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C-Alkynylation of Cyclopropanols

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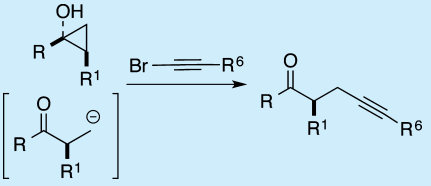
Supporting Information

ABSTRACT: Alkynylation of cyclopropanols with 1-bromo-1-alkynes has been devised for easy access to synthetically useful alk-4-yn-1-ones. This method broadens the utility of attractively functionalized cyclopropanols as a new class of homoenolate equivalent in C−C bond formation.

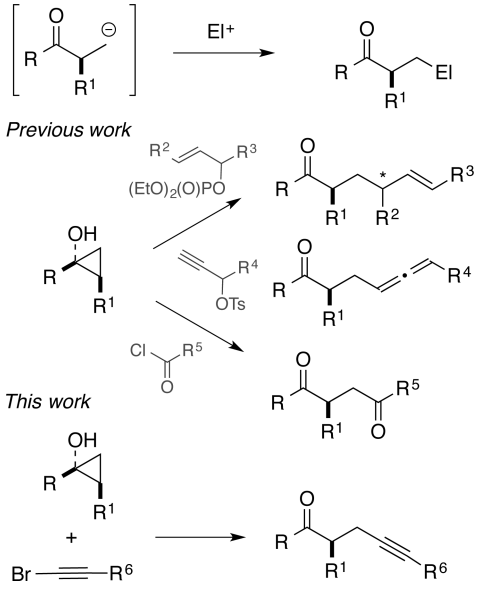


Alkylation of ketones, esters, and other carboxylic acid derivatives is a staple of frequently utilized C−C bond-forming reactions. Asymmetric alkylation reactions of carboxylic acid derivatives are typically achieved under the aegis of chiral auxiliaries.[1,2] Recent advances in organocatalysis offer a convenient method for enantioselective alkylation of aldehydes.[3] Analogous C−C bond formation of homoenolates gives a useful alternative but has received less attention. Previous work was limited primarily to homoenolates bearing less electrophilic esters, amides, and nitriles.[4] The keto homoenolates are prone to cyclize to the corresponding cyclopropoxides, thus requiring a more demanding balance between stability and reactivity for applications to C−C bond formation. Keto homoenolates are more advantageous than ester homoenolates for the rapid assembly of two large segments.

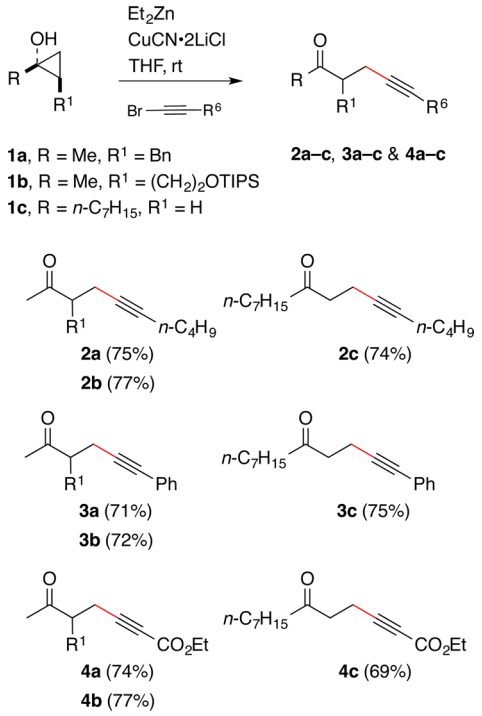
We recently combined ring opening of readily available cyclopropanols[5] with transmetalation to shift the otherwise unfavorable equilibrium for in situ generation of β-keto homoenolates. Specifically, we first developed S_N2' alkylation of cyclopropanols with allylic halides or propargylic sulfonates and C-acylation of cyclopropanols.[6] We report herein facile alkynylation of cyclopropanols with 1-bromo-1-alkynes for the preparation of alk-4-yn-1-ones to broaden the utility of cyclopropanols as a homoenolate equivalent (Scheme 1).

Cross-coupling of cyclopropanols with readily available bromoalkynes[7] was next chosen to utilize cyclopropanols as a new class of attractively functionalized keto homoenolates. The use of bromoalkynes or alkynyliodoniium salts as electrophilic alkynes was well documented in combination with various

Scheme 1. Homoenolate Alkylation and Acylation



Scheme 2. Alkynylation of Cyclopropanols 1a−c



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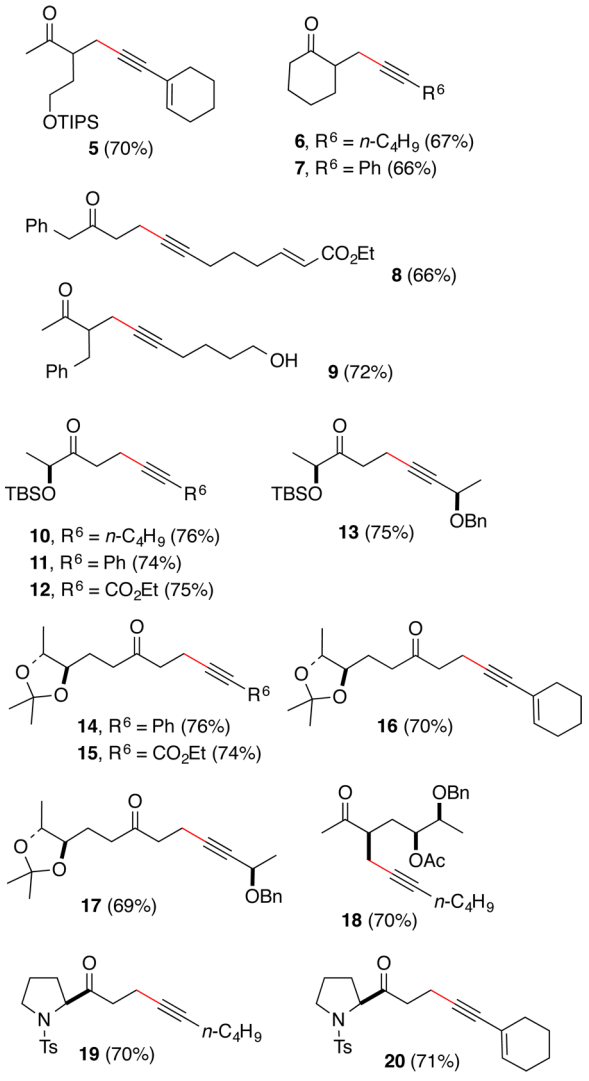
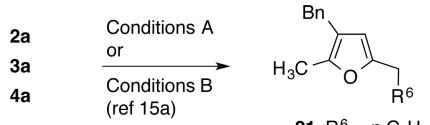


Figure 1. Additional examples of alkynylation.

nucleophiles, including mixed zinc−copper reagents,[8] for C−C and C−heteroatom bond formation.[9−11] Notwithstanding the aforementioned S_N2' alkylation and *C*-acylation reactions of cyclopropanols, the reactivity profile of cyclopropanols as a homoenolate equivalent in the C−C bond formation remains to be fully defined.[12] Additionally, the resulting adducts, γ-alkynones, have long been known to be valuable intermediates for organic synthesis. The juxtaposition of the keto and alkyne functionalities in alk-4-yn-1-ones is well suited for elaboration, especially in light of recent progress in gold- and platinum-catalyzed transformations of alkynes.[13]

By adaptation of coupling reaction conditions for S_N2' alkylation of cyclopropanols, a THF solution of cyclopropanol **1a** was treated at rt with commercially available Et_2Zn, followed by CuCN·2LiCl and 1-bromo-1-hexyne, to yield the expected coupling product **2a** in 75% yield (Scheme 2). Both Et_2Zn and CuCN·2LiCl were required, and in their absence, a complex mixture was found with no alkynylation product. Substituents on 1-bromo-1-alkynes exerted little influence: irrespective of the nature of R^6 (an alkyl, phenyl, or ester group), the resultant γ-alkynones **2a**, **3a**, and **4a** were isolated in comparable yields. Similarly, the alkynylation reactions of cyclopropanols **1b** and **1c** proceeded cleanly. Additional examples show a wide substrate scope and compatibility with common functional

Scheme 3. Preparation of Furans from γ-Alkynones

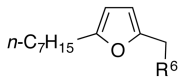


Conditions A:
p-TsOH (1.2 equiv)
toluene, 85 °C
Conditions B:
Ph_3PAuCl (2 mol %), AgOTf (2 mol %)
p-TsOH (0.05 equiv)
toluene, rt

21, R^6 = *n*-C_4H_9
22, R^6 = Ph
23, R^6 = CO_2Et
24, R^6 = H

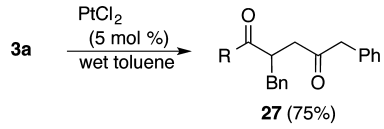
entry	alkynones	conditions	time (h)	product(s)/ yield (%)
1	**2a**	**A**	5.5	**21** (75)
2	**3a**	**A**	7	**22** (33)[a]
3	**3a**	**B**	1.5	**22** (70)
4	**4a**	**A**	12	**23** (70)[b,c]
5	**4a**	**B**	1	**23** (90)

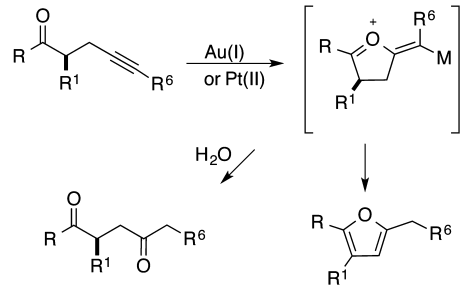
a. recovered **2a** (60%); *b*. Decarboxylation also occurred to give **24** (28%); c. At 110 °C (7 h) was obtained a mixture of **23** (9%) and **24** (83%).



25, R^6 = CO_2Et (72%)
26, R^6 = Ph (83%)

Scheme 4. Elaboration of γ-Alkynones





groups, such as an enyne and an α,β-unsaturated ester (e.g., **12**, **15**, **16**, and **20**), under mild conditions (Figure 1). An alcohol substituent (e.g., **9** from 6-bromo-5-hexyn-1-ol) is also tolerated and can thus be introduced without a protecting group. Also included is the convenient preparation of enantiopure adducts **10**−**20**.

As for synthetic applications, cyclization of the γ-alkynone adducts to furans was selected in part owing to the utility of attractively substituted furans.[14] Furans are embedded in a number of natural products and have been employed as useful intermediates in organic synthesis. Among a plethora of known methods for preparing furans, cyclization of γ-alkynones to furans is a reliable approach and has been effected under acidic or basic conditions, as well as by transition-metal-catalyzed cycloisomerization reactions.[15,16] The latter method allows easy preparation of furans under mild reaction conditions, but ready access to judiciously substituted γ-alkynones has been lacking.

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As shown in Scheme 3, the present method denotes a convergent, efficient route to both functionalized γ-alkynones and 2,5-disubstituted/2,3,5- trisubstituted furans.

Cyclization of **2a** took place smoothly under conventional acidic conditions (the use of *p*-TsOH) in toluene at 85 °C to give 2,3,5-trisubstituted furan **21** in 75% yield (Scheme 3, entry 1). The corresponding cyclization of **3a** having a phenylacetylene was significantly slower under identical conditions (Scheme 3, entry 2). An effective solution was found in Au(I) catalysis by the method of Krause to yield **22** in 70% yield at rt (Scheme 3, entry 3).[15a] When alkynoate **4a** was subjected to acidic conditions, formation of **23** (70%) was accompanied by that of **24** (28%) due to surprisingly facile decarboxylation of the former (Scheme 3, entry 4). A satisfactory result was again available by Au(I)-catalyzed cycloisomerization of **4a** (Scheme 3, entry 5). 2,5-Disubstituted furans **25** and **26** were also easily prepared from **4c** and **15** under similar conditions.

In addition to the aforementioned preparation of substituted furans, 1,4-diketones are readily accessible from γ-alkynones by employing wet toluene, as exemplified by the synthesis of **27** (Scheme 4). 1,4-Diketones have been utilized as a useful precursor to a number of structural motifs.[6b] A common intermediate is presumed to be involved in the formation of furans and 1,4-diketones.

In conclusion, a convenient cross-coupling reaction between cyclopropanols and 1-bromo-1-alkynes offers a versatile method for preparing attractively functionalized alk-4-yn-1-ones. Segment coupling is particularly useful for building a rapid increase in molecular complexity due to an expedient bond connection under mild conditions and with operational simplicity. Synthetic applications of chiral γ-alkynones, which capitalize on directing effects of resident stereocenters, are currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data for key intermediates. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01789.

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Notes

The authors declare no competing financial interest.

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