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Oxidative difunctionalization of alkynoates via cascade radical addition, aryl migration, and decarboxylation

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ABSTRACT

A cascade radical oxidative difunctionalization of alkynoates with simple ethers for the construction of tri-substituted olefins is developed. The reaction undergoes cascade radical addition to C–C triple bond, 1,4-aryl migration, and decarboxylation to deliver a variety of difunctionalized alkenes in moderate to good yields. This procedure also represents a promising strategy for the direct functionalization of the α-Csp^3-H bonds in ether derivatives.

Introduction

Direct difunctionalization of alkynes has emerged as a promising and powerful approach for the construction of various valuable organic compounds due to its high efficiency in the cascade formation of carbon–carbon or carbon–heteroatom bonds.[1] For example, some excellent difunctionalization reactions such as sulfonylation,[2] oxysulfurization,[3] halogenation,[4] phosphorylation,[5] trifluoromethylation,[6] *ispo*-carboacylation,[7] etc, catalyzed by transition-metals or reacted under metal-free conditions have been developed delivering a series of functional derivatives. In this field, the difunctionalization of readily available alkynoates via cascade radical cyclization has been proved to be a fascinating strategy in the construction of 3-functionalized coumarins. Through 6-*endo*/5-*exo* cyclization, a variety of 3-phosphorated,[8] sulfonylated,[9] trifluoromethylated,[6c] thiocyanated,[10] and acylated[11] coumarins were obtained in good yields with excellent selectivity (Scheme 1a). Besides, alkynoates could also undergo radical oxidation-tandem cyclization/dearomatization in the presence of Langlois' reagent as the CF_3 radical source to synthesize 3-trifluoromethyl oxaspiro[4.5]trienones (Scheme 1b).[12a]

Construction of C–C bonds via direct C–H functionalization has drawn great attention during the recent decade owing to its step- and atom-economy with environmental sustainability. Among them, the direct functionalization of Csp^3-H bonds is an interesting while challenging task for their relatively strong bond dissociation energy (BDE) and the low polarity. Gratefully, radical reaction provides a promising avenue to the direct functionalization of inert Csp^3-H bonds, a lot of excellent results have been reported recently.[13] Simple ethers are important basic chemical feedstock and widely used solvents. Moreover, α-functionalized ether derivatives frequently exist in numerous biologically active molecules and natural products.[14] Thus, the direct functionalization of ethers becomes an urgent task. In other words, the α-C(sp^3)-H bonds of ethers are relatively weak and easy to generate α-carbon centered radicals under oxidative conditions.[15] Here, we reported our recent achievements in the α-functionalization of simple ethers with alkynoates as the radical acceptors to access tri-substituted olefins.

Results and discussion

Initially, phenyl 3-phenylpropiolate (**1a**) was chosen as substrate catalyzed by CuI in the presence of DTBP (di-*tert*-butyl peroxide) as the oxidant in THF under air at 110 °C to optimize the reaction conditions. To our surprise, neither coumarin derivative nor oxaspiro[4.5]trienone analogue was detected after 16 h, but an unexpected oil compound **3aa** was isolated in 62% yield. In fact, after GCMS and NMR analysis, we found that the obtained product was 2-diphenylvinyl tetrahydrofuran (**3aa**). Thus, the reaction must undergo aryl migration and decarboxylation process. Encouraged by this exciting result, we further optimized the reaction

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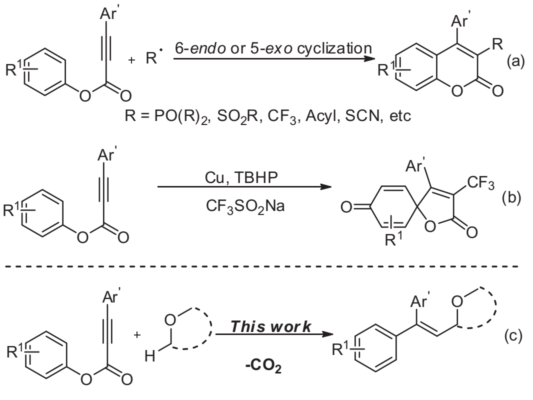
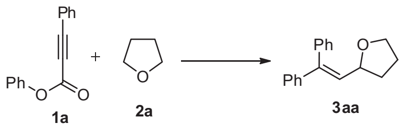


Scheme 1. Radical difunctionalization of alkynoates.

conditions and some of them are listed in Table 1. The results showed that, CuBr is a better catalyst than CuI, and **3aa** could be obtained in 78% yield. The reaction became sluggish if the amount of oxidant was decreased (Table 1, entry 2). Copper(II) catalyst, as $Cu(OAc)_2$ was inferior to CuBr. Control experiment indicated that, this aryl migration/decarboxylation process could proceed without copper-catalyst while in a low yield (Table 1, entry 4). Other common peroxides, such as TBHP, delivered only traces of the corresponding alkene (Table 1, entry 5) and the BPO resulted in lower yield (Table 1, entry 6).

With the optimized reaction conditions in hand, the scope of alkynoates was investigated as shown in Table 2. As expected, all substrates ran smoothly under the standard procedure to produce the corresponding tri-substituted alkenes in moderate to good yields (**3aa**–**3la**, Table 2). Halogen substituents such as F, Cl, and I could be well tolerated in this transformation to afford the desired products in 66–81% yields, respectively (**3ca**, **3da**, **3ea**, **sia**, **3ja**, and **3ka**, Table 2), providing more chance for further functionalization or modification of these compounds. Particularly noteworthy is the tolerance of iodo-in our procedure (**3ka**). Under the limits of detection, no deiodination or other related by-products were found in the crude reaction mixtures. The reaction was not sensitive to the electronic nature of the substituents on phenyls, for alkynoates with either electron-withdrawing or electron-donating substituent reacting smoothly. The steric hindrance has little influence on the reaction, for alkynoates with *meta*-substituted aryls, the yields of corresponding products were slightly lower than those with *para*-substituted ones (e.g., **3ea** vs **3da**, Table 2). Finally, substrates bearing different aryls were also employed to investigate the stereoselectivity of the reaction (**3ga**–**3la**, Table 2). The results showed that the reactions of those alkynoates afforded the corresponding stereoisomers mixtures, with the *E*/*Z* ratios nearly 1:1, as determined by ^{1}H NMR.

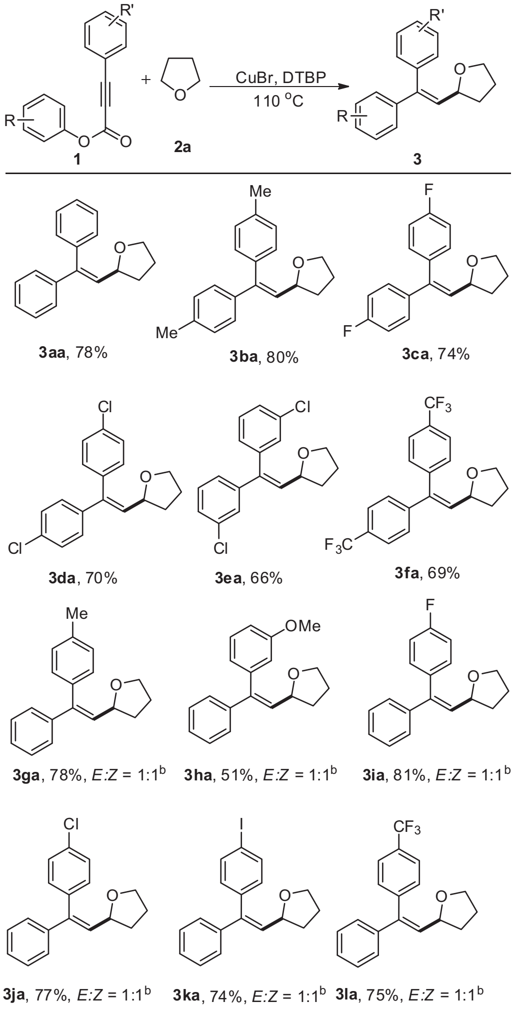
Table 1
The optimization of reaction conditions



Entry	Catalyst	Oxidant	Yield[a] (%)
1	CuI	DTBP	62
2	CuBr	DTBP	78(52)[b]
3	$Cu(OAc)_2$	DTBP	58
4	–	DTBP	32(39)[c]
5	CuBr	TBHP	Trace
6	CuBr	BPO	55

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (2 mL), catalyst (10 mol %) and oxidant (4 equiv) at 110 °C for 16 h. Isolated yields.
[b] DTBP (3 equiv).
[c] 40 h.

Table 2
Scope of the alkynoates[a]



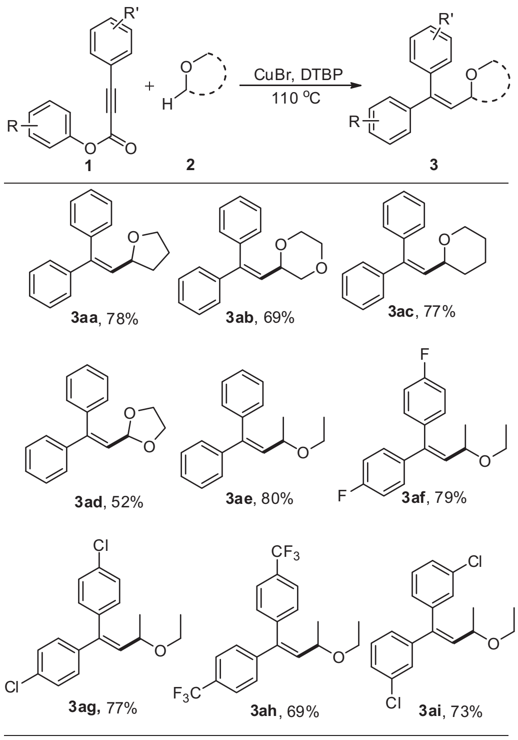
3aa, 78% **3ba**, 80% **3ca**, 74%
3da, 70% **3ea**, 66% **3fa**, 69%
3ga, 78%, *E*:*Z* = 1:1[b] **3ha**, 51%, *E*:*Z* = 1:1[b] **3ia**, 81%, *E*:*Z* = 1:1[b]
3ja, 77%, *E*:*Z* = 1:1[b] **3ka**, 74%, *E*:*Z* = 1:1[b] **3la**, 75%, *E*:*Z* = 1:1[b]

[a] Reaction conditions: **1** (0.2 mmol), **2a** (2 mL), CuBr (10 mol %) and DTBP (4 equiv) at 110 °C for 16 h. Isolated yields.
[b] Determined by ^{1}H NMR.

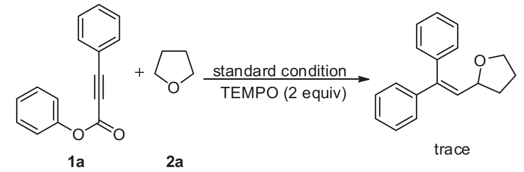
Owing to the diversity of ether compounds, we next investigated the applicability of various simple ether derivatives with different alkynoates in this transformation (Table 3). To our delight, common simple ethers such as 1,4-dioxane, tetrahydropyrane, 1,3-dioxolane, and diethyl ether all reacted smoothly with alkynoates to generate the corresponding alkenes in moderate to good yields (52–80% yields) (**3ab**–**3ae**, Table 3).

To gain some insights into the mechanism of the reaction, control experiments were carried out as shown in Scheme 2. When the radical scavenger, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added under the standard conditions, the reaction was obviously inhibited, which suggests a radical intermediate is involved (Scheme 2). Thus, the proposed reaction mechanism is outlined in Scheme 3. Firstly, copper(I)-promoted homolytic cleavage of DTBP gives *tert*-butoxyl radical,[15d,16] which abstracts one α-H from THF to generate radical intermediate **A**. Then the addition of radical **A** to the triple bond of alkynoate **1a** forms radical intermediate **B**. Next, the *ipso*-cyclization of **B** gives a spiro intermediate **C**.[12] Sub-

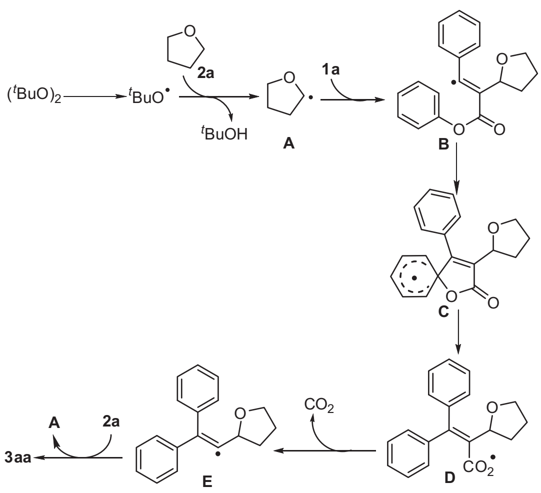
Table 3
Scope of the ethers[a]



[a] Reaction conditions: **1** (0.2 mmol), **2** (2 mL), CuBr (10 mol %), and DTBP (4 equiv) at 110 °C for 16 h. Isolated yields.



Scheme 2. Mechanism of study.



Scheme 3. Proposed mechanism.

sequent 1,4-migration of the aryl group on the ester moiety results in carboxyl radical **D**, which is ready to undergo the decarboxylative process with the release of CO_2 to afford radical intermediate **E**. Finally, hydrogen abstraction of **2a** by intermediate **E** produces the product **3aa** together with a radical intermediate **A** for the next cycle.

Conclusions

In summary, we have developed a radical cascade difunctionalization reaction of aryl alkynoates with ethers to access tri-substituted olefins through radical addition, aryl migration, and decarboxylation processes.[17] Different substituted alkynoates and various simple ethers all reacted well, leading to the corresponding tri-substituted olefins in moderate to good yields. This procedure gives a new avenue to the direct functionalization of the α-C (sp^3)-H bonds in ether derivatives.

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Supplementary data

Supplementary data (experimental details and the characterization data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.12.092.

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