Res Chem Intermed
DOI 10.1007/s11164-016-2859-2

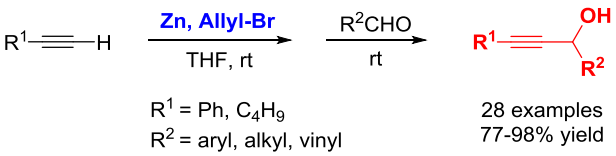
Alkynylation of aldehydes mediated by zinc and allyl bromide: a practical synthesis of propargylic alcohols

Ji-Cai Zhou[1] · Lei Zhao[1] · Yuan Li[1] · Ding-Qiang Fu[1] · Zi-Cheng Li[1] · Wen-Cai Huang[1]

Received: 20 November 2016 / Accepted: 30 December 2016

Abstract A practical synthesis of propargylic alcohols was developed by alkynylation of aldehydes mediated by zinc and allyl bromide. Aromatic, aliphatic and vinyl aldehydes react with phenylacetylene or 1-hexyne to obtain various propargylic alcohols at room temperature in up to 98% yield. This method is characterized with inexpensive materials, wide substrate scope, and mild reaction conditions, and is also easy to scale up. In addition, this protocol is applicable to the alkynylation of α-ketone esters and epoxides to generate α-tertiary-hydroxy esters and α-alkynyl alcohols, respectively.

Graphical Abstract



Keywords Alkynylation · Zinc · Propargylic alcohol · α-Tertiary-hydroxy ester · α-Alkynyl alcohol

Introduction

Propargylic alcohols are versatile precursors for the synthesis of natural products and pharmaceutically relevant compounds [1–3]. Especially, they can be transformed to important carbocycles and heterocycles such as 1*H*-indenes [4], pyrazoles

✉ Wen-Cai Huang
hwc@scu.edu.cn

[1] Department of Pharmaceutical and Bioengineering, School of Chemical Engineering, Sichuan University, Chengdu 610065, People's Republic of China

Published online: 07 February 2017

[5], isoxazoles [6], tetrazoles [7], benzofurans [8] and β-lactams [9]. Different processes have been developed to prepare structurally diverse propargylic alcohols over the past decades, among which alkynylation of aldehydes is a straightforward and very useful method [10–16]. In most cases, organometallic reagents such as diethylzinc [17–21], dimethylzinc [22–24] and *n*-butyllithium [25, 26] are needed to abstract the active hydrogen of terminal alkynes to form metal acetylides, followed by nucleophilic addition to aldehydes to afford propargylic alcohols. However, there are some recognized limitations of this approach because these alkylmetal reagents are sensitive toward air and moisture and thus inconvenient to handle.

Recently, some progress has been made in the alkynylation of aldehydes without the use of the strong bases mentioned above. ZnO, a cheap and efficient catalyst, has been reported to promote the direct addition of terminal alkynes to aldehydes under solvent- and base-free conditions at 120 °C [27]; however, the comparatively high temperature may limit the generality of this methodology. Similarly, a copper-silver nanoparticles-catalyzed addition of terminal alkynes to aldehydes at 100 °C in good yields has also been reported, but the substrate scope is limited to aromatic aldehydes and aromatic alkynes [28]. In contrast to the traditional reaction medium, a novel protocol using a Bu_4NOH/H_2O/DMSO catalytic system was developed to achieve the alkynylation of aldehydes and ketones to generate propargylic alcohols [29]. With a strong base solution as the solvent, the reaction system may not be applicable to sensitive substrates such as esters, amides and epoxides. More recently, the direct use of the inexpensive and easily manageable zinc powder in combination with MeI [30], EtI [31] or ^{i}PrI [32] to promote the addition of alkynes to aldehydes was disclosed, but 8 or 12 equiv of alkyl iodides and two different solvents must be used to accomplish this two-step transformation.

Considering the importance of propargylic alcohols in organic synthesis, inexpensive and practical methods to achieve the direct alkynylation of aldehydes are still in urgent need.

In our previous work, it was found that the combination of Zn (6 equiv), ^{i}PrI (6 equiv), H_8BINOL (0.4 equiv) and $Ti(O^{i}Pr)_4$ (1 equiv) could accomplish the enantioselective alkyne addition to aromatic, aliphatic and vinyl aldehydes to afford various chiral propargylic alcohols at room temperature with up to 98% yield and 98% enantiomeric excess [32]. When lower amounts of allyl bromide (Allyl-Br) were used in place of ^{i}PrI, propargylic alcohol could still be obtained, but the *ee* value decreased significantly (Table 1, entries 1–2). Inspired by these results, we envisioned that high yields of racemic propargylic alcohols may be obtained via further investigation of this addition reaction. Here, we report our findings on the practical synthesis of a variety of propargylic alcohols by the alkynylation of aldehydes mediated by Zn and allyl bromide under mild conditions.

Experimental

THF was distilled over sodium and benzophenone under nitrogen. Toluene, dichloromethane and ether were dried over a 4A molecular sieve before use. Aldehydes, acetophenone, methyl phenylglyoxylate, epoxides and alkynes were

distilled or recrystallized before use. Zinc powder was activated with dilute HCl, dried at 90 °C for 2 h under vacuum, and stored under nitrogen. All the other reagents and solvents were purchased from the commercial sources and used as received. All the reactions were performed under nitrogen and monitored by TLC. ^{1}H NMR spectra were recorded on a Bruker AVANCE III spectrometer (400 MHz) in $CDCl_3$ with TMS as an internal standard.

General procedure for the synthesis of propargylic alcohols

To a dry 10-mL round-bottom flask was added activated zinc powder (3 mmol, 3equiv), then dry THF (1 mL), allyl bromide (3 mmol, 3 equiv), and an alkyne (3 mmol, 3 equiv) were added in turn via a syringe under nitrogen. After the mixture was stirred at room temperature for 2–3 h and all the zinc powder disappeared, an aldehyde (1 mmol, 1 equiv) was added via a syringe and the stirring was continued for 10–20 h. When TLC showed the aldehyde had been consumed, saturated ammonia chloride solution (0.5 mL) was added to quench the reaction. After extraction with methylene chloride (2× 10 mL) and concentration under vacuum, the residue was purified by column chromatography on silica gel with hexane/ethyl acetate (15/1) as the eluent to afford the pure product.

Spectral data of synthesized compounds

1,3-Diphenylprop-2-yn-1-ol ***(1a)*** Pale-yellow oil, 96% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.51 (m, 2H), 7.49–7.43 (m, 2H), 7.40–7.35 (m, 2H), 7.34–7.26 (m, 4H), 5.65 (s, 1H), 2.69 (s, 1H).

1-(2-Chlorophenyl)-3-phenylprop-2-yn-1-ol ***(1b)*** Pale-yellow oil, 96% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.78 (m, 1H), 7.47–7.42 (m, 2H), 7.38–7.34 (m, 1H), 7.32–7.20 (m, 5H), 6.02 (s, 1H), 2.94 (s, 1H).

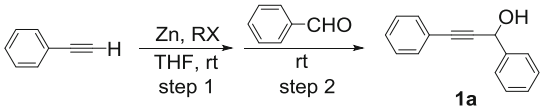
1-(3-Chlorophenyl)-3-phenylprop-2-yn-1-ol ***(1c)*** Pale-yellow oil, 98% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.43–7.33 (m, 3H), 7.26–7.14 (m, 5H), 5.57 (s, 1H), 2.51 (s, 1H).

1-(2, 4-Chlorophenyl)-3-phenylprop-2-yn-1-ol ***(1d)*** Colorless oil, 98% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.4 Hz, 1H), 7.50–7.43 (m, 2H), 7.40 (d, J = 2.0 Hz, 1H), 7.36–7.27 (m, 4H), 5.98 (d, J = 4.0 Hz, 1H), 2.68 (d, J = 4.0 Hz, 1H).

3-Phenyl-1-(o-tolyl) prop-2-yn-1-ol ***(1e)*** Pale-yellow oil, 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.75 (m, 1H), 7.48–7.43 (m, 2H), 7.33–7.28 (m, 3H), 7.22–7.25 (m, 2H), 7.20–7.17 (m, 1H), 5.83 (s, 1H), 2.49 (s, 3H), 2.28 (s, 1H).

1-(4-Nitrophenyl)-3-phenylprop-2-yn-1-ol ***(1f)*** Brown-yellow oil, 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 8.8 Hz, 2H), 7.49–7.42 (m, 2H), 7.38–7.28 (m, 3H), 5.79 (s, 1H), 2.86 (s, 1H).

Table 1 Optimization of reaction conditions for the addition of phenylacetylene to benzaldehyde[a]



Entry	Zn (equiv)	RX (equiv)	Alkyne (equiv)	Solvent[b] (mL)	Additive (equiv)	Reaction times[c] (h)	Isolated yield (%)
1[d]	6	Allyl-Br 6	4	THF 1 + Et_2O 10	$Ti(O^iPr)_4$ 1	24 + 16	93
2[e]	3	Allyl-Br 3	2	THF 1 + Et_2O 10	$Ti(O^iPr)_4$ 1	24 + 16	81
3	3	Allyl-Br 3	2	THF 1 + Et_2O 10	/	24 + 16	65[f]
4	3	Allyl-Br 3	3	THF 1 + Et_2O 10	/	24 + 16	92
5	3	Allyl-Br 3	3	THF 10	/	24 + 16	90
6	3	Allyl-Br 3	3	THF 5	/	24 + 16	89
7	3	Allyl-Br 3	3	THF 1	/	24 + 16	91
8	3	Allyl-Br 3	3	THF 1	/	5 + 12	94
9	3	Allyl-Br 3	3	THF 1	/	2 + 10	96
10	3	Allyl-Br 3	3	THF 1	/	2 + 8	90
11	3	Allyl-Br 3	3	THF 1	LiCl 1	2 + 10	88
12	3	Allyl-Br 3	3	THF 1	KI 1	2 + 10	85
13	3	Allyl-Br 3	3	THF 1	CuCl 1	2 + 10	70
14	3	Allyl-Br 3	3	THF 1	$CuCl_2$ 1	2 + 10	50
15	3	Allyl-Br 3	3	Toluene 1	/	2 + 10	No product
16	3	Allyl-Br 3	3	CH_2Cl_2 1	/	2 + 10	No product
17	3	Allyl-Br 3	3	Et_2O 1	/	2 + 10	No product
18	3	Bn-Br 3	3	THF 1	/	2 + 10	50
19	3	Bn-Cl 3	3	THF 1	/	2 + 10	No product
20	2	Allyl-Br 2	2	THF 1	/	2 + 10	53
21	2	Allyl-Br 2	3	THF 1	/	2 + 10	67
22	2	Allyl-Br 2	4	THF 1	/	2 + 10	78
23	3	Allyl-Br 3	4	THF 1	/	2 + 10	94
24	6	Allyl-Br 6	6	THF 1	/	2 + 10	95

[a] The reaction was conducted at room temperature (26 °C) in two steps: step 1 involved the reaction of Zn, RX and phenylacetylene to generate organozinc, then 1.0 mmol (1 equiv) of benzaldehyde was added to accomplish the addition reaction (step 2). After work-up, the product was isolated by column chromatography on silica gel

[b] Different solvents may be used for step 1 and step 2

[c] Reaction times for step 1 and step 2

[d] 0.4 equiv of (*S*)-H_8BINOL was used and the *ee* value of the product was 64%

[e] 0.4 equiv of (*S*)-BINOL was used and the *ee* value of the product was 49%

[f] Some addition product of allyl group to benzaldehyde was detected by TLC

1-(2-Nitrophenyl)-3-phenylprop-2-yn-1-ol ***(1g)*** Pale-yellow oil, 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, $J = 8.0$, 2.0 Hz, 2H), 7.64 (t, $J = 8.0$ Hz, 1H), 7.50–7.39 (m, 3H), 7.33–7.25 (m, 3H), 6.22 (s, 1H), 3.63 (s, 1H).

1-(Furan-2-yl)-3-phenylprop-2-yn-1-ol ***(1h)*** Brown–red oil, 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.46 (m, 2H), 7.43 (dd, $J = 2.0$, 0.8 Hz, 1H), 7.35–7.28 (m, 3H), 6.52 (d, $J = 3.2$ Hz, 1H), 6.37 (dd, $J = 3.2$, 2.0 Hz, 1H), 5.69 (s, 1H), 2.64 (s, 1H).

1-(Benzo[d] [1,3] dioxol-5-yl)-3-phenylprop-2-yn-1-ol ***(1i)*** Pale-yellow oil, 91% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.43 (m, 2H), 7.34–7.28 (m, 3H), 7.12 (d, $J = 1.2$ Hz, 1H), 7.07 (d, $J = 8.0$ Hz, 1H), 6.81 (d, $J = 8.0$ Hz, 1H), 5.97 (s, 2H), 5.59 (s, 1H), 2.33 (s, 1H).

1,5-Diphenyl-pent-1-en-4-yn-3-ol ***(1j)*** Pale-yellow oil, 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, $J = 7.2$, 2.0 Hz, 2H), 7.43 (d, $J = 7.2$ Hz, 2H), 7.36–7.28 (m, 6H), 6.84 (d, $J = 7.6$ Hz, 1H), 6.39 (dd, $J = 7.6$, 2.0 Hz, 1H), 5.29 (d, $J = 7.6$ Hz, 1H), 2.12 (s, 1H).

1-Phenylpent-1-yn-3-ol ***(1k)*** Pale-yellow oil, 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.40 (m, 2H), 7.34–7.28 (m, 3H), 4.55 (t, $J = 6.4$ Hz, 1H), 2.04 (s, 1H), 1.87–1.78 (m, 2H), 1.08 (t, $J = 7.2$ Hz, 3H).

1-Phenylhex-1-yn-3-ol ***(1l)*** Pale-yellow oil, 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.38 (m, 2H), 7.33–7.27 (m, 3H), 4.61 (t, $J = 6.4$ Hz, 1H), 2.04 (s, 1H), 1.83–1.75 (m, 2H), 1.62–1.49 (m, 2H), 0.99 (t, $J = 7.2$ Hz, 3H).

4-methyl-1-phenylpent-1-yn-3-ol ***(1m)*** Pale-yellow oil, 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.40 (m, 2H), 7.33–7.28 (m, 3H), 4.40 (d, $J = 5.6$ Hz, 1H), 1.98 (td, $J = 8.4$, 2.8 Hz, 1H), 1.29–1.15 (m, 1H), 1.07 (dd, $J = 8.8$, 2.8 Hz, 6H).

1-Phenylono-1-yn-3-ol ***(1n)*** Colorless oil, 95% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.38 (m, 2H), 7.35–7.30 (m, 3H), 4.59 (t, $J = 8.0$ Hz, 1H), 2.02 (s, 1H), 1.88–1.74 (m, 2H), 1.56–1.44 (m, 2H), 1.42–1.22 (m, 6H), 0.89 (t, $J = 7.2$ Hz, 3H).

1-Cyclohexyl-3-phenyl-prop-2-yn-1-ol ***(1o)*** Pale-yellow oil, 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.39 (m, 2H), 7.34–7.26 (m, 3H), 4.37 (d, $J = 5.6$ Hz, 1H), 1.92 (d, $J = 8.8$ Hz, 3H), 1.79 (d, $J = 8.8$ Hz, 2H), 1.73–1.60 (m, 2H), 1.34–1.21 (m, 3H), 1.20–1.08 (m, 2H).

1-Phenylhept-2-yn-1-ol ***(2a)*** Colorless oil, 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, $J = 7.2$ Hz, 2H), 7.34–7.28 (m, 3H), 5.44 (s, 1H), 2.28 (t, $J = 6.4$, 2H), 2.11 (s, 1H), 1.58–1.48 (m, 2H), 1.47–1.36 (m, 2H), 0.91 (t, $J = 7.2$ Hz, 3H).

1-(2-Chlorophenyl)hept-2-yn-1-ol ***(2b)*** Colorless oil, 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, $J = 7.2$, 1.6 Hz, 1H), 7.37 (dd, $J = 7.2$, 1.6 Hz,

1H), 7.33–7.23 (m, 2H), 5.81 (t, $J = 1.6$ Hz, 1H), 2.27 (td, $J = 7.2$, 2.0 Hz, 2H), 2.04 (s, 1H), 1.57–1.48 (m, 2H), 1.46–1.36 (m, 2H), 0.91 (t, $J = 7.2$ Hz, 3H).

1-(3-Chlorophenyl)hept-2-yn-1-ol ***(2c)*** Colorless oil, 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.40–7.37 (m, 1H), 7.33–7.26 (m, 2H), 5.42 (s, 1H), 2.28 (td, $J = 7.2$, 2.0 Hz, 2H), 2.04 (s, 1H), 1.58–1.49 (m, 2H), 1.47–1.37 (m, 2H), 0.92 (t, $J = 7.2$ Hz, 3H).

1-(o-Tolyl)hept-2-yn-1-ol ***(2d)*** Colorless oil, 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.62 (m, 1H), 7.31–7.09 (m, 3H), 5.61 (s, 1H), 2.39 (s, 3H), 2.26 (t, $J = 6.4$ Hz, 2H), 2.04 (s, 1H), 1.58–1.48 (m, 2H), 1.46–1.38 (m, 2H), 0.92 (t, $J = 7.2$ Hz, 3H).

1-(4-Nitrophenyl)hept-2-yn-1-ol ***(2e)*** Brown-yellow oil, 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, $J = 8.0$ Hz, 2H), 7.71 (d, $J = 8.0$ Hz, 2H), 5.54 (s, 1H), 2.39 (s, 1H), 2.28 (td, $J = 6.4$, 2.0 Hz, 2H), 1.57–1.48 (m, 2H), 1.46–1.37 (m, 2H), 0.92 (t, $J = 7.2$ Hz, 3H).

1-(2-Nitrophenyl)hept-2-yn-1-ol ***(2f)*** Pale-yellow oil, 86% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, $J = 7.2$, 2.0 Hz, 2H), 7.66 (t, $J = 7.6$ Hz, 1H), 7.49 (t, $J = 7.6$ Hz, 1H), 5.97 (s, 1H), 3.11 (s, 1H), 2.24 (td, $J = 7.2$, 2.0 Hz, 2H), 1.56–1.46 (m, 2H), 1.44-1.33 (m, 2H), 0.90 (t, $J = 7.2$ Hz, 3H).

1-(Furan-2-yl)hept-2-yn-1-ol ***(2g)*** Pale brown-red oil, 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, $J = 0.8$ Hz, 1H), 6.43 (d, $J = 0.8$ Hz, 1H), 6.35 (dd, $J = 3.2$, 2.0 Hz, 1H), 5.44 (d, $J = 5.0$ Hz, 1H), 2.28 (td, $J = 5.0$, 2.0 Hz, 3H), 1.58–1.49 (m, 2H), 1.48–1.37 (m, 2H), 0.92 (t, $J = 7.2$ Hz, 3H).

1-(Benzo[d] [1, 3] dioxol-5-yl)hept-2-yn-1-ol ***(2h)*** Pale-yellow oil, 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, $J = 1.6$ Hz, 1H), 7.00 (dd, $J = 8.0$, 1.2 Hz, 1H), 6.79 (d, $J = 8.0$ Hz, 1H), 5.96 (s, 2H), 5.39–5.32 (m, 1H), 2.27 (td, $J = 7.2$, 2.0 Hz, 2H), 2.08 (s, 1H), 1.56–1.49 (m, 2H), 1.47–1.37 (m, 2H), 0.92 (t, $J = 7.2$ Hz, 3H).

1-Phenylnon-1-en-4-yn-3-ol ***(2i)*** Pale-yellow oil, 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, $J = 7.2$ Hz, 2H), 7.32 (t, $J = 7.6$ Hz, 2H), 7.25 (t, $J = 7.6$ Hz, 1H), 6.75 (d, $J = 6.4$ Hz, 1H), 6.30 (dd, $J = 6.4$, 2.0 Hz, 1H), 5.04 (s, 1H), 2.27 (t, $J = 5.6$ Hz, 2H), 1.97 (s, 1H), 1.57–1.48 (m, 2H), 1.47–1.39 (m, 2H), 0.92 (t, $J = 7.2$ Hz, 3H).

Non-4-yn-3-ol ***(2j)*** Colorless oil, 78% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30 (s, 1H), 2.21 (t, $J = 5.2$ Hz, 2H), 1.70 (s, 1H), 1.69–1.60 (m, 2H), 1.53–1.46 (m, 2H), 1.44–1.36 (m, 2H), 1.00 (t, $J = 7.2$ Hz, 3H), 0.91 (t, $J = 7.2$ Hz, 3H).

Dec-5-yn-4-ol ***(2k)*** Colorless oil, 77% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36 (tt, $J = 6.6$, 2.0 Hz, 1H), 2.21 (td, $J = 6.6$, 2.0 Hz, 2H), 1.78 (s, 1H), 1.73–1.58 (m, 2H), 1.53–1.35 (m, 6H), 0.93 (dt, $J = 7.2$, 2.4 Hz, 6H).

Tridec-5-yn-7-ol ***(2l)*** Colorless oil, 86% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 (t, $J = 6.4$ Hz, 1H), 2.21 (td, $J = 6.4$, 1.6 Hz, 2H), 1.77 (s, 1H), 1.71–1.59 (m, 2H), 1.53–1.37 (m, 6H), 1.35–1.24 (m, 6H), 0.93–0.85 (m, 6H).

1-Cyclohexylhept-2-yn-1-ol ***(2m)*** Colorless oil, 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (d, $J = 6.4$ Hz, 1H), 2.22 (t, $J = 6.4$ Hz, 2H), 1.88–1.80 (m, 2H), 1.79–1.66 (m, 4H), 1.52–1.47 (m, 2H), 1.44–1.35 (m, 2H), 1.28–1.18 (m, 3H), 1.17–0.99 (m, 3H), 0.91 (t, $J = 7.2$ Hz, 3H).

2,4-Diphenylbut-3-yn-2-ol ***(3a)*** Yellow oil, 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04–7.96 (m, 2H), 7.60–7.52 (m, 3H), 7.50–7.37 (m, 5H), 2.60 (s, 1H), 1.58 (s, 3H).

Methyl 2-hydroxy-2, 4-diphenylbut-3-ynoate ***(4a)*** Pale-yellow oil, 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.72 (m, 2H), 7.56–7.51 (m, 2H), 7.44–7.30 (m, 6H), 4.25 (s, 1H), 3.82 (s, 3H).

Methyl 2-hydroxy-2-phenyloct-3-ynoate ***(4b)*** Colorless oil, 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.63 (m, 2H), 7.40–7.30 (m, 3H), 4.12 (s, 1H), 3.77 (s, 3H), 2.33 (t, $J = 7.2$ Hz, 2H), 1.61–1.52 (m, 2H), 1.50–1.39 (m, 2H), 0.93 (t, $J = 7.2$ Hz, 3H).

1,4-Diphenylbut-3-yn-1-ol ***(5a)*** Pale-yellow oil, 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.43 (m, 4H), 7.40–7.34 (m, 2H), 7.33–7.27 (m, 4H), 4.08 (t, $J = 6.8$ Hz, 1H), 3.85 (d, $J = 6.8$ Hz, 2H), 1.82 (s, 1H).

2-(Phenylethynyl)cyclohexan-1-ol ***(5b)*** Pale-yellow oil, 60% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.39 (m, 2H), 7.33–7.28 (m, 3H), 4.47 (d, $J = 7.2$ Hz, 1H), 2.38–2.23 (m, 1H), 2.23–1.81 (m, 3H), 1.72–1.65 (m, 2H), 1.61–1.46 (m, 4H), 1.37–1.24 (m, 1H).

2-(Hex-1-yn-yl)cyclohexan-1-ol ***(5c)*** Colorless oil, 40% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22 (dt, $J = 7.2$, 2.0 Hz, 1H), 2.21 (td, $J = 6.8$, 2.0 Hz, 2H), 2.18–2.09 (m, 1H), 1.81–1.66 (m, 4H), 1.65–1.52 (m, 4H), 1.49–1.45 (m, 2H), 1.43–1.38 (m, 3H), 0.91 (t, $J = 7.2$ Hz, 3H).

Results and discussion

To begin the study, phenylacetylene and benzaldehyde were chosen as the model substrates, and the variations of reaction conditions and experimental results are summarized in Table 1 (entries 3–24).

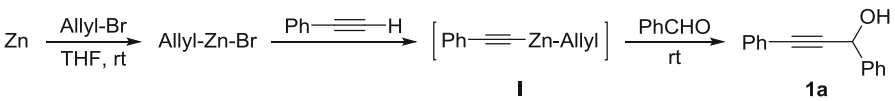
First, the reaction was performed without the addition of $Ti(O^iPr)_4$ and chiral ligand, racemic product **1a** was obtained in moderate yield (entry 3). We reasoned that a lower amount of phenylacetylene (2 equiv) than that of allyl bromide and Zn (3 equiv) may result in an unsatisfactory yield because the remaining allylzinc bromide which did not react with phenylacetylene may attack the benzaldehye competitively to produce a by-product. To testify our hypothesis, we carried out a

control experiment in which the operations were the same as that in entry 3 except that no phenylacetylene was added; the results revealed that the addition product was the same major by-product as in entry 3. Hence, the amount of phenylacetylene was increased from 2 equiv to 3 equiv, and the yield of **1a** improved significantly to 92% (entry 4).

To simplify the operation and minimize the amount of solvent, we avoided the addition of ether in step 2 and lowered the volume of THF stepwise to 1 mL, and no obvious decrease of the yield was observed (entries 5–7). Based on the observation that activated zinc powder reacted with allyl bromide quickly in THF and disappeared in about 1 h, we shortened the reaction times of step 1 and step 2, and slight increases of yield were observed which may have resulted from less deterioration of the active intermediate and product **1a** (entries 8–9). However, when the reaction time of step 2 was reduced from 10 to 8 h, the yield decreased by 6% (entry 10). Next, halides such as lithium chloride, potassium iodide, copper chloride and cuprous chloride were used as additives, but the yields of **1a** were all lower than 96% (entries 11–14). THF, toluene, dichloromethlene and ether were also used as the solvent for the two-step transformation, but, unfortunately, the zinc powder could not react completely and no product was detected by TLC (entries 15–17). Thus, THF was necessary for the effective generation and reaction of the organozinc reagent involved in the transformation. Moreover, the possibility of employing benzyl bromide or benzyl chloride in place of allyl bromide to promote the addition reaction was also investigated, but when benzyl bromide was used, **1a** was separated in 50% yield (entry 18), and when benzyl chloride was used, no product was detected (entry 19). Finally, the molar ratios of Zn, allyl bromide and phenylacetylene to benzaldehyde were varied, the results showing that lower molar ratios than that in entry 9 led to lower yields of **1a** (entries 20–22) and higher molar ratios did not increase the yield (entries 23–24). Therefore, the optimized reaction conditions for the direct addition of phenylacetylene to benzaldehyde mediated by Zn and allyl bromide were determined as listed in entry 9.

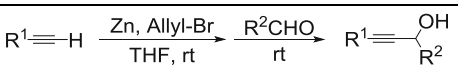
In agreement with the above experimental observations, a tentative mechanism that accounts for the synthesis of propargylic alcohol **1a** has been proposed in Scheme 1. Initially, zinc reacts with allyl bromide in THF to provide allylzinc bromide [33], then it abstracts the active hydrogen of phenylacetylene to form the active intermediate **I** which attacks the carbonyl group of benzaldehyde, leading to the formation of compound **1a**.

With the optimal reaction conditions and tentative mechanism established, the addition reactions of phenylacetylene or 1-hexyne to various aldehydes, including substituted benzaldehydes, aliphatic and vinyl aldehydes, were performed, and the results are set out in Table 2.



Scheme 1 Plausible steps in the formation of propargylic alcohol **1a**

Table 2 Addition of alkynes to aldehydes mediated by Zn and allyl bromide[a]



Entry	R^1	R^2	Product	Isolated yield (%)
1	Ph	Ph	**1a**	96
2	Ph	2-ClC_6H_4	**1b**	96
3	Ph	3-ClC_6H_4	**1c**	98
4[b]	Ph	2,4-$Cl_2C_6H_3$	**1d**	98
5	Ph	2-MeC_6H_4	**1e**	93
6[b]	Ph	4-$NO_2C_6H_4$	**1f**	93
7[b]	Ph	2-$NO_2C_6H_4$	**1g**	94
8	Ph	2-furanyl	**1h**	94
9[b]	Ph	piperonyl	**1i**	91
10	Ph	cinnamyl	**1j**	93
11[c]	Ph	ethyl	**1k**	81
12[c]	Ph	*n*-propyl	**1l**	80
13[c]	Ph	*i*-propyl	**1m**	80
14[c]	Ph	*n*-hexyl	**1n**	95
15[c]	Ph	cyclohexyl	**1o**	93
16[d]	*n*-butyl	Ph	**2a**	85
17[d]	*n*-butyl	2-ClC_6H_4	**2b**	85
18[d]	*n*-butyl	3-ClC_6H_4	**2c**	88
19[d]	*n*-butyl	2-MeC_6H_4	**2d**	84
20[b,d]	*n*-butyl	4-$NO_2C_6H_4$	**2e**	88
21[b,d]	*n*-butyl	2-$NO_2C_6H_4$	**2f**	86
22[d]	*n*-butyl	2-furanyl	**2g**	90
23[b,d]	*n*-butyl	piperonyl	**2h**	90
24[d]	*n*-butyl	cinnamyl	**2i**	88
25[e]	*n*-butyl	ethyl	**2j**	78
26[e]	*n*-butyl	*n*-propyl	**2k**	77
27[f]	*n*-butyl	*n*-hexyl	**2l**	86
28[f]	*n*-butyl	cyclohexyl	**2m**	92

[a] Conditions of entry 9 in Table 1 were applied unless indicated otherwise

[b] The solid aldehyde was dissolved in 0.5 mL of THF and then added via syringe

[c] The reaction times were 2 h + 16 h

[d] The reaction times were 3 h + 12 h

[e] The reaction times were 3 h + 20 h

[f] The reaction times were 3 h + 16 h

It can be seen from Table 2 that most of the reactions proceeded smoothly to afford propargylic alcohols in good yields. The addition of phenylacetylene to aromatic, heteroaromatic or cinnamic aldehydes gave the desired products **1a**–**1j** in 91–98% yields and it appears that the position and electronic property of the substituents of aromatic aldehydes have a very limited effect on the results of this reaction. Although the phenylacetylene addition to propanal, *n*-butanal and *iso*-butanal gave slightly lower yields (**1k**–**1m**), it is noteworthy that when heptanal and cyclohexanecarboxaldehyde were employed, the yields were 95 and 93% respectively (**1n**, **1o**). When 1-hexyne was subjected to this reaction, the yields ranged from 84 to 90% for aromatic, heteroaromatic and cinnamic aldehydes (**2a**–**2i**) and from 77 to 92% for aliphatic aldehydes (**2j**–**2m**).

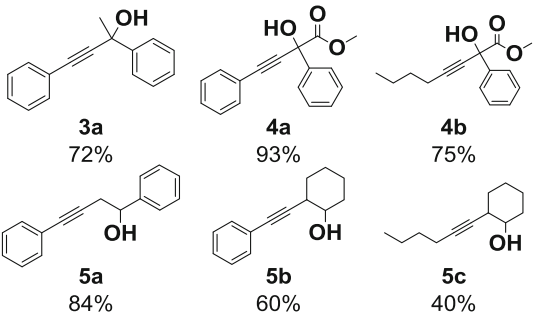


Fig. 1 Products of the addition of alkynes to ketone, α-ketone ester and epoxides[a] (a For compound **3a**, the molar ratios of ketone:Zn:allyl bromide:alkyne were 1:6:6:6 and the reaction times were 3 h + 16 h. For compound **4b**, the reaction times were 2 h + 12 h and for compounds **5b** and **5c**, the reaction times were 2 h + 16 h)

With the good results obtained from aldehydes, we attempted similar transformations with other substrates and the results are shown in Fig. 1. Unless indicated otherwise, the conditions of entry 9 in Table 1 were applied for these addition reactions. Initially, acetophenone was subjected to the alkynylation process, but incomplete conversion of the ketone was observed owing to its lower reactivity than aldehyde. When the molar ratios of Zn, allyl bromide and phenylacetylene to ketone were increased from 3 equiv to 6 equiv, **3a** was obtained in 72% yield. Then, methyl phenylglyoxylate was employed in place of aldehyde. To our delight, α-tertiary-hydroxy esters **4a** and **4b** were obtained in 93 and 75% yields, respectively. It is noteworthy that the ester group is tolerable to this transformation. Epoxide is another important electrophilic reagent with wide synthetic utility and the direct addition of alkyne to it will afford α-alkynyl alcohol, an analogue of propargylic alcohol. We envisioned that our protocol was also applicable to the alkyne addition to epoxide under mild conditions, hence, the addition of phenylacetylene to styrene oxide was conducted under the standard reaction conditions. As shown in Fig. 1, the reaction proceeded smoothly, providing compound **5a** in 84% yield. Also, the alkynylation of cyclohexene oxide provided **5b** and **5c** in moderate yields. Generally, the addition of phenylacetylene to styrene oxide involved the use of active intermediates such as phenylethynyl lithium [34–36] and phenylethynyldifluoroborane [37] and suffered from harsh reaction conditions and low yield. To the best of our knowledge, there has thus far been no report on the Zn-promoted alkynylation of epoxide with alkyne, so our methodology provides a practical and convenient synthesis of α-alkynyl alcohol via the direct alkynlation of epoxide.

To demonstrate practical utility, the reaction of 10.20 mL phenylacetylene and 3.09 mL benzaldehyde was carried out at the 30-mmol scale. The operations were the same as that of entry 9 in Table 1 except that an ice-water bath was used to cool the flask when allyl bromide was added in batches and the reaction times were prolonged to 3 and 14 h for step 1 and step 2, respectively. Finally, 6.03 g of **1a** was isolated after column chromatography and the yield was 96%. The result suggests that the alkynylation of aldehydes mediated by Zn and allyl bromide is easy to scale up.

Conclusion

In summary, we have developed a practical method for the direct alkynylation of aldehydes mediated by Zn and allyl bromide, and a variety of propargylic alcohols could be obtained by the reaction of terminal alkynes and aromatic, aliphatic and vinyl aldehydes. These reactions proceeded under very mild conditions (at room temperature) in high yields (77–98%). Furthermore, when α-ketone esters and epoxides were subjected to this protocol, α-tertiary-hydroxy esters and α-alkynyl alcohols could also be obtained in moderate to high yields.

Acknowledgement We thank the Analytical and Testing Center of Sichuan University for NMR measurements.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. E. Gayon, H. Gerard, E. Vrancken, J.M. Campagne, Synlett **26**, 2336 (2015)
2. Q. Wang, L. Pu, Synlett **24**, 1340 (2013)
3. E.B. Bauer, Synthesis **44**, 1131 (2012)
4. B.V.S. Reddy, B.B. Reddy, K.V.R. Rao, J.S. Yadav, Tetrahedron Lett. **51**, 5697 (2010)
5. S.-X. Xu, L. Hao, T. Wang, Z.-C. Ding, Z.-P. Zhan, Org. Biomol. Chem. **11**, 294 (2013)
6. C.R. Reddy, J. Vijaykumar, E. Jithender, G.P.K. Reddy, R. Grée, Eur. J. Org. Chem. **2012**, 5767 (2012)
7. X.-R. Song, Y.-P. Han, Y.-F. Qiu, Z.-H. Qiu, X.-Y. Liu, P.-F. Xu, Y.-M. Liang, Chem. Eur. J. **20**, 12046 (2014)
8. W.-T. Li, W.-H. Nan, Q.-L. Luo, RSC Adv. **4**, 34774 (2014)
9. I. Nakamura, T. Araki, M. Terada, J. Am. Chem. Soc. **131**, 2804 (2009)
10. D.E. Frantz, R. Fässler, C.S. Tomooka, E.M. Carreira, Acc. Chem. Res. **33**, 373 (2000)
11. P.G. Cozzi, R. Hilgraf, N. Zimmermann, Eur. J. Org. Chem. **2004**, 4095 (2004)
12. G. Lu, Y.-M. Li, X.-S. Li, A.S.C. Chan, Coord. Chem. Rev. **249**, 1736 (2005)
13. B.M. Trost, A.H. Weiss, Adv. Synth. Catal. **351**, 963 (2009)
14. M. Turlington, L. Pu, Synlett **23**, 649 (2012)
15. L. Pu, Acc. Chem. Res. **47**, 1523 (2014)
16. T. Bauer, Coord. Chem. Rev. **299**, 83 (2015)
17. N. Oguni, T. Omi, Tetrahedron Lett. **25**, 2823 (1984)
18. M. Kitamura, S. Suga, K. Kawai, R. Noyori, J. Am. Chem. Soc. **108**, 6071 (1986)
19. G. Gao, R.-G. Xie, L. Pu, Proc. Nat. Acad. Sci. **101**, 5417 (2004)
20. M. Turlington, Y.-H. Du, S.G. Ostrum, V. Santosh, K. Wren, T. Lin, M. Sabat, L. Pu, J. Am. Chem. Soc. **133**, 11780 (2011)
21. T. Bauer, M. Majdecki, S. Smoliński, J. Jurczak, Curr. Org. Chem. **18**, 1218 (2014)
22. A.-L. Zhang, L.-W. Yang, N.-F. Yang, J. Zhang, J. Organomet. Chem. **775**, 88 (2015)
23. Y. Yang, S.-F. Zhu, Q.-L. Zhou, J. Am. Chem. Soc. **130**, 14052 (2008)
24. B.M. Trost, V.S. Chan, D. Yamamoto, J. Am. Chem. Soc. **132**, 5186 (2010)
25. J.G. Kim, P.J. Walsh, Angew. Chem. Int. Ed. **45**, 4175 (2006)
26. R.S. Ramón, S. Gaillard, A.M.Z. Slawin, A. Porta, A. D'Alfonso, G. Zanoni, S.P. Nolan, Organometallics **29**, 3665 (2010)
27. M. Hosseini-Sarvari, Z. Mardaneh, Bull. Korean Chem. Soc. **32**, 4297 (2011)
28. C. Wang, N. Deng, L. Wang, D. Xu, X. Yao, Chin. J. Org. Chem. **36**, 1034 (2016)

29. E. Yu. Schmidt, N.A. Cherimichkina, I.A. Bidusenko, N.I. Protzuk, B.A. Trofimov, Eur. J. Org. Chem. **2014**, 4663 (2014)
30. W. Zhang, Y. Cao, W. Chen, G. Zhao, L. Pu, Tetrahedron Lett. **56**, 6430 (2015)
31. S. Chen, W. Liu, X. Wu, J. Ying, X. Yu, L. Pu, Chem. Commun. **51**, 358 (2015)
32. W.-C. Huang, W. Liu, X.-D. Wu, J. Ying, L. Pu, J. Org. Chem. **80**, 11480 (2015)
33. X. Peng, Allylzinc Bromide, in e-EROS Encyclopedia of Reagents for Organic Synthesis (John Wiley. New York (2008). doi:10.1002/047084289X.rn00886
34. C.R. Pitts, S. Bloom, R. Woltornist, D.J. Auvenshine, L.R. Ryzhkov, M.A. Siegler, T. Lectka, J. Am. Chem. Soc. **136**, 9780 (2014)
35. R.D. Grigg, J.W. Rigoli, S.D. Pearce, J.M. Schomaker, Org. Lett. **14**, 280 (2012)
36. M. Shindo, T. Sugioka, K. Shishido, Tetrahedron Lett. **45**, 9265 (2004)
37. D.E. Kaufmann, N. Ocal, Sci. Synth. **6**, 635 (2004)