom flask fitted with condenser and vacuum adaptor. Dioxane (10 mL, degassed) was added. Diisopropylamine (50 mmol, 7.07 mL) was added dropwise over 60 min at room temperature with aggressive stirring. The mixture was then heated gently to 60 °C. After 16 h, a clear solution was obtained, which was then cooled to room temperature and charged with (*S*)-H_8BINOL (1.47 g, 5 mmol). The solution was heated at 60 °C for 17 h and then at 80 °C for 24 h. After the same workup as in the preparation of (*S*)-**4**, the oily residue was dissolved in a minimal amount of ethyl acetate and passed through an alumina column eluted with hexanes/acetone

(5%). This chromatography purification was repeated two more times to give pure (*S*)-**5** as a light powdery white solid in 60% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.26 (s, 2H), 6.70 (s, 2H), 3.87 (d, J = 14.7 Hz, 2H), 3.77 (d, J = 14.4 Hz, 2H), 3.15 (septet, J = 6.6 Hz, 4H), 2.70 (m, 4H), 2.44 (m, 2H), 2.13 (m, 2H), 1.69 (m, 8H), 1.07 (d, J = 6.6 Hz, 12H), 1.06 (d, J = 6.6 Hz, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 135.1, 128.3, 126.5, 123.8, 119.4, 48.4, 47.2, 29.2, 26.8, 23.3, 19.9, 19.4. $[\alpha]^{25}_D$ −54.9 (*c* 0.925, THF) mp 184−188 °C. HRMS calcd for $C_{34}H_{52}N_2O_2$ + H: 521.4102. Found for MH^+: 521.4106.

Synthesis and Characterization of (*S*)-6. Dicyclohexylamine (75 mmol) was added to paraformaldehyde (75 mmol) under nitrogen at 0 °C. The resulting mixture was stirred at room temperature for an additional 1 h and heated at 60 °C for 2 d. Then, at room temperature (*S*)-H_8BINOL (880 mg, 3 mmol) and degassed dioxane (20 mL, degassed) were added. The reaction mixture was heated at 70 °C for 24 h and further heated at reflux for another 12 h. The reaction was shown to be complete by ^{1}H NMR spectroscopy. After the same workup and purification as in the preparation of (*S*)-**4**, the product was further purified by recrystallization in ethanol. Two crops of (*S*)-**6** were obtained as a white solid in 55% yield. One additional column chromatography was necessary to fully purify (*S*)-**6**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.26 (s, 2H), 6.62 (s, 2H), 3.99 (d, J = 14.1 Hz, 2H), 3.79 (d, J = 14.4 Hz, 2H), 2.91 (m, 2H), 2.66 (m, 6H), 2.43 (m, 2H), 2.10 (m, 4H), 1.69 (m, 24H), 1.22 (m, 16H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4, 135.2, 128.3, 126.7, 124.0, 120.0, 57.3, 49.8, 31.6, 30.0, 29.5, 26.9, 26.4, 26.3, 23.6. $[\alpha]^{25}_D$ −4.5 (*c* 0.785, THF). Mp 234−238 °C. HRMS calcd for $C_{46}H_{68}N_2O_2$ + H: 681.5354. Found for MH^+: 681.5362.

Synthesis and Characterization of (*S*)-7. Paraformaldehyde (301 mg, 10.0 mmol, 5 equiv) was added to a 2-neck round-bottom flask fitted with condenser under nitrogen. The flask was then charged with dioxane (6 mL, degassed), and the mixture was cooled to 0 °C. Benzyl methylamine (10.0 mmol, 5 equiv) was added dropwise into the mixture cautiously over 15−20 min. The ice bath was removed, and the mixture was warmed to room temperature for 1 h. The mixture was then heated gently to 75 °C for 12 h, which gave a yellow-colored solution. This solution was cooled to room temperature, and (*S*)-H_8BINOL (590 mg, 2.01 mmol) was added. After the reaction solution was reheated to 75 °C for 12 h, CH_2Cl_2 (50 mL) was added to this mixture at room temperature. The organic fraction was then washed with $NaHCO_3$ (saturated, aq) (3 × 35 mL) and H_2O (2 × 35 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residual oil was dissolved in a minimal amount of ethyl acetate and passed through an alumina column eluted with hexanes/ethyl acetate (5%). Multiple column chromatography was sometimes needed which gave (*S*)-**7** as a white powder in >70% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.67 (s, 2H), 7.29 (m, 10H), 6.82 (s, 2H), 3.99 (d, J = 13.5 Hz, 2H), 3.68 (d, J = 12.6 Hz, 2H), 3.66 (d, J = 13.5 Hz, 2H), 3.57 (d, J = 12.6 Hz, 2H), 2.81 (m, 4H), 2.49 (m, 2H), 2.23 (m, 8H), 1.79 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.3, 137.1, 135.6, 129.4, 128.3, 128.2, 127.2, 124.0, 118.9, 61.4, 61.3, 40.9, 29.2, 26.9, 23.2, 23.1. $[\alpha]^{25}_D$ −19.0 (*c* 0.81, THF). Mp 90−95 °C. Anal. Calcd for $C_{38}H_{44}N_2O_2$: C, 81.39; H, 7.91; N, 5.00. Found: C, 80.59; H, 7.90; N, 4.85. HRMS calcd for $C_{38}H_{44}N_2O_2$ + H: 561.3481. Found for MH^+: 561.3473.

Synthesis and Characterization of (*S*)-8. Paraformaldehyde (50 mmol, 1.5 g) was placed into a 2-neck, 50 mL round-bottom flask equipped with stir bar, condenser, and vacuum adaptor. At 0 °C, benzyl ethylamine was added dropwise to the flask with vigorous stirring. After the addition was complete, the mixture was stirred for 25 min and then warmed to room temperature for 50 min. The reaction mixture was heated at 50 °C for 18 h and then cooled to room temperature. (*S*)-H_8BINOL (736 mg, 2.5 mmol) and dioxane (5 mL, degassed) were added. The reaction mixture was heated at 95−100 °C for 24 h. After the same workup as the preparation of (*S*)-**3**, a residual oil was obtained that was purified twice by column chromatography on alumina eluted with hexanes/acetone (5−10%). The resulting crystals were recrystallized from ethanol to give pure (*S*)-**8** in 55% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.73 (s, 2H), 7.29 (m, 10H), 6.78 (s, 2H), 3.98 (d, J = 13.8 Hz, 2H), 3.77 (d, J = 13.2 Hz, 2H), 3.63 (d, J = 13.8 Hz, 2H), 3.54 (d, J = 13.2 Hz, 2H), 2.77 (m, 4H), 2.64 (m, 2H), 2.49 (m, 4H), 2.17 (m, 2H), 1.71 (m, 8H), 1.10 (t, J = 7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.3, 137.3, 135.6, 129.5, 128.5, 128.2, 127.1, 124.0, 119.1, 57.5, 57.2, 46.2, 29.2, 26.9, 23.2, 10.9. $[\alpha]^{25}_D$ −17.6 (*c* 0.785, THF). Mp 76−82 °C. HRMS calcd for $C_{40}H_{48}N_2O_2$ + H: 589.3789. Found for MH^+: 589.3787.

Synthesis and Characterization of (*S*)-9. Under nitrogen, paraformaldehyde (1.5 g, 50 mmol) was placed into a 2-neck, 50 mL round-bottom flask equipped with stir bar, condenser, and vacuum adaptor. Dioxane (5 mL, degassed) was then added, and the slurry was chilled to 0 °C. Benzyl isopropylamine was added dropwise into the mixture with vigorous stirring. After the addition was complete, the mixture was stirred for 25 min and then warmed to room temperature for 50 min. The reaction mixture was heated at 60−65 °C for 18 h. Then, (*S*)-H_8BINOL (734 mg, 2.49 mmol) and dioxane (5 mL, degassed) were added at room temperature. The reaction mixture was heated at 90−100 °C for 24 h. After the same workup as the preparation of (*S*)-**3**, the resulting oily residue was purified twice by column chromatography on alumina eluted with hexanes/acetone (5−8%) and hexanes/acetone (4−10%), respectively. The resulting crystals were recrystallized from ethanol to give pure (*S*)-**9** in 45% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.76 (s, 2H), 7.23 (m, 10H), 6.76 (s, 2H), 3.94 (d, J = 13.8 Hz, 2H), 3.71 (d, J = 13.5 Hz, 2H), 3.60 (d, J = 13.8 Hz, 2H), 3.52 (d, J = 13.2 Hz, 2H), 3.05 (septet, J = 6.6 Hz, 2H), 2.74 (m, 4H), 2.44 (m, 2H), 2.10 (m, 2H), 1.65 (m, 8H), 1.11 (d, J = 6.9 Hz, 6H), 1.06 (d, J = 6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) 152.5, 138.2, 135.6, 129.4, 123.9, 119.0, 53.7, 52.2, 47.8, 29.3, 26.9, 23.3, 18.0, 15.4. $[\alpha]^{25}_D$ −17.9 (*c* 0.90, THF). Mp 165−168 °C. HRMS calcd for $C_{42}H_{52}N_2O_2$ + H: 617.4122. Found for MH^+: 617.4112.

Synthesis and Characterization of (*S*)-10. Under nitrogen, thiomorpholine (5.0 mL, 50 mmol) was mixed with paraformaldehyde (1.5 g, 50 mmol) at 0 °C. The mixture was warmed to room temperature after 30 min and then gently heated to 50 °C for 12 h. The resulting slurry was further heated at 75−80 °C for 5 h to give a homogeneous solution. To the solution at room temperature were added (*S*)-H_8BINOL (508.2 mg, 2 mmol) and dioxane (10 mL, degassed). The reaction solution was heated at 80 °C for 16 h. After the same workup as the preparation of (*S*)-**3**, the crude solid was recrystallized from ethanol, which gave pure (*S*)-**10** (crop 1, 65% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.37 (s, 2H), 6.71 (s, 2H), 3.79 (d, J = 13.8 Hz, 2H), 3.62 (d, J = 13.8 Hz, 2H), 2.82 (m, 8H), 2.67 (m, 8H), 2.36 (m, 2H), 2.16 (m, 2H), 1.67 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.1, 135.8, 128.6, 127.5, 123.9, 117.8, 62.2, 54.3, 29.1, 27.7, 26.9, 23.2, 23.1. $[\alpha]^{25}_D$ −50.8 (*c* 0.715, THF). Mp 162−176 °C. HRMS calcd for $C_{30}H_{40}N_2O_2S_2$ + H: 525.2604. Found for MH^+: 525.2611.

Synthesis and Characterization of (*S*)-11. Under nitrogen, paraformaldehyde (901 mg, 30.0 mmol) was added to a 2-neck round-bottom flask fitted with condenser. Then at 0 °C, piperidine (3 mL, 30.0 mmol) was added dropwise cautiously over 15−20 min with vigorous stirring. After the addition was complete, the mixture was warmed to room temperature for 30 min and then heated at 80 °C for 9 h. The resulting amber-colored viscous solution was cooled to room temperature, and (*S*)-H_8BINOL (2.06 g, 7 mmol) and dioxane (15 mL, degassed) were added. The reaction solution was reheated at 80 °C for 12 h. Upon completion of the reaction, ethyl acetate was added to this mixture. The organic fraction was washed with $NaHCO_3$ (saturated, aq) (3 × 35 mL) and H_2O (2 × 35 mL). Then, the

organic layer was dried over Na_2SO_4, filtered, and evaporated. The resulting crude crystals were recrystallized in acetone to give pure (*S*)-**11** as a white powder in 81% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.06 (s, 2H), 6.78 (s, 2H), 3.77 (d, J = 14.1 Hz, 2H), 3.51 (d, J = 13.8 Hz, 2H), 2.70 (m, 4H), 2.39 (m, 9H), 2.15 (m, 2H), 1.61 (m, 22H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 135.4, 128.2, 126.8, 124.0, 118.7, 62.2, 53.7, 29.2, 26.9, 25.6, 24.0, 23.2. $[\alpha]^{25}_D$ −72.2 (*c* 0.835, THF). Mp 128−133 °C. HRMS calcd for $C_{32}H_{44}N_2O_2$ + H: 489.3476. Found for MH^+: 489.3480.

Synthesis and Characterization of (*S*)-12. Method A. (1) Preparation of pyrrolidinomethanol. Paraformaldehyde (15.0 g, 0.5 moL) was added into a 2-necked round-bottom flask equipped with a stir bar and condenser. The vessel was flushed under nitrogen for 15 min and then cooled to 0 °C. Pyrrolidine (42 mL, 0.5 mol) was added dropwise through a side arm over 30 min with caution. After complete addition, the mixture was stirred for 1 h. The ice bath was then removed, and the mixture was stirred at room temperature for 1 h. It was then heated at 70 °C overnight to give a homogeneous syrup-like liquid. (2) Preparation of (*S*)-**12**. (*S*)-H_8BINOL (2.519 g, 8.56 mmol) was dissolved in dioxane (20 mL, degassed) in a 100 mL 2-neck round-bottom flask equipped with stir bar and condenser. Pyrrolidinomethanol (20 mL) was added into this solution, and the flask was flushed with nitrogen. After 15 min, the mixture was heated at 60 °C for 15 h. After the reaction was complete as shown by TLC, the mixture was diluted with ethyl acetate (120 mL) and washed with $NaHCO_3$ (satd., aq) (3 × 80 mL) and H_2O (3 × 100 mL). The organic fraction was dried over Na_2SO_4, filtered, and evaporated. The residue was recrystallized from ethanol to give (*S*)-**12** in 70% yield (crop 1).

Method B. Alternatively, the reaction could be conducted in one pot by preparing an appropriate amount of pyrrolidinomethanol (10−20 equiv relative to (*S*)-H_8BINOL). Step one could be carried out in dioxane (to allow for safer addition) in a 2-neck, round-bottom flask equipped with stir bar, condenser, and vacuum adaptor. After pyrrolidinomethanol was prepared, (*S*)-H_8BINOL and degassed dioxane were introduced at room temperature. The reaction was allowed to proceed for 8−12 h. The reaction was monitored by TLC and ^{1}H NMR.

Characterization of (*S*)-12. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.91 (bs, 2H), 6.70 (s, 2H), 4.03 (d, J = 13.8 Hz, 2H), 3.76 (m, 2H), 3.62 (d, J = 13.8 Hz, 2H), 2.72 (m, 2H), 2.61 (m, 8H), 2.37 (m, 2H), 2.18 (m, 2H), 1.84 (m, 2H), 1.72 (m, 16H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 135.5, 127.7, 127.1, 124.1, 119.6, 67.9, 58.8, 53.3, 29.2, 26.9, 25.5, 23.6, 23.2, 23.2. $[\alpha]^{25}_D$ −56.4 (*c* 1.07, THF). Mp 152−156 °C. Anal. Calcd for $C_{30}H_{40}N_2O_2$: C, 78.22; H, 8.75; N, 6.08. Found: C, 78.20; H, 9.00; N, 6.03. HRMS calcd for $C_{30}H_{40}N_2O_2$ + H: 461.3168. Found for MH^+: 461.3177.

Synthesis and Characterization of (*S*)-13. (1) Thiazolidine was prepared by stirring 2-aminoethanethiol hydrochloride (88 mmol) with paraformaldehyde (88 mmol) in water (60 mL) for 20 h. Then, a solution of $NaHCO_3$ (88 mmol) in water (55 mL) was added rapidly in one addition. KCl was added to saturate the solution which resulted in a pinkish color. It was extracted with diethyl ether (4 × 150 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and evaporated. This gave a clear yellow oil, which was shown to be thiazolidine of high purity by ^{1}H NMR spectroscopy and was used without further purification in the next step. (2) Under nitrogen, thiazolidine (88 mmol) was stirred with paraformaldehyde (88 mmol) and heated at 55−62 °C for 12 h. Then, (*S*)-H_8BINOL (1.1 g, 4.1 mmol) and dioxane (15 mL, degassed) were added at room temperature. The reaction mixture was reheated at 60 °C for 10 h. It was then worked up in the same manner as for the preparation of (*S*)-**3**. The resulting oily reside was separated twice by column chromatography on silica gel eluted with hexane/acetone (5%) and hexanes (10−12%), respectively, to give the impure crystals of (*S*)-**13**. Recrystallization from acetone yielded pure (*S*)-**13** in 50% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.52 (s, 2H), 6.74 (s, 2H), 4.05 (m, 4H), 3.82 (d, J = 13.5 Hz, 2H), 3.71 (d, J = 13.5 Hz, 2H), 3.13 (t, J = 6.6 Hz, 4H), 2.98 (t, J = 6.3 Hz, 4H), 2.70 (m, 4H), 2.35 (m, 2H), 2.18 (m, 2H), 1.70 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0, 136.5, 124.3, 119.0, 58.6, 56.4, 56.2, 29.4, 29.2, 27.2, 23.4, 23.3. $[\alpha]^{25}_D$ −42.8 (*c* 0.995, THF). Mp 186−188 °C. HRMS calcd for $C_{28}H_{36}N_2O_2S_2$ + H: 497.2291. Found for MH^+: 497.2294.

Synthesis and Characterization of (*S*)-14. (1) Under nitrogen, (*S*)-2-(methoxymethyl)pyrrolidine (5.4 mL, 43.7 mmol), prepared according to Kipphardt's method and vacuum distillation through a Vigreux column,[14] was mixed with paraformaldehyde (1.31 g, 43.7 mmol) at 0 °C for 1 h. The mixture was then heated at 65 °C for overnight, resulting in a thick yellowish solution. At room temperature, (*S*)-H_8BINOL (650 mg, 2.2 mmol) and dioxane (10 mL, degassed) were added, and the reaction mixture was reheated at 65−70 °C for 18 h. The reaction was shown to be complete by TLC and NMR. After the same workup as in the preparation of (*S*)-**3,** a thick yellow oily residue was obtained. After repeated column chromatography on silica gel eluted with CH_2Cl_2/MeOH, the NMR and HRMS spectra still showed impurities that could not be completely removed. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.52 (bs, 2H), 6.71 (s, 2H), 4.24 (d, J = 13.8 Hz, 2H), 3.64 (d, J = 13.8 Hz, 2H), 3.46 (m, 2H), 3.29 (s, 6H), 3.11 (m, 2H), 2.77 (m, 6H), 2.49 (m, 2H), 2.33 (m, 2H), 2.21 (m, 2H), 1.97 (m, 2H), 1.72 (m, 16H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.1, 135.2, 127.4, 126.5, 123.6, 119.4, 75.6, 63.2, 58.7, 58.5, 54.4, 29.0, 28.4, 26.7, 23.1, 23.1, 22.7. $[\alpha]^{25}_D$ −82.1 (*c* 1.13, THF). Mp 68−80 °C. HRMS calcd for $C_{46}H_{68}N_2O_2$ + H: 549.3698. Found for MH^+: 549.3691. The mass spectrum gave an additional signal at 116.1073 corresponding to the starting (*S*)-2-(methoxymethyl)pyrrolidine ([MH^+] = 116.1075).

Synthesis and Characterization of (*S*)-15. (1) 2-Methylpyrrolidine was prepared from the commercially available 2-methyl-1-pyrroline. 2-Methyl-1-pyrroline (5 mL, 53 mmol) was added to a mixed solvent of MeOH (120 mL) and H_2O (30 mL) in a round-bottom flask equipped with a stir bar. $NaBH_4$ (64 mmol, 1.2 equiv) was then added in small quantities with vigorous stirring at room temperature. The mixture was allowed to stir at room temperature for 15 h. TLC (eluted with 5:1 CH_2Cl_2/MeOH) showed the complete consumption of the starting material. The reaction mixture was cooled with an ice bath and quenched with a *slow* addition of 2 M HCl until pH = 1−3. The solution was then stirred at room temperature for 1 h and adjusted to pH = 13 with 2 M NaOH. CH_2Cl_2 (3 × 100 mL) was used for extraction, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude compound was then stirred with solid KOH pellets and dried over sodium metal under nitrogen at 40−50 °C for 12 h. The subsequent distillation over a glass fractionating column gave 2-methylpyrrolidine. (2) Under nitrogen, 2-methylpyrrolidine (4.4 mL, 43.1 mmol) was added dropwise over 20 min to a 2-necked round-bottom for containing paraformaldehyde (43 mmol) and equipped with a stir bar, a condenser, and a vacuum adaptor at 0 °C. The resulting reaction mixture was heated at 60 °C for 7.5 h. Then, (*S*)-H_8BINOL (3 mmol) and dioxane (20 mL, degassed) were added at room temperature. The reaction mixture was reheated at 70 °C for 24 h. Following the workup as described for (*S*)-**12** (basic aqueous and aqueous extraction using ethyl acetate followed by recrystallization from ethanol), (*S*)-**15** was obtained as a white solid in 57% yield from two crops. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.98 (s, 2H), 6.70 (s, 2H), 4.33 (m, 1H), 4.12 (m, 1H), 3.45 (m, 1H), 3.21 (m, 1H), 3.06 (m, 2H), 2.75 (m, 4H), 2.49 (m, 3H), 2.25 (m, 5H), 2.01 (m, 2H), 1.61 (m, 12H), 1.42 (m, 2H), 1.16 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 135.3, 127.5, 126.7, 123.9, 119.8, 60.0, 59.8, 59.6, 57.0, 57.0, 56.9, 56.9, 53.8, 53.8, 32.8, 29.2, 26.8, 23.2, 23.2, 21.6, 21.6, 18.9, 18.8, 18.8, 18.7. This compound contains a mixture of diastereomers.

(14) Enders, D.; Fey, P.; Kipphardt, H. *Org. Synth.* **1987**, *65*, 173.

See the NMR spectra in Supporting Information for more details. $[\alpha]^{25}_{D}$ −43.6 (*c* 0.735, THF). Mp 162−166 °C. HRMS calcd for $C_{32}H_{44}N_2O_2$ + H: 489.3476. Found for MH^+: 489.3477.

Synthesis and Characterization of (*S*)-16. (1) Octahydro-1*H*-indole was prepared by adapting the method reported by Jessup.[15] Pd/C (10 mol % Pd) was wetted with 50% water in a Parr reactor equipped with a stir bar. Indoline (25, 42, or 84 mmol) and ethanol (30 or 100 mL) were charged into the vessel. The vessel was closed, and hydrogen gas was flushed through the mixture 3 times. Finally, the vessel was loaded with H_2 (∼600 psi) and placed in a 100 °C bath. After 13 h, the reactor was cooled to room temperature, and TLC (ninhydrin stain) showed no starting material. The mixture was filtered through a packed Celite pad and rinsed with chloroform and ethanol. The organics were concentrated, redissolved in NaOH (50 mL), and extracted with chloroform. After it was dried over Na_2SO_4, the solution was filtered and concentrated. It was then vacuum distilled over molecular sieves (4 Å) at 40−60 °C to give octahydro-1*H*-indole. (2) Under nitrogen, octahydro-1*H*-indole (43.5 mmol) was mixed with paraformaldehyde (43.5 mmol) in dioxane (5 mL, degassed) and heated at 50 °C for 16 h. Then (*S*)-H_8BINOL (2.4 mmol) and dioxane (5 mL, degassed) were added at room temperature and reheated at 60−70 °C for 18 h. After the same workup as described for (*S*)-**12**, a residual oil was obtained, which yielded impure crystals after evaporation. Recrystallization from ethanol (seeded with a small amount of the impure crystal) yielded pale yellow-whitish impure crystals. Upon column chromatography on silica gel eluted with hexanes/ethyl acetate (95:5 to 90:10), (*S*)-**16** was obtained as a diastereomeric mixture in 70% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.30 (bs, 2H), 6.73 (s, 2H), 4.27 (m, 1H), 4.13 (d, J = 13.5 Hz, 1H), 3.45 (d, J = 13.5 Hz, 1H), 3.27 (m, 2H), 3.07 (m, 2H), 2.73 (bs, 4H), 2.59−2.67 (m, 2H), 2.35−2.51 (m, 4H), 2.12 (bs, 2H), 1.22−1.93 (m, 30H). ^{13}C NMR (75 MHz, $CDCl_3$) 153.1, 152.9, 152.8, 135.7, 135.6, 128.1, 127.0, 126.9, 124.1, 124.0, 120.0, 63.6, 63.4, 63.3, 57.5, 51.9, 38.3, 38.2, 29.5, 28.8, 28.7, 28.5, 28.3, 27.1, 26.1, 25.3, 25.1, 24.9, 24.3, 24.0, 23.6, 23.5, 21.5, 21.3, 21.1. This compound contains a mixture of diastereomers. See the NMR spectra in Supporting Information for more details. $[\alpha]^{25}_{D}$ −22.4 (*c* 1.14, THF). Mp 122−128 °C. HRMS calcd for $C_{38}H_{52}N_2O_2$ + H: 569.4102. Found for MH^+: 569.4103.

Synthesis and Characterization of (*S*)-17. (1) Under nitrogen, imidazole (11.33 g, 166.5 mmol) was added to an ice cold mixture of paraformaldehyde (5 g, 166.5 mmol) and 1,4-dioxane (45 mL, degassed) in a 2-neck round-bottom flask equipped with a stir bar, a condenser and a vacuum adapter. The mixture was warmed to room temperature and stirred for 2 h. It was then heated at 70 °C for 12 h. After removal of dioxane under reduced pressure, imidazole methanol was obtained as a moist white solid. ^{1}H NMR (300 MHz $CDCl_3$) δ 5.41 (s, 2H), 6.93 (s, 1H), 7.08 (s, 1H), 7.32 (s, 1H), 8.94 (s, 1H). (2) Imidazole methanol (10 g, 102 mmol, 30 equiv), (*S*)-H_8BINOL (1.0 g, 3.4 mmol), and 1,4-dioxane (6 mL, degassed) were combined in a screw cap-sealed vial. [NOTE: The vial and contents were placed under nitrogen and sealed. Electrical tape was placed around the vial to prevent potential evaporative loss and also as a precautionary safety measure.] The reaction mixture was heated at 135 °C for 8 h. [NOTE: The vial was placed behind a blast shield, although no breakage of vial occurred.] Ethyl acetate was added to dilute the *warm reaction* mixture, and the organic solution was washed with a saturated aqueous $NaHCO_3$ solution (3 × 25 mL) and water (2 × 25 mL) [NOTE: It was found that the reaction mixture could be difficult to handle after cooling to room temperature; to bypass this issue, caution was taken to handle the warm reaction mixture—still nonviscous—after 8 h reaction time]. After recyrstallization from ethanol, (*S*)-**17** was obtained in 82% yield (1.27 g). ^{1}H NMR (300 MHz $CDCl_3$) δ 7.38 (s, 2H), 6.94 (s, 2H), 6.89 (s, 2H), 6.76 (s, 2H), 5.11 (d, J = 15.0 Hz, 2H), 5.00 (d, J = 14.7 Hz, 2H), 3.48 (s, 2H), 2.67 (m, 4H), 2.16 (m, 4H), 1.68 (m, 8H). ^{13}C NMR (75 MHz $CDCl_3$) δ 150.0, 137.5, 136.9, 130.1, 129.6, 128.3, 121.0, 120.7, 119.3, 45.1, 29.2, 27.1, 22.9, 22.8. $[\alpha]^{20}_{D}$ −36.4 (*c* 1.01, $CHCl_3$). Mp 248−250 °C (decomposition). HRMS calcd for $C_{28}H_{30}N_4O_2$ + H: 455.2447; Found for MH^+: 455.2442.

Optical Rotation Studies of (*S*)-17. In order to determine whether the reaction conditions caused racemization of (*S*)-**17**, the reaction was conducted in 2 screw cap-sealed vials. In each sealed vial were combined imidazole methanol (3.3 g, 34 mmol, 30 equiv), (*S*)-H_8BINOL (0.33 g, 1.2 mmol), and 1,4-dioxane (2 mL, degassed). Both sealed vials were heated at 135 °C. After 4 h, one of the sealed vials was removed from the heat and (*S*)-**17** was isolated upon purification. The optical rotation was recorded: $[\alpha]^{20}_{D}$ −34.4 (*c* 1.07, $CHCl_3$). The second sealed vial was removed from the heat after 8 h. Upon isolation of (*S*)-**17** the optical rotation was found to be undiminished: $[\alpha]^{20}_{D}$ −34.8 (*c* 1.13, $CHCl_3$). The high optical purity of (*S*)-**17** was supported by studying the ^{1}H NMR spectra of (*S*)-**17** and racemic **17** in the presence of 1 equiv (*S*)-mandelic acid (see Supporting Information).

Synthesis and Characterization of (*S*)-29. (1) (*S*)-3,3′-DiformylH$_8$BINOL (480 mg, 1.37 mmol) was dissolved in CH_2Cl_2 (30 mL) and combined with naphthalen-1-yl methylamine (6.85 mmol, 5 equiv). The reaction mixture was stirred at room temperature for 4 h and was then concentration under vacuum. The residue was passed through a silica gel column eluted with hexanes/ethyl acetate (4−20%) to give the corresponding Schiff base (818 mg, 1.37 mmol). (2) The Schiff base was dissolved in ethanol (absolute, 50 mL) and cooled down to 0 °C. $NaBH_4$ (4 equiv) was added in small portions, and the solution was then stirred at room temperature for 2 h to complete the reaction. The product mixture was cooled to 0 °C to which was added ∼1.2 N HCl (20 mL) portionwise to quench the reaction. Water (20 mL) was added, and the mixture was stirred for about 2 h at room temperature. The solution was then basified to pH ∼8−9. Extraction with CH_2Cl_2 (3 × 50 mL) followed by evaporation gave an oily yellow solid. Column chromatography purification of the product on silica gel gave (*S*)-**29** in 80% yield as whitish to slight yellow crystals. The compound could be further purified by recrystallization from ethanol which gave 30% recovered yield from 2 crops. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.30 (bs, 2H), 8.02 (d, J = 8.7 Hz, 3H), 7.86 (m, 2H), 7.78 (d, J = 7.5 Hz, 3H), 7.45 (m, 10H), 6.79 (s, 2H), 4.27 (bs, 4H), 4.14 (d, J = 13.5 Hz, 1H), 4.03 (d, J = 13.5 Hz, 1H), 2.74 (m, 6H), 2.44 (m, 4H), 2.19 (m, 4H), 1.73 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 135.9, 134.4, 133.3, 131.5, 128.7, 128.4, 128.1, 127.4, 126.7, 126.4, 125.7, 125.3, 124.2, 123.1, 119.6, 52.6, 50.2, 29.3, 27.0, 23.3, 23.2. $[\alpha]^{25}_{D}$ −33.4 (*c* 0.52, THF). Mp 112−116 °C. HRMS calcd for $C_{46}H_{68}N_2O_2$ + H: 633.3476. Found for MH^+: 633.3471.

General Procedures for the Asymmetric Arylzinc Addition to Aldehydes Catalyzed by the H$_8$BINOL-AM Compounds. Prior to use for catalysis, all the H_8BINOL-AM compounds were dissolved in dry THF and pumped under vacuum to dryness.

Asymmetric Reaction of Methyl 4-Iodobenzoate with Aldehydes. Under nitrogen to a 25 mL round-bottom flask (flame-dried under vacuum) were added Li(acac) (24 mg, 0.22 mmol, 0.24 equiv), methyl 4-iodobenzoate (524 mg, 2.0 mmol, 2.2 equiv), and NMP (1.5 mL) sequentially. This mixture was cooled to 0 °C, and diethylzinc (115 μL, 1.1 mmol, 1.20 equiv) was added dropwise. The mixture was stirred at 0 °C for 18 h. A solution of a H_8BINOL-AM (0.181 mmol, 0.2 equiv) in CH_2Cl_2 (20 mL) was added. The reaction mixture was stirred at 0 °C for 1 h. The solution was warmed to room temperature for 15 min and then cooled back to 0 °C. An aldehyde (0.91 mmol) was

(15) Cui, Y.; Kwok, S.; Bucholtz, A.; Davis, B.; Whitney, R. A.; Jessop, P. G. *New J. Chem.* **2008**, *32*, 1027–1037.

added, and the reaction was monitored by TLC. Upon completion, ammonium chloride (3 mL, saturated, aq) was added dropwise to quench the reaction. The resulting mixture was transferred into a separatory funnel and combined with additional ammonium chloride (30 mL, saturated, aq). Diethyl ether was used to extract the mixture three times (3 × 60 mL). The organic fractions were combined and washed with water (2 × 75 mL). It was then dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel eluted with hexanes (or petroleum ether)/ethyl acetate (0−12%) to give the alcohol products as either an oil or solid.

Asymmetric Reaction of 3-Iodoanisole with Aldehydes. Under nitrogen to a 10 mL round-bottom flask (flame-dried under vacuum) were added Li(acac) (24 mg, 0.22 mmol, 0.24 equiv), 3-iodoanisole (238 μL, 2.0 mmol, 2.2 equiv), and NMP (1.5 mL) sequentially. This mixture was cooled to 0 °C, and diethylzinc (115 μL, 1.1 mmol, 1.20 equiv) was added dropwise. The mixture was stirred at 0 °C for 12 h. A solution of a H_8BINOL-AM (0.091 mmol, 0.1 equiv) in THF (5 mL) was added. The resulting reaction mixture was stirred at 0 °C for 1 h and then warmed to room temperature. An aldehyde (0.91 mmol) was added, and the reaction was monitored by TLC. Upon completion, ammonium chloride (3 mL, saturated, aq) was added dropwise to quench the reaction. The resulting mixture was transferred into a separatory funnel and combined with additional ammonium chloride (30 mL, saturated, aq). Diethyl ether was used to extract the mixture three times (3 × 60 mL). The organic fractions were combined and washed with water (2 × 75 mL). It was then dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel eluted with hexanes (or petroleum ether)/ethyl acetate (0−12%) to give the alcohol products as either an oil or solid.

Asymmetric Reaction of 3-Iodobenzonitrile with Aldehydes. Under nitrogen to a 25 mL round-bottom flask (flame-dried under vacuum) were added Li(acac) (37 mg, 0.35 mmol, 0.38 equiv), 3-iodobenzonitrile (663 mg, 2.89 mmol, 3.2 equiv), and NMP (1.5 mL) sequentially. It was then cooled to 0 °C, and diethylzinc (167 μL, 1.59 mmol, 1.75 equiv) was added dropwise. The resulting mixture was stirred at 0 °C for 2 h. It was then warmed to room temperature and stirred for 34 h. A solution of a H_8BINOL-AM (178 mg, 0.362 mmol, 0.4 equiv) in THF (25 mL) was added. It was stirred at room temperature for 2 h. An aldehyde (0.91 mmoL) was added and the reaction was monitored by TLC. Upon completion, ammonium chloride (3 mL, saturated, aq) was added dropwise to quench the reaction. The resulting mixture was transferred into a separatory funnel and combined with additional ammonium chloride (30 mL, saturated, aq). Diethyl ether was used to extract the mixture three times (3 × 60 mL). The organic fractions were combined and washed with water (2 × 75 mL). It was then dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel eluted with hexanes (or petroleum ether)/ethyl acetate (0−12%) to give the alcohol products as either oil or solid.

Asymmetric Reaction of 2-Iodothiophene with Aldehydes. Under nitrogen to a 10 mL round-bottom flask (flame-dried under vacuum) were added Li(acac) (24 mg, 0.22 mmol, 0.24 equiv), 2-iodothiophene (221 μL, 2.0 mmol, 2.2 equiv), and NMP (1.5 mL) sequentially. Diethylzinc (115 μL, 1.1 mmol, 1.20 equiv) was added dropwise and was stirred at room temperature for 6−12 h. A H_8BINOL-AM (0.091 mmol, 0.1 equiv) and THF (5 mL) were added. After the reaction mixture was stirred for 1 h, an aldehyde (0.91 mmol) was added, and the reaction was monitored by TLC. Upon completion, ammonium chloride (3 mL, saturated, aq) was added dropwise to quench the reaction. The resulting mixture was transferred into a separatory funnel and combined with additional ammonium chloride (30 mL, saturated, aq). Diethyl ether was used to extract the mixture three times (3 × 60 mL). The organic fractions were combined and washed with water (2 × 75 mL). The organic fraction was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel eluted with hexanes (or petroleum ether)/ethyl acetate (1−8%) to give the alcohol products as either oil or solid.

Asymmetric Reaction of Iodobenzene with p-Anisaldehyde. Under nitrogen to a 10 mL round-bottom flask (flame-dried under vacuum) were added Li(acac) (24 mg, 0.22 mmol, 0.24 equiv), iodobenzene (224 μL, 2.0 mmol, 2.2 equiv), and NMP (1.5 mL) sequentially. Diethylzinc (115 μL, 1.1 mmol, 1.20 equiv) was added dropwise, and the mixture was stirred at room temperature for 3 h. A H_8BINOL-AM (0.091 mmol, 0.1 equiv) and THF (5 mL) were added, and it was then stirred for 1 h. *p*-Anisaldehyde (0.91 mmol) was added, and the reaction was monitored by TLC. Upon completion, ammonium chloride (3 mL, saturated, aq) was added dropwise to quench the reaction. The resulting mixture was transferred into a separatory funnel and combined with additional ammonium chloride (30 mL, saturated, aq). Diethyl ether was used to extract the mixture three times (3 × 60 mL). The organic fractions were combined and washed with water (2 × 75 mL). It was then dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel eluted with hexanes (or petroleum ether)/ethyl acetate (1−8%) to give the alcohol product as either oil or solid.

Asymmetric Reaction of 2-Bromothiophene with Benzaldehyde. Under nitrogen to a 10 mL round-bottom flask (flame-dried under vacuum) were added Li(acac) (24 mg, 0.22 mmol, 0.24 equiv), 2-bromothiopene (238 μL, 2 mmol, 2.2 equiv), and NMP (1.5 mL) sequentially. Diethylzinc (115 μL, 1.1 mmol, 1.20 equiv) was added dropwise, and the mixture was stirred at room temperature for 6−12 h. A solution of (*S*)-**12** (45 mg, 0.091 mmol, 0.1 equiv) in THF (5 mL) was added, and the resulting mixture was stirred for 1 h. Benzaldehyde (0.91 mmoL) was added, and the reaction was monitored by TLC. Upon completion, ammonium chloride (3 mL, saturated, aq) was added dropwise to quench the reaction. The resulting mixture was transferred into a separatory funnel and combined with additional ammonium chloride (30 mL, saturated, aq). Diethyl ether was used to extract the mixture three times (3 × 60 mL). The organic fractions were combined and washed with water (2 × 75 mL). It was then dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel eluted with hexanes (or petroleum ether)/ethyl acetate (1−8%) to give the alcohol products as either oil or solid.

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Supporting Information Available: Synthesis, characterization, and ee determination of the chiral alcohol products, $^1H/^{13}C$ NMR spectra of the ligands, preparation of (*S*)-**28**, the ee correlation experiment, the absolute configuration assignment for compound **24**, and details of the NMR spectroscopic studies. This material is available free of charge via the Internet at http://pubs.acs.org.