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Difunctionalization of Alkynones by Base-Mediated Reaction with α,α-Dithioketones

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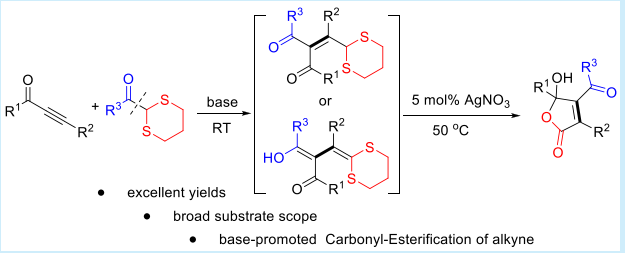
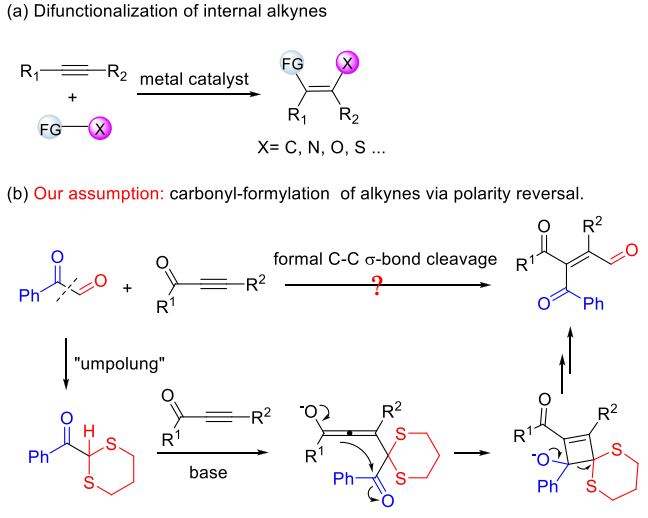
ABSTRACT: A novel 1,2-difunctionalization of alkynones via an umpolung strategy for the synthesis of tetrasubstituted olefins has been developed. This procedure is realized by a formal C−C σ-bond cleavage reaction of cyclic α,α-dithioketones and subsequent deprotection. Notable features of this approach include excellent yields, mild reaction conditions, a broad substrate scope, and operational simplicity.



Alkynes, one of the most prevalent classes of organic compounds, are widely used as building blocks for the synthesis of many functional materials and pharmaceutical molecules.[1] Arguably, among the various transformation reactions of alkynes, one-pot 1,2-difunctionalization of internal alkynes is an efficient approach for the synthesis of tetrasubstituted alkene derivatives, especially those bearing four functional groups (Scheme 1a).[2] Most of these reactions required transition metal catalysis. For instance, Gaunt's group creatively realized Cu-catalyzed electrophilic carbotriflation of alkynes to form highly substituted tetrasubstituted alkenyl triflates.[2a] A gold-catalyzed intermolecular difunctionalization of alkynes with aryl diazonium salts without any external oxidants and photosensitizers under visible-light irradiation

Scheme 1. Difunctionalization of Alkynes



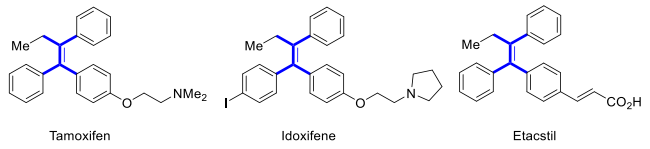


Figure 1. Biologically active compounds containing tetrasubstituted olefins.

was presented by Hashmi's group.[2b] In addition, a few studies concerning transition metal-free difunctionalization of internal alkynes have also been reported. For example, Greaney and co-workers developed the efficient metal-free aminoarylation of internal alkynes to yield tetrasubstituted enaminoates in a single step.[2c] A practical multicomponent synthesis of highly substituted vinyl ethers via iodo(III) etherification of alkynes with iodine(III) electrophiles and alcohols was disclosed by Yoshikai's group.[2d] Although great progress has been made in the past few decades, almost all of the reported alkyne difunctionalization reactions are simultaneous incorporations of two functional groups of opposite polarity onto the different carbon atoms of the C≡C bonds. In this context, installing two functional groups of the same polarity on the internal alkynes remains a challenge and has rarely been reported except with the help of transition metal catalysis.[3]

Carbonyl and formyl functional groups are important and are used flexibly for subsequent modification and transformations.[4] Thus, installing carbonyl and formyl groups

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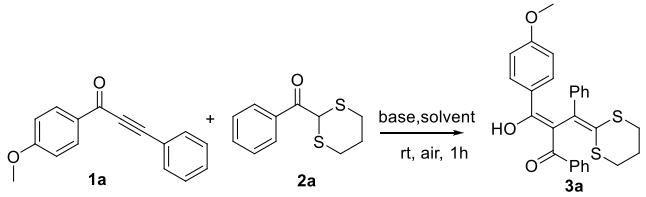
Table 1. Optimization of the Synthesis of 3a



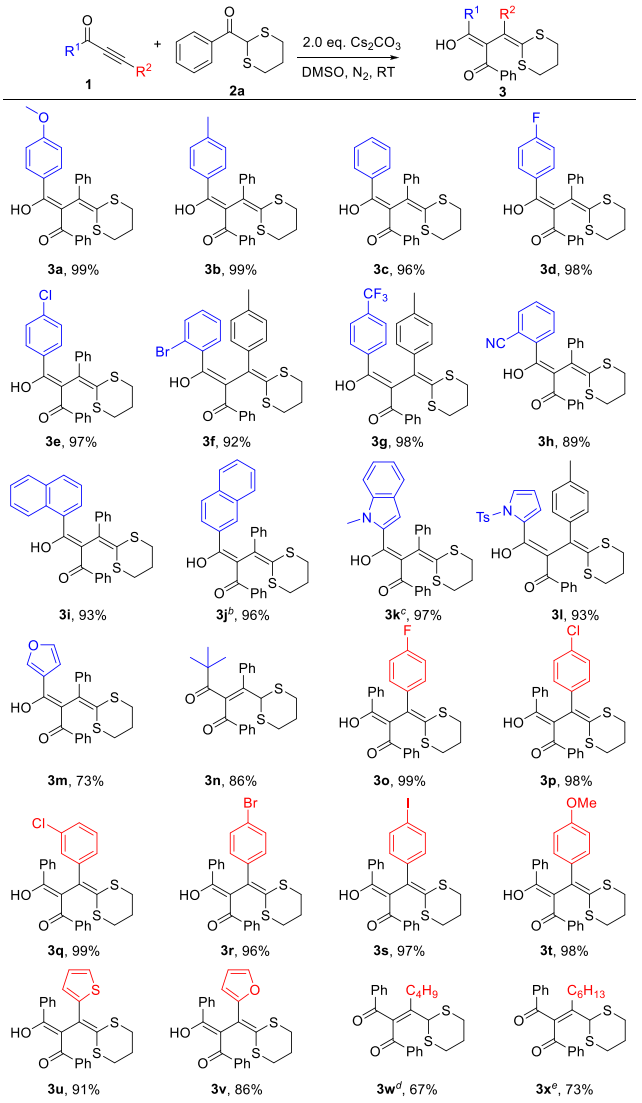
entry	1a:2a	base	solvent	yield[a,b] (%)
1	1:1	2.0 equiv of Cs_2CO_3	DMSO	76
2	1:1.2	2.0 equiv of Cs_2CO_3	DMSO	75
3	1:1	2.0 equiv of CsF	DMSO	20
4	1:1	2.0 equiv of K_2CO_3	DMSO	25
5	1:1	2.0 equiv of ^tBuOK	DMSO	72
6	1:1	2.0 equiv of Cs_2CO_3	DMSO	99[c]
7	1:1	2.0 equiv of Cs_2CO_3	DMF	67[c]
8	1:1	2.0 equiv of Cs_2CO_3	DMA	87[c]
9	1:1	2.0 equiv of Cs_2CO_3	toluene	NR[c,d]
10	1:1	1.5 equiv of Cs_2CO_3	DMSO	94[c]

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), solvent (2.0 mL), base, reaction in air, 1 h. [b]Isolated yields. [c]N_2. [d]No reaction.

simultaneously on the adjacent carbon atoms of C≡C bonds is very appealing, and they serve as a platform for producing various highly functionalized tetrasubstituted alkenes. However, installation of these groups is a great challenge because of their identical electrophilic character. Phenylglyoxal, an ideal bifunctional molecule containing both carbonyl and formyl groups, makes it possible to introduce carbonyl and formyl groups across C≡C bonds via formal C−C σ-bond cleavage reactions. Nevertheless, phenylglyoxal has rarely been examined as the bifunctional group source in organic synthesis despite its high reactivity. We considered trying to reverse the electronic property of the formyl carbon in phenylglyoxal through the strategy of polarity reversal, that is the protection of the formyl group with 1,3-dithiane,[5] because the 1,3-dithianes are usually regarded as precursors of sulfur-stabilized acyl anion equivalents (umpolung reactivity) and widely used as nucleophiles in alkylation, epoxide ring opening, and Michael addition reactions.[6] We envisaged that such protected phenylglyoxal might undergo nucleophilic attack to electron deficient alkynes such as alkynones, followed by intramolecular addition to the C═O bond of phenylglyoxal to give a cyclobutenol intermediate. In addition, ring opening of the cyclobutenol intermediate might give rise to difunctionalized alkynes bearing both carbonyl and thiolyl groups simultaneously (Scheme 1b). It is known that tetrasubstituted olefins have been widely explored for liquid crystal and materials research[7] and are found in many pharmaceutical compounds such as Tamoxifen,[8] idoxifene,[9] and etacstil[10] (Figure 1). We report herein a base-promoted 1,2-difunctionalization of alkynes via the C−C σ-bond cleavage reaction of cyclic α,α-dithioketones, which provides potential access to tetrasubstituted olefins.

To test our hypothesis, we carried out the investigation by employing 1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-one (**1a**) to react with (1,3-dithian-2-yl)(phenyl)methanone (**2a**) using Cs_2CO_3 as the base and DMSO as the solvent at room temperature (Table 1). The desired product **3a** was isolated in 76% yield (entry 1). According to ^1H NMR, the H signal of the enol−OH shifted to 17−18 ppm, indicating the formation of a hydrogen bond with the carbonyl oxygen. To further

Scheme 2. Scope of Alkynone 1 for the Bifunctionalization Reaction[a]



[a]Reactions were conducted by employing **1** (0.3 mmol) to react with **2a** (0.3 mmol) in 3 mL of DMSO with 2.0 equiv of Cs_2CO_3 at room temperature under N_2. Isolated yields. The isomer ratios were taken from the ^1H NMR spectrum. [b]Keto:enol ratio of 1:0.7. [c]Keto:enol ratio of 0.3:1. [d]Keto:enol ratio of 1:0.3. [e]Keto:enol ratio of 1:0.4.

optimize the reaction conditions, we screened other parameters systematically. The same yield of **3a** was obtained when the **1a**:**2a** was changed to 1:1.2 (entry 2). A survey of different bases was conducted, including CsF, K_2CO_3, and ^tBuOK, and the yields of **3a** all decreased dramatically (entries 3−5, respectively). An almost quantitative yield of the desired product **3a** was obtained when the reaction was conducted under a nitrogen atmosphere (entry 6). Conducting the reaction in solvents such as DMF, DMA, and toluene decreased the yield (entries 7−9, respectively). In addition, decreasing the loading of Cs_2CO_3 impaired this reaction with a lower yield of 94% (entry 10). On the basis of the experimental data presented above, 2.0 equiv of Cs_2CO_3 as the base and DMSO as the solvent at room temperature under a N_2 atmosphere proved to be the optimized reaction conditions.

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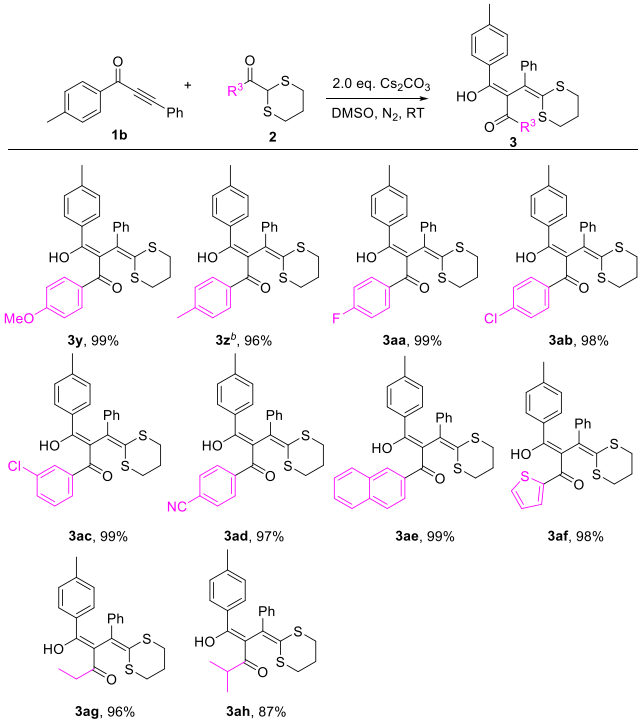
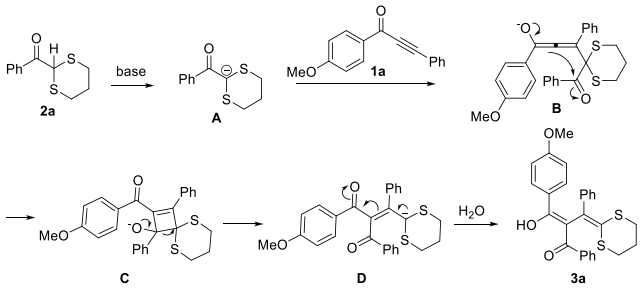
Scheme 3. Scope of α,α-Dithioketone 2 for the Bifunctionalization Reaction[a]



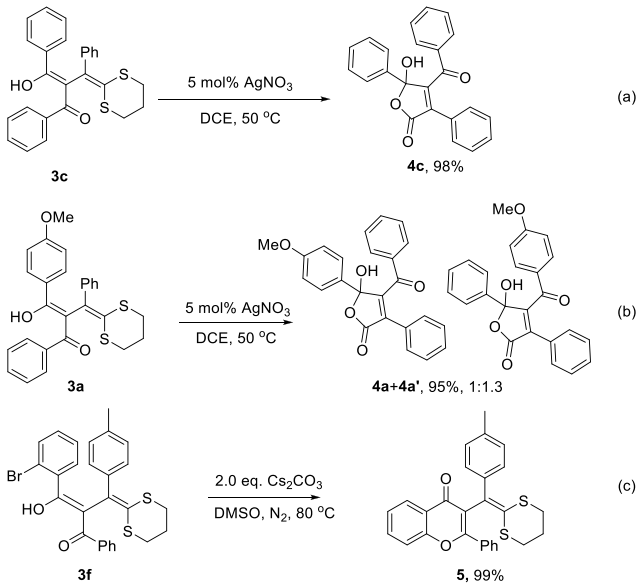
[a]Reactions were conducted by employing **1b** (0.3 mmol) to react with **2** (0.3 mmol) in 3 mL of DMSO with 2.0 equiv of Cs_2CO_3 at room temperature under N_2. Isolated yields. [b]Keto:enol ratio of 0.1:1. The isomer ratio was taken from the ^1H NMR spectrum.

Scheme 4. Possible Mechanism for the Formation of 3a



With the optimized conditions in hand (Table 1, entry 6), we investigated the substrate scope of ynones. As shown in Scheme 2, we explored ynones with different substituents (R^1) attached to the carbonyl and found that alkynones with both electron-donating and electron-withdrawing groups on the phenyl ring were compatible, offering excellent yields of the desired products **3a**−**3h**. X-ray crystallographic analysis unambiguously confirmed the structure of **3b** as a *Z* form in the enol form. Subsequently, the sterically demanding 1-naphthyl- and 2-naphthyl-substituted ynones were also explored and gave the corresponding products **3i** and **3j** with high yields of 93% and 96%, respectively. The ^1H NMR spectrum of **3j** showed that two isomers were obtained because of keto−enol isomerization. Notably, heteroaryl motifs such as *N*-methyl-2-indolyl, *N*-tosyl-2-pyrrolyl, and 3-furyl were well tolerated, providing products **3k**−**3m**, respectively. Even the alkyl R^1 substituent (^{t}Bu) worked well to furnish the desired product **3n**, albeit with a reduced yield. For R^2 substituents

Scheme 5. Transformations of Products



adjacent to the triple bond, various electron-withdrawing groups such as 4-F, 4-Cl, 3-Cl, 4-Br, and 4-I and an electron-donating group (4-OMe) introduced onto the aryl ring were all suitable substrates to produce **3o**−**3t** in high yields. Similarly, substrates with 2-thienyl and 2-furyl groups could also be employed in this transformation. An alkyl-substituted R^2 group (C_4H_9 and C_6H_{13}) also resulted in the corresponding products **3w** and **3x** in 67% and 73% yields, respectively.

Finally, the substituent scope of R^3 in the α,α-dithioketone was examined (Scheme 3). Various electron-withdrawing and electron-donating aryl groups were found to be suitable for this reaction, delivering good yields of the products (**3y**−**3ac**). Notably, the strong electron-withdrawing group CN could also be introduced into the desired product **3ad**. Dithioketones with naphthyl and thienyl substitution also provided the products **3ae** and **3af** in 99% and 98% yields, respectively. Alkyl-substituted R^3 groups (*n*-Pr and *i*-Pr) also worked smoothly, providing the corresponding products **3ag** and **3ah** in 96% and 87% yields, respectively.

On the basis of the literature precedent,[6] a possible mechanistic pathway for the formation of product **3a** is depicted in Scheme 4. First, dithioacetal **2a** is readily deprotonated to form carbanion **A** in the presence of a base, which subsequently attacks alkynone **1a** resulting in allene intermediate **B**. Following that, an intramolecular nucleophilic addition/four-membered ring-opening cascade occurs to provide intermediate **D**, which undergoes further hydrolysis to afford product **3a**.

To demonstrate the versatility of the strategy, further transformations of the products were carried out. At first, we tried to dethioacetalize the products. Due to the enol isomerization, the product **3c** mainly exists in an enol structure. As a result, under the hydrolysis condition, the corresponding carboxylic acid was produced and further nucleophilic addition gave the highly functionalized γ-hydroxybutenolide **4c**[11] (Scheme 5a). When the substituents R^1 and R^3 of substrates **1** and **2** were different, a mixture of two isomers (**4a** and **4a′**) was obtained (Scheme 5b). Indeed, γ-hydroxybutenolide is a vital core extensively found in natural products and bioactive molecules. At 80 °C, **3f** bearing an *o*-

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bromo-substituted phenyl ring could be converted to chromone derivative **5** almost quantitatively (Scheme 5c).

In summary, we have developed a versatile and highly efficient base-promoted alkyne difunctionalization reaction via the formal C−C σ-bond cleavage reaction of cyclic α,α-dithioketones. This reaction proceeds under mild conditions with a broad substrate scope, yielding tetrasubstituted olefins in excellent yields. This procedure represents the first example of installing two electrophiles on the triple bond simultaneously without transition metal catalysis with operational simplicity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01640.

Experimental procedures, characterization data, and spectroscopic data for all new compounds (PDF)

Accession Codes

CCDC 2081029 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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