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Highly Enantioselective Phenylacetylene Additions to Both Aliphatic and Aromatic Aldehydes

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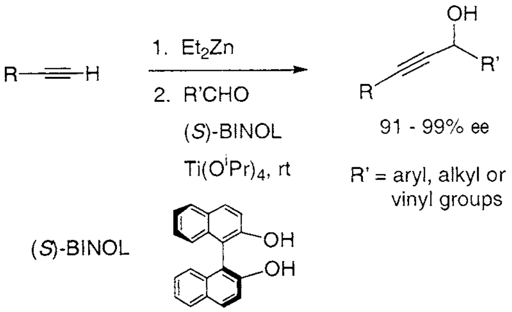
ABSTRACT



The readily available and inexpensive BINOL in combination with $Ti(O^iPr)_4$ is found to catalyze the reaction of an alkynylzinc reagent with various types of aldehydes including aliphatic aldehydes, aromatic aldehydes, and other α,β-unsaturated aldehydes to generate chiral propargyl alcohols with 91–99% ee at room temperature. No previous chiral catalysts have exhibited such a broad scope of enantioselectivity with respect to the type of aldehydes for this reaction.

In recent years, significant progress has been made in developing the catalytic enantioselective alkynylzinc addition to aldehydes.[1−9] This process allows the synthesis of propargyl alcohols that are versatile functional precursors to many chiral organic compounds.[10−15] In 1994, Ishizaki and Hoshino found that ligands **1** were effective for the addition of alkynylzinc reagents to aldehydes.[3] Up to 90−95% ee was observed for the reaction of alkynylzincs with benzaldehyde, cyclohexanecarbaldehyde, and trimethyl acetaldehyde, but the scope of the enantioselectivity was very limited. Carreira and co-workers discovered a catalyst based on the chiral

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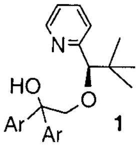
amino alcohol **2** for the alkynylzinc addition to aldehydes.[4] High enantioselectivity in the range of 90−99% ee was achieved for the reaction of alkynylzincs with a variety of *aliphatic* aldehydes at 60 °C. It utilized a catalytic amount of both the chiral ligand **2** and $Zn(OTf)_2$. However, this reaction was not suitable for the addition to aromatic aldehydes because of a significant Cannizzaro reaction.



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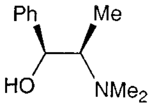

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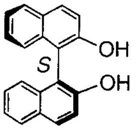
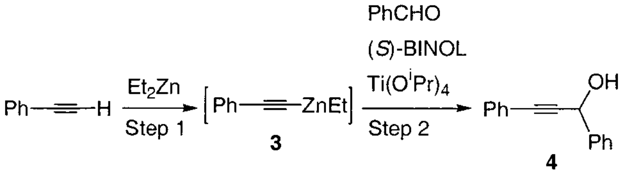


BINOL

Recently, we[5] and Chan[6] have found that 1,1′-bi-2-naphthol (BINOL) in combination with $Ti(O^iPr)_4$[16] can catalyze the alkynylzinc addition to aromatic aldehydes with high enantioselectivity. We have further demonstrated that the BINOL−$Ti(O^iPr)_4$ catalyst system is also highly enantioselective for the phenylacetylene addition to aliphatic aldehydes as well as α,*β*-unsaturated aldehydes. Herein, these results are reported.

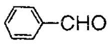
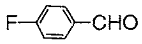
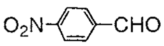
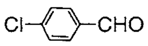
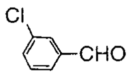
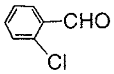
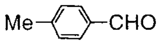
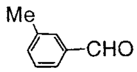
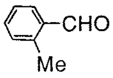
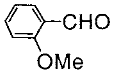
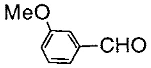
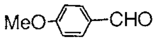
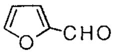
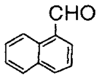
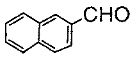
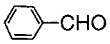
We conducted the asymmetric alkynylzinc addition in two steps: (1) treatment of a terminal alkyne with diethylzinc in refluxing toluene; (2) addition of (*S*)-BINOL, $Ti(O^iPr)_4$, an aldehyde, and a second solvent. Scheme 1 shows this two-step reaction using phenylacetylene, diethylzinc, and benzaldehyde catalyzed by (*S*)-BINOL and $Ti(O^iPr)_4$. The first step probably generated the alkynylzinc intermediate **3**, which then added to benzaldehyde in the presence of the catalyst to form the chiral propargyl alcohol **4**. Earlier, we reported the following reaction condition that gave excellent enantioselectivity for this reaction.[5] A toluene solution (2 mL) of phenylacetylene (1.1 mmol) and diethylzinc (1.0 mmol) was heated at reflux under nitrogen for 5 h. It was then combined with (*S*)-BINOL (0.10 mmol), CH_2Cl_2 (8 mL), $Ti(O^iPr)_4$ (0.25 mmol), and benzaldehyde (0.5 mmol) at room temperature. After 4 h, compound **4** was isolated in 77% yield and 96% ee.

Scheme 1. Reaction of Phenylacetylene with Benzaldehyde in the Presence of Diethylzinc, (*S*)-BINOL, and $Ti(O^iPr)_4$



The above procedure was used to carry out the alkynylzinc addition to other aromatic aldehydes, and the results are summarized in Table 1.[5] The reactions of phenylacetylene with *ortho*-, *meta*-, or *para*-substituted benzaldehydes containing electron-donating or electron-withdrawing substituents showed excellent enantioselectivity (entries 1−12). High enantioselectivity was also observed for the additions to other

Table 1. Reaction of Terminal Alkynes with Aromatic Aldehydes in the Presence of Diethylzinc, (*S*)-BINOL, and $Ti(O^iPr)_4$[a]

entry	aldehyde	isolated yield (%)	ee (%)
1		77	96
2		74	96
3		79[b]	97
4		81	92
5		79	92
6[c,d]		95	92
7[c,d]		93	97
8		77	94
9		81	96
10		73	93
11		78	93
12[c,d]		97	94
13[d]		72	92
14		71[b]	92
15		77	98
16[e]		75	92

[a] Phenylacetylene was used with the reagent ratio of phenylacetylene:Et_2Zn:$Ti(O^iPr)_4$:BINOL:aldehyde = 2:2:0.5:0.2:1 unless otherwise indicated. [b] Determined by ^1H NMR. [c] Phenylacetylene:Et_2Zn:$Ti(O^iPr)_4$:BINOL:aldehyde = 4:4:1:0.4:1. [d] Previously unpublished result. [e] Triisopropylsilylacetylene was used in place of phenylacetylene.

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[16] Selected examples for the application of BINOL+Lewis acids in asymmetric catalysis: (a) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236−1256. (b) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1993**, *115*, 7039−7040. (c) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1994**, *116*, 4077−4078. (d) Keck, G. E.; Tatbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467−8468. (e) Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **1993**, *115*, 7001−7002. (f) Aoki, S.; Mikami, K.; Terada, M.; Nakai, T. *Tetrahedron* **1993**, *49*, 1783−1792. (g) Mikami, K. *Pure Appl. Chem.* **1996**, *68*, 639−644. (h) Mikami, K.; Terada, M.; Motoyama, Y.; Nakai, T. *Tetrahedron: Asymmetry* **1991**, *2*, 643−646. (i) Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812−2820. (j) Mori, M.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 6233−6236. (k) Zhang, F.-Y.; Yip, C.-W.; Cao, R.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 585−589. (l) Sakane, S.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1985**, *26*, 5535−5538.

Table 2. Attempted Reactions of Phenylacetylene with Nonyl Aldehyde (Tol = toluene)[a]

entry	conditions for step 1	conditions for step 2	phenylacetylene/ diethylzinc (mol %)	Ti(O^{i}Pr)$_4$ (mol %)	BINOL (mol %)	ee (%)
1	2 mL of Tol, reflux 5 h	8 mL of CH_2Cl_2, rt, 4 h	200/200	50	20	75
2	2 mL of Tol, reflux 5 h	4 mL of Tol, rt, 4 h	200/200	50	20	75
3	2 mL of Tol, reflux 5 h	8 mL of THF, rt, 4 h	200/200	50	20	79
4	2 mL of Tol, reflux 5 h	8 mL of Et_2O, rt, 4 h	200/200	50	20	83
5	2 mL of Tol, reflux 5 h	8 mL of Et_2O, 0 °C, 4 h	200/200	50	20	59
6	2 mL of Tol, reflux 5 h	8 mL of Et_2O, reflux, 4 h	200/200	50	20	77
7	2 mL of Tol, reflux 5 h	8 mL of Et_2O, MS, rt, 4 h	200/200	50	20	83
8	2 mL of Tol, reflux 5 h	8 mL of Et_2O, rt, 4 h	200/200	50	20	63[b]
9	2 mL of Tol, reflux 5 h	8 mL of Et_2O, rt, 4 h	200/200	140	20	68
10	2 mL of Tol, reflux 1 h	8 mL of Et_2O, rt, 4 h	200/200	50	20	89[c]
11	2 mL of Tol, reflux 0.5 h	8 mL of Et_2O, rt, 4 h	200/200	50	20	82[d]
12	2 mL of Tol, reflux 1 h	8 mL of Et_2O, rt, 4 h	400/400	50	20	85
13	2 mL of Tol, reflux 1 h	8 mL of Et_2O, rt, 4 h	200/200	100	40	84[e]
14	2 mL of Tol, reflux 1 h	8 mL of Et_2O, rt, 4 h	400/400	100	40	91[f]
15	1 mL of Tol, reflux 1 h	8 mL of Et_2O, rt, 4 h	400/400	100	40	91[g]

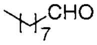
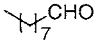
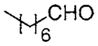
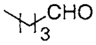
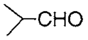
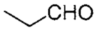
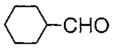
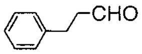
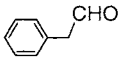
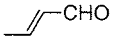
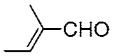
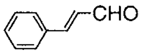
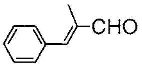
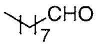
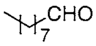
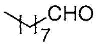
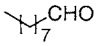
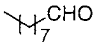
[a] Redistilled nonyl aldehyde was used unless otherwise indicated. [b] Ti(O^{t}Bu)$_4$ was used. [c] Yield: 54%. [d] Yield: 9%. [e] Yield: 35.9%. [f] Yield: 96%. [g] Undistilled aldehyde was used. Yield: 66%.

aromatic aldehydes such as 2-furaldehyde, 1-naphthaldehyde, and 2-naphthaldehyde (entries 13−15). The reaction of triisopropylsilylacetylene with benzaldehyde gave high ee as well (entry 16).

However, when the conditions for the highly enantioselective addition to aromatic aldehydes were applied to the reaction of aliphatic aldehydes, low enantioselectivity was observed. For example, only 75% ee was observed for the reaction of nonyl aldehyde, a linear aliphatic aldehyde (Table 2, entry 1). Various conditions were explored for the reaction of phenylacetylene with nonyl aldehyde, and the results are summarized in Table 2. We first varied the methylene chloride solvent used in step 2 (entries 2−4). It was found that diethyl ether improved the ee to 83% (entry 4). We then examined the effect of temperature on this reaction, but found only decreased ee values at either higher or lower temperatures (entries 4−6). Addition of molecular sieves had no effect on the enantioselectivity (entry 7). In entry 8, Ti(O^{t}Bu)$_4$ was used in place of Ti(O^{i}Pr)$_4$, which gave lower ee. Increasing the amount of Ti(O^{i}Pr)$_4$ in entry 9 could not improve the enantioselectivity. Increased ee (89%) was observed when the refluxing time in the first step was reduced to 1 h, but the yield was also reduced (54%, entry 10). Further decreasing the refluxing time in the first step to 30 min gave very low yield (9%) as well as lower ee (82%) (entry 11). To increase the yield, we increased the amount of phenylacetylene and diethylzinc which, however, gave lower ee values (entry 12). Increasing the amount of BINOL and Ti(O^{i}Pr)$_4$ also showed no improvement (entry 13). Therefore, we increased the amount of all reagents which indeed led to both high enantioselectivity (91% ee) and excellent yield (96%) (entry 14). The same enantioselectivity was observed for the use of undistilled nonyl aldehyde (entry 15).

The following gives the experimental procedure for entry 15 of Table 2. Under nitrogen, a toluene (1 mL) solution of phenylacetylene (2.0 mmol, 226 μL) and diethylzinc (2.0

Table 3. Results for the Addition of Phenylacetylene to Aliphatic and α,β-Unsaturated Aldehydes[a]

entry	aldehyde	isolated yield (%)	ee (%)
1		66	91
2[b]		96	91
3		70	93
4		91	93
5		84	97
6		60	94
7		58	95
8		99	93
9[c]		93	91
10		92	96
11		93	96
12		89	97
13		96	99
14[b,d]		94	94
15[b,e]		92	96
16[b,f]		92	95
17[f]		77	96
18[g]		96	96

[a] Conditions of entry 15 in Table 2 were used with undistilled aldehydes unless otherwise indicated. [b] Redistilled aldehyde was used. 2 mL of toluene was used in the first step. [c] Aldehyde was added dropwise. [d] Phenylacetylene:Et_2Zn:Ti(O^{i}Pr)$_4$:BINOL:aldehyde = 6:6:1.5:0.6:1. [e] Phenylacetylene:Et_2Zn:Ti(O^{i}Pr)$_4$:BINOL:aldehyde = 6:6:2:0.8:1. [f] Phenylacetylene:Et_2Zn:Ti(O^{i}Pr)$_4$:BINOL:aldehyde = 6:6:2.5:1:1. [g] The same conditions as entry 17 in this table except that redistilled aldehyde was used.

mmol, 210 μL) in a 25-mL flask was heated at reflux for 1 h. Then, (*S*)-BINOL (0.20 mmol, 57.2 mg), Et_2O (8 mL), and Ti(O^{i}Pr)$_4$ (0.50 mmol, 150 μL) were added sequentially at room temperature and stirred for 1 h. Nonyl aldehyde (0.50 mmol, 91 μL, undistilled) was added and the stirring continued for an additional 4 h. The reaction was quenched with saturated ammonium chloride. The resulting mixture was extracted with methylene chloride and the extract was dried over magnesium sulfate. After removal of the volatile solvent under reduced pressure, the residue was passed through a short silica gel column to afford the product 1-phenylundec-1-yn-3-ol in 66% yield. The ee was determined to be 91% by HPLC (ChiralDiacel OD column).

We applied the above conditions to the reaction of phenylacetylene with other aliphatic aldehydes. As the results summarized in Table 3 demonstrate, highly enantioselective alkynylzinc additions to various aliphatic aldehydes were achieved (91−95% ee, entries 1−9). In addition, the reactions of various α,β-unsaturaed aldehydes also exhibited very high enantioselectivity (96−99% ee, entries 10−13). In entries 14−18, we further increased the ratio of the reagents versus the aldehyde, which boosted the ee up to 96% for the reaction of phenylacetylene with nonyl aldehyde.

The effect of the ee of BINOL on the ee of the propargyl alcohol product generated from the reaction of phenylacetylene with benzaldehyde was studied. Figure 1 shows a small negative nonlinear effect in this reaction. It indicates that the reaction may involve both the monomeric BINOL catalyst and its aggregates.[17]

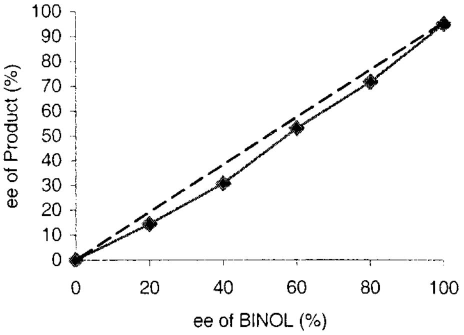


Figure 1. The relation of the enantiomeric purity of BINOL with that of the propargyl alcohol product for the reaction of phenylacetylene with benzaldehyde.

In summary, we have demonstrated that the readily available and inexpensive BINOL ligand in combination with Ti(O^{i}Pr)$_4$ is a highly enantioselective catalyst for the reaction of an alkynylzinc reagent with various types of aldehydes, including aliphatic aldehydes, aromatic aldehydes, and α,β-unsaturated aldehydes. No previous catalysts have exhibited such a broad scope of enantioselectivity with respect to the type of aldehydes for this reaction. In the BINOL−Ti(O^{i}Pr)$_4$-catalyzed reaction, after the preparation of the alkynylzinc, the asymmetric addition to aldehydes proceeds at room temperature with 91−99% ee. This simple catalyst system is practical for the asymmetric synthesis of various types of chiral propargyl alcohols.

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Supporting Information Available: Experimental conditions for determining the enantiomeric purity of the propargyl alcohol products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[17] For a recent mechanistic study on the BINOL−Ti(IV) catalyzed organozinc addition, see: Balsells, J.; Davis, T. J.; Carroll, P.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10336−10348.