

Article

Highly Enantioselective Addition of Phenylethynylzinc to Aldehydes Catalyzed by Chiral Cyclopropane-Based Amino Alcohols

Bing Zheng ¹, Zhiyuan Li ², Feipeng Liu ¹, Yanhua Wu ¹, Junjian Shen ¹, Qinghua Bian ^{1,*}, Shicong Hou ^{1,*} and Ming Wang ¹

¹ Department of Applied Chemistry, China Agricultural University, 2 West Yuanmingyuan Road, Beijing 100193, China; E-Mails: bing17609@gmail.com (B.Z.); liufeipeng0302@163.com (F.L.); wyh64964478@sina.com (Y.W.); sjj06137@163.com (J.S.); wangmin@cau.edu.cn (M.W.)

² Yanlin Agriculture Bureau, 20 Huadu Avenue, Yanlin 461200, Henan, China; E-Mail: caulizhiyuan@163.com

* Authors to whom correspondence should be addressed; E-Mails: bianqinghua@cau.edu.cn (Q.B.); houshc@cau.edu.cn (S.H.); Tel.: +86-010-6273-1356 (Q.B.); Tel.: +86-010-6273-1881 (S.H.); Fax: +86-010-6282-0325 (Q.B. & S.H.).

Received: 18 November 2013; in revised form: 28 November 2013 / Accepted: 29 November 2013 / Published: 11 December 2013

Abstract: The enantioselective addition of phenylethynylzinc to aldehydes catalyzed by a series of cyclopropane-based amino alcohol ligands **7** was investigated. The reactions afforded chiral propargylic alcohols in high yields (up to 96%) and with excellent enantioselectivities (up to 98% *ee*) under mild conditions. Furthermore, studies on the structural relationship show that the matching of the chiral center configuration is crucial to obtain the high enantioselectivity.

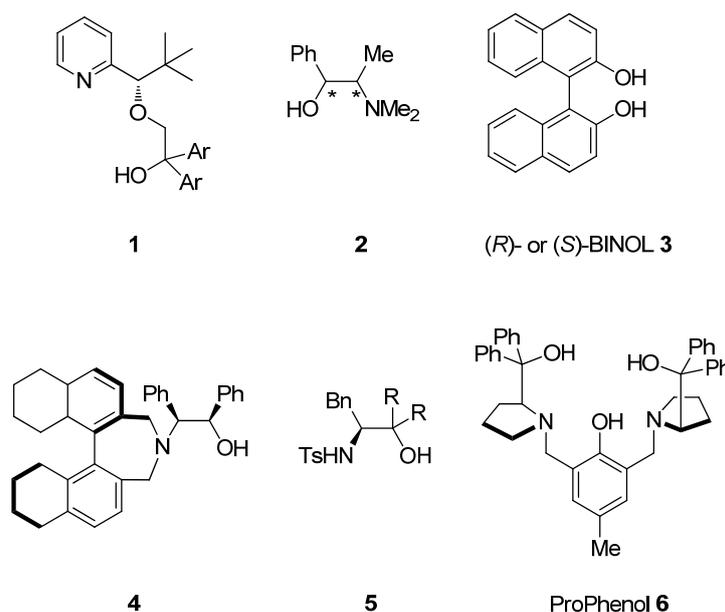
Keywords: alkynylation; aldehydes; cyclopropane-based; amino alcohols; asymmetric catalysis

1. Introduction

The catalytic enantioselective addition of alkynylzinc to aldehydes is one of the most useful carbon-carbon bond-forming reactions because the resulting propargylic alcohols are versatile, useful building blocks and important precursors for fine chemicals, pharmaceuticals, and natural products [1–7].

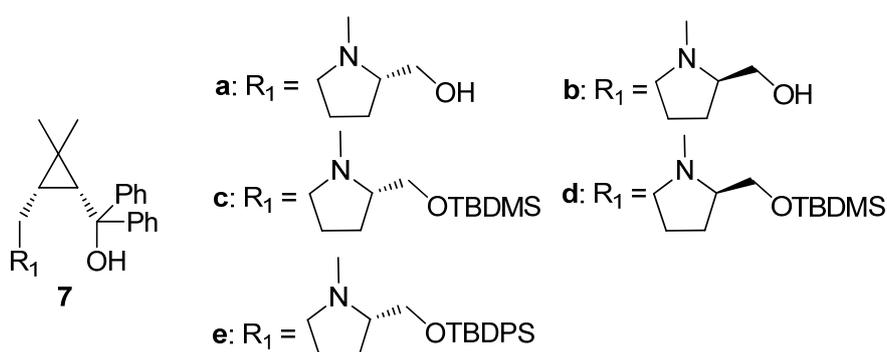
In 1994, Hoshino reported the first example of the addition of alkynylzinc reagents to cyclohexanecarbaldehyde and benzaldehyde using the ligand **1**, which afforded the corresponding products with high enantioselectivity [8]. Subsequently, various other catalytic systems were reported, including (+)- or (-)-*N*-methylephedrine **2** by Carreira [9–14], (*R*)- or (*S*)-BINOL **3** and their derivatives by Pu [15–24], amino alcohols **4**, and β -sulfonamide alcohols by Chan [25–28], sulfonamide alcohols **5** and a bifunctional catalyst by Wang [29–36], and ProPhenol **6** by Trost [37–40] (Figure 1).

Figure 1. Chiral ligands for the enantioselective addition of alkynylzinc to aldehydes.



Recently, we have developed a series of chiral cyclopropane-based ligands bearing amino alcohols, bisoxazolines, and amide alcohols (Figure 2). These ligands were proven to be very effective in some stereoselective reactions, including dialkylzinc addition to aldehydes and ketoesters, nitroaldol (Henry) reaction, Diels-Alder additions [41–47]. In this study, we focused on the structural relationship of our cyclopropane-based ligands amino alcohol **7** in the phenylethynylzinc addition to various aldehydes. It is noteworthy that the desired chiral propargylic alcohols were achieved with high to excellent yield (80%–96%). Importantly, high enantioselectivities (84%–98%) and broad substrate tolerance are also observed without any additives.

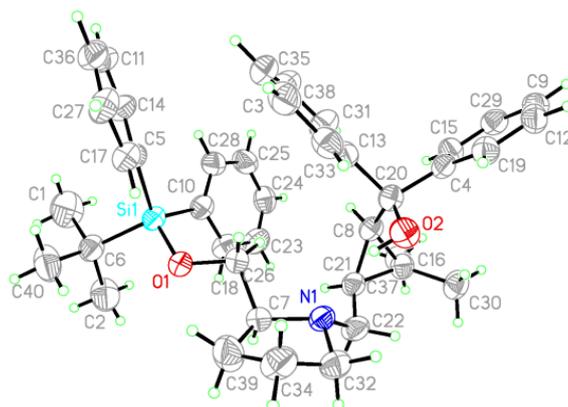
Figure 2. Cyclopropane amino alcohol **7a–e**.



2. Results and Discussion

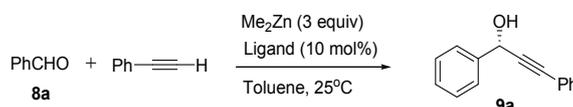
The chiral ligands **7** were easily synthesised from commercially available (+)-*cis*-methyl chrysanthemate and (*R*) or (*S*)-prolinol according to a previously reported procedure [44]. The absolute configuration of ligands **7** was (*1R, 3S*), as confirmed by X-ray crystallography analysis of ligand **7e** (Figure 3). This configuration is identical to that of the starting material, (+)-*cis*-methyl chrysanthemate.

Figure 3. X-ray crystallographic structure of ligand **7e**.



An initial study on the structural relationship of the cyclopropane-based ligands **7** in the addition of phenylethynylzinc to benzaldehyde was performed (Table 1).

Table 1. Ligand survey for the addition of phenylethynylzinc to benzaldehyde ^a.



Entry	Ligand	Time (h)	Yield (%) ^b	<i>Ee</i> (%) ^c	Config. ^d
1	7a	20	89	10	<i>S</i>
2	7b	20	90	16	<i>S</i>
3	7c	20	94	80	<i>S</i>
4	7d	20	90	22	<i>S</i>
5	7e	20	91	79	<i>S</i>

^a All reactions were run on a 1 mmol scale; ^b Isolated yields after chromatographic purification;

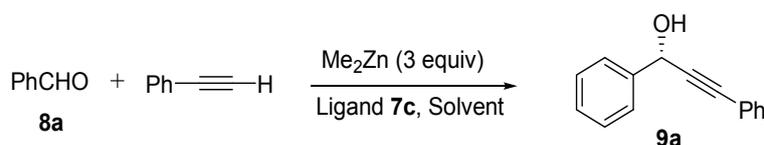
^c Enantiomeric excess determined by HPLC on a Chiralcel OD-H column; ^d Absolute configuration assigned by comparing their specific rotations or the HPLC elution order with literature data.

The results indicated that varying the substitution on the pyrrolidine ring of the ligands significantly affected the enantioselectivity of the reaction. The *ee* value was significantly increased when the hydroxyl group in the prolinol of ligand **7a** was protected with a *tert*-butyldimethylsilyl chloride (TBDMSCl; ligand **7c**) or *tert*-butyldiphenylsilyl chloride (TBDPSCI; ligand **7e**) moiety (entry 1 vs. entries 3 and 5). Furthermore, the cyclopropane-based amino alcohol **7d**, which was synthesized from (*R*)-prolinol, afforded the corresponding (*S*)-propargyl alcohol with only 22% *ee*, whereas ligand **7c**, which was prepared from (*S*)-prolinol, exhibited a higher *ee* (80%). This result showed that the match of the cyclopropane configuration with the additional chiral center on the pyrrolidine was crucial to

achieve high enantioselectivity. Therefore, the cyclopropane-based amino alcohol **7c** was the ligand of choice, providing the propargylic alcohol product with 80% *ee* (entry 3).

Attempts were made to optimize the reaction conditions by employing the addition of phenylethynylzinc to benzaldehyde. (Table 2). Early optimization showed that temperature significantly affected the *ee* value. A decrease in the reaction temperature from room temperature to 0 °C increased the *ee* values (entry 1 vs. entry 2). However, a further decrease in the temperature to −10 and −20 °C reduced both the enantioselectivity and yield (entries 3 and 4). It was interesting to note that the results were almost equally good when the amount of ligand was increased to 20 mol% (entry 6 vs. entry 2). Moreover, both the yield and enantioselectivity of the reaction decreased when the amount of ligand was reduced to 5 mol% (entry 7 vs. entry 2). Although previous studies [47] showed that the addition of polyethylene glycol dimethyl ether (DiMPEG) can significantly promote asymmetric induction, our additive to this reaction only slightly reduced the enantioselectivity (entry 5 vs. entry 2), because the DiMPEG would impact the generation of our unique catalyst system. Finally, the effects of the solvent on this reaction were investigated. Reaction in heptane gave lower enantioselectivity than in toluene (entry 8 vs. entry 2), this may be due to the poor solubility of Zn-amino alcohol complexes. Finally, the optimized reaction conditions were considered as following: **8a** (0.5 mmol) with phenylacetylene (1.5 mmol) and Me₂Zn (1.5 mmol) in toluene at 0 °C for 48 h (Table 2, entry 2).

Table 2. Reaction optimization for the addition of phenylethynylzinc to benzaldehyde ^a.



Entry	Ligand (mol %)	Solvent	Time (h)	Temp (°C)	Yield (%) ^b	<i>Ee</i> (%) ^c
1	10	Toluene	20	25	94	80
2	10	Toluene	48	0	91	93
3	10	Toluene	48	−10	83	86
4	10	Toluene	48	−20	40	79
5 ^d	10	Toluene	48	0	95	90
6	20	Toluene	48	0	97	94
7	5	Toluene	48	0	75	85
8	10	Heptane	48	0	80	83

^a All reactions were run on a 1 mmol scale; ^b Isolated yields after chromatographic purification;

^c Enantiomeric excess determined by HPLC on a Chiracel OD-H column; ^d With the addition of 10 mol % DiMPEG.

With the optimal condition in hand, we continued to explore the scope of this reaction. The addition of phenylethynylzinc to various aldehydes was investigated (Table 3). The results revealed that ligand **7c** was a highly enantioselective catalyst for the addition of alkynylzinc to aldehydes. *Ortho*-, *meta*-, and *para*-substituted benzaldehydes containing either electron-donating or electron-withdrawing substituents gave uniformly high *ee* (90%–98%, entries 1 to 13). In particular, the result (98% *ee*) obtained from 2-methylbenzaldehyde was remarkable (entry 5). High enantioselectivity was also

observed for the addition to other aromatic aldehydes such as 1-naphthaldehyde and 2-naphthaldehyde (entries 14 and 15). A favorable result (entries 16 and 17) was also obtained when the aliphatic aldehydes **8p** and **8q** were used as substrates.

Table 3. Substrate scope for the addition of phenylethynylzinc to aldehydes ^a.

Entry	R	Product	Yield (%) ^b	Ee (%) ^c
1	Ph	9a	91	93
2	<i>p</i> -FC ₆ H ₄	9b	90	94
3	<i>o</i> -BrC ₆ H ₄	9c	96	94
4	<i>p</i> -NO ₂ C ₆ H ₄	9d	92	93
5	<i>o</i> -CH ₃ C ₆ H ₄	9e	91	98
6	<i>m</i> -CH ₃ C ₆ H ₄	9f	89	95
7	<i>p</i> -CH ₃ C ₆ H ₄	9g	90	95
8	<i>o</i> -CH ₃ OC ₆ H ₄	9h	81	96
9	<i>m</i> -CH ₃ OC ₆ H ₄	9i	80	94
10	<i>p</i> -CH ₃ OC ₆ H ₄	9j	85	97
11	<i>o</i> -ClC ₆ H ₄	9k	95	90
12	<i>m</i> -ClC ₆ H ₄	9l	93	93
13	<i>p</i> -ClC ₆ H ₄	9m	92	93
14	1-Naphthyl	9n	91	98
15	2-Naphthyl	9o	80	92
16	Cyclohexyl	9p	92	84
17	Isopropyl	9q	91	88

^a All reactions were run on a 0.5 mmol scale; ^b Isolated yields after chromatographic purification; ^c Enantiomeric excess determined by HPLC on a Chiracel OD-H column.

3. Experimental

3.1. General Methods and Materials

All reactions were performed under a nitrogen atmosphere. Solvents were dried according to standard procedures and were then distilled prior to use. All reagents were purchased commercially and used without further purification, unless stated otherwise. ¹H- and ¹³C-NMR spectra were recorded using a Bruker DP-X300 MHz spectrometer (Bruker, Fallanden, Switzerland), and referenced internally to Me₄Si. High-resolution mass spectra were obtained on an Agilent MS using the time-of-flight mass spectrometry technique (Agilent Technologies, Waldbronn, Germany). The optical rotations were determined on a Perkin-Elmer PE-341 polarimeter (Perkin-Elmer, Waltham, MA, USA). Crystallographic data were obtained using a Rigaku RAPID-S image plate X-Ray diffractometer (Rigaku Denki Co., Ltd, Tokyo, Japan). Enantiomeric excesses (*ee*) were determined on an Agilent 1100 HPLC system using a chiral Chiralcel OD-H column (Daicel Chiral Technologies (China) Co., Ltd., Shanghai, China) and isopropanol-hexanes as the eluent.

3.2. X-Ray Crystallographic Data of the Ligand 7e

CCDC 808539 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via <http://www.ccdc.cam.ac.uk/conts/retrieving.html> (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk). This text may be included in the General subsection of the Experimental or as a suitably referenced endnote.

3.3. General Procedure for the Asymmetric Alkynylation of Aldehydes

Phenylacetylene (0.165 mL, 1.5 mmol, 3 equiv) was added to a solution of Me₂Zn (1.25 mL, 1.2 M in toluene, 1.5 mmol, 3 equiv) in dry toluene (1.75 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred for 30 min, then was transferred via syringe to another Schlenk tube containing neat ligand **7** (0.05 mmol, 0.1 equiv). After stirring for 30 min, an aldehyde (0.5 mmol) was added at 0 °C. The reaction mixture was stirred at 0 °C for 48 h and then quenched with saturated aqueous NH₄Cl (5 mL). The organic phase was separated, and the aqueous phase was extracted with Et₂O. The combined organic layers were dried over anhydrous Na₂SO₄. The solvents were removed under reduced pressure. Flash chromatography (silica gel, 10% ether in hexanes) afforded the pure propargylic alcohols. The enantiomeric excess was determined by HPLC on a Chiralcel OD-H column. The absolute configurations of the products were assigned by comparing their specific rotations or their HPLC elution order with literature data.

(*S*)-1,3-Diphenylprop-2-yn-1-ol (**9a**). 91% yield. $[\alpha]_D^{20} = -3.8$ ($c = 1.52$, CHCl₃). ¹H-NMR (CDCl₃): δ 7.80–7.76 (m, 2H), 7.65–7.62 (m, 2H), 7.57–7.46 (m, 6H), 5.85 (d, $J = 5.8$ Hz, 1H), 2.47 (d, $J = 5.9$ Hz, 1H). ¹³C-NMR (CDCl₃): δ 140.6, 131.7, 128.6, 128.5, 128.3, 128.2, 126.7, 122.3, 88.7, 86.6, 65.0. HRMS (TOF) calcd. for C₁₅H₁₂NaO [M+Na]⁺: 231.0786; found: 231.0776. 93% *ee* (80:20 *n*-hexane-2-propanol, 1.0 mL/min, 254 nm). Retention time: $t_{\text{minor}} = 8.13$ min, $t_{\text{major}} = 10.27$ min.

(*S*)-1-(4-Fluorophenyl)-3-phenylprop-2-yn-1-ol (**9b**). 90% yield. $[\alpha]_D^{20} = -4.0$ ($c = 1.50$, CHCl₃). ¹H-NMR (CDCl₃): δ 7.62–7.57 (m, 2H), 7.49–7.45 (m, 2H), 7.35–7.32 (m, 3H), 7.11–7.05 (m, 2H), 5.67 (d, $J = 6.0$ Hz, 1H), 2.34 (d, $J = 6.1$ Hz, 1H). ¹³C-NMR (CDCl₃): δ 164.2, 136.4, 131.6, 128.6, 128.4, 128.3, 122.1, 115.4, 88.5, 86.7, 64.2. HRMS (TOF) calcd. for C₁₅H₁₁FNao [M+Na]⁺: 249.0692; found: 249.0685. 94% *ee* (80:20 *n*-hexane-2-propanol, 1.0 mL/min, 254 nm). Retention time: $t_{\text{minor}} = 6.45$ min, $t_{\text{major}} = 12.47$ min.

(*S*)-1-(2-Bromophenyl)-3-phenylprop-2-yn-1-ol (**9c**). 96% yield. $[\alpha]_D^{20} = +71.9$ ($c = 1.01$, CHCl₃). ¹H-NMR (CDCl₃): δ 7.85 (dd, $J = 1.7, 7.7$ Hz, 1H), 7.59 (dd, $J = 1.2, 8.0$ Hz, 1H), 7.49–7.21 (m, 7H), 6.02 (d, $J = 5.5$ Hz, 1H), 2.56 (d, $J = 5.6$ Hz, 1H). ¹³C-NMR (CDCl₃): δ 139.4, 132.9, 131.7, 129.8, 128.6, 128.2, 127.8, 122.7, 122.2, 87.6, 86.6, 64.5. HRMS (TOF) calcd. for C₁₅H₁₁BrNaO [M+Na]⁺: 308.9891; found: 308.9894. 94% *ee* (80:20 *n*-hexane-2-propanol, 1.0 mL/min, 254 nm). Retention time: $t_{\text{major}} = 6.44$ min, $t_{\text{minor}} = 6.92$ min.

(*S*)-1-(4-Nitrophenyl)-3-phenylprop-2-yn-1-ol (**9d**). 92% yield. $[\alpha]_D^{20} = -12.8$ ($c = 1.00$, CHCl₃). ¹H-NMR (CDCl₃): δ 8.27 (dd, $J = 2.0, 6.8$ Hz, 1H), 7.82–7.78 (m, 2H), 7.49–7.45 (m, 2H),

7.37–7.34 (m, 3H), 5.80 (d, $J = 5.6$ Hz, 1H), 2.45 (d, $J = 5.7$ Hz, 1H). $^{13}\text{C-NMR}$ (CDCl_3): δ 147.9, 147.4, 131.8, 129.1, 128.4, 127.4, 123.8, 121.7, 87.7, 87.4, 64.1. HRMS (TOF) calcd for $\text{C}_{15}\text{H}_{12}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 254.0817; found: 254.0813. 93% *ee* (80:20 *n*-hexane-2-propanol, 1.0 mL/min, 254 nm). Retention time: $t_{\text{minor}} = 9.50$ min, $t_{\text{major}} = 27.68$ min.

(*S*)-1-(2-Methylphenyl)-3-phenylprop-2-yn-1-ol (**9e**). 91% yield. $[\alpha]_{\text{D}}^{20} = +13.6$ ($c = 0.73$, CHCl_3). $^1\text{H-NMR}$ (CDCl_3): δ 7.74–7.71 (m, 1H), 7.48–7.45 (m, 2H), 7.33–7.30 (m, 3H), 7.27–7.20 (m, 3H), 5.84 (s, 1H), 2.50 (s, 3H), 2.18 (br, 1H). $^{13}\text{C-NMR}$ (CDCl_3): δ 138.3, 136.0, 131.7, 130.8, 128.5, 128.4, 128.2, 126.5, 126.2, 122.5, 88.5, 86.4, 62.9, 19.0. HRMS (TOF) calcd. for $\text{C}_{16}\text{H}_{14}\text{NaO}$ $[\text{M}+\text{Na}]^+$: 245.0942; found: 245.0938. 98% *ee* (80:20 *n*-hexane-2-propanol, 1.0 mL/min, 254 nm). Retention time: $t_{\text{minor}} = 6.29$ min, $t_{\text{major}} = 9.72$ min.

(*S*)-1-(3-Methylphenyl)-3-phenylprop-2-yn-1-ol (**9f**). 89% yield. $[\alpha]_{\text{D}}^{20} = -6.8$ ($c = 1.11$, CHCl_3). $^1\text{H-NMR}$ (CDCl_3): δ 7.49–7.40 (m, 4H), 7.33–7.30 (m, 4H), 7.17 (d, $J = 7.6$ Hz, 1H), 5.66 (d, $J = 5.8$ Hz, 1H), 2.39 (s, 3H), 2.23 (d, $J = 6.1$ Hz, 1H). $^{13}\text{C-NMR}$ (CDCl_3): δ 140.5, 138.4, 131.7, 129.2, 128.55, 128.53, 128.3, 127.4, 123.7, 122.4, 88.8, 86.5, 65.1, 21.4. HRMS (TOF) calcd. for $\text{C}_{16}\text{H}_{14}\text{NaO}$ $[\text{M}+\text{Na}]^+$: 245.0942; found: 245.0938. 95% *ee* (80:20 *n*-hexane-2-propanol, 1.0 mL/min, 254 nm). Retention time: $t_{\text{minor}} = 7.12$ min, $t_{\text{major}} = 11.27$ min.

(*S*)-1-(4-Methylphenyl)-3-phenylprop-2-yn-1-ol (**9g**). 90% yield. $[\alpha]_{\text{D}}^{20} = -5.9$ ($c = 0.76$, CHCl_3). $^1\text{H-NMR}$ (CDCl_3): δ 7.52–7.45 (m, 4H), 7.33–7.20 (m, 5H), 5.66 (s, 1H), 2.37 (s, 3H), 2.26 (br, 1H). $^{13}\text{C-NMR}$ (CDCl_3): δ 138.2, 137.8, 131.7, 129.3, 128.5, 128.3, 126.7, 122.5, 88.9, 86.4, 64.9, 21.1. HRMS (TOF) calcd. for $\text{C}_{16}\text{H}_{14}\text{NaO}$ $[\text{M}+\text{Na}]^+$: 245.0942; found: 245.0948. 95% *ee* (80:20 *n*-hexane-2-propanol, 1.0 mL/min, 254 nm). Retention time: $t_{\text{minor}} = 6.53$ min, $t_{\text{major}} = 9.69$ min.

(*S*)-1-(2-Methoxyphenyl)-3-phenylprop-2-yn-1-ol (**9h**). 81% yield. $[\alpha]_{\text{D}}^{20} = +12.3$ ($c = 2.03$, CHCl_3). $^1\text{H-NMR}$ (CDCl_3): δ 7.65 (dd, $J = 1.8, 7.6$ Hz, 1H), 7.49–7.46 (m, 2H), 7.33–7.29 (m, 4H), 7.00–6.92 (m, 2H), 5.93 (s, 1H), 3.91 (s, 3H), 3.07 (br, 1H). $^{13}\text{C-NMR}$ (CDCl_3): δ 156.8, 131.7, 129.6, 128.9, 128.3, 128.1, 127.9, 122.7, 120.8, 110.9, 88.5, 85.9, 61.5, 55.5. HRMS (TOF) calcd. for $\text{C}_{16}\text{H}_{14}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 261.0891; found: 261.0895. 96% *ee* (80:20 *n*-hexane-2-propanol, 1.0 mL/min, 254 nm). Retention time: $t_{\text{minor}} = 9.19$ min, $t_{\text{major}} = 10.16$ min.

(*S*)-1-(3-Methoxyphenyl)-3-phenylprop-2-yn-1-ol (**9i**). 80% yield. $[\alpha]_{\text{D}}^{20} = -12.9$ ($c = 1.04$, CHCl_3). $^1\text{H-NMR}$ (CDCl_3): δ 7.49–7.45 (m, 2H), 7.33–7.29 (m, 4H), 7.21–7.18 (m, 2H), 6.91–6.88 (m, 1H), 5.66 (s, 1H), 3.83 (s, 3H), 2.27 (br, 1H). $^{13}\text{C-NMR}$ (CDCl_3): δ 159.7, 142.2, 131.7, 129.6, 128.5, 128.2, 122.3, 118.9, 114.0, 112.1, 88.7, 86.4, 64.8, 55.2. HRMS (TOF) calcd. for $\text{C}_{16}\text{H}_{14}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$: 261.0891; found: 261.0885. 94% *ee* (80:20 *n*-hexane-2-propanol, 1.0 mL/min, 254 nm). Retention time: $t_{\text{minor}} = 11.43$ min, $t_{\text{major}} = 14.51$ min.

(*S*)-1-(4-Methoxyphenyl)-3-phenylprop-2-yn-1-ol (**9j**). 85% yield. $[\alpha]_{\text{D}}^{20} = -5.3$ ($c = 1.16$, CHCl_3). $^1\text{H-NMR}$ (CDCl_3): δ 7.55 (dd, $J = 2.1, 6.7$ Hz, 2H), 7.49–7.46 (m, 2H), 7.33–7.31 (m, 3H), 6.93 (dd, $J = 2.0, 6.7$ Hz, 2H), 5.65 (d, $J = 6.0$ Hz, 1H), 3.83 (s, 3H), 2.18 (d, $J = 6.2$ Hz, 1H). $^{13}\text{C-NMR}$ (CDCl_3): δ 159.7, 133.0, 131.7, 128.5, 128.3, 128.1, 122.5, 114.0, 89.0, 86.5, 64.7, 55.3. HRMS

(TOF) calcd. for $C_{16}H_{14}NaO_2$ $[M+Na]^+$: 261.0891; found: 261.0887. 97% *ee* (80:20 *n*-hexane-2-propanol, 1.0 mL/min, 254 nm). Retention time: $t_{minor} = 10.05$ min, $t_{major} = 14.41$ min.

(*S*)-1-(2-Chlorophenyl)-3-phenylprop-2-yn-1-ol (**9k**). 95% yield. $[\alpha]_D^{20} = +12.1$ ($c = 1.20$, $CHCl_3$). 1H -NMR ($CDCl_3$): δ 7.85–7.82 (m, 1H), 7.49–7.26 (m, 8H), 6.05 (d, $J = 4.5$ Hz, 1H), 2.53 (d, $J = 5.1$ Hz, 1H). ^{13}C -NMR ($CDCl_3$): δ 137.9, 132.8, 131.7, 129.75, 129.67, 128.6, 128.4, 128.3, 127.2, 122.3, 87.6, 86.6, 62.4. HRMS (TOF) calcd. for $C_{15}H_{11}ClNaO$ $[M+Na]^+$: 265.0396; found: 265.0396. 90% *ee* (97:3 *n*-hexane-2-propanol, 1.0 mL/min, 254 nm). Retention time: $t_{minor} = 29.93$ min, $t_{major} = 34.49$ min.

(*S*)-1-(3-Chlorophenyl)-3-phenylprop-2-yn-1-ol (**9l**). 93% yield. $[\alpha]_D^{20} = -8.6$ ($c = 1.54$, $CHCl_3$). 1H -NMR ($CDCl_3$): δ 7.56 (t, $J = 0.5$ Hz, 1H), 7.44–7.41 (m, 3H), 7.29–7.24 (m, 5H), 5.60 (s, 1H), 3.10 (s, 1H). ^{13}C -NMR ($CDCl_3$): δ 142.4, 134.3, 131.7, 129.8, 128.7, 128.4, 128.2, 126.8, 124.7, 122.0, 88.0, 86.9, 64.2. HRMS (TOF) calcd. for $C_{15}H_{11}ClNaO$ $[M+Na]^+$: 265.0396; found: 265.0393. 93% *ee* (80:20 *n*-hexane-2-propanol, 1.0 mL/min, 254 nm). Retention time: $t_{minor} = 6.05$ min, $t_{major} = 13.35$ min.

(*S*)-1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-ol (**9m**). 92% yield. $[\alpha]_D^{20} = -9.0$ ($c = 1.01$, $CHCl_3$). 1H -NMR ($CDCl_3$): δ 7.57–7.32 (m, 9H), 5.67 (s, 1H), 2.30 (br, 1H). ^{13}C -NMR ($CDCl_3$): δ 139.0, 134.1, 131.7, 128.7, 128.6, 128.3, 128.0, 122.0, 88.2, 86.8, 64.2. HRMS (TOF) calcd. for $C_{15}H_{11}ClNaO$ $[M+Na]^+$: 265.0396; found: 265.0390. 93% *ee* (80:20 *n*-hexane-2-propanol, 1.0 mL/min, 254 nm). Retention time: $t_{minor} = 5.96$ min, $t_{major} = 12.43$ min.

(*S*)-1-(1-Naphthyl)-3-phenylprop-2-yn-1-ol (**9n**). 91% yield. $[\alpha]_D^{20} = +35.3$ ($c = 1.00$, $CHCl_3$). 1H -NMR ($CDCl_3$): δ 8.36 (d, $J = 8.4$, 2H), 7.92–7.84 (m, 3H), 7.58–7.46 (m, 5H), 7.32–7.29 (m, 3H), 6.34 (s, 1H), 2.45 (br, 1H). ^{13}C -NMR ($CDCl_3$): δ 135.5, 133.8, 131.6, 130.4, 129.2, 128.6, 128.4, 128.1, 126.3, 125.7, 125.1, 124.5, 123.9, 122.3, 88.6, 87.1, 63.1. HRMS (TOF) calcd. for $C_{19}H_{14}NaO$ $[M+Na]^+$: 281.0942; found: 281.0938. 98% *ee* (80:20 *n*-hexane-2-propanol, 1.0 mL/min, 254 nm). Retention time: $t_{minor} = 9.46$ min, $t_{major} = 15.77$ min.

(*S*)-1-(2-Naphthyl)-3-phenylprop-2-yn-1-ol (**9o**). 80% yield. $[\alpha]_D^{20} = +8.6$ ($c = 0.70$, $CHCl_3$). 1H -NMR ($CDCl_3$): δ 8.06 (s, 1H), 7.91–7.87 (m, 3H), 7.73 (dd, $J = 1.7, 8.4$ Hz, 1H), 7.52–7.49 (m, 4H), 7.35–7.33 (m, 3H), 5.87 (d, $J = 6.2$ Hz, 1H), 2.35 (d, $J = 6.2$ Hz, 1H). ^{13}C -NMR ($CDCl_3$): δ 138.0, 133.3, 133.2, 131.8, 128.7, 128.6, 128.3, 128.2, 127.7, 126.3, 125.5, 124.6, 122.4, 88.7, 87.0, 65.3. HRMS (TOF) calcd. for $C_{19}H_{14}NaO$ $[M+Na]^+$: 281.0942; found: 281.0938. 92% *ee* (80:20 *n*-hexane-2-propanol, 1.0 mL/min, 254 nm). Retention time: $t_{minor} = 9.34$ min, $t_{major} = 21.95$ min.

(*S*)-1-Cyclohexyl-3-phenylprop-2-yn-1-ol (**9p**). 92% yield. $[\alpha]_D^{20} = +7.9$ ($c = 0.71$, $CHCl_3$). 1H -NMR ($CDCl_3$): δ 7.45–7.41 (m, 2H), 7.33–7.28 (m, 3H), 4.38 (t, $J = 5.9$, 1H), 1.95–1.90 (m, 2H), 1.86–1.78 (m, 3H), 1.72–1.64 (m, 2H), 1.32–1.11 (m, 5H). ^{13}C -NMR ($CDCl_3$): δ 131.7, 128.27, 128.24, 122.8, 89.3, 85.7, 67.7, 44.3, 28.6, 28.2, 26.4, 25.92, 25.90. HRMS (TOF) calcd. for $C_{15}H_{18}NaO$ $[M+Na]^+$: 237.1255; found: 237.1250. 84% *ee* (80:20 *n*-hexane-2-propanol, 1.0 mL/min, 254 nm). Retention time: $t_{minor} = 4.35$ min, $t_{major} = 6.32$ min.

(*S*)-4-Methyl-1-phenylpent-1-yl-3-ol (**9q**). 91% yield. $[\alpha]_D^{20} = +1.6$ ($c = 1.35$, CHCl_3). $^1\text{H-NMR}$ (CDCl_3): δ 7.45–7.42 (m, 2H), 7.33–7.28 (m, 3H), 4.40 (d, $J = 5.6$, 1H), 2.01–1.95 (m, 1H), 1.87 (br, 1H), 1.07 (t, $J = 6.7$, 6H). $^{13}\text{C-NMR}$ (CDCl_3): δ 131.7, 128.28, 128.23, 122.7, 88.9, 85.6, 68.4, 34.7, 18.1, 17.5. HRMS (TOF) calcd. for $\text{C}_{12}\text{H}_{14}\text{NaO}$ $[\text{M}+\text{Na}]^+$: 197.0942; found: 197.0941. 88% *ee* (80:20 *n*-hexane-2-propanol, 1.0 mL/min, 254 nm). Retention time: $t_{\text{minor}} = 4.22$ min, $t_{\text{major}} = 5.71$ min.

4. Conclusions

The cyclopropane-based amino alcohol **7c** successfully promotes the enantioselective alkynylation of aldehydes and affords chiral propargylic alcohols in high yields and high enantiomeric excess (up to 98% *ee*) without requiring any additives. In addition, studies on the structural relationship show that the matching of the cyclopropane configuration with the additional chiral center on pyrrolidine is crucial to obtain high enantioselectivity.

Supplementary Materials

Supplementary materials can be accessed at: <http://www.mdpi.com/1420-3049/18/12/15422/s1>.

Acknowledgments

We thank the National Basic Research Program of China (81102340) and the National Key Technology Research and Development Program (2012BAK25B03-3) for the financial support that they provided.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Trost, B.M.; Quintard, A. Asymmetric catalytic alkynylation of acetaldehyde: Application to the synthesis of (+)-tetrahydropyrenophorol. *Angew. Chem. Int. Ed. Engl.* **2012**, *51*, 6704–6708.
2. Chinkov, N.; Warm, A.; Carreira, E.M. Asymmetric autocatalysis enables an improved synthesis of efavirenz. *Angew. Chem. Int. Ed.* **2011**, *50*, 2957–2961.
3. Tan, L.; Chen, C.; Tillyer, R.D.; Grabowski, E.J.J.; Reider, P.J. A novel highly enantioselective ketone alkynylation reaction mediated by chiral zinc aminoalkoxides. *Angew. Chem. Int. Ed.* **1999**, *38*, 711–713.
4. Reber, S.; Knöpfel, T.F.; Carreira, E.M. Enantioselective total synthesis of (*R*)-strongyloidiols A and B. *Tetrahedron* **2003**, *59*, 6813–6817.
5. Escorihuela, J.; Altava, B. C_2 symmetrical nickel complexes derived from α -amino amides as efficient catalysts for the enantioselective addition of dialkylzinc reagents to aldehydes. *Tetrahedron* **2013**, *69*, 551–558.
6. Rachwalski, M.; Jarzynski, S. Aziridine ring-containing chiral ligands as highly efficient catalysts in asymmetric synthesis. *Tetrahedron* **2013**, *24*, 421–425.

7. Turlington, M.; Du, Y.; Ostrum, S.G.; Santosh, V.; Wren, K.; Lin, T.; Sabat, M.; Pu, L. From highly enantioselective catalytic reaction of 1,3-diynes with aldehydes to facile asymmetric synthesis of polycyclic compounds. *J. Am. Chem. Soc.* **2011**, *133*, 11780–11794.
8. Ishizaki, M.; Hoshino, O. Efficient ligands, chiral 2-[2,2-dimethyl-1-(2-pyridyl)propoxy]-1,1-diarylethanol for highly enantioselective addition of alkynylzinc reagents to various aldehydes. *Tetrahedron* **1994**, *5*, 1901–1904.
9. Frantz, D.E.; Fässler, R.; Carreira, E.M. Facile enantioselective synthesis of propargylic alcohols by direct addition of terminal alkynes to aldehydes. *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807.
10. Anand, N.K.; Carreira, E.M. A simple, mild, catalytic, enantioselective addition of terminal acetylenes to aldehydes. *J. Am. Chem. Soc.* **2001**, *123*, 9687–9688.
11. Sasaki, H.; Boyall, D.; Carreira, E.M. Facile, asymmetric addition of acetylene to aldehydes: *In Situ* generation of reactive zinc acetylide. *Helv. Chim. Acta* **2001**, *84*, 964–971.
12. Boyall, D.; Frantz, D.E.; Carreira, E.M. Efficient enantioselective additions of terminal alkynes and aldehydes under operationally convenient conditions. *Org. Lett.* **2002**, *4*, 2605–2606.
13. El-Sayed, E.; Anand, N.K.; Carreira, E.M. Asymmetric synthesis of γ -hydroxy α,β -unsaturated aldehydes via enantioselective direct addition of propargyl acetate to aldehydes. *Org. Lett.* **2001**, *3*, 3017–3020.
14. Boyall, D.; López, F.; Sasaki, H.; Frantz, D.; Carreira, E.M. Enantioselective addition of 2-methyl-3-butyn-2-ol to aldehydes: Preparation of 3-hydroxy-1-butynes. *Org. Lett.* **2000**, *2*, 4233–4236.
15. Gao, G.; Moore, D.; Xie, R.-G.; Pu, L. Highly enantioselective phenylacetylene additions to both aliphatic and aromatic aldehydes. *Org. Lett.* **2002**, *4*, 4143–4146.
16. Moore, D.; Pu, L. BINOL-catalyzed highly enantioselective terminal alkyne additions to aromatic aldehydes. *Org. Lett.* **2002**, *4*, 1855–1857.
17. Xu, M.-H.; Pu, L. A new 1,1'-binaphthyl-based catalyst for the enantioselective phenylacetylene addition to aromatic aldehydes without using a titanium complex. *Org. Lett.* **2002**, *4*, 4555–4557.
18. Moore, D.; Huang, W.-S.; Xu, M.-H.; Pu, L. Greatly enhanced enantioselectivity by an apparently remote steric effect in the 1,1'-binaphthyl-catalyzed alkynylzinc addition to aldehydes. *Tetrahedron Lett.* **2002**, *43*, 8831–8834.
19. Liu, L.; Pu, L. 3,3'-Functionalized octahydro-BINOL: A facile synthesis and its high enantioselectivity in the alkyne addition to aldehydes. *Tetrahedron* **2004**, *60*, 7427–7430.
20. Li, Z.-B.; Pu, L. BINOL-salen-catalyzed highly enantioselective alkyne additions to aromatic aldehydes. *Org. Lett.* **2004**, *6*, 1065–1068.
21. Wang, Q.; Chen, S.-Y.; Yu, X.-Q.; Pu, L. 1,1'-Binaphthyl ligands with bulky 3,3'-thertiaryalkyl substituents for the asymmetric alkyne addition to aromatic aldehydes. *Tetrahedron* **2007**, *63*, 4422–4428.
22. Yue, Y.; Turlington, M.; Yu, X.-Q.; Pu, L. 3,3'-Anisyl-substituted BINOL, H₄BINOL, and H₈BINOL ligands: Asymmetric synthesis of diverse propargylic alcohols and their ring-closing metathesis to chiral cycloalkenes. *J. Org. Chem.* **2009**, *74*, 8681–8689.
23. Chen, X.; Chen, W.; Wang, L.; Yu, X.-Q.; Huang, D.-S.; Pu, L. Synthesis of a C₁ symmetric BINOL-terpyridine ligand and highly enantioselective methyl propiolate addition to aromatic aldehydes. *Tetrahedron* **2010**, *66*, 1990–1993.

24. Gao, G.; Wang, Q.; Yu, X.-Q.; Xie, R.-G.; Pu, L. Highly enantioselective synthesis of γ -hydroxy- α , β -acetylenic esters by asymmetric alkyne addition to aldehydes. *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 122–125.
25. Lu, G.; Li, X.; Chan, W.L.; Chan, A.S.C. Titanium-catalyzed enantioselective alkynylation of aldehydes. *Chem. Commun.* **2002**, *21*, 172–173.
26. Li, X.; Lu, G.; Kwok, W.H.; Chan, A.S.C. Highly enantioselective alkynylzinc addition to aromatic aldehydes catalyzed by self-assembled titanium catalysts. *J. Am. Chem. Soc.* **2002**, *124*, 12636–12637.
27. Lu, G.; Li, X.; Zhou, Z.; Chan, W.L.; Chan, A.S.C. Enantioselective alkynylation of aromatic aldehydes catalyzed by new chiral amino alcohol-based ligands. *Tetrahedron* **2001**, *12*, 2147–2152.
28. Ruan, J.; Lu, G.; Xu, L.; Li, Y.-M.; Chan, A.S.C. Catalytic asymmetric alkynylation and arylation of aldehydes by an H₈-binaphthyl-based amino alcohol ligand. *Adv. Synth. Catal.* **2008**, *350*, 76–84.
29. Xu, Z.; Wang, R.; Xu, J.; Da, C.-S.; Yan, W.-J.; Chen, C. Highly enantioselective addition of phenylacetylene to aldehydes catalyzed by a β -sulfonamide alcohol–titanium complex. *Angew. Chem. Int. Ed.* **2003**, *42*, 5747–5749.
30. Kang, Y.-F.; Liu, L.; Wang, R.; Yan, W.-J.; Zhou, Y.-F. The use of bifunctional catalyst systems in the asymmetric addition of alkynylzinc to aldehydes. *Tetrahedron* **2004**, *15*, 3155–3159.
31. Xu, Z.; Chen, C.; Xu, J.; Miao, M.; Yan, W.; Wang, R. Highly enantioselective addition of phenylacetylene to aldehydes catalyzed by a camphor sulfonamide ligand. *Org. Lett.* **2004**, *6*, 1193–1195.
32. Han, Z.-J.; Da, C.-S.; Xu, Z.-Q.; Ni, M.; Wang, R. The asymmetric addition of phenylacetylene to aldehydes catalyzed by l-leucine derived chiral sulfonamide alcohol ligands. *J. Mol. Cat. A* **2005**, *236*, 32–37.
33. Ni, M.; Wang, R.; Han, Z.-J.; Mao, B.; Da, C.-S.; Liu, L.; Chen, C. Synthesis of new C₂-symmetrical bissulfonamide ligands and application in the enantioselective addition of alkynylzinc to aldehydes and ketones. *Adv. Synth. Catal.* **2005**, *347*, 1659–1665.
34. Xu, Z.; Lin, L.; Xu, J.; Yan, W.; Wang, R. Asymmetric addition of phenylacetylene to aldehydes catalyzed by β -sulfonamide alcohol-titanium complex. *Adv. Synth. Catal.* **2006**, *348*, 506–514.
35. Lin, L.; Jiang, X.; Liu, W.; Qiu, L.; Xu, Z.; Xu, J.; Chan, A.S.C.; Wang, R. Highly enantioselective synthesis of γ -hydroxy- α , β -acetylenic esters catalyzed by a β -sulfonamide alcohol. *Org. Lett.* **2007**, *9*, 2329–2332.
36. Qiu, L.; Wang, Q.; Lin, L.; Liu, X.D.; Jiang, X.X.; Zhao, Q.Y.; Hu, G.W.; Wang, R. Highly enantioselective addition of terminal alkynes to aldehydes catalyzed by a new chiral β -sulfonamide alcohol/Ti(OiPr)₄/Et₂Zn/R₃N catalyst system. *Chirality* **2009**, *21*, 316–323.
37. Trost, B.M.; Weiss, A.H.; von Wangelin, A.J. Dinuclear Zn-catalyzed asymmetric alkynylation of unsaturated aldehydes. *J. Am. Chem. Soc.* **2006**, *128*, 8–9.
38. Trost, B.M.; Sieber, J.D.; Qian, W.; Dhawan, R.; Ball, Z.T. Asymmetric total synthesis of soraphen A: A flexible alkyne strategy. *Angew. Chem. Int. Ed. Engl.* **2009**, *48*, 5478–5481.

39. Trost, B.M.; Chan, V.S.; Yamamoto, D. Enantioselective prophenol-catalyzed addition of 1,3-diyne to aldehydes to generate synthetically versatile building blocks and diyne natural products. *J. Am. Chem. Soc.* **2010**, *132*, 5186–5192.
40. Trost, B.M.; O'Boyle, B.M. Exploiting orthogonally reactive functionality: Synthesis and stereochemical assignment of (–)-ushikulide A. *J. Am. Chem. Soc.* **2008**, *130*, 16190–16192.
41. Zhong, J.C.; Wang, M.A.; Guo, H.C.; Bian, Q.H.; Wang, M. Design and synthesis of 1,4-amino alcohol ligands with a chiral cyclopropane backbone for asymmetric diethylzinc addition to aromatic aldehydes. *Synlett* **2006**, *11*, 1667–1670.
42. Zhong, J.C.; Wang, M.A.; Guo, H.C.; Yin, M.M.; Wang, M. Asymmetric diethylzinc addition and phenyl transfer to aldehydes using chiral *cis*-cyclopropane-based amino alcohols. *Tetrahedron Asymmetry* **2007**, *18*, 734–741.
43. Zhong, J.C.; Hou, S.C.; Bian, Q.H.; Yin, M.M.; Na, R.S.; Zheng, B.; Li, Z.Y.; Liu, S.Z.; Wang, M. Highly enantioselective zinc/amino alcohol-catalyzed alkynylation of aldehydes. *Chem. Eur. J.* **2009**, *15*, 3069–3071.
44. Li, Z.Y.; Wang, M.; Bian, Q.H.; Zheng, B.; Mao, J.Y.; Li, S.N.; Liu, S.Z.; Wang, M.A.; Zhong, J.C.; Guo, H.C. Highly enantioselective addition of trimethylsilylacetylene to aldehydes catalyzed by a zinc-amino-alcohol complex. *Chem. Eur. J.* **2011**, *17*, 5782–5786.
45. Zheng, B.; Wang, M.; Li, Z.Y.; Bian, Q.H.; Mao, J.Y.; Li, S.N.; Liu, S.Z.; Zhong, J.C.; Guo, H.C. Asymmetric Henry reaction catalyzed by a Zn-amino alcohol system. *Tetrahedron Asymmetry* **2011**, *22*, 1156–1160.
46. Mao, J.Y.; Nie, X.; Wang, M.; Wang, Q.; Zheng, B.; Bian, Q.H.; Zhong, J.C. Catalytic asymmetric nitroaldol (Henry) reactions with copper(II)/cyclopropane-based bisoxazoline complexes. *Tetrahedron Asymmetry* **2012**, *23*, 965–971.
47. Dahmen, S. Enantioselective alkynylation of aldehydes catalyzed by [2.2]paracyclophane-based ligands. *Org. Lett.* **2004**, *6*, 2113–2116.

Sample Availability: Samples of the compounds **7a–d** are available from the authors.

© 2013 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (<http://creativecommons.org/licenses/by/3.0/>).