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Unprecedented Consecutive, Competitive Nucleophilic Addition to Construct Densely Functionalized Propargylic Alcohols

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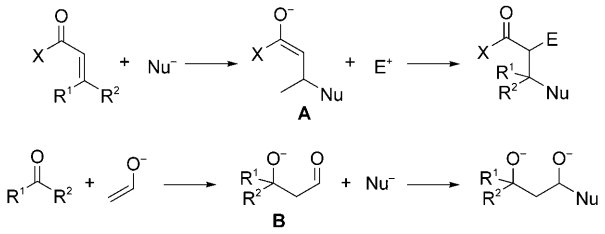
Tandem C–C bond formation through consecutive nucleophilic addition to construct organic compounds is one of the most attractive strategies in organic synthesis.[1] The classical route, as exemplified by the reaction shown in Scheme 1

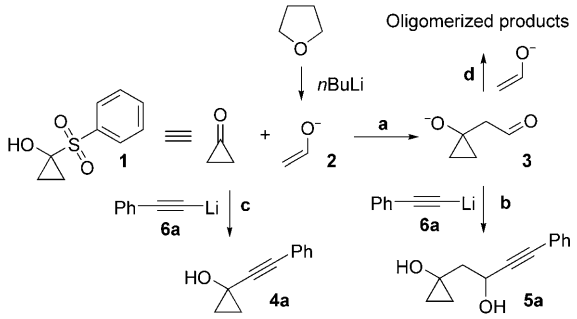


Scheme 1. Tandem C–C bond formation by consecutive nucleophilic additions.

(top), provides an efficient approach to introduce both α,β substituents at the enone or at an α,β-unsaturated ester. The key intermediate (enolate **A**) acts as the new nucleophile in the last step.[2] Herein we described a new tandem reaction involving two consecutive nucleophilic additions to successively introduce two substituents on acetaldehyde,[3] leading to a series of propargylic alcohol derivatives with multiple functionalities that are malleable for further transformation and modification. In this process, the in-situ-generated intermediate (aldehyde **B**) was used as the new electrophile in the last step (Scheme 1, bottom). This is the first report, to the best of our knowledge, of a process involving two consecutive, competitive nucleophilic addition reactions to establish two C–C bonds in one-pot reaction.[4]

While investigating the reaction of the new cyclopropanone surrogate 1-(benzenesulfonyl) cyclopropanol **1**,[5a] with lithium phenyl ethynilide in THF at low temperature to construct 1-alkynyl cyclopropanol **4a**,[5b] we accidentally obtained an unexpected product **5a** in 5% yield. The structure of compound **5a** was identified to be 1-(2-hydroxy-4-phenyl-but-3-ynyl)cyclopropanol, which has a -$CH_2CH(OH)$- subunit between the cyclopropanol and the alkynyl functionalities, indicating the participation of the lithium enolate of acetaldehyde in the reaction. Ring-opening and decomposition of THF with various organometallic reagents to generate acetaldehyde enolates have been reported,[6] but little study of its reactivity and synthetic utility has ever been undertaken.[6c] Meanwhile, this reaction is unprecedented with a consecutive, competitive nucleophilic addition process to construct densely functionalized propargylic alcohol derivatives from simple reactants, and would be worthy of further study.

The proposed mechanism for the preparation of **5a** (shown in Scheme 2) starts from the nucleophilic addition of the enolate **2** to the cylopropanone intermediate (route a), giving a new aldehyde intermediate **3**, which was then selectively trapped by lithium alkynilide to provide product **5a** (route b). However, there are two other competitive process existed, either to construct 1-alkynyl cyclopropanol **4** (route c) or to give oligomerized products (route d). Therefore, an efficient method should be devised in which the



Scheme 2. Proposed mechanism to synthesize compound **5a**.

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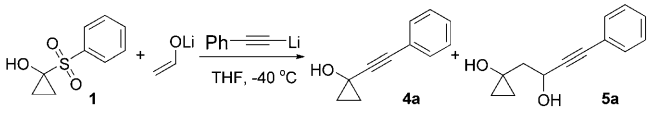
first competitive nucleophilic attack must be controlled to favor the addition of lithium enolate **2** to the ketone (route a), and the second nucleophilic attack to favor the addition of lithium alkynylide (route b) to the intermediate **3**. We envisioned that the difference of nucleophilicity between lithium enolate **2** (sp^3 or sp^2 carbon) and lithium alkynylide (sp carbon)[7,8] would leave some space for us to tune the reaction factors to get optimal conditions for the formation of 1-(2-hydroxy-but-3-ynyl)cyclopropanol (**5**).

The reaction of compound **1**, lithium enolate **2**, and phenylacetylene (**6a**) was chosen as the model system for our initial investigation. In the event, the consecutive nucleophilic addition of enolate **2** (1.1 equiv) and lithium phenyl ethynylide (2.1 equiv) to compound **1** (0.5 mmol, 1 equiv) in THF at −40 °C (2 h) afforded a mixture of 1-phenylethynyl cyclopropanol (**4a**) in 16% yield and diol **5a** in 39% yield (Table 1, entry 1). The effect of different ratios of **2**/**6a** on

Table 1. Examination of the reaction of compound **1**, enolate **2** and lithium phenyl ethynylide **6a**.[a]



	6a [equiv]	**2** [equiv]	*t* [h]	Yield [%] of **4a**	Yield [%] of **5a**
1	2.1	1.1	2	16	39
2	2.1	2.2	2	14	49
3	2.1	2.7	2	9	54
4	2.1	3.0	2	11	52
5[b]	2.1	2.7	2	20	49
6	4.2	5.4	4	37	62
7	3.5	5.4	4	22	77
8	3.0	5.4	4	18	73

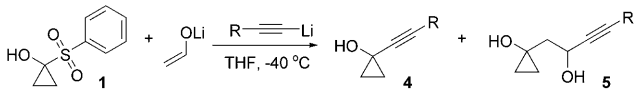
[a] Unless otherwise noted, all reactions were carried out at the 0.5 mmol scale in THF at −40 °C. [b] 1 equivalent of HMPA was added.

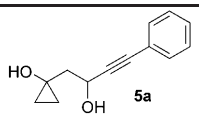
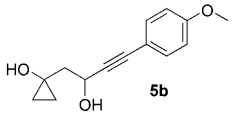
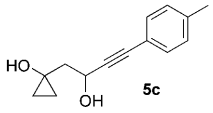
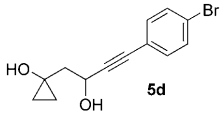
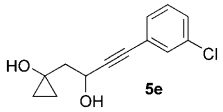
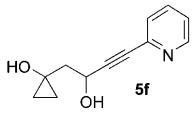
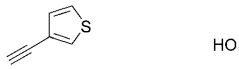
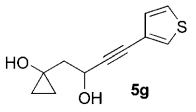
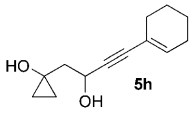
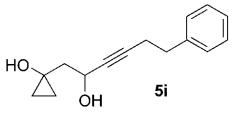
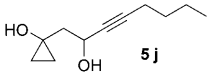
the yield of the two products was then examined. A relatively good result (54% yield of **5a** with 9% yield of **4**, Table 1, entry 3) was obtained when the ratio of **2**/**6a** was adjusted to 2.7:2.1. Increasing the amount of enolate **2** and lithium alkynylide enhanced the reaction yield greatly (Table 1, entry 6). Rational examination then identified a set of best conditions (**1** (1 equiv), **6a** (3.5 equiv), **2** (5.4 equiv) in THF (10 mL) at −40 °C for 4 h, Table 1, entry 7) to give the desired product **5a** in 77% yield. The use of other additive, such as hexamethylphosphoramide (HMPA), proved to be fruitless in this reaction (Table 1, entry 5).[9]

With this standard procedure in hand, we explored the scope and limitations of the reaction by examining other terminal alkynes. As shown in Table 2, a range of 3-alkynyl-2-hydroxy cyclopropanols were readily obtained. Both aromatic and aliphatic terminal alkynes were able to undergo the corresponding consecutive nucleophilic addition. Electron-rich aromatic or heteroaromatic terminal alkynes displayed relatively high reactivity and gave higher conversion (Table 2, Entries 2, 3, and 7). The *p*-methoxy phenylacetylene underwent the consecutive nucleophilic addition to give the product **5b** in highest yield (81%). Electron-deficient terminal aromatic alkynes exhibited relatively low reactivity (Table 2, entries 4–6). Alkene-substituted and aliphatic alkynes, such as 4-phenyl-1-butyne and 1-hexyne, also worked effectively in the reaction (Table 2, entries 8–10). It is notable that the reactivity of electron-rich and electron-deficient aryl aldehyde exhibited similar reactivity in the reaction.

To further evaluate this methodology, a number of different carbonyl-containing substrates, including aromatic alde-

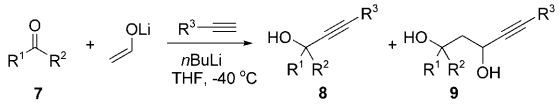
Table 2. Preparation of a series of 3-alkynyl-2-hydroxy cyclopropanol derivatives **5**.[a]



	Alkyne (**6**)	Product **5**	Yield [%][b]
1	PhC≡CH	 **5a**	77 (22)
2	*p*-MeOPhC≡CH	 **5b**	81 (18)
3	*p*-MePhC≡CH	 **5c**	77 (22)
4	*p*-BrPhC≡CH	 **5d**	64 (26)
5	*m*-ClPhC≡CH	 **5e**	70 (18)
6		 **5f**	55 (7)
7		 **5g**	72 (11)
8		 **5h**	64 (18)
9	$PhCH_2CH_2C\equiv CH$	 **5i**	60 (7)
10	1-hexyne	 **5j**	63 (15)

[a] Unless otherwise noted, all reactions were carried out at the 0.5 mmol scale in THF at −40 °C for 4 h, with the ratio of **1**/**6**/**2** = 1:3.5:5.4. [b] The figure in the parentheses is the % yield of compound **4**.

Table 3. The reaction of different aldehydes, ketone with enolate **2** and lithium alkynilide.[a]



	Reactant **7**	Product **9**	*syn*/*anti*	Yield [%][b]
1			2.3:1[c] (**9a**)	63 (21)
2			2.3:1[c] (**9b**)	69 (26)
3			2.3:1[c] (**9c**)	65 (22)
4	R=NO_2	**9a** R^3=Ph, **9b** R^3=4-MePh, **9c** R^3=3-ClPh, **9d** R^3=Ph$(CH_2)_2$	1.9:1[c] (**9d**)	53 (13)
5			2.3:1[d] (**9e**)	65 (16)
6		**9e** R^3=Ph, **9f** R^3=4-MePh	2:1[d] (**9f**)	66 (18)
7			2.3:1[c] (**9g**)	63 (22)
8	R=Cl	**9g** R^3=Ph, **9h** R^3=4-MePh	1.5:1[c] (**9h**)	67 (16)
9			2:1[d] (**9i**)	74 (17)
10		**9i** R^3=Ph, **9j** R^3=4-MePh	1.8:1[d] (**9j**)	77 (16)
11			1.5:1[d] (**9k**)	57 (25)
12		**9k** R^3=Ph, **9l** R^3=4-MePh	1.5:1[d] (**9l**)	60 (28)
13[e]		**9m**	**9m**	40 (50)
14[f]		**9n**	2:1[d] (**9n**)	20 (53)

[a] Unless otherwise noted, all reactions were carried out at the 0.5 mmol scale in THF at −40 °C for 4 h, with the ratio of **7**/**6**/**2** = 1:2.4:3.4. [b] The figure in the parentheses is the % yield of compound **8**. [c] The *syn*/anti ratio was determined by ^{1}H NMR spectroscopy. [d] The *syn*/anti ratio was determined by the separated yields. [e] The ratio of **7**/**6**/**2** = 1:2.1:8.0. [f] The ratio of **7**/**6**/**2** = 1:1.2:4.8.

hydes, ketones, and aliphatic aldehydes, were also examined.[9] The optimal reaction conditions were slightly modified according to different substrates to get a higher conversion.[9] All these results are summarized in Table 3. While utilizing various aromatic aldehydes as electrophile, as shown, almost all of the alkynyl-substituted 1,3-diol products were obtained in a moderate to good yield with the *syn*/*anti* ratio ranging from 1.5:1 to 2.5:1.[10] The heterocyclic furan-2-carbaldehyde underwent the consecutive nucleophilic addition to give the desired product with the highest yield (Table 3, entry 10). Coupling of aromatic ketone or aliphatic aldehyde with enolate **2** and lithium alkynilide provided the corresponding diols in relatively low yields (table 3, entries 13 and 14).

Propargylic alcohol derivatives are important synthetic intermediates in organic synthesis. Multiple functionalities in compound **5** and **9** would make them even more versatile as structural motifs for further elaboration. As shown in Scheme 3 (top), reduction of the triple bond in **5a** by Pd/C hydrogenation, followed by Lewis acid induced cyclopropane fragmentation, provides a keto–oxepane product **11** in 40% yield (Equation c).[11] Meanwhile, **9f** was treated with $AuCl_3$ in CH_2Cl_2 at room temperature to yield a dienone product **12** in 45% yield, which can be used to construct dihydropyridine and pyridine derivatives. (Scheme 3, bottom).[12]

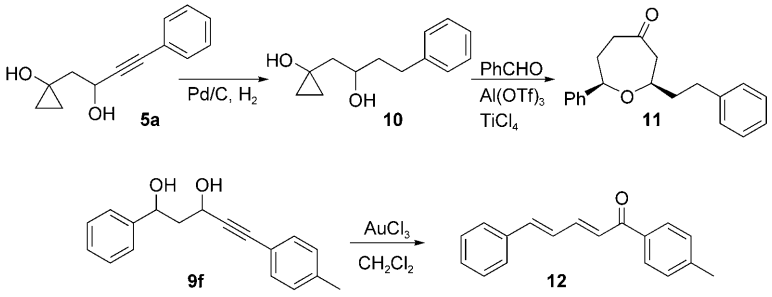
In conclusion, we have developed an efficient one-pot process to construct a series of polyfunctionalized propargylic alcohol derivatives from the simple materials without functional protection. A variety of electrophiles including cyclopropanone, and aromatic aldehydes have been successfully employed in the reaction. Further study to broaden the applicability of the new methodology and to explore its synthetic utility is in progress.

Experimental Section

Preparation of the solution of the lithium enolate of acetaldehyde (2) in THF: A solution of *n*BuLi in hexane (1.93 mL, 2.8 m) was added into dry THF (6 mL) by syringe; the resulting solution was then maintained at RT for 3 h. After the brown color disappeared, the freshly prepared lithium enolate of acetaldehyde (**2**) was used directly in the following reaction.

General procedure for the preparation of 1-(2-hydroxy-but-3-ynyl) cyclopropanol (5): *n*BuLi (1.25 mL, 2.8 m) was added over a period of 30 min by syringe to a solution of terminal alkyne (3.5 mmol) in THF (10 mL) at −30 °C. The freshly prepared enolate **2** and a solution of 1-(benzenesufonyl)cyclopropanol 1 (99 mg, 0.5 mmol) in THF (5 mL) was then added successively at −70 °C. After the reaction was stirred for 4 h at a temperature below −40 °C, saturated NH_4Cl (10 mL) was added slowly to quench the reaction. Usual workup followed by flash chromatography over silica gel gave compound **4** (petroleum ether(PE)/ethyl acetate(EA) = 30:1) and diol derivative **5** (PE/EA = 20:1).

General procedure for the preparation of alkynyl-substituted 1,3-diol derivatives 9: *n*BuLi (0.4 mL, 2.8 m in hexane) was added over a period



Scheme 3. Further transformation of compound **5a** and **9f**

of 30 min by syringe to a solution of terminal alkyne (1.05 mmol) in THF (10 mL) at −30 °C. The freshly prepared enolate **2** and a solution of the phenylacetaldehyde **7a** (0.5 mmol) in THF (5 mL) was then added successively at −70 °C. The reaction was maintained below −40 °C for 4 h. Then, saturated NH_4Cl (10 mL) was added slowly to quench the reaction. The usual workup and removal of solvents, followed by flash chromatography over silica gel gave **8** (PE/EA = 30:1) and the desired 1,3-diols compound **9** (PE/EA = 10:1).

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Keywords: cyclopropanone · nucleophilic addition · propargylic alcohol · tandem reactions

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[9] Optimization of the reaction conditions is summarized in the Supporting Information.
[10] The "1,3-syn dihydroxy" stereochemistry of the product **9aa** (major isomer in **9a**) were deduced from the NOE correlation spectrum of 1,3-dioxane derivative of **9aa**, see the Supporting Information for the details.
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