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BINOL-Catalyzed Highly Enantioselective Terminal Alkyne Additions to Aromatic Aldehydes

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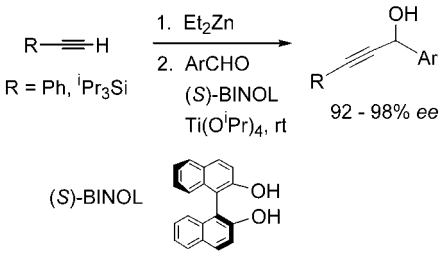
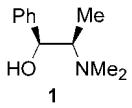
ABSTRACT



The readily available BINOL ligand in combination with $Ti(O^iPr)_4$ was found to catalyze the highly enantioselective reaction (92–98% ee) of terminal alkynes with aromatic aldehydes that contain a variety of substituents and substitution patterns. After the preparation of the zinc acetylide reagent, the catalytic asymmetric addition to aldehydes proceeded at room temperature with excellent stereocontrol. This simple catalyst system is practical for the asymmetric synthesis of chiral propargylic alcohols.

Optically active propargylic alcohols are versatile precursors for the synthesis of many chiral organic compounds.[1] Addition of metalated terminal alkynes to carbonyls is a very useful method to generate various types of propargylic alcohols. Recently, Carreira and co-workers discovered a highly enantioselective catalyst based on the chiral amino alcohol **1** for the alkynylzinc addition to *aliphatic* aldehydes.[2] Other chiral compounds have also been used to carry out



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the asymmetric reaction of terminal alkynes with carbonyl compounds, but only limited enantioselectivity has been observed.[3] Thus, one of the current challenges in this area is to develop generally enantioselective as well as practical catalysts for the reaction of terminal alkynes especially with *aromatic* aldehydes.

In our laboratory, we are interested in studying the applications of 1,1′-bi-2-naphthol (BINOL) and its derivatives.[4] In recent years, optically pure BINOL has become a cheap and broadly applicable chiral compound. Direct use of the *unmodified* BINOL ligand in combination with metal salts in asymmetric catalysis has resulted in a series of exciting discoveries. Among these are the nitro aldol reaction,[5] the allylstannane addition,[6] the ene reaction,[7] the

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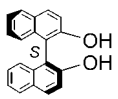
Table 1. Results for the Reaction of Phenylacetylene with Benzaldehyde (Tol = toluene)

entry	conditions for step 1	solvent in step 2	$Ti(O^iPr)_4$ (mol %)	BINOL (mol %)	temp for step 2	major product	ee of **3** (%)
1	Tol (5 mL), BINOL, rt	Tol (5 mL)	25	10	rt	**4**	~85
2	CH_2Cl_2 (5 mL), BINOL, rt	CH_2Cl_2 (5 mL)	25	10	rt	**4**	~88
3	THF (5 mL), BINOL, rt	THF (5 mL)	25	10	rt	**4**	~70
4	ether (5 mL), BINOL, rt	ether (5 mL)	25	10	rt	**4**	~78
5	CH_2Cl_2 (5 mL), reflux	CH_2Cl_2 (5 mL)	25	10	rt	**4**	~85
6	CH_2Cl_2 (5 mL), BINOL, reflux	CH_2Cl_2 (5 mL)	25	10	rt	**4**	ND
7	CH_2Cl_2 (5 mL), BINOL $Ti(O^iPr)_4$, reflux	CH_2Cl_2 (5 mL)	25	10	rt	**4**	ND
8	Tol (5 mL), reflux	Tol (5 mL)	25	10	rt	**3**	80
9	Tol (1 mL), reflux	Tol (1 mL) + CH_2Cl_2 (4 mL)	25	10	rt	**3**	85
10	Tol (1 mL), reflux	Tol (1 mL) + CH_2Cl_2 (4 mL)	25	10	0 °C	**3**	62
11	Tol (1 mL), reflux	Tol (1 mL) + CH_2Cl_2 (4 mL)	25	10	42 °C	**3**	48
12	Tol (1 mL), reflux	Tol (1 mL) + CH_2Cl_2 (4 mL)	25	10	12 °C	**3**	78
13	Tol (1 mL), reflux	Tol (1 mL) + CH_2Cl_2 (4 mL)	100	10	rt	**3**	87
14	Tol (1 mL), reflux	Tol (1 mL) + CH_2Cl_2 (4 mL)	10	10	rt	**3**	70
15	Tol (1 mL), reflux	Tol (1 mL) + CH_2Cl_2 (4 mL)	50	20	rt	**3**	91
16	Tol (2 mL), reflux	Tol (2 mL) + CH_2Cl_2 (8 mL)	25	10	rt	**3**	92
17	Tol (2 mL), reflux	Tol (2 mL) + CH_2Cl_2 (18 mL)	25	10	rt	**3**	90
18	Tol (2 mL), reflux	Tol (2 mL) + CH_2Cl_2 (48 mL)	25	10	rt	**3**	80
19	**Tol (2 mL), reflux**	**Tol (2 mL) + CH_2Cl_2 (8 mL)**	**50**	**20**	**rt**	**3**	**96**

Diels−Alder reaction,[8] and others.[9,10] In a number of cases, the combination of BINOL with a Ti(IV) complex has shown



BINOL

high catalytic activity as well as excellent enantioselectivity.[6−9] We have investigated the asymmetric alkynylzinc addition catalyzed by BINOL and $Ti(O^iPr)_4$ and found that this simple catalyst system is highly enantioselective for the reaction of *aromatic* aldehydes. During the preparation of this paper, Chan and co-workers independently reported the use of BINOL and a partially hydrogenated BINOL in combination with $Ti(O^iPr)_4$ (1.5 equiv versus aldehyde) to carry out the reaction of phenylacetylene with a variety of aldehydes in the presence of dimethylzinc at 0 °C.[11] They also observed that BINOL showed high enantioselectivity for a few aldehydes, but their experimental procedure is very different from the work described below. Both procedures have their own practical advantages.

We first studied the asymmetric reaction of phenylacetylene with benzaldehyde. This reaction involves two steps: (1) treatment of phenylacetylene with diethylzinc with or without BINOL and $Ti(O^iPr)_4$; (2) addition of benzaldehyde, (*S*)-BINOL and $Ti(O^iPr)_4$ (Scheme 1). The first step probably generates the zinc phenylacetylide intermediate **2** which can then add to benzaldehyde in the presence of the catalyst. In this reaction, besides the desired propargylic alcohol **3**, the side product **4** was observed under certain conditions as the result of the ethyl addition to benzaldehyde.

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

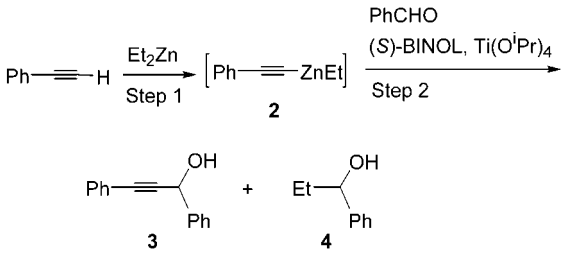


Table 1 summarizes our attempts for this reaction. In these experiments, 1.1 mmol of phenylacetylene was reacted with 1.0 mmol of diethylzinc and 0.5 mmol of benzaldehyde. We found that in order to generate **3** as the major product and avoid the ethyl addition side product **4**, it was necessary to reflux phenylacetylene with diethylzinc in toluene in step 1 (entry 8). This condition may be more favorable for the formation of the zinc acetylide **2**.[3b] Treatment of phenyl-

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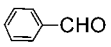
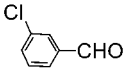
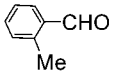
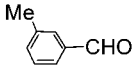
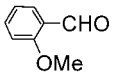
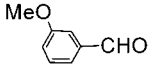
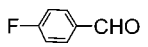
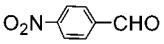
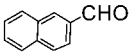
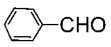
acetylene with diethylzinc at lower temperatures in various solvents with or without BINOL and $Ti(O^iPr)_4$ in step 1 mainly led to the side product **4** (entries 1−7). Comparison of entry 5 with entry 8 revealed that although refluxing in toluene in step 1 gave much higher yield of **3**, the enantioselectivity was higher when the reaction was carried out in CH_2Cl_2. Therefore, we tested the use of a combined solvent of toluene and CH_2Cl_2 for step 2. Indeed, higher enantioselectivity was achieved in entry 9 than entry 8. We also varied the temperature in step 2 in order to optimize the reaction condition. However, only reduced enantioselectivity was observed at either higher or lower temperatures (entries 10−12). Thus, the room-temperature condition seems most suitable for the reaction. We found that increasing the amount of $Ti(O^iPr)_4$ only gave slightly increased enantioselectivity (entry 13) and reducing $Ti(O^iPr)_4$ decreased the enantioselectivity (entry 14). Increasing both $Ti(O^iPr)_4$ and BINOL led to significantly higher enantioselectivity (entry 15). We then studied the effect of the reagent concentration on this reaction. In entry 16, the amount of solvent was doubled which improved this reaction over entry 9. However, further diluting the reaction mixture reduced the enantioselectivity (entries 17, 18). Finally, by combining the conditions in entry 15 with entry 16, we obtained the optimized enantioselectivity (96% ee) and yield in entry 19. No side product was observed in this experiment.

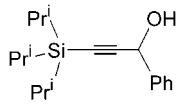
The optimized procedure for the reaction of benzaldehyde with phenylacetylene is given here. Under nitrogen, phenylacetylene (1.1 mmol, 121 μL) and diethylzinc (1.0 mmol, 102 μL) were added to a 25 mL flask containing toluene (2 mL, distilled over sodium). This solution was heated under reflux for 5 h during which a white precipitate was generated. It was then combined with (*S*)-BINOL (0.10 mmol, 28.6 mg, >99% ee) and CH_2Cl_2 (8 mL, dried with activated alumina and stored over molecular sieves). After the mixture was stirred at room temperature for 15 min, $Ti(O^iPr)_4$ (0.25 mmol, 74 μL) was added and the stirring continued for another hour. Benzaldehyde (0.5 mmol, 50 μL) was then added, and the reaction mixture was stirred for 4 h. Concentrated ammonium chloride was added to quench the reaction, and the mixture was extracted with CH_2Cl_2 and dried with sodium sulfate. After column chromatography on silica gel using 2−10% ethyl acetate in hexanes to elute, compound **3** was isolated in 77% yield. The enantiomeric purity of the propargylic alcohol product **3** was determined to be 96% ee by using an HPLC Chiralcel OD column. The configuration of this propargylic alcohol was *R* as determined by comparing its optical rotation with the literature data.[1g]

The above procedure was applied to the reaction of terminal alkynes with a variety of aromatic aldehydes. As the results summarized in Table 2 show, highly enantioselective reactions of phenylacetylene with *ortho*-, *meta*-, or *para*-substituted benzaldehydes containing electron-donating or electron-withdrawing substituents have been achieved by using the BINOL-based catalyst (entries 1−9). The additions to 2-naphthaldehyde and 1-naphthaldehyde also gave very high enantioselectivity (entries 10 and 11). In entry 12, we studied the reaction of triisopropylsilylacetylene with benzaldehyde which showed excellent enantioselectivity. This reaction is particularly useful, since the triisopropylsilyl group in the resulting chiral propargylic alcohol **5** can be easily removed for further derivatization.

Table 2. Results for the Terminal Alkyne Additions to Aldehydes in the Presence of Diethylzinc, (*S*)-BINOL, and $Ti(O^iPr)_4$

entry	alkyne	aldehyde	isolated yield (%)	*ee* (%)
1	PhC≡CH		77	96
2	PhC≡CH		79	92
3	PhC≡CH		81	92
4	PhC≡CH		81	96
5	PhC≡CH		77	94
6	PhC≡CH		73	93
7	PhC≡CH		78	93
8	PhC≡CH		74	96
9	PhC≡CH		79[a]	97
10	PhC≡CH		77	98
11	PhC≡CH		71[a]	92
12	$^iPr_3SiC$≡CH		75	92

[a] Determined by ^1H NMR.



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In summary, the readily available BINOL ligand has been found to catalyze the highly enantioselective reaction of terminal alkynes with *aromatic* aldehydes that have a variety of substituents as well as substitution patterns. After the preparation of the zinc acetylide reagent, the catalytic asymmetric addition to aldehydes proceeds at room temperature with excellent stereocontrol. This simple catalyst system is practical for the asymmetric synthesis of chiral propargylic alcohols containing aromatic rings.

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

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