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Oxidative Difunctionalization of Alkynoates through Alkylation and Migration Decarboxylative Arylation

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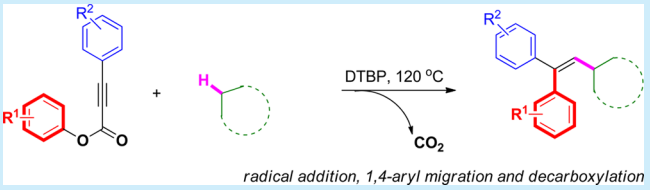
Supporting Information

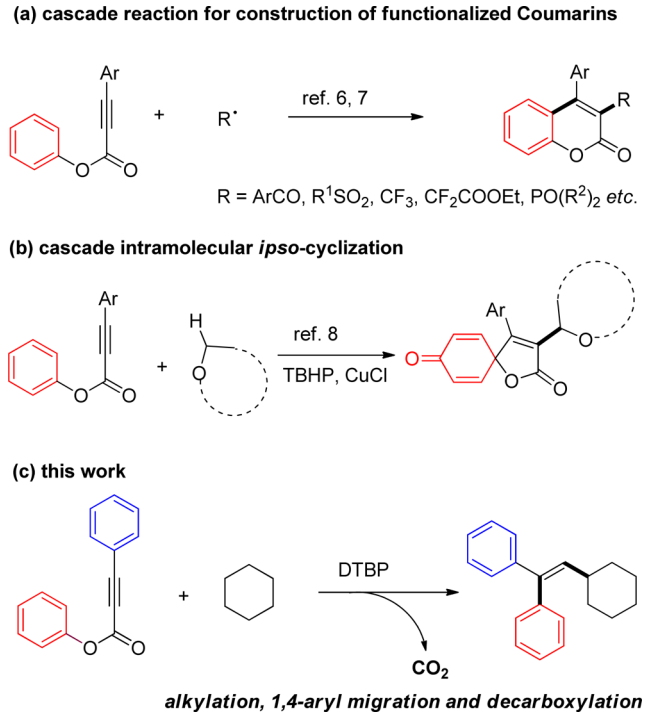
ABSTRACT: A cascade oxidative difunctionalization reaction of alkynoates for the construction of trisubstituted olefins has been developed. The process undergoes alkylation of a C−C triple bond, 1,4-aryl migration, and decarboxylation, which demonstrates a multistep radical cascade reaction for the difunctionalization of alkynoates and also represents a strategy of direct decarboxylation of esters.



The development of efficient methodologies for the construction of carbon−carbon bonds has become one of the most active areas in modern organic chemistry.[1] Radical-mediated functionalization of the sp^3 C−H bonds has been demonstrated to be a powerful and versatile tool for carbon−carbon formation to assemble molecules with a wide range of structural varieties.[2] In recent decades, significant achievements have been made in the area of C(sp^3)−H bond functionalization. In particular, such reactions show advantages in the synthesis of complex molecules, which may form multiple C−C bonds in one process. Many ingenious applications of such radical cascade reactions in the total synthesis of natural products have been well explored.[3]

Aryl alkynoate represents an important and extremely valuable synthetic block in organic synthesis. It is because that acetylene bond is a privileged motif, which can easily react with radical partners and allows the various introductions of different functional groups.[4,5] Furthermore, the site-specifically generated reactive radical intermediates could undergo cyclization reactions to construct functionalized heterocycles via intramolecular cross-coupling with sp^2 C of aromatic rings. In recent years, several examples have been developed on the related cascade reactions of aryl alkynoates. The first type, which was most studied, was cascade functionalization of an alkyne and subsequent cyclization with *ortho*-C(sp^2) on an aromatic moiety affording varieties of functionalized Coumarins (Scheme 1a).[6,7] Functionalization of an alkyne and *ipso*-cyclization represented the other type of reaction on alkynoates, which gave spiro compounds as target products (Scheme 1b).[8] Also, aryl alkynoates could undergo [2 + 2]-cycloaddition with ketene silyl acetals to give polysubstituted four-membered ring compounds with good yields.[9] However, to the best of our knowledge, alkylation of alkynoate triggers migration and decarboxylation of the ester moiety to assemble trisubstituted olefins has not been explored. Notably, Tunge and co-workers explored the relevant Pd-catalyzed allylation via decarboxylative coupling of ester.[10] The Gooßen group demonstrated the decarboxylative coupling of alcohols with oxalate esters.[11] Herein, we reported an unprecedented cascade radical difunctionalization reaction of alkynoates, which proceeds through alkylation with cycloalkanes, 1,4-aryl migration, and decarboxylation to afford trisubstituted olefins

Scheme 1. Reactions of Alkynoates



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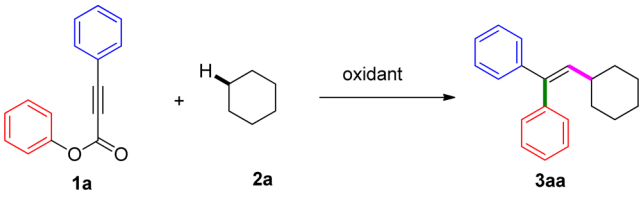
(Scheme 1c). This process contains one C−H, one C−O, and two C−C bond cleavages, along with two new C−C bond formations.

Our previous study showed that alkyl radicals could be easily in situ generated from the reaction of oxidant DTBP and alkanes.[12] Thus, we selected phenyl 3-phenylpropiolate **1a** and cyclohexane **2a** as model compounds to carry out the cascade reaction in the presence of 3.0 equiv of DTBP with cyclohexane (1.5 mL) as solvent at 120 °C for 24 h (entry 1, Table 1). The

Table 1. Optimization of the Reaction Conditions[a]



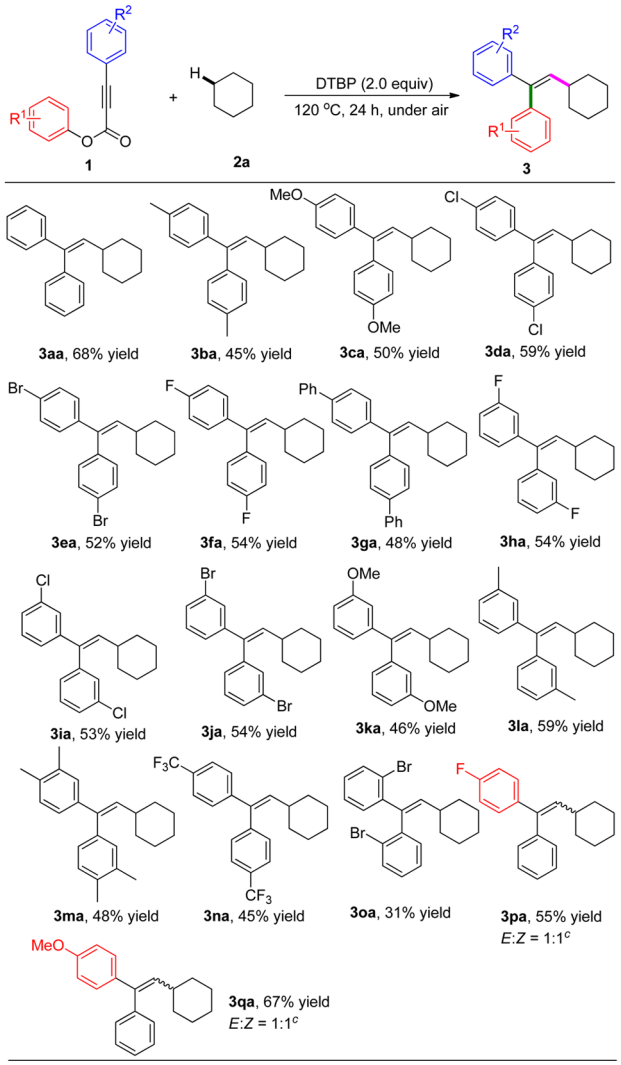
entry	oxidant (equiv)[b]	temp (°C)	t (h)	yield (%)[c]
1	DTBP (3.0)	120	24	43
2	TBHP (3.0)	120	24	9
3	TBPB (3.0)	120	24	34
4	$K_2S_2O_8$ (3.0)	120	24	trace
5	DCP (3.0)	120	24	19
6	H_2O_2 (3.0)	120	24	N.R.
7	DTBP (1.0)	120	24	30
8	DTBP (2.0)	120	24	58
9	DTBP (2.0)	120	48	55
10[d]	DTBP (2.0)	120	24	44
11[e]	DTBP (2.0)	120	24	68
12[e]	DTBP (2.0)	140	24	46
13[e]	DTBP (2.0)	120	24	trace[f]
14[e]	DTBP (2.0)	120	24	48[g]

[a]Reaction conditions: **1a** (0.2 mmol), cyclohexane **2a** (1.5 mL), oxidant under air. [b]DTBP: di-*tert*-butyl peroxide; H_2O_2: 30% aqueous solution; TBHP: *tert*-butyl hydroperoxide 5.5 M in decane; TBPB: *tert*-butyl peroxybenzoate; DCP: dicumyl peroxide. [c]Isolated yields based on **1a**. [d]1 mL of cyclohexane used. [e]2 mL of cyclohexane used. [f]20 mol % $Pd(OAc)_2$ was added. [g]20 mmol % $Cu(OAc)_2{\cdot}H_2O$ was added.

reaction could happen and afford the desired product **3aa** in 43% yield. To find the best oxidant, the reactions performed in the presence of different oxidants other than DTBP were investigated. Application of other oxidants, such as TBHP, TBPB, and DCP (entries 2, 3 and 5), was rather unsuccessful, as no improved yields were obtained. Even no desired product was found at all when $K_2S_2O_8$ or H_2O_2 was used for this reaction (entries 4 and 6). To further optimize the reaction conditions, the amount of cyclohexane, reaction time, and temperature were examined. Noticeably, 2.0 equiv of DTBP were sufficient for the completion of this reaction with increased yield (58%, entry 8). The results in entries 10 and 11 disclosed that 2 mL of cyclohexane were needed, and the best result was obtained (68% yield). It did not result in any improvement of the yield when prolonging the reaction time to 48 h or increasing the temperature to 140 °C (entries 9 and 12). Finally, the attempts to use metal catalysts, such as $Pd(OAc)_2$ (entry 13) and $Cu(OAc)_2$ (entry 14), were also unsuccessful. Even almost no product was detected when $Pd(OAc)_2$ was used.

With the optimized conditions in hand, we then set out to investigate the substrate generality of this radical reaction by using various types of alkynoates to react with cyclohexane **2a**. As presented in Scheme 2, this radical reaction showed a broad

Scheme 2. Reaction Scope of Aryl Alkynoates with Cyclohexane 2a[a,b]



[a]Reaction conditions: **1** (0.2 mmol), cyclohexane **2a** (2.0 mL), DTBP (2.0 equiv), at 120 °C under air for 24 h. [b]Isolated yields. [c]Determined by ^{1}H NMR.

substrate scope, and halo, methyl, and methoxyl groups could be well tolerated in this reaction to afford the expected substituted olefins with up to 68% chemical yield. The position of substituents on aromatic rings had an obvious effect on the results of the reactions, as the substrates with *para* and *meta* substituents gave the same level of yields (**3ea** and **3ja**, 52% and 54% respectively) while a dramatically lower yield was obtained from the substrate bearing an *ortho*-substituted aromatic ring (**3oa**, 25%). In general, the alkynoates with electron-withdrawing groups gave slightly better results (**3da**, **3fa**, **3ha**) compared with the alkynoates associated with electron-donating groups (**3ba**, **3ca**). Substrates bearing different aromatic rings were also employed to investigate the stereoselectivity of the reaction (**3pa**, **3qa**). Reactions of **3pa** and **3qa** afforded the products as a 1:1 mixture of stereoisomers. Finally,

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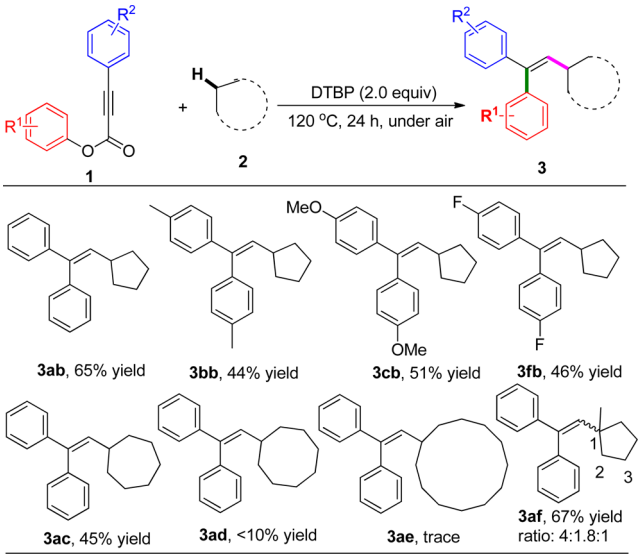
it should be mentioned that the starting materials remained in most cases of these reactions.

We then carried out the study of another line of substrate generality by using various cycloalkanes **2** (Scheme 3). Several

Scheme 3. Reaction Scope of Cycloalkane with Aryl Alkynoates[a,b]



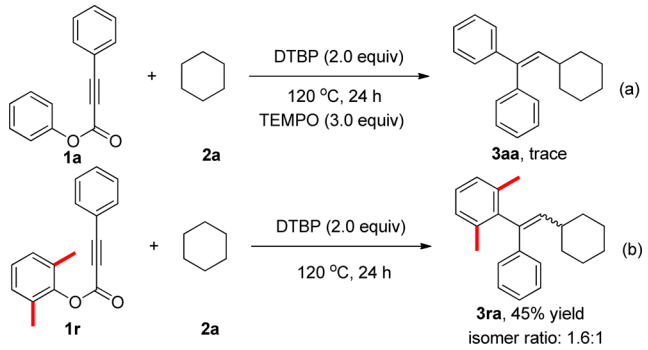
[a]Reaction conditions: **1** (0.2 mmol), cycloalkane **2** (2.0 mL), DTBP (2.0 equiv), at 120 °C under air for 24 h. [b]Isolated yields.

cycloalkanes have been employed to react with phenyl 3-phenylpropiolate **1a**. These radical reactions could afford the corresponding product **3** bearing five- (**3ab**) and seven-membered (**3ac**) rings with up to 65% yield. It is noteworthy that cyclopentane could also react smoothly with electron-rich (**1b** and **1c**) or electron-poor (**1f**) alkynoates to afford the expected products. Unfortunately, the yield decreased dramatically when the larger cycloalkanes were used as substrates, and almost no product was obtained at all in the case of cyclododecane (**2e**). The reaction also showed poor regioselectivity when the coupling partner cycloalkane contains several potential reaction sites (**2f**), and a mixture of regioisomers was obtained (**3af**, the ratio of mixture = 4:1.8:1).

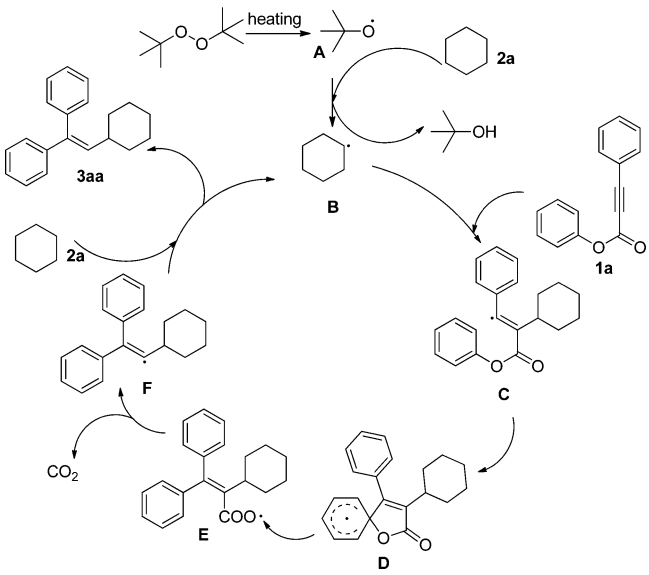
Then two control experiments were carried out to gain insight into the reaction mechanism. First, a reaction of **1a** and **2a** with the addition of radical-trapping reagent 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) under the standard conditions was performed, and the formation of desired product **3aa** was suppressed (Scheme 4a). This suggests the reaction might be a radical process. Interestingly, the reaction with aryl alkynoate with an *ortho*-occupied aromatic ring (**1r**) could also work well in this system to afford the expected product **3ra** in 45% yield (Scheme 4b), which implies that no neighboring group participation happens during the migration of the aryl group.

Based on the above experimental results and the previous reports,[7] a possible mechanism for the cascade radical reaction was proposed in Scheme 5. Initially, homolysis of DTBP generates *tert*-butoxy radical intermediate **A** under heating. Subsequent hydrogen abstraction of cyclohexane **2a** by a *tert*-butoxy radical affords cyclohexane radical intermediate **B**,[12] which adds to the C−C triple bond of alkynoates resulting in intermediate **C**.[7] Then, intermediate **C** undergoes *ipso*-

Scheme 4. Investigation of the Reaction Mechanism



Scheme 5. Proposed Mechanism



cyclization to give spiro intermediate **D**.[8] Subsequent migration of the aryl group on the ester moiety gives the carboxyl radical **E**, which is ready to undergo the decarboxylative process with release of the CO_2 to afford intermediate **F**. Finally, hydrogen abstraction of cyclohexane **2a** by the radical intermediate **F** gives the desired product **3aa** and cyclohexane radical intermediate **B** for next cycle.

In summary, we have explored an unexpected radical cascade difunctionalization reaction of aryl alkynoates which proceeded through cleavage of the sp^3 C−H bond of cycloalkanes, alkylation of alkynoates, 1,4-aryl migration, and decarboxylation. This complex radical process tolerated a wide range of substrates, affording trisubstituted olefins with moderate chemical yields. It is worth noting that this process involves one C−H, one C−O, and two C−C bond cleavages, along with two new C−C bond formations. This reaction also could be viewed as the direct decarboxylation of ester, which enriches the content of decarboxylative reactions. Further studies directed toward the development of new radical precursors for this system are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures, full spectroscopic data for compounds **3**, copies of ^{1}H NMR and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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