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BINOL−Salen-Catalyzed Highly Enantioselective Alkyne Additions to Aromatic Aldehydes

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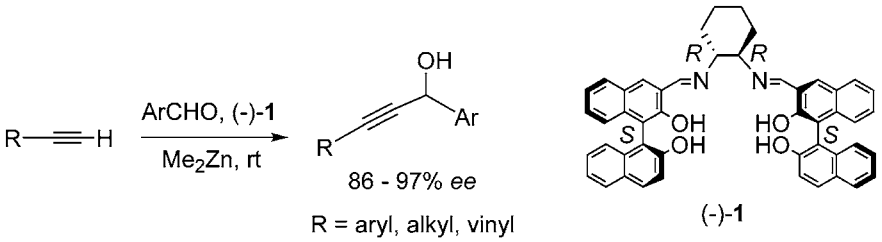
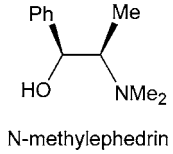
ABSTRACT

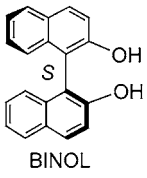


The BINOL−Salen compound (−)-1 can catalyze the addition of both aryl- and alkylalkynes to aromatic aldehydes at room temperature with high enantioselectivity (86−97% ee). The conditions for this catalytic process are both mild and simple. Unlike most other BINOL-based catalysts, using ligand (−)-1 not only avoids heating or cooling but also does not require the addition of Ti(O^{i}Pr)$_4$.

The catalytic asymmetric alkyne addition to carbonyl compounds has attracted intense research activity in recent years because this process can provide a very convenient route to chiral propargylic alcohols that have diverse synthetic applications.[1−3] Among the catalytic methods developed for the asymmetric alkyne addition to aldehydes,[4−10] two are currently considered the most practical. One was developed by Carreira and co-workers, which used *N*-methylephedrin, $Zn(OTf)_2$, and Et_3N.[5] In this method, the zinc alkynylides were generated in situ in the presence of substoichiometric amounts of Zn(II) salts. The other method was developed by us,[6,7a−c] which used 1,1′-bi-2-naphthol (BINOL), Et_2Zn, and Ti(O^{i}Pr)$_4$. The alkynylzincs in this method were generated by treating terminal alkynes with Et_2Zn. The chiral



N-methylephedrin



BINOL

ligands in both methods are commercially available and inexpensive. They can conduct the highly enantioselective

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(7) Other reports on BINOL-catalyzed alkyne additions involving both R_2Zn and Ti(O^{i}Pr)$_4$: (a) Lu, G.; Li, X.; Chan, W. L.; Chan, A. S. C. *J. Chem. Soc., Chem. Commun.* **2002**, 172−173. (b) Li, X.-S.; Lu, G.; Kwok, W. H.; Chan, A. S. C. *J. Am. Chem. Soc.* **2002**, *124*, 12636−12637. (c) Lu, G.; Li, X.-S.; Chen, G.; Chan, W. L.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2003**, *14*, 449−452. (d) Liu, Q.-Z.; Xie, N.-S.; Luo, Z.-B.; Cui, X.; Cun, L.-F.; Gong, L. Z.; Mi, A.-Q.; Jiang, Y. Z. *J. Org. Chem.* **2003**, *68*, 7921−7924. (e) Moore, D.; Huang, W.-S.; Xu, M.-H.; Pu, L. *Tetrahedron Lett.* **2002**, *43*, 8831−8834. (f) Mashall, J. A.; Bourbeau, M. P. *Org. Lett.* **2003**, *5*, 3197−3199.

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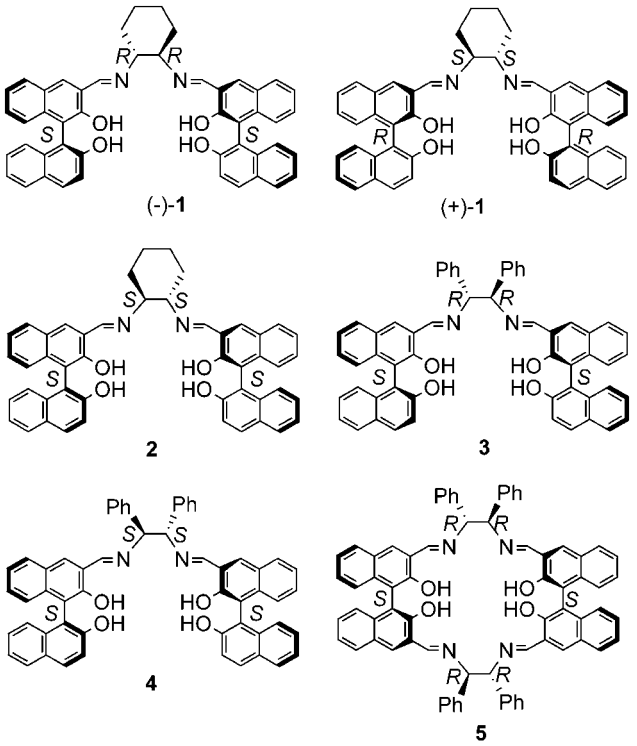
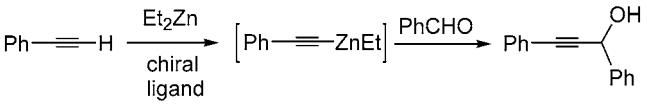
synthesis of a variety of propargylic alcohols. Limitations have also been identified for these methods. Carreira's method can catalyze the alkyne addition to aliphatic aldehydes with high enantioselectivity, but it is not catalytic for the addition to benzaldehyde. Our BINOL method can catalyze the alkyne addition to aromatic, aliphatic, and α,β-unsaturated aldehydes with high enantioselectivity,[6,7f] but it requires the use of both Et_2Zn and $Ti(O^iPr)_4$. Therefore, the search of efficient catalysts continues for the asymmetric alkyne additions. Herein, we report our finding of a highly enantioselective alkyne addition to aromatic aldehydes catalyzed by a BINOL−Salen ligand in the absence of $Ti(O^iPr)_4$.

BINOL−Salens are a class of compounds made from the condensation of the 3-aldehyde function of BINOL with amines. Since 1993, Katsuki has used BINOL−Salen-based manganese complexes for the asymmetric epoxidation of alkenes.[11] In recent years, Kozlowski has further developed BINOL−Salen-based bifunctional metal complexes for asymmetric catalysis.[12] We prepared enantiomerically pure BINOL−Salen ligands **1**−**4** by using Kozlowski's method.[12] Compounds (−)-**1** and (+)-**1** are a pair of enantiomers. Compounds (−)-**1**/**2** and **3**/**4** are two pairs of diastereomers with the configuration of the chiral carbon centers inverted. We also prepared the macrocyclic BINOL−Salen **5** by following Brunner's procedure.[13]



Compounds **1**−**5** were used to catalyze the reaction of phenylacetylene with benzaldehyde in the presence of Et_2Zn. The reactions were conducted at room temperature in toluene

Scheme 1. Asymmetric Reaction of Phenylacetylene with Benzaldehyde



by the sequential treatment of phenylacetylene with Et_2Zn, a chiral ligand, and then benzaldehyde (Scheme 1). As the results summarized in Table 1 show, compound (−)-**1** gave the highest enantioselectivity among the five ligands. The low enantioselectivity of compound **2** indicated a mismatched chirality between the BINOL units and the chiral carbon centers. Replacement of the cyclohexyl groups of (−)-**1** with the diphenyl groups of **3** and **4** also gave very low enantioselectivity. The macrocycle **5** was a poor chiral ligand for this reaction.

Table 1. Results for the Reaction of Phenylacetylene with Benzaldehyde in the Presence of Ligands (−)-**1**−**5** and Et_2Zn in Toluene at Room Temperature

entry	ligand	phenylacetylene (equiv)	Et_2Zn (equiv)	ee (%)
1	(−)-**1** (15 mol %)	2.1	2.0	79
2	**2** (15 mol %)	2.1	2.0	<10
3	**3** (15 mol %)	2.1	2.0	<10
4	**4** (15 mol %)	2.1	2.0	13
5	**5** (15 mol %)	2.1	2.0	17

We then explored the conditions for the use of ligand (−)-**1** in the reaction of phenylacetylene with benzaldehyde. Table 2 summarizes these experiments. In entries 1−4, various solvents including toluene, THF, diethyl ether, and methylene chloride were tested, among which, toluene was found to be the best. Increasing the amount of phenylacetylene versus Et_2Zn led to reduction in enantioselectivity (entry 5). This indicated that the phenylethynyl ethylzinc intermediate, as shown in Scheme 1, should be more favorable in the addition to the aldehyde than bisphenylethynylzinc that could be generated from the reaction of excess phenylacetylene with Et_2Zn. Reducing the amount of ligand (−)-**1** from 15 to 11 mol % in entry 6 led to reduction in ee. Increasing the amount

(8) A BINOL derivative-catalyzed alkyne addition without using titanium was reported but with lower enantioselectivity than this work: Xu, M.-H.; Pu, L. *Org. Lett.* **2002**, *4*, 4555−4557.

(9) (a) Lu, G.; Li, X. S.; Jia, X.; Chan, W. L.; Chan, A. S. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5057−5058. (b) Jiang, B.; Chen, Z.-L.; Xiong, W.-N. *J. Chem. Soc., Chem. Commun.* **2002**, 1524−1525. (c) Xu, Z. Q.; Wang, R.; Xu, J. K.; Da, C. S.; Yan, W. J.; Chen, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5747−5749.

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(11) (a) Sasaki, H.; Irie, R.; Katsuki, T. *Synlett* **1993**, 300−302. (b) Katsuki, T. *Coord. Chem. Rev.* **1995**, *140*, 189−214.

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(13) (a) Brunner, H.; Schiessling, H. *Angew Chem., Int. Ed. Engl.* **1994**, *33*, 125−126. (b) Brunner, H.; Schiessling, H. *Bull. Soc. Chim. Belg.* **1994**, *103*, 119−126.

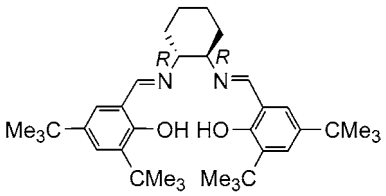
Table 2. Conditions for the Reaction of Phenylacetylene with Benzaldehyde in the Presence of Ligand (−)-**1**

entry	ligand (−)-**1** (mol %)	*T* (°C)	solvent	phenylacetylene (equiv)	R_2Zn (equiv)	ee (%)
1	15	rt	toluene	2.1	Et_2Zn (2.0)	79
2	15	rt	THF	2.1	Et_2Zn (2.0)	57
3	15	rt	ether	2.1	Et_2Zn (2.0)	39
4	15	rt	CH_2Cl_2	2.1	Et_2Zn (2.0)	29
5	15	rt	toluene	3.0	Et_2Zn (2.0)	45
6	11	rt	toluene	2.0	Et_2Zn (2.0)	71
7	22	rt	toluene	2.0	Et_2Zn (2.0)	87
8	30	rt	toluene	2.0	Et_2Zn (2.0)	87
9	30	rt	toluene	3.0	Et_2Zn (3.0)	87
10	22	0	toluene	2.0	Et_2Zn (2.0)	80
11	**22**	**rt**	**toluene**	**2.0**	**Me_2Zn (2.0)**	**92**

of ligand (−)-**1** to 22 mol % in entry 7 gave enhanced ee, but further increasing the amount of the ligand to 30 mol % did not lead to a further increase in ee (entry 8). In entry 9, the amounts of ligand (−)-**1**, phenylenacetylene, and Et_2Zn were increased, but no effect on the enantioselectivity was observed. Reducing the reaction temperature from room temperature to 0 °C gave reduced enantioselectivity (entry 10). Replacement of Et_2Zn with Me_2Zn boosted the enantioselectivity to 92% ee (entry 11). The configuration of the propargylic alcohol product was *S* as determined by comparing with the literature.[10]

We also used (+)-**1** to catalyze the reaction of phenylacetylene with benzaldehyde. Under the conditions of entry 11 in Table 2, (+)-**1** gave the propargylic alcohol product with 92% ee. The configuration of the product was *R*, the enantiomer of the product from (−)-**1** as expected.

Earlier, Cozzi found that Jacobsen's Salen ligand **6** could catalyze the alkyne addition to ketones with up to 81% ee.[14] We tested the use of **6** in the asymmetric phenylacetylene addition to benzaldehyde by applying the conditions of entry 11 in Table 2. However, only 39% ee was observed. This shows that BINOL units of ligand (−)-**1** are necessary for the high enantioselectivity.



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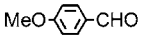
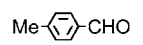
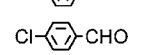
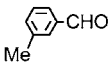
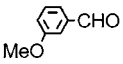
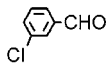
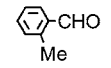
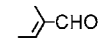
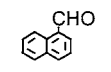
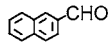
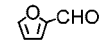
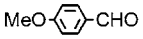
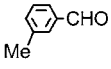
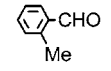
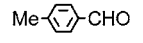
Ligand (−)-**1** was used to catalyze the reaction of alkynes with a variety of aldehydes by applying the optimized conditions of entry 11 in Table 2.[15] As shown by the results summarized in Table 3, high enantioselectivity has been achieved for the addition of both aromatic and aliphatic alkynes to aromatic aldehydes. The addition to a vinyl

(14) Cozzi, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 2895−2898.

Table 3. Results for the Alkyne Additions to Aldehydes Catalyzed by (−)-**1**

entry	alkyne	aldehyde	isolated yield (%)	ee (%)
1	PhC≡CH		-	92
2[a]	PhC≡CH		84	92
3	PhC≡CH		85	94
4	PhC≡CH		82	91
5	PhC≡CH		61	89
6	PhC≡CH		80	92
7	PhC≡CH		72	89
8	PhC≡CH		67	86
9	PhC≡CH		80	87
10	PhC≡CH		75	94
11	PhC≡CH		87	97
12	PhC≡CH		61	91
13	PhC≡CH		90	89
14	$Cl(CH_2)_3C{\equiv}CH$		60	95
15	$Cl(CH_2)_3C{\equiv}CH$		72	95
16	$Cl(CH_2)_3C{\equiv}CH$		72	90
17	$Cl(CH_2)_3C{\equiv}CH$		76	89
18	$Cl(CH_2)_3C{\equiv}CH$		74	96
19			64	86

[a] (+)-**1** was used.

aldehyde gave excellent stereocontrol as well (entry 10). Very good enantioselectivity was also observed for the reaction of an alkenyl alkyne with benzaldehyde (entry 19).

In summary, we have discovered that the BINOL−Salen compound (−)-**1** can catalyze the addition of both aromatic and aliphatic alkynes to aromatic aldehydes with high enantioselectivity. The conditions of this catalytic process are both mild and simple. Unlike most other BINOL-based

(15) A typical experimental procedure for the alkyne addition to aldehydes catalyzed by (−)-**1** is given below. Under nitrogen, an alkyne (0.5 mmol) and Me_2Zn (0.5 mmol) were added to a 10 mL flask containing toluene (1 mL, distilled over sodium). After the solution was stirred at room temperature for 1 h, ligand (−)-**1** (0.054 mmol, 38.2 mg) was added and the mixture stirred for another 1 h. Then, an aldehyde (0.25 mmol) was added and the reaction was allowed to proceed at room temperature for 18 h. 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 eluted 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.

catalysts,[6−8] using ligand (−)-**1** not only avoids heating or cooling but also does not require the addition of $Ti(O^iPr)_4$.

Acknowledgment. We thank the National Institutes of Health (R01GM58454/R01EB002037) for partial support of this research.

Supporting Information Available: Conditions to determine the enantiomeric purity of the propargyl alcohol products are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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