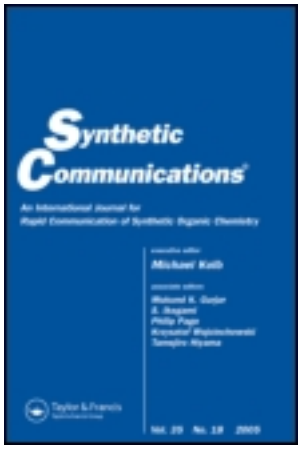

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Enantioselective Synthesis of Chiral Propargylic Alcohols Catalyzed by Bifunctional Zinc-Based Complexes

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ENANTIOSELECTIVE SYNTHESIS OF CHIRAL PROPARGYLIC ALCOHOLS CATALYZED BY BIFUNCTIONAL ZINC-BASED COMPLEXES

Xinhua Lu, Guanlei Xie, Tingyi Li, Xiaoming Qu, and Jincheng Mao

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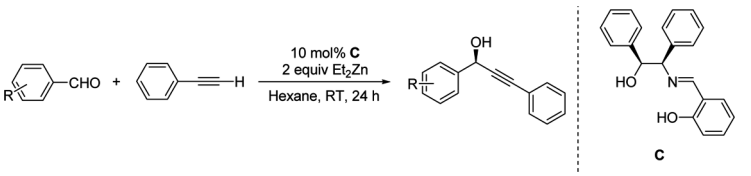
GRAPHICAL ABSTRACT



Abstract *This work demonstrates an efficient way to prepare chiral propargylic alcohols by asymmetric addition of terminal Zn-acetylide to aldehydes catalyzed by bifunctional zinc-based complexes. The corresponding products with moderate to good yields and enantioselectivities were obtained in the absence of moisture-sensitive* $Ti(O^iPr)_4$.

Keywords Alkyne; asymmetric addition; bifunctional complexes; enantioselectivities

INTRODUCTION

Chiral secondary propargylic alcohols were important and useful building blocks in the synthesis of many natural products and pharmaceuticals.[1,2] However, the most effective and straightforward way is asymmetric alkynylation of aldehydes, which can simultaneously form a new C-C bond and a stereogenic center in one step.[3–6] In past decades, various excellent chiral ligands in combination with different central metals have been developed for such an enantioselective transformation process, such as alkyl zinc–catalyzed asymmetric alkynylation of aldehydes,[7] titanium-catalyzed enantioselective alkynylide addition to aldehydes,[8] $Zn(OTf)_2$-meditated enantioselective additions,[9] $InBr_3$-catalyzed alkynylation of aldehydes,[10] vanadium-mediated asymmetric additions,[11] and copper-promoted enantioselective addition of terminal alkynes to aldehydes.[12] Among them, alkylzinc-mediated

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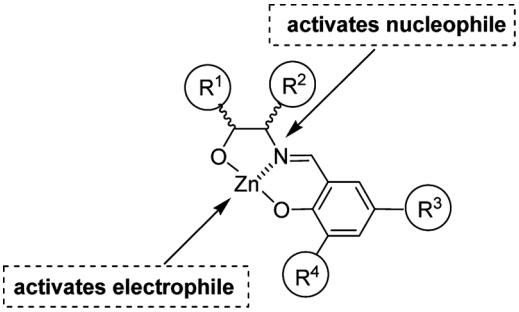


Figure 1. Design of possible bifunctional zinc-based catalysts for asymmetric alkynylation reaction.

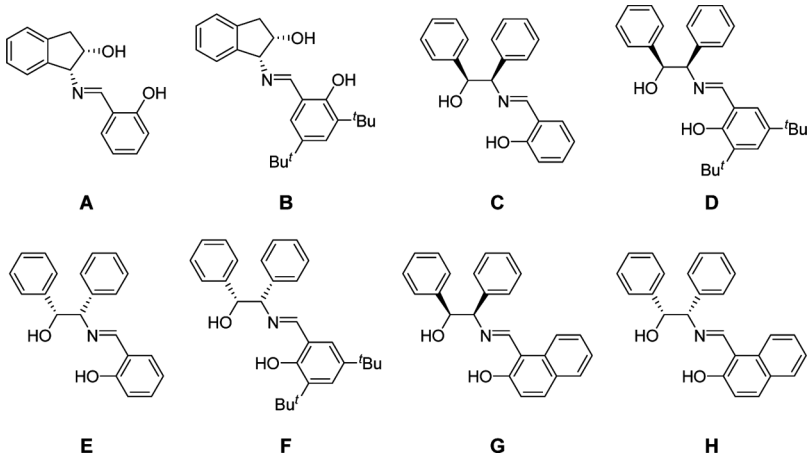


Figure 2. Chiral ligands evaluated in this research.

asymmetric addition of phenylacetylene to aldehydes is most attractive.[13] Although great effort has been made in this field, development of novel readily available chiral catalysts is still desirable. Based on our interest in such catalytic reactions,[14–19] here we report our recent findings in this asymmetric transformation using the bifunctional zinc-based catalysts (Fig. 1).

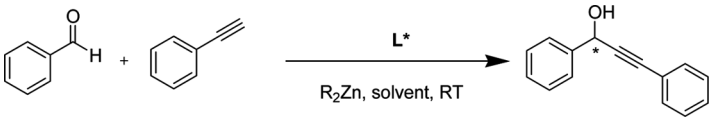
We know that bifunctional catalysts have been developed for various asymmetric transformation processes.[20–22] However, this concept for the design of catalysts has not been extensively applied in asymmetric addition reactions.[23] When this bifunctional catalyst was employed in this reaction, the Lewis-acid part could activate the electrophilic substrate, such as aldehyde, and the Lewis-base part could activate the nuclephilic substrate, such as metal acetylide. In this way, double activations could make this catalyst efficient for the asymmetric alkynylation of aldehydes.

RESULTS AND DISCUSSION

Based on commercially available chiral amino alcohols, ligands **A–H** were easily prepared in one-step reaction with good yields. Then, we applied these stable

ligands to the asymmetric addition of Zn-phenylacetylide to benzaldehyde as the model reaction, and the related results are listed in Table 1. Using toluene as the solvent, ligand **C** gave the best enantioselectivity (48% *ee*) (entries 1–8, Table 1). At the same time, additional Lewis acid $Ti(O^iPr)_4$ was employed in the reaction. However, less than 5% *ee* was obtained, although the yield of the desired product was very high (91%) (entry 9, Table 1). After screening different solvents (entries 10–12, Table 1), we found that hexane afforded the greatest enantioselectivity (entry 11, Table 1). When 1 equiv. of 1,2-dimethoxyethane (DME) and hexamethylphosphoramide (HMPA) were employed as the additives, we did not get the enhanced *ee* values

Table 1. Asymmetric addition of Zn-phenylacetylide to benzaldehyde using various chiral ligands[a]



Entry	Ligand (mol%)	Solvent	PhCCH (equiv)	R_2Zn (equiv)	Yield (%)[b]	*Ee* (%)[c]	Config.
1	**A** (10)	Toluene	2.0	Me (2.0)	26	18	*R*
2	**B** (10)	Toluene	2.0	Me (2.0)	29	31	*R*
3	**C** (10)	Toluene	2.0	Me (2.0)	34	48	*R*
4	**D** (10)	Toluene	2.0	Me (2.0)	25	40	*R*
5	**E** (10)	Toluene	2.0	Me (2.0)	33	43	*S*
6	**F** (10)	Toluene	2.0	Me (2.0)	17	21	*S*
7	**G** (10)	Toluene	2.0	Me (2.0)	15	35	*R*
8	**H** (10)	Toluene	2.0	Me (2.0)	13	32	*S*
9[d]	**C** (10)	Toluene	2.0	Me (2.0)	91	<5	*R*
10	**C** (10)	DCM	2.0	Me (2.0)	82	15	*R*
11	**C** (10)	Hexane	2.0	Me (2.0)	26	53	*R*
12	**C** (10)	THF	2.0	Me (2.0)	17	20	*R*
13[e]	**C** (10)	Hexane	2.0	Me (2.0)	89	9	*R*
14[f]	**C** (10)	Hexane	2.0	Me (2.0)	30	52	*R*
15	**C** (10)	Hexane	2.0	Et (2.0)	83	60	*R*
16	**C** (10)	Hexane	3.0	Et (3.0)	80	40	*R*
17	**C** (10)	Hexane	4.0	Et (4.0)	85	44	*R*
18	**C** (10)	Hexane	1.4	Et (1.4)	67	51	*R*
19	**C** (20)	Hexane	2.0	Et (2.0)	84	59	*R*
20	**C** (40)	Hexane	2.0	Et (2.0)	75	61	*R*
21	**C** (5)	Hexane	2.0	Et (2.0)	76	28	*R*
22[g]	**C** (10)	Hexane	2.0	Et (2.0)	62	26	*R*
23[h]	**C** (10)	Hexane	2.0	Et (2.0)	47	0	*R*

[a]All the reactions were performed under argon at room temperature for 24 h. Alkyne/Me_2Zn/benzaldehyde/ligand 1:1:0.5:0.05.

[b]Isolated yield.

[c]The enantiomeric excess was determined by chiral HPLC analysis of the corresponding products on a Chiralcel OD-H column.

[d]0.2 mmol $Ti(O^iPr)_4$ was used.

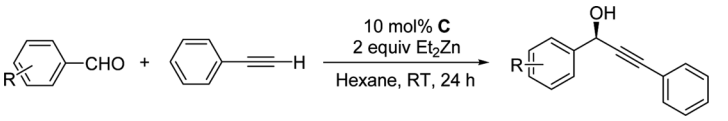
[e]1 mmol HMPA was added.

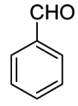
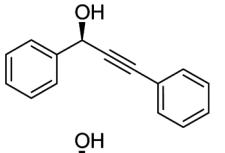
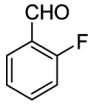
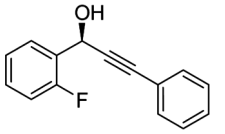
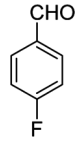
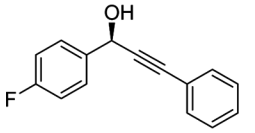
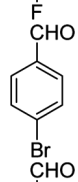
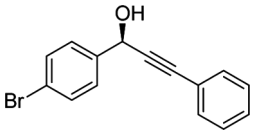
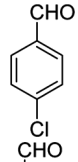
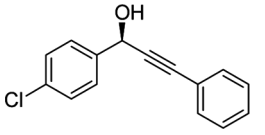
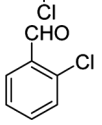
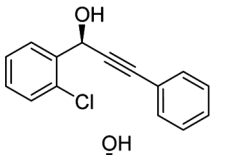
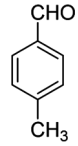
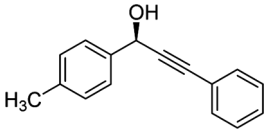
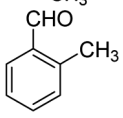
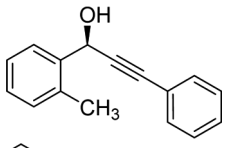
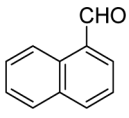
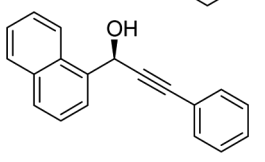
[f]1 mmol DME was added.

[g]Reaction was carried out at 0 °C.

[h]Reaction was carried out at 60 °C.

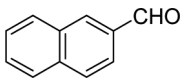
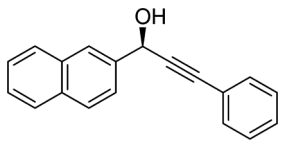
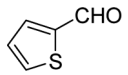
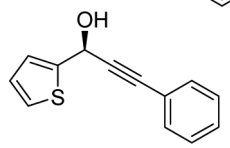
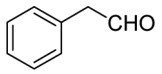
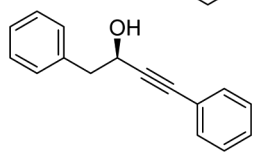
Table 2. Results for asymmetric alkynylzinc additions to various aldehydes catalyzed by ligand **C**[a]



Entry	Substrate	Product	Yield (%)[b]	*Ee* (%)[c]	Config.
1			83	60	*R*
2			64	39	*R*
3			72	43	*R*
4			63	41	*R*
5			76	52	*R*
6			73	32	*R*
7			72	48	*R*
8			67	47	*R*
9			70	56	*R*

(*Continued*)

Table 2. Continued

Entry	Substrate	Product	Yield (%)[b]	*Ee* (%)[c]	Config.
10			76	60 [90][d]	*R*
11			51	50	*R*
12			56	50	*R*

[a]All the reactions were performed under argon at room temperature for 24 h. Alkyne/Et_2Zn/benzaldehyde/**C** 1:1:0.5:0.05.

[b]Isolated yield.

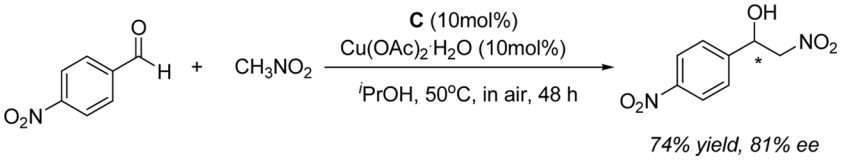
[c]The enantiomeric excess was determined by chiral HPLC analysis of the corresponding products on a Chiralcel OD-H column.

[d]The *ee* in parentheses was determined after simple recrystallization.

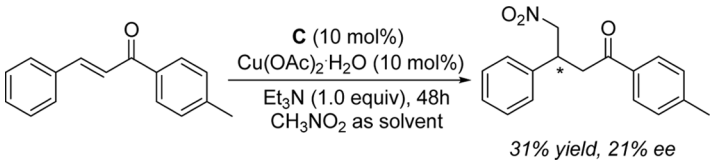
(entries 13 and 14, Table 1). Replacement of Me_2Zn with Et_2Zn led to better yield (83%) and better enantioselectivity (60% *ee*) (entry 15, Table 1). Varying the amount of phenylacetylene and diethyl zinc did not improve results (entries 16–18, Table 1). To our surprise, higher or lower loading of ligand **C** did not afford better results (entries 19–21, Table 1). Changing reaction temperatures did not lead to enhanced enantioselectivities (entries 22 and 23, Table 1).

The influence of various aromatic aldehyde substrates on the reactivity and enantioselectivity was studied under the standard conditions. As shown by the results summarized in Table 2, moderate yields and enantioselectivities were achieved for the addition of Zn-phenylacetylide to aromatic aldehydes (entries 1–11, Table 2). Substituents of aromatic aldehydes containing an electron-withdrawing group at the *ortho*- or *para*-position have little effect on the enantiomeric excess. It is noteworthy that for β-naphthaldehyde, the desired product was obtained with good enantioselectivity (90%) after simple recrystallization (entry 10, Table 2). In addition, promising enantioselectivity (50%) can also be obtained with aliphatic aldehyde (entry 12, Table 2).

In addition, we performed different asymmetric reactions using **C** as the ligand to test its possible catalytic performances. One selected reaction is copper-catalyzed asymmetric Henry reaction of 4-nitrobenzaldehyde and nitromethane. In air, the desired product was obtained in good yield and enantioselectivity in the presence of $Cu(OAc)_2 \cdot H_2O$ using **C** as the ligand (Scheme 1). The other reaction is copper-catalyzed asymmetric Michael addition reaction of 4′-methylchalcone and nitromethane. The promising result was acquired using $Cu(OAc)_2 \cdot H_2O$/**C** catalytic system as shown in Scheme 2. Thus, it shows that our catalytic system may be efficient in various enantioseletive catalytic processes.



Scheme 1. Copper-catalyzed asymmetric Henry reaction in the presence of ligand **C**.



Scheme 2. Copper-catalyzed asymmetric Michael addition reaction in the presence of ligand **C**.

CONCLUSIONS

In summary, we have developed a bifunctional zinc-based complex for the enantioselective reaction of phenylacetylene with various aldehydes for the synthesis of optically active propargylic alcohols. Using 10 mol% of easily prepared amino alcohol derivative **C** as the chiral ligand, the desired products were obtained in moderate to good yields and enantioselectivities. Thus, the easily available catalyst made this catalytic process potentially practical and useful. Further studies on highly effective asymmetric addition reactions using novel catalysts are in progress in our laboratory.

EXPERIMENTAL

All manipulations were carried out under an argon atmosphere in dried and degassed solvents. All solvents were dried and degassed by the standard methods and all aldehydes, dimethyl zinc, and diethyl zinc were commercially available. Melting points were determined using a standard melting-point apparatus and are uncorrected. The reactions were monitored by thin-layer chromatography (TLC). NMR spectra were measured in $CDCl_3$ on a Varian-Inova 400 NMR spectrometer (400 MHz) with tetramethylsilane (TMS) as an internal reference. Optical rotations were measured with a HORIBA SEPA-200 highly sensitive polarimeter. Enantiomeric excess (*ee*) determination was carried out using a chiral OD-H column (solvent, hexane/isopropanol; flow rate, 1 $cm^3 min^{-1}$; UV detection, 254 nm). High-resolution mass spectra (HRMS) were measured with electron impact (EI).

General Procedure for the Addition of Zinc-Phenylacethylene to Aldehydes

All manipulations were carried out under an argon atmosphere using dried and degassed solvent. The ligand **C** (0.05 mmol) was suspended in dry hexane (2.0 mL) at

room temperature. Then, a solution of diethyl zinc (1.0 M in hexane, 1.0 mL, 1.0 mmol) was added. After the mixture was stirred at room temperature for 1.5 h, phenylacetylene (1.0 mmol) was added, and the stirring continued for another 1.5 h. The yellow solution was cooled to 0 °C and treated with benzaldehyde (50 μL, 0.5 mmol); then the resultant mixture was allowed to warm up to room temperature naturally and stirred for 20 h. After the reaction was completed, it was cooled to 0 °C again and quenched by 5% aqueous HCl (2 mL). The mixture was extracted with ethyl acetate (EtOAc) (2 × 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography (silica gel H, EtOAc–petroleum ether = 1:6) to give the pure product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J = 7.2 Hz, 2H), 7.48–7.25 (m, 8H), 5.69 (s, 1H), 2.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.1, 132.2, 129.2, 129.1, 128.9, 128.8, 127.2, 122.9, 89.1, 87.2, 65.6.

Chiral HPLC Chromatography Data

1,3-Diphenylprop-2-yn-1-ol. Yield 83%; 60% *ee* determined by HPLC analysis (Chiralcel OD-H column, IPA–hexane 20:80). Retention time: t_{minor} = 9.53 min, t_{major} = 6.42 min.

1-(2-Fluorophenyl)-3-phenylprop-2-yn-1-ol. Yield 64%; 39% *ee* determined by HPLC analysis (Chiralcel OD-H column, IPA–hexane 20:80). Retention time: t_{minor} = 7.02 min, t_{major} = 5.77 min.

1-(4-Fluorophenyl)-3-phenylprop-2-yn-1-ol. Yield 72%; 43% *ee* determined by HPLC analysis (Chiralcel OD-H column, IPA–hexane 20:80). Retention time: t_{minor} = 11.58 min, t_{major} = 5.91 min.

1-(4-Bromophenyl)-3-phenylprop-2-yn-1-ol. Yield 63%; 41% *ee* determined by HPLC analysis (Chiralcel OD-H column, IPA–hexane 20:80). Retention time: t_{minor} = 13.49 min, t_{major} = 6.25 min.

1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-ol. Yield 76%; 52% *ee* determined by HPLC analysis (Chiralcel OD-H column, IPA–hexane 20:80). Retention time: t_{minor} = 12.62 min, t_{major} = 6.03 min.

1-(Naphthalen-4-yl)-3-phenylprop-2-yn-1-ol. Yield 70%; 56% *ee* determined by HPLC analysis (Chiralcel OD-H column, IPA–hexane 20:80). Retention time: t_{minor} = 15.21 min, t_{major} = 9.04 min.

1-(2-Chlorophenyl)-3-phenylprop-2-yn-1-ol. Yield 73%; 32% *ee* determined by HPLC analysis (Chiralcel OD-H column, IPA–hexane 20:80). Retention time: t_{minor} = 6.22 min, t_{major} = 5.77 min.

3-Phenyl-1-p-tolylprop-2-yn-1-ol. Yield 72%; 48% *ee* determined by HPLC analysis (Chiralcel OD-H column, IPA–hexane 20:80). Retention time: t_{minor} = 9.22 min, t_{major} = 5.62 min.

3-Phenyl-1-o-tolylprop-2-yn-1-ol. Yield 67%; 47% *ee* determined by HPLC analysis (Chiralcel OD-H column, IPA–hexane 20:80). Retention time: t_{minor} = 9.16 min, t_{major} = 5.49 min.

1,4-Diphenylbut-3-yn-2-ol. Yield 56%; 50% *ee* determined by HPLC analysis (Chiralcel OD-H column, IPA–hexane 20:80). Retention time: $t_{minor} = 9.15$ min, $t_{major} = 5.53$ min.

1-(Naphthalen-3-yl)-3-phenylprop-2-yn-1-ol. Yield 76%; 60% *ee* determined by HPLC analysis (Chiralcel OD-H column, IPA–hexane 20:80). Retention time: $t_{minor} = 7.74$ min, $t_{major} = 5.57$ min.

3-Phenyl-1-(thiophen-2-yl)prop-2-yn-1-ol. Yield 51%; 50% *ee* determined by HPLC analysis (Chiralcel OD-H column, IPA–hexane 20:80). Retention time: $t_{minor} = 9.46$ min, $t_{major} = 6.16$ min.

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