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ARTICLE

Metal-Free Synthesis of Homopropargylic Alcohols from Aldehydes

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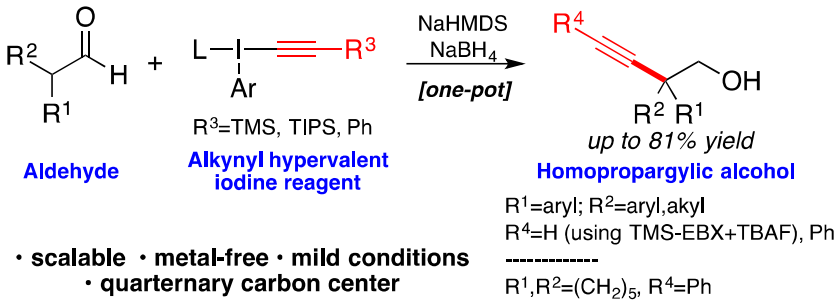
Graphical abstract



Abstract

The synthesis of homopropargylic alcohols under metal-free and mild condition is described. This transformation is based on a one-pot procedure involving sequential α-alkynylation of acyclic aldehydes using hypervalent iodine reagents and borohydride reduction. The chemistry exhibit broad substrate scope and good scalability, providing a

convenient route for the α-alkynylation of aldehydes along with the formation of a quaternary carbon center. The applicability of the method is demonstrated by the gram-scale synthesis of the key synthetic precursor of botulinum toxin inhibitors.

Keywords: Hypervalent iodine, α-alkynylation, aldehyde, homopropargylic alcohol

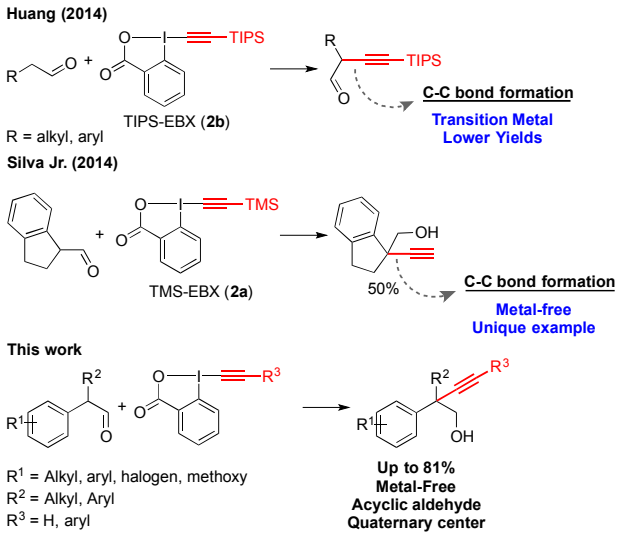
Introduction

Acetylenes are extremely versatile functional groups, which have been applied in several fields, including materials science and biochemistry.[1] The presence of a vicinal hydroxyl group results in homopropargylic alcohols, a class of compounds that associate the exquisite reactivity of both alkynes and alcohols and, therefore, has been extensively used as building blocks in organic synthesis.[2]

Transition-metal-catalyzed alkynylations have been used for the nucleophilic transfer of acetylenes to a variety of substrates *via* cross-coupling[3] reactions and generation of acetylenes anions[4]. However, the polarity inversion (*umpolung*) or the acetylene group allows the alkynylation of enols and related nucleophiles, expanding the structural diversity of substrates. Alkynyl hypervalent iodine reagents are a convenient source of electrophilic acetylenes[5] and EthynylBenziodoXolone-based reagents (EBX) emerged as user-friendly, low-toxicity electrophilic acetylene source.[5-6] Waser and co-workers developed the trimethylsilyl-EBX (TMS-EBX, **2a**)[7], a widely used alkynylation reagent that have been used to gain entry to several previously inaccessible compounds[8] and complex natural products[9]. The use of EBXs in α-alkynylation reactions became an important transformation and the scope of this type of strategy includes non-stabilized and stabilized enolates.[7,10]

Huang and co-workers reported the synthesis of allenes via pyrrolidine/AuCl-catalyzed reaction of aldehydes with triisopropyl-EBX (TIPS-EBX, **2b**).[11] The authors reported the

inefficient formation of monoalkynyl aldehydes as coproducts (Scheme 1). Our group developed a method for the alkynylation of non-stabilized enolates using TMS-EBX. During the examination of the reaction scope, the α-alkynylation of 2,3-dihydro-1*H*-indene-1-carbaldehyde, followed by reduction with sodium borohydride, produced the corresponding homopropargylic alcohol (Scheme 1)[10g]. In this work, we report the practical and scalable synthesis of homopropargylic alcohols from aldehydes via the one-pot α-alkynylation/reduction strategy.



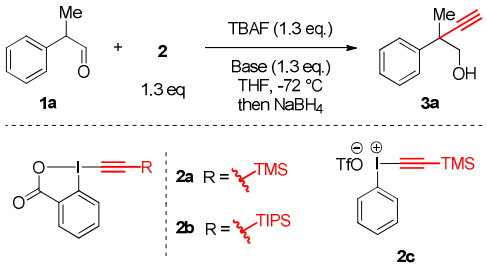
Scheme 1. Synthetic methods of α-alkynylation of aldehydes

Results and discussion

The conversion of aldehydes into homopropargylic alcohols was based on a one-pot reaction involving sequential α-alkynylation and borohydride reduction. Reaction conditions were optimized using the model substrate 2-phenylpropionaldehyde (**1a**) and the hypervalent iodine reagent TMS-EBX (**2a**) as the electrophilic acetylene source. Reactions were carried out by deprotecting **2a** with fluoride (i.e., TBAF) at –72 ºC to produce EBX *in*

situ. The enolisation of the aldehyde is a key step in alkynylation. Potassium carbonate was not able to deprotonate **1a** and the starting material was fully recovered (entry 1, Table 1). The use of *t*-BuOK resulted in formation of the alkynylated aldehyde, which was detected by CG-MS but could not be isolated; one-pot reduction using $NaBH_4$ gave the homopropargylic alcohol **3a** in 40% yield (entry 2). The deprotonation of **1a** with *t*-BuOK at 25 ºC had no effect in the reaction yield (entry 3). Higher yields were achieved when used hexamethyldisilazane bases (entries 4-6); the use of NaHMDS allowed the obtaining of **3a** in 85% yield (entry 6). Attempts to replace **2a** by the more stable TIPS-EBX (**2b**) or the Ochiai's reagent (**2c**) resulted in lower yields and longer reaction time (entries 7 and 8). The α-alkynylation of aldehydes upon enolate formation is prone to direct self-aldol reaction. However, EBX-type reagents are so reactive that α-alkynylation outcompetes the aldol reaction explaining the lack of aldol products in this transformation.

Table 1. Optimization of reaction conditions for the synthesis of the homopropargylic alcohol **3a.**[a]



Entry	Base	**2**	Yield (%)
1	K_2CO_3	**2a**	n.r.[b]

2	*t*-BuOK	**2a**	40
3[c]	*t*-BuOK	**2a**	43
4	LiHMDS	**2a**	63
5	KHMDS	**2a**	60
6	NaHMDS	**2a**	85
7	NaHMDS	**2b**	77[d]
8	NaHMDS	**2c**	55[e]

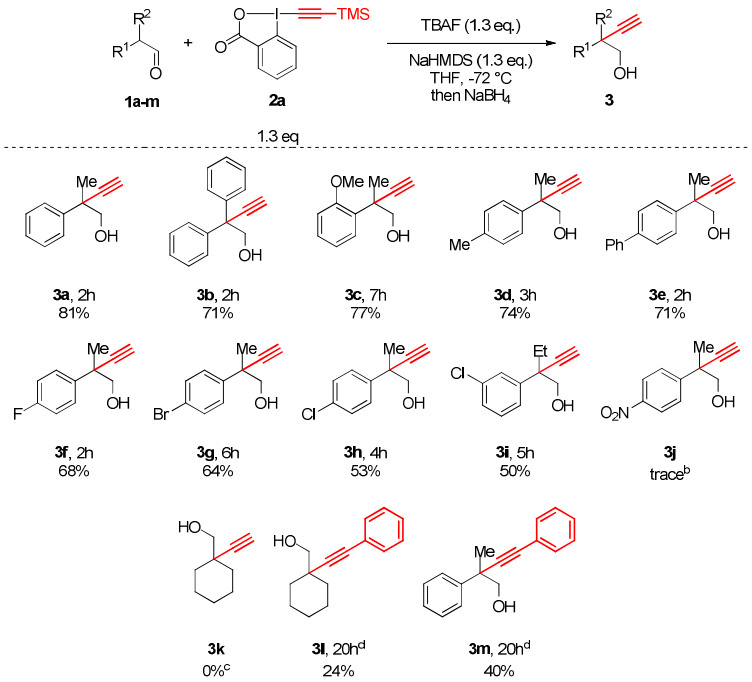
[a] The reaction of **1** (0.20 mmol) with **2a** (0.26 mmol) was performed in THF (0.1 mol L^{-1}) at –72 ºC in the presence of NaHMDS (0.26 mmol), under N_2 atmosphere, and monitored for 2 h. The product was reduced in the presence of $NaBH_4$ (1.0 mmol) at 25 ºC. [b] n.r. = no reaction. [c] The deprotonation step was carried out at 25 ºC for 45 min. [d] The alkynylation step was carried out for 4 h. [e] The alkynylation step was carried out for 8 h.

The scope of this method was evaluated as shown in Table 2. Aromatic aldehydes bearing electron-donating substituents in the *ortho* or *para* positions were converted into the corresponding propargylic alcohols contain a chiral quaternary carbon center in roughly 70% yield. Formation of product **3c** (*o*-OMe) was slower compared to other compounds probably due to the steric hindrance of the *ortho* substituent of the aromatic ring. Interestingly, the *para* regioisomer could not be obtained due to the decomposition of the starting material in the presence of TMS-EBX. Aldehydes bearing a halogen atom give the

products in lower yields in long time reaction (entries 6-9). The lower purified yields of **3h** and **3i** are probably caused by product decomposition.

2-(4-Nitrophenyl)acetaldehyde (**1j**) and the aliphatic aldehyde cyclohexanecarbaldehyde (**1k**, R^1,R^2=cyclohexyl) did not react under the reaction conditions optimized for the synthesis of **3a.** The alkynylation of the aliphatic aldehyde **1l** was achieved in 24% yield by using phenyl-EBX (**2d**), which can be used within the 0 ºC → 25 ºC temperature range. The alkynylation of **1a** (model aldehyde used to optimize the reaction conditions) with phenyl-EBX produced the homopropargylic alcohol **3m** in 40% yield.

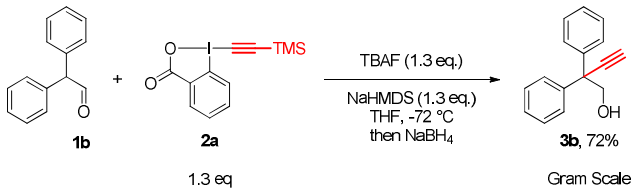
Table 2. Scope of the α-alkynylation of aldehydes in the presence of TMS-EBX[a]



[a] The reaction of **1** (0.50 mmol) with **2a** (0.65 mmol) was performed in THF (0.1 mol L^{-1}) at –72 ºC in the presence of NaHMDS (0.65 mmol) and under N_2 atmosphere, for the indicated period of time. The product was reduced by $NaBH_4$ (2.5 mmol) at 25 ºC; isolated yields are reported. [b] Detected by a GC-MS. [c] The starting material was recovered. [d] The reaction was performed at 0 ºC for 8 h and 25 ºC overnight in the absence of TBAF and **2d**.

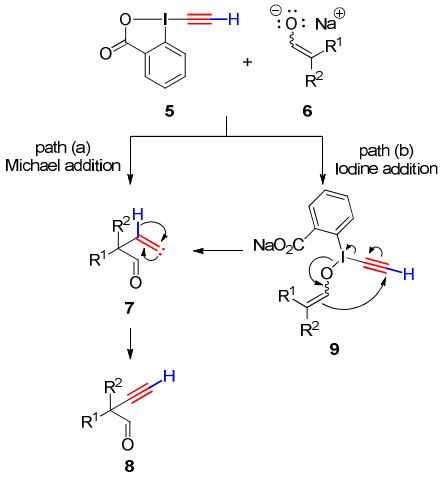
Reports on the synthesis of homopropargylic alcohols such as **3** are scarce. Compound **3a** was synthesized via ring-opening of 2-methyleneoxetanes in the presence of a trimethylaluminium complex,[12] the Yamaguchi alkynylation of 2,2-diphenyloxirane led to compound **3b,**[13] and compounds analogues of **3l** were synthesized in eight steps.[14] Consequently, the methodology described here represents a powerful and convenient method for the synthesis of homopropargylic alcohols from simple feedstock aldehydes.

To illustrate the scalability of this approach, a gram-scale reaction was carried out. 2,2-Diphenylpropargylic alcohol (**3b**) has been used as building blocks for the synthesis of botulinum neurotoxin inhibitors. Using one gram of aldehyde **1b**, the homopropargylic alcohol **3b** was obtained in 72% yield, without modification of the optimized conditions (Scheme 2).



Scheme 2. Gram-scale synthesis of 2,2-diphenyl-homopropargylic alcohol.

The proposed mechanism of electrophilic alkynylation is shown in Scheme 3. According to Ochiai, EBX (**5**) is obtained by reaction of TMS-EBX (**2a**) with TBAF. Nucleophilic attack of the enolate **6** on the terminal carbon of **5** furnishes the carbene **7**. Following 1,2-hydride shift of carbene **7** leads to the alkynylated product **8** (Scheme 3, path a).[15] An alternative mechanism was proposed by Waser and co-authors to explains the enantioselectivity in the alkynylation of carbonyl compounds using TMS-EBX in asymmetric phase-transfer conditions. Nucleophilic attack of the oxygen atom of enolate **6** on the iodine atom of **5** furnishes the intermediate **9**, which undergoes a rearrangement to generate the carbene **7.** Following 1,2-hydride shift of carbene **7** leads to the alkynylated product **8** (Scheme 3, path b).[10e]



Scheme 3. Mechanism proposed for the α-alkynylation of aldehydes. Path a) Mechanism proposed by Ochiai; Michael addition from the enolate to the terminal *sp* carbon.[15] Path b) Mechanism proposed by Waser and co-authors based on direct iodine addition.[10e]

In conclusion, we developed a method for the α-alkynylation of aldehydes using a one-pot method based on α-alkynylation with the hypervalent iodine reagent TMS-EBX followed by borohydride reduction. Under the optimized reaction conditions, homopropargylic alcohols derived from electron-rich aromatic aldehydes were isolated in roughly 70% yields. The first example of aliphatic propargylic alcohol was obtained using phenyl-EBX as source of electrophilic acetylene. The scalability of the method was illustrated by the gram-scale synthesis of the synthetic precursor of inhibitors of botulinum neurotoxin. Using this framework, versatile synthetic building blocks bearing a quaternary carbon center and an acetylene moiety can be conveniently obtained from aldehydes.

Experimental section

General considerations

Commercial reagents were used without further purification, unless otherwise noted. All solvents used for reactions and chromatography were dried and purified by standard methods. TLC analyses were performed using silica gel 60-F254 plates, with detection by UV-absorption (254 nm) and by using *p*-anisaldehyde or sulfuric vaniline solutions. Flash column chromatography was performed using silica gel 200−400 Mesh. All NMR analyses were recorded using $CDCl_3$ as solvent and TMS as internal standard; chemical shifts are reported in ppm. Infrared spectra were registered on a Perkin-Elmer 1750-FT spectrometer. High-resolution mass spectra HRMS (ESI-TOF) were obtained using a Bruker MicroTOF-QII mass spectrometer equipped with an electrospray ionization source operating in positive mode. Preparations of substrates **1c-j**[16] and **2a-d**[10e] were performed as reported in the literature.

*2-(3-Chlorophenyl)butanal (**1i**):* Following a general procedure,[16] to a schlenk flask equipped with a magnetic stir bar was added the (methoxymethyl)triphenylphosphonium chloride (5.14 g, 15 mmol, 1.3 eq.). The flask was evacuated and filled with N_2 for 3 times and THF (15 mL) was added by syringe. The suspension was cooled to -72 ˚C in an ethanol/dry ice bath. Slowly by a syringe, *n*BuLi (2.5 M in THF, 6.0 mL, 15 mmol) was added to the stirring solution under an atmosphere of N_2. The reaction was allowed to stir under N_2 at –72 ˚C for 30 min, then at rt for 30 min. Then, the mixture was recooled to -72 ˚C, and the solution of 3-chloropropiophenone (1.68 g, 10 mmol, 1.0 eq.) in minimal anhydrous THF was added by cannula. After stirring under N_2 for 24 h, the reaction was quenched with H_2O (50 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 x 50 mL). The organic solutions were combined, washed with brine (100 mL), dried over anhydrous Mg_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (silica flash, ethyl acetate 10% in hexanes) to afford the 1-chloro-3-(1-methoxybut-1-en-2-yl)benzene in a E/Z isomers ratio 56:44. 1-chloro-3-(1-methoxybut-1-en-2-yl)benzene. 0.983 g, yield 50%, colorless oil, R_f = 0.54 (ethyl acetate 10% in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (t, 1.3 H, J = 1.8 Hz), 7.37 (t, 0.5 H, J = 1.2 Hz), 7.34 (t, 0.8 H, J = 1.2 Hz), 7.12-7.26 (m, 7H), 6.29 (s, 1H, minor diast.), 6.10 (s, 1.3 H, major diast.), 3.71 (s, 3H, minor diast.), 3.65 (s, 4H, major diast.), 2.49 (qd, 2H, J = 0.6 and 7.5 Hz, minor diast.), 2.30 (qd, 2.7H, J = 1.2 and 7.2 Hz, minor diast.), 0.96-1.02 (m, 7.3H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 145.5, 144.6, 141.5, 139.3, 134.1, 133.8, 129.5, 129.1, 128.1, 126.1, 126.0, 125.8, 125.6, 123.7, 120.3, 116.7, 60.1, 60.0, 25.5, 20.0, 14.1, 13.0 ppm. IR (neat) 2966, 2933, 2874, 1648, 1592, 1561, 1477, 1463, 1417,

1261, 1250, 1224, 1205, 1146, 1112, 1079, 1066, 1039, 781 cm^{-1}. HRMS (ESI) *m/z* calculated for $C_{11}H_{14}ClO$ $(M + H)^+$ 197.0728, found 197.0730.

The 1-chloro-3-(1-methoxybut-1-en-2-yl)benzene (0.39 g, 2.0 mmol) was dissolved in a 4:1 mixture of acetone and H_2O (10 mL) and the resultant solution was cooled to 0 ˚C in an ice bath. HBr (48% in water, 2 mL) was added to the solution and the reaction mixture was stirred at rt for 24 h. The solution was neutralized with sat. aq. $NaHCO_3$ and this aqueous solution was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica flash, ethyl acetate 10% in hexanes) to afford the 2-(3-Chlorophenyl)butanal (**1i**). 0.25 g, yield 69%, colorless oil, R_f = 0.26 (ethyl acetate 10% in hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 9.66 (d, 1H, J = 2.1 Hz), 7.26-7.31 (m, 2H), 7.19-7.31 (m, 1H), 7.06-7.10 (m, 1H), 3.37-3.42 (m, 1H), 2.04-2.18 (m, 1H), 1.67-1.82 (m, 1H), 0.91 (t, 3H, J = 7.5 Hz) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 200.2, 138.3, 134.8, 130.2, 128.9, 127.7, 127.0, 60.4, 22.9, 11.7 ppm. IR (neat) 2967, 2933, 2877, 2852, 1725, 1596, 1573, 1478, 1463, 1431, 1382, 1081, 999, 962, 783 cm^{-1}. HRMS (ESI-TOF) *m/z* calculated for $C_{10}H_{12}ClO$ $(M + H)^+$ 183.0572, found 183.0575.

General procedure for the α-alkynylation of aldehydes using TMS-EBX (**2a**): To a schlenk flask equipped with a magnetic stir bar was added the aldehyde (0.50 mmol, 1.0 eq.). The flask was evacuated and filled with N_2 for 3 times and THF (0.1 M, 5 mL) was added by syringe. The reaction was then cooled to -72 °C in an ethanol/dry ice bath and NaHMDS (1M in THF, 0.65 mL, 0.65 mmol, 1.3 eq.) was added by syringe. The reaction was stirred

at -72 °C for 20 min and the 2a (0.22 g, 0.65 mmol, 1.3 eq.) was added followed by addition of TBAF (1M in THF, 0.65 mL, 0.65 mmol, 1.3 eq.). The reaction was stirred at -72 °C for the indicated time. After this time, $NaBH_4$ (0.094 g, 2.5 mmol, 5.0 eq.) was added and the mixture warmed up to rt. After 2 h the reaction was quenched with sat. aq. NH_4Cl (10 mL) and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (30 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography.

*2-methyl-2-phenylbut-3-yn-1-ol (**3a**):*[12] The general procedure was employed **1a** (0.067 g, 0.50 mmol), and the alkynylation step was completed in 4h. 0.068 g, yield 85%, colorless oil, purified by column chromatography (silica flash, ethyl acetate 15% in hexanes), R_f = 0.36 (ethyl acetate 20% in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53-7.57 (m, 2H), 7.25-7.40 (m, 3H), 3.66-3.78 (m, 2H), 2.47 (s, 1H), 1.63 (s, 1H), 1.58 (sl, 1H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 141.6, 128.5, 127.2, 126.4, 87.3, 72.7, 71.8, 43.3, 25.0 ppm.

*2,2-diphenylbut-3-yn-1-ol (**3b**):* [17] The general procedure was employed **1b** (0.099 g, 0.50 mmol), and the alkynylation step was completed in 2h. 0.079 g, yield 70%, colorless oil, purified by column chromatography (silica flash, ethyl acetate 10% in hexanes), R_f = 0.12 (ethyl acetate 10% in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43-7.47 (m, 4H), 7.23-7.36 (m, 6H), 4.19 (s, 2H), 2.66 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 141.6, 128.4, 127.7, 127.2, 86.3, 74.7, 69.5, 52.4 ppm.

*2-(2-methoxyphenyl)-2-methylbut-3-yn-1-ol (**3c**):* The general procedure was employed **1c** (0.082 g, 0.5 mmol), and the alkynylation step was completed in 7h. 0.073 g, yield 77%, colorless oil, purified by column chromatography (silica flash, 5% ethyl ether and 40% dichloromethane in hexanes), R_f = 0.26, (5% ethyl ether and 40% dichloromethane in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (dd, 1H, J = 1.8 and 7.5 Hz), 7.24-7.30 (m, 1H), 6.96 (td, 1H, J = 0.9 and 7.5 Hz), 6.90 (dd, 1H, J = 0.9 and 8.1 Hz), 3.91-4.07 (m, 2H), 3.84 (s, 3H), 2.52 (s, 1H), 1.68 (s, 3H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 157.4, 129.7, 128.7, 128.5, 120.7, 111.7, 88.1, 73.1, 68.6, 55.1, 44.1, 23.5 ppm. IR (neat) 3435, 3293, 2882, 2937, 2838, 1599, 1582, 1491, 1463, 1436, 1386, 1290, 1245, 1179, 1071, 1030, 788, 755 cm^{-1}. HRMS (ESI-TOF) *m/z* calculated for $C_{12}H_{15}O_2$ $(M + H)^+$ 191.1067, found 191.1060.

*2-methyl-2-(p-tolyl)but-3-yn-1-ol (**3d**):* The general procedure was employed **1d** (0.074 g, 0.50 mmol), and the alkynylation step was completed in 3h. 0.064 g, yield 74%, colorless oil, purified by column chromatography (silica flash, ethyl acetate 10% in hexanes), R_f = 0.18 (ethyl acetate 10% in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.44 (m, 2H), 7.16-7.25 (m, 2H), 3.63-3.74 (m, 2H), 2.45 (s, 1H), 2.34 (s, 3H), 1.61 (s, 3H) ppm. ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 138.6, 136.8, 129.2, 126.3, 87.5, 72.5, 71.8, 42.9, 25.0, 20.9 ppm. IR (neat) 3546, 3401, 3305, 2873, 2925, 2872, 1513, 1460, 1409, 1379, 1043, 1021, 816 cm^{-1}. HRMS (ESI-TOF) *m/z* calculated for $C_{12}H_{14}O$ $(M + Na)^+$ 197.0937, found 197.0945.

*2-([1,1'-biphenyl]-4-yl)-2-methylbut-3-yn-1-ol (**3e**):* The general procedure was employed 1e (0.10 g, 0.50 mmol), and the alkynylation step was completed in 4h. 0.084 g, yield 71%,

colorless oil, purified by column chromatography (silica flash, ethyl acetate 20% in hexanes), R_f = 0.51 (ethyl acetate 30% in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57-7.64 (m, 5H), 7.41-7.46 (m, 3H), 7.32-7.37 (m 1H), 3.71-3.80 (m, 2H), 2.49 (s, 1H), 1.66 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 140.7, 140.6, 140.1, 128.8, 127.3, 127.2, 127.1, 126.9, 87.3, 72.8, 71.8, 43.0, 25.0 ppm. IR (neat) 3401, 3287, 2918, 2875, 1486, 1403, 1077, 1045, 840, 768, 730, 694 cm^{-1}. HRMS (ESI-TOF) *m/z* calculated for $C_{17}H_{17}O$ $(M + H)^+$ 237.1274, found 237.1266.

*2-(4-fluorophenyl)-2-methylbut-3-yn-1-ol (**3f**):* The general procedure was employed **1f** (0.076 g, 0.50 mmol), and the alkynylation step was completed in 2h. 0.061 g, yield 68%, colorless oil, purified by column chromatography (silica flash, ethyl acetate 20% in hexanes), R_f = 0.39 (ethyl acetate 20% in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49-7.54 (m, 2H), 7.02-7.07 (m, 2H), 3.64-3.73 (m, 2H), 2.48 (s, 1H), 1.61 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 163.5, 160.2, 137.4, 128.1, 128.0, 115.4, 115.1, 87.1, 72.9, 71.8, 42.8, 25.1 ppm. IR (neat) 3436, 2981, 2935, 1721, 1605, 1511, 1225, 1160, 1063, 835 cm^{-1}. HRMS (ESI-TOF) *m/z* calculated for $C_{11}H_{11}FONa$ $(M + Na)^+$ 201.0686, found 201.0694.

*2-(4-bromophenyl)-2-methylbut-3-yn-1-ol (**3g**):* The general procedure was employed **1g** (0.093 g, 0.50 mmol), and the alkynylation step was completed in 6h. 0.065 g, yield 64%, colorless oil, purified by column chromatography (silica flash, ethyl acetate 10% in hexanes), R_f = 0.21 (ethyl acetate 10% in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46-7.50 (m, 2H), 7.40-7.44 (m, 2H), 3.68-3.69 (m, 2H), 2.48 (s, 1H), 1.60 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 140.8, 131,5, 128.3, 121.2, 86.7, 73.1, 71.6, 43.0, 24.9

ppm. IR (neat) 3392, 3297, 2978, 2935, 2876, 1488, 1398, 1100, 1043, 1010, 822, 645 cm^{-1}. HRMS (ESI-TOF) *m/z* calculated for $C_{11}H_{11}{}^{79}BrO$ $(M+H)^+$ 239.0067 and $C_{11}H_{11}{}^{81}BrO$ $(M + H)^+$ 241.0046, found 239.0059 (^{79}Br) and 241.0038 (^{81}Br).

*2-(4-chlorophenyl)-2-methylbut-3-yn-1-ol (**3h**):* The general procedure was employed **1j** (0.084 g, 0.50 mmol), and the alkynylation step was completed in 4h. 0.051 g, yield 52%, colorless oil, purified by column chromatography (silica flash, ethyl acetate 10% in hexanes), R_f = 0.15 (ethyl acetate 10% in hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 7.46-7.50 (m, 2H), 7.30-7.35 (m, 2H), 3.66-3.72 (m, 2H), 2.48 (s, 1H), 1.60 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 140.3, 133.1, 128.6, 127.9, 86.8, 73.1, 71.6, 42.9, 25.0 ppm. IR (neat) 3401, 3300, 2934, 2978, 2876, 1492, 1462, 1401, 1284, 1262, 1098, 1071, 1043, 1014, 827 cm^{-1}. HRMS (ESI-TOF) *m/z* calculated for $C_{11}H_{12}ClO$ $(M + H)^+$ 195.0572, found 195.0580.

*2-(3-chlorophenyl)-2-ethylbut-3-yn-1-ol (**3i**):* The general procedure was employed **1i** (0.10 g, 0.50 mmol), and the alkynylation step was completed in 5h. 0.052 g, yield 50%, colorless oil, purified by column chromatography (silica flash, ethyl acetate 10% in hexanes), R_f = 0.25 (ethyl acetate 10% in hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 7.52-7.53 (m, 1H), 7.39 (dt, 1H, J = 1.5 and 7.2 Hz), 7.24-7.33 (m, 2H), 3.76 (s, 2H), 2.55 (s, 1H), 1.93-2.05 (m, 1H), 1.71-1.89 (m, 1H), 0.87 (t, 3H, J = 1.8 Hz) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 142.2, 134.4, 129.7, 127.4, 127.3, 125.0, 85.0, 74.8, 70.91, 49.3, 30.4, 9.1 ppm. IR (neat) 3400, 3300, 2970, 2934, 2879, 2850, 1596, 1571, 1473, 1414, 1380, 1299, 1261, 1196, 1080, 1052, 999, 785 cm^{-1}. HRMS (ESI-TOF) *m/z* calculated for $C_{12}H_{13}ClONa$ $(M + Na)^+$ 231.0547, found 231.0540.

General procedure for the α-alkynylation of aldehydes using Ph-EBX (**2d**)*:* To a schlenk flask equipped with a magnetic stir bar was added the aldehyde (0.50 mmol). The flask was evacuated and filled with N_2 for 3 times and THF (0.1 M, 5 mL) was added by syringe. The reaction was kept at rt and NaHMDS (1M in THF, 0.65 mL, 0.65 mmol, 1.3 eq.) was added by syringe. The reaction was stirred at rt for 20 min and **2d** (0.23 g, 0.65 mmol, 1.3 eq.) was added. The reaction was kept stirred for 20 h. After this time, the reaction was cooled to 0 °C and $NaBH_4$ (5.0 eq.) was added and the mixture warmed up to rt. After 2 h the reaction was quenched with sat. aq. NH_4Cl (10 mL) and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (30 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography.

*(1-(phenylethynyl)cyclohexyl)metanol (**3l**)*:[18] The general procedure was employed **1l** (0.056 g, 0.50 mmol). 0.026 g, yield 24%, yellow oil, purified by column chromatography (silica flash, ethyl acetate 10% in hexanes), R_f = 0.15 (ethyl acetate 10% in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28-7.44 (m, 5H), 3.52 (s, 2H), 1.65-1.83 (m, 6H), 1.21-1.31 (m, 5H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 131.7, 128.9, 128.2, 127.8, 92.7, 84.5, 71.6, 40.7, 34.2, 26.2, 22.8 ppm.

*2-methyl-2,4-diphenylbut-3-yn-1-ol (**3m**):* The general procedure was employed **1a** (0.067 g, 0.50 mmol). 0.047 g, yield 40%, colorless oil, purified by column chromatography (silica flash, 5% ethyl ether and 40% dichloromethane in hexanes), R_f = 0.29 (5% ethyl ether and 40% dichloromethane in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60-7.62 (m, 2H), 7.48-7.51 (m, 2H), 7.29-7.41 (m, 6H), 3.74-3.83 (m, 2H), 1.71 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (75

MHz, $CDCl_3$): δ 142.3, 131.7, 128.5, 128.3, 128.1, 127.1, 126.5, 123.0, 92.3, 84.9, 71.9, 43.9, 25.1 ppm. IR (neat) 3401, 3031, 3082, 2977, 2931, 2873, 1598, 1491, 1444, 1071, 1044, 1028, 757 cm^{-1}. HRMS (ESI-TOF) *m/z* calculated for $C_{17}H_{16}ONa$ $(M + Na)^+$ 237.1274, found 237.1264.

Gram-scale preparation of compound (**3b**): To a schlenk flask equipped with a magnetic stir bar was added the aldehyde (1.00 g, 5.10 mmol, 1.0 eq.). The flask was evacuated and filled with N_2 for 3 times and THF (0.1 M, 50 mL) was added by syringe. The reaction was then cooled to -72 °C in an ethanol/dry ice bath and NaHMDS (1M in THF, 6.63 mL, 6.63 mmol, 1.3 eq.) was added slowly by syringe. The reaction was stirred at -72 °C for 20 min and the **2a** (2.28 g, 6.63 mmol, 1.3 eq.) was added followed by addition of TBAF (1M in THF, 6.63 mL, 6.63 mmol, 1.3 eq.). The reaction was stirred at -72 °C for 2h. After this time, $NaBH_4$ (0.965 g, 25.5 mmol, 5.0 eq.) was added and the mixture warmed up to rt. After 2 h the reaction was quenched with sat. aq. NH_4Cl (100 mL) and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (300 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (silica flash, ethyl acetate 10% in hexanes) to furnishes product 2a in 72% yield (0.815 g).

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Author contributions

L.F.S.Jr. proposed the concept and directed the research. B.V.M.T. carried out the experiments. B.V.M.T. wrote the main manuscript text and prepared the figures.

Notes

The authors declare no competing financial interest.

Supporting information

The Supporting Information is available free of charge on the ACS Publications website.

^{1}H and ^{13}C spectra of all compounds.

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