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# Chiral Macrocycle-Catalyzed Highly Enantioselective Phenylacetylene Addition to Aliphatic and Vinyl Aldehydes

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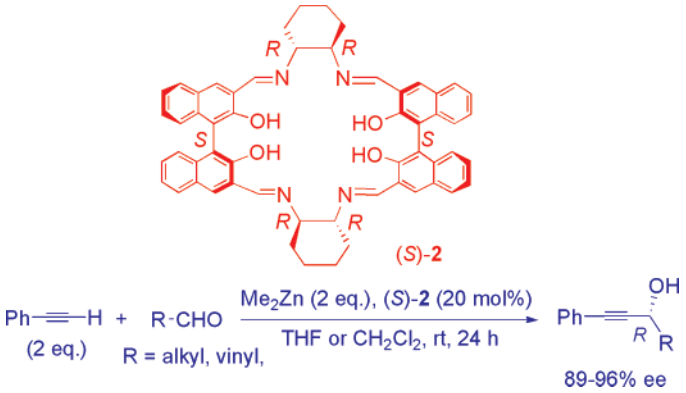
*Received January 16, 2007*




The 1,1′-binaphthyl macrocycle (*S*)-**2** is found to be an excellent catalyst for the alkyne addition to aldehydes. In the presence of (*S*)-**2** (20 mol %) and $Me_2Zn$ (2 equiv) in THF at room temperature, the addition of phenylacetylene to linear or branched aliphatic aldehydes and vinyl aldehydes gave various propargylic alcohols with 89−96% ee.

## Introduction

Organic macrocycles have been extensively employed in the host−guest chemistry and have shown enhanced binding ability and selectivity in molecular recognition over their acyclic analogues because of their preorganized binding sites.[1−3] However, many fewer of them have been used in asymmetric catalysis except for the work on metalloporphyrin complexes.[4] Chiral 1,1′-binaphthyl-based macrocycles such as (*S*)-**1** and (*S*)-**2** can be readily prepared from the one-step and four-component condensation of (*S*)-3,3′-diformyl-1,1′-bi-2-naphthol with the corresponding chiral diamines.[5,6] The Cu(II) complex of (*S*)-**1** was used to catalyze the cyclopropanation of styrene with ethyl diazoacetate by Brunner and Schiessling, but only low enantioselectivity (36.6% ee) was observed.[5b] Previously, we found that the imine-reduced derivatives of (*S*)-**1** and (*S*)-**2** were highly enantioselective fluorescent sensors for the recognition of chiral carboxylic acids.[6] The unique macrocyclic chiral structure of these compounds and their multiple imine and hydroxyl groups

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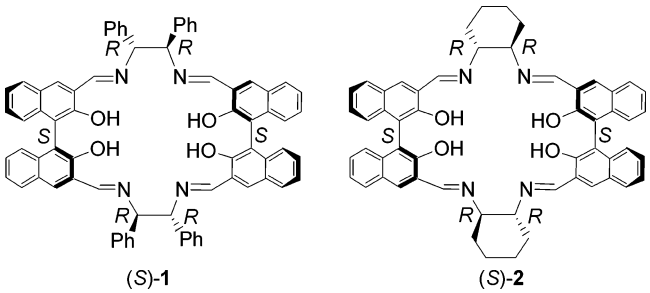
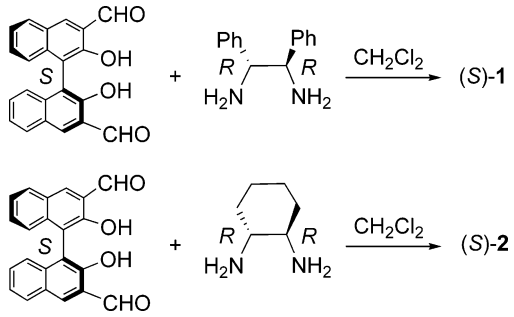
10.1021/jo070091j CCC: $37.00 
Published on Web 05/11/2007

have prompted us to study the application of their Lewis acid complexes in asymmetric catalysis.



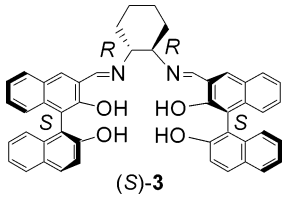

In our laboratory, we have been working on the development of chiral catalysts for the asymmetric alkyne addition to aldehydes. Intense research activity has been conducted in this area in recent years because this process can produce the synthetically very useful chiral propargylic alcohols.[7−9] A number of highly enantioselective catalysts have been developed for this reaction.[10−13] Among these, we have demonstrated that 1,1′-bi-2-naphthol (BINOL) in combination with $Et_2Zn$ and $Ti(O^iPr)_4$ can catalyze the alkyne addition to aromatic, aliphatic, and α,β-unsaturated aldehydes with high enantioselectivity.[12a,b] This method requires a pre-preparation of the alkynylzinc reagent by heating the alkyne with diethylzinc in toluene at reflux. Later, we found that the addition of the Lewis base HMPA allowed the formation of the alkynylzinc reagent to take place at room temperature.[12c,d] That is, this process uses BINOL, $Et_2Zn$, $Ti(O^iPr)_4$, and HMPA for the asymmetric synthesis of propargylic alcohols. To further develop efficient catalysts for the asymmetric alkyne addition to aldehydes, we have explored the use of functionalized BINOL catalysts. Many functional BINOL compounds have also been synthesized and studied by numerous research laboratories.[14−16] Herein, our work on using the functional BINOL-based macrocycles (*S*)-**1** and (*S*)-**2** for the asymmetric alkyne addition to aldehydes is reported. We have demonstrated that the macrocycle (*S*)-**2** in combination with $Me_2Zn$ is highly enantioselective for the reaction of phenylacetylene with linear or branched aliphatic aldehydes and vinyl aldehydes.

**SCHEME 1. Synthesis of the Bis(binaphthyl) Macrocycles (*S*)-1 and (*S*)-2**




## Results and Discussion

Earlier, we reported that the acyclic BINOL-Salen compound (*S*)-**3**[16a] in combination with $Me_2Zn$ can catalyze the reaction of alkynes with aromatic aldehydes to form propargylic alcohols with high enantioselectivity.[17] However, when (*S*)-**3** (21 mol %) in combination with $Me_2Zn$ was used to catalyze the reaction of phenylacetylene with octyl aldehyde, an aliphatic aldehyde, in THF at room temperature, only 61% ee was observed.




We then prepared the chiral macrocycles (*S*)-**1** and (*S*)-**2** according to Scheme 1.[5,6] We used these macrocycles to catalyze the reaction of phenylacetylene with octyl aldehyde under the same conditions as for (*S*)-**3**, and obtained the corresponding propargylic alcohol with 71% and 74% ee, respectively. Thus, from the acyclic compound to the macrocycles, a significant improvement was observed.

Encouraged by the above results, we examined a variety of conditions for the reaction of phenylacetylene with isovaleraldehyde by using the chiral macrocycles (*S*)-**1** and (*S*)-**2** in combination with $Me_2Zn$ as the catalysts (Scheme 2). The results of the reactions are summarized in Table 1. We first varied the

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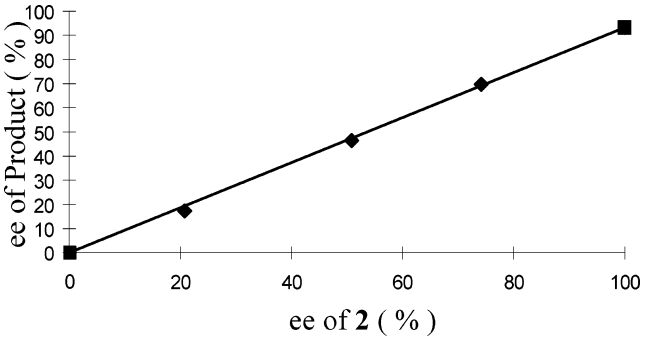
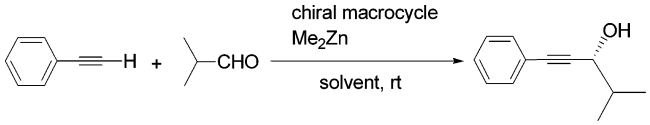



**FIGURE 1.** The relationship of the enantiomeric purity of **2** with that of the propargylic alcohol product for the reaction of phenylacetylene with isovaleraldehyde.

**SCHEME 2. Reaction of Phenylacetylene with Isovaleraldehyde in the Presence of the Chiral Macrocycles and $Me_2Zn$.**




amount of $Me_2Zn$ used in the reaction (entries 1−3). It was found that with 2 equiv of $Me_2Zn$ the ee was 87% (entry 2). Further increasing the amount of zinc to 2.5 equiv did not change the ee but gave a significant amount of 3-methyl-2-butanol because of the competing $Me_2Zn$ addition to the aldehyde. Addition of molecular sieves decreased the enantioselectivity to 85% (entry 4). Reducing the loading of the catalyst to 10% decreased the ee to 82% (entry 5). Ligand (*S*)-**1** showed a slightly lower selectivity than (*S*)-**2** (entry 6). We also varied the solvent from THF to methylene chloride, toluene, and diethyl ether but observed significant reduction in enantioselectivity especially in toluene and diethyl ether (entries 7−9). The concentration effect was explored. It was found that the ee of the product was enhanced while the concentration was reduced (entries 10−13). It reached a maximum (93% ee) when 6 mL of THF ($6.0 \times 10^{-3}$ M catalyst) was used (entry 13). Further increasing the solvent to 10 mL resulted in lower ee (entry 14). There was almost no desired reaction observed after 2 d when the solvent was increased to 20 mL (entry 15). If the catalyst concentration was kept unchanged while the amounts of other reagents were doubled, the ee of the product became slightly lower (entry 16). When 6 mL of methylene chloride ($6.0 \times 10^{-3}$ M catalyst) was used (entry 17), a similar ee was obtained.

Thus, entry 13 in Table 1 is identified as the optimized reaction procedure. We applied this procedure to the reaction of phenylacetylene with various aldehydes. As the results summarized in Table 2 demonstrate, (*S*)-**2** is a highly enantioselective catalyst for the reaction of linear and branched aliphatic aldehydes (89−95% ee, entries 1−8). The configuration for the product of entry 8 (nonyl aldehyde) is assigned to be *R* by comparing its HPLC data with those reported previously.[12a] Excellent results were obtained for the reaction of vinyl aldehydes as well (87−96% ee, entries 9−12). This macrocycle also showed good enantioselectivity for the reaction of phenylacetylene with benzaldehyde (81% ee).

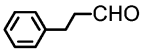
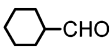
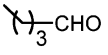
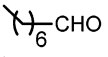
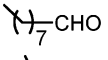
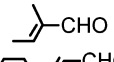
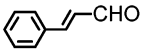
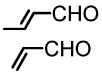
The effect of the ee of **2** on the ee of the propargylic alcohol product in the reaction of phenylacetylene with isovaleraldehyde was studied. This gave an almost linear relationship (Figure 1).

**TABLE 1. Attempted Reactions of Phenylacetylene with Isovaleraldehyde, Using the Chiral Macrocycles[a]**

| entry | solvent (mL) | $Me_2Zn$ (equiv) | ligand (mol %) | ee (%) |
|---|---|---|---|---|
| 1 | THF (2) | 1.6 | (*S*)-**2** (20) | 83 |
| 2 | THF (2) | 2 | (*S*)-**2** (20) | 87 |
| 3 | THF (2) | 2.5 | (*S*)-**2** (20) | 87 |
| 4[b] | THF (2) | 2 | (*S*)-**2** (20) | 85 |
| 5 | THF (2) | 2 | (*S*)-**2** (10) | 82 |
| 6 | THF (2) | 2 | (*S*)-**1** (20) | 84 |
| 7 | toluene (2) | 2 | (*S*)-**2** (20) | 13 |
| 8 | $Et_2O$ (2) | 2 | (*S*)-**2** (20) | 31 |
| 9 | $CH_2Cl_2$ (2) | 2 | (*S*)-**2** (20) | 83 |
| 10 | THF (2.5) | 2 | (*S*)-**2** (20) | 89 |
| 11 | THF (3.5) | 2 | (*S*)-**2** (20) | 91 |
| 12 | THF (4.5) | 2 | (*S*)-**2** (20) | 91.5 |
| **13** | **THF (6)** | **2** | **(*S*)-2 (20)** | **93** |
| 14 | THF (10) | 2 | (*S*)-**2** (20) | 92 |
| 15 | THF (20) | 2 | (*S*)-**2** (20) | NR |
| 16 | THF (10) | 2 | (*S*)-**2** (10) | 91 |
| 17 | $CH_2Cl_2$ (6) | 2 | (*S*)-**2** (20) | 94 |

[a] 2 equiv of phenylacetylene was used at room temperature. [b] 4 Å MS were added.

**TABLE 2. Results for the Addition of Phenylacetylene to Aldehydes Catalyzed by (*S*)-2**

| entry | aldehydes | yield (%) | ee (%) |
|---|---|---|---|
| 1 |  | 72 | 93 |
| 2[a] |  | - | 93 |
| 3 |  | 76 | 91 |
| 4 |  | 68 | 89 |
| 5 |  | 54 | 95 |
| 6 |  | 67 | 93 |
| 7 |  | 64 | 93 |
| 8 |  | 76 | 93 |
| 9 |  | 52 | 91 |
| 10 |  | 79 | 96 |
| 11 |  | 76 | 96 |
| 12 |  | 67 | 87 |

[a] (*R*)-**2**, the enantiomer of (*S*)-**2** made of (*R*)-binaphthyl and (*S*,*S*)-cyclohexane-1,2-diamine, was used for the reaction.

It indicates that the reaction may involve the monomeric complex of **2** rather than its aggregate. The concentration effect also supports this hypothesis. The NMR spectroscopic study of the reaction yields no conclusive results for the mechanism of this catalytic process.

In summary, we have discovered that the readily available chiral macrocycle (*S*)-**2** is an excellent catalyst for the asymmetric reaction of phenylacetylene with linear or branched aliphatic aldehydes and vinyl aldehydes. The high enantioselectivity, the easily available catalyst, and the mild reaction conditions make this catalytic method potentially very useful.

## Experimental Section

**Synthesis and Characterization of (*S*)-2.** Similar to the reaction reported by Brunner and Schiessling,[5a] the four-component con-

densation of (*S*)-3,3′-diformyl-1,1′-bi-2-naphthol and (*R*,*R*)-1,2-cyclohexanediamine occurred at room temperature in $CH_2Cl_2$ to form the chiral macrocyclic Schiff base (*S*)-**2**. The crude mixture was passed through an alumina column eluted with $CH_2Cl_2$. The solvent was evaporated and the residue was redissolved in acetone. The insoluble in the solution was removed by filtration. After removal of the solvent, the pure Schiff base (*S*)-**7** was obtained as a yellow powder. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.54 (s, 4H), 7.83 (s, 4H), 7.63(dd, $J$ = 6.6, 1.8 Hz, 4H), 7.21−7.09 (m, 8H), 3.43−3.39 (m, 4H), 2.02−1.81 (m, 8H), 1.61−1.42 (m, 8H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 165.0, 154.8, 135.3, 133.3, 129.0, 127.8, 127.3, 124.8, 122.8, 121.3, 116.3, 70.2, 32.8, 24.9. Mp >250 °C dec. MS calcd for $C_{56}H_{49}N_4O_4$ ($MH^+$) 841.3, found 841.6.

**The General Procedure for the Macrocycle Catalyzed Alkyne Addition to Aldehydes.** Under nitrogen, (*S*)-**2** (32 mg, 0.038 mmol) was added to THF (6 mL) in a 10 mL flask, followed by the addition of phenylacetylene (0.38 mmol) and dimethylzinc (0.38 mmol). Then, an aldehyde (0.19 mmol) was added and the reaction was allowed to proceed at room temperature for 24 h and monitored by thin layer chromatography. Water was added to quench the reaction, and the mixture was extracted with diethyl ether and dried with sodium sulfate. After column chromatography on silica gel, eluting with 2−10% ethyl acetate in hexanes, the propargylic alcohol product was isolated. The enantiomeric purity of the product was determined by using HPLC Chiralcel OD column.

**Acknowledgment.** Partial support of this work from the National Institutes of Health (R01GM58454/ R01EB002037-05) is gratefully acknowledged.

**Supporting Information Available:** Analytical data for the catalytic addition products. This material is available free of charge via the Internet at http://pubs.acs.org.

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