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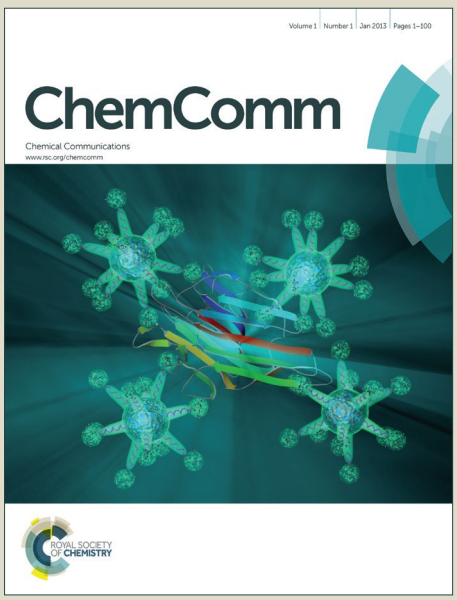

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ARTICLE TYPE

Synthesis of 3-Alkyl Spiro[4,5]trienones by Copper-Catalyzed Oxidative *ipso*-Annulation of Activated Alkynes with Unactivated Alkanes

Xuan-Hui Ouyang,[a] Ren-Jie Song,*[a] Bang Liu,[a] and Jin-Heng Li*[a]

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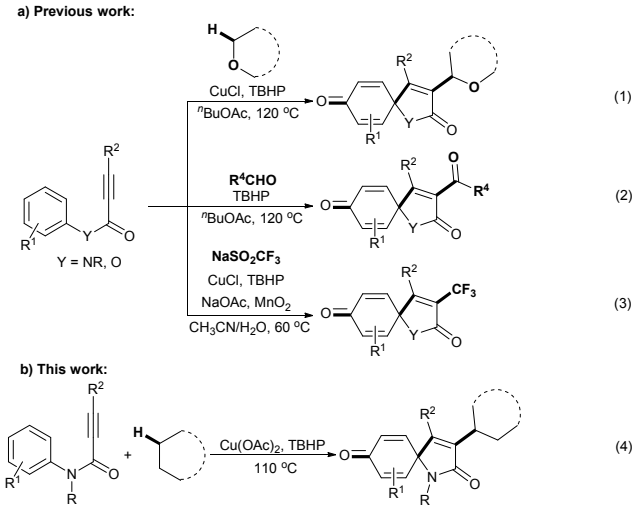
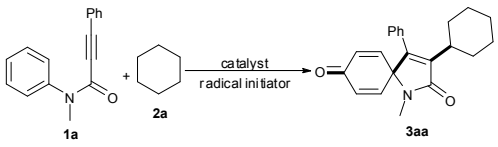
A Cu-catalyzed oxidative *ipso*-annulation of activated alkynes with unactivated alkanes for the synthesis of 3-alkyl spiro[4,5]trienones is described. This method allows the formation of two carbon-carbon bonds and one carbon-oxygen bond in a single reaction through a sequence of C-H oxidative coupling, *ispo*-carbocyclization and dearomatization.

Spirocyclohexadienones represent an essential part of the skeleton of numerous natural compounds and pharmaceuticals[1], as well as valuable intermediates in organic synthesis[1,2]. Generally, the spirocyclohexadienone structures are constructed via the oxidative spiro cyclization of phenol derivatives[3], transition-metal-catalyzed intramolecular nucleophilic *ipso*-carbocyclization of 5-(4-hydroxyaryl)-1-alkenes or 5-(4-hydroxyaryl)-1-alkynes,[4] and the electrophilic *ipso*-cyclization of 5-(4-methoxyaryl)-1-alkynes.[5] However, these transformations are restrict to a limited substrate scope, especially the attack functional reagents. Recently, attractive approaches for the synthesis of spirocyclohexadienones via the oxidative radical coupling strategy were developed (Scheme 1a). We have reported radical oxidative *ipso*-carbocyclization of alkynes with aldehydes or ethers for the synthesis of 3-substituted spiro[4,5]trienones (Eqs 1 and 2, Scheme 1).[8] Very recently, Liu, Liang and co-workers reported copper-catalyzed difunctionalization of activated alkynes leading to 3-trifluoromethly spiro[4,5]trienones *via* radical oxidation/tandem cyclization/dearomatization (Eq 3, Scheme 1).[9] Although only few approaches have been developed, this strategy would offer a new door for the incorporation of diverse attack functional reagents that extends beyond the existing transformations to access spirocyclohexadienones.



Scheme 1 Oxidative Radical Difunctionalization of Alkynes Leading to Spiro[4,5]trienones.

Table 1 Screening of Optimal Conditions[a]



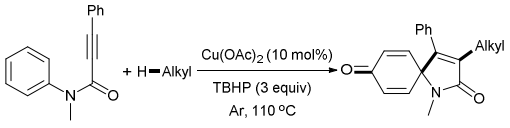
Entry	[Cu]	[O] (equiv)	T [°C]	Yield (%)[b]
1	$Cu(OAc)_2$ (10)	TBHP (3)	110	57 (82)
2	$CuCl_2$ (10)	TBHP (3)	110	30 (80)
3	CuOAc (10)	TBHP (3)	110	22 (76)
4	Cu_2O (10)	TBHP (3)	110	28 (59)
5	CuI (10)	TBHP (3)	110	20 (62)
6	$Cu(acac)_2$ (10)	TBHP (3)	110	trace
7	$Cu(OAc)_2$ (10)	—	110	0
8[c]	$Cu(OAc)_2$ (10)	TBHP (3)	110	8 (81)
9	$Cu(OAc)_2$ (10)	DTBP (3)	110	11 (73)
10	$Cu(OAc)_2$ (10)	TBPB (3)	110	28 (68)
11	$Cu(OAc)_2$ (10)	DCP (3)	110	28 (70)
12	$Cu(OAc)_2$ (10)	$K_2S_2O_8$ (3)	110	0
13	$Cu(OAc)_2$ (10)	TBHP (2)	110	41 (77)
14	$Cu(OAc)_2$ (10)	TBHP (5)	110	53 (81)
15	$Cu(OAc)_2$ (5)	TBHP (3)	110	45 (69)
16	$Cu(OAc)_2$ (15)	TBHP (3)	110	53 (79)
17	$Cu(OAc)_2$ (10)	TBHP (3)	130	55 (81)
18	$Cu(OAc)_2$ (10)	TBHP (3)	80	23 (87)

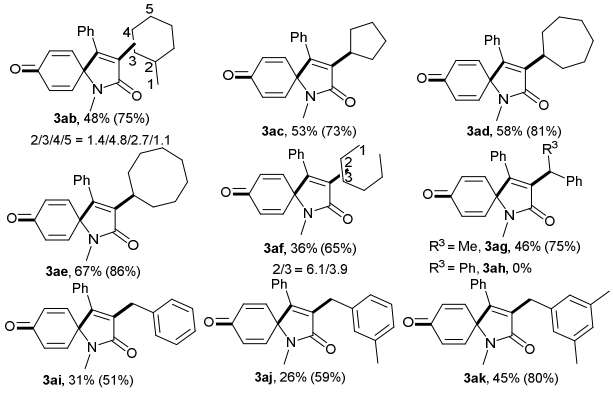
[a] Reaction conditions: **1a** (0.2 mmol), [Cu], oxidant and cyclohexane **2a** (1 mL) for 36 h under argon atmosphere. The number in parentheses is the yield based on recovered starting materials. DTBP = di-*tert*-butyl peroxide, TBHP = *tert*-butyl hydroperoxide (5M in decane), TBPB = *tert*-butyl peroxybenzoate, DCP = dicumylperoxide. [b] Isolated yield. [c] TBHP (70% in water) was added.

Direct C(sp^3)-H functionalization for the construction of C-C bonds has emerged as an efficient and straightforward method in modern organic synthesis.[6] Despite recent efforts, the establishment of general and mild strategies for the engagement of unreactived C(sp^3)-H bonds in C-C bond forming reactions still remains a formidable challenge.[7] To the best of our knowledge, approach for the difunctionalization of activated alkynes with unactivated simple alkanes to generate spiro[4,5]trienones has never been reported. Herein, we report a copper-catalyzed oxidative difunctionalization of activated alkynes with unactivated alkanes to 3-alkyl spiro[4,5]trienones *via* a C-H oxidative radical coupling, *ispo*-carbocyclization and dearomatization tandem process (Eq 4, Scheme 1).

Our investigation began with oxidative difunctionalization of activated alkynes with unactivated alkanes in the presence of catalytic amount of copper salt and oxidant. (Table 1). In the presence of $Cu(OAc)_2$ and TBHP, *N*-methyl-*N*,3-diphenylpropiolamide **1a** successfully underwent the *ipso*-annualtion reaction with cyclohexane **2a**, furnishing the desired 3-cyclohexyl-1-methyl-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione **3aa** in 57% yield (entry 1). Encouraged by these results, a series of other Cu salts, namely $CuCl_2$, CuOAc, Cu_2O, CuI and $Cu(acac)_2$ were tested (entries 3-7): all the copper salts showed catalytic activity, but they were less effective than $Cu(OAc)_2$ (entry 1 *vs* entries 2-6). It should be noted that no detectable amounts of product **3aa** was observed in the absence of oxidant (entry 7). A number of other oxidants, such as TBHP (70% in water) DTBP, TBPB, DCP and $K_2S_2O_8$, were subsequently examined, and they were less effective than DTBP (entry1 *vs* entries 8-12). Further, $K_2S_2O_8$ had no effect the reaction (entry 12). Screening on the amount of TBHP and $Cu(OAc)_2$ reaveled that combined 10 mol% of $Cu(OAc)_2$ with 2 equivalents of TBHP gave the best results (entry 1*vs* entries 13-16). Finally, the effect of reaction temperature were investigated: higher reaction temperature (at 130 °C) did not improve the yield compared with the results at 110 °C (entry 17), but lower temperature (at 80 °C) dramatically reduced the yield (entry 18).

Table 2 Scope of Alkanes (**2**)[a]

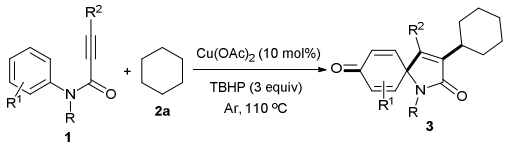


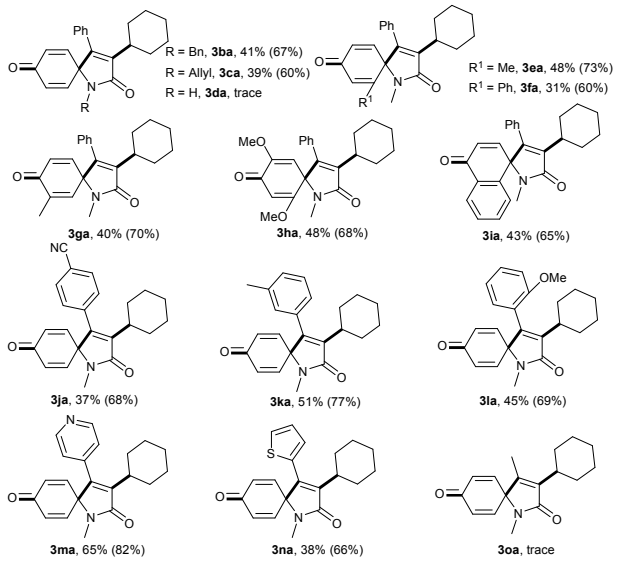


[a] Reaction conditions: **1a** (0.2 mmol), $Cu(OAc)_2$ (10 mol%), TBHP (3 equiv, 5 M in decane) and **2** (1 mL) at 110 °C under argon atmosphere for 36 h, isolated yield. The number in parentheses is the yield based on recovered starting materials.

With the optimal conditions in hand, the substrate scope of this Cu-catalyzed tandem reaction of alkanes **2** with respect to *N*-methyl-*N*,3-diphenylpropiolamide **1a** was first investigated (Table 2). In the presence of $Cu(OAc)_2$ and TBHP, a variety of cycloalkanes, such as methylcyclohexane **1b**, cyclopentane **1c**, cycloheptane **1d**, cyclooctane **1e** could successfully reacted with *N*-methyl-*N*,3-diphenylpropiolamide **1a**, allowing easy access to the corresponding products **3ab-ae** in moderate yields. For example, the reaction between *N*-methyl-*N*,3-diphenylpropiolamide **1a** and cyclooctane **2e** successfully generated product **3ae** in 67% yield. Gratifyingly, a straight-chain alkane **2f** was found to be viable for the reaction, providing the product **3af** in 36% yield. Notably, ethylbenzene **2g** was tested under the optimal conditions, affording the corresponding product 1-methyl-4-phenyl-3-(1-phenylethyl)-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione **3ag** in 46% yield. Unfortunately, diphenylmethane **2h** was not a suitable substrate more because of the steric effect. Furthermore, toluene derivatives showed good compatibility (Products **3al-ak**).

Table 3 Scope of *N*-Arylpropiolamides (**1**)[a]



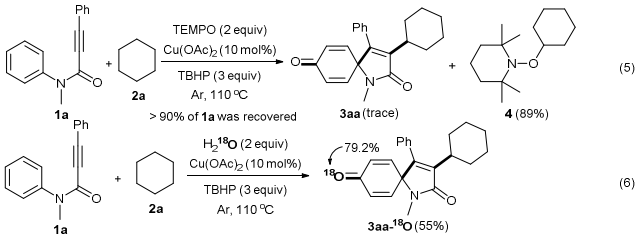


[a] Reaction conditions: **1** (0.2 mmol), $Cu(OAc)_2$ (10 mol%), TBHP (3 equiv, 5 M in decane) and cyclohexane **2a** (1 mL) at 110 °C under argon atmosphere for 36 h. The number in parentheses is the yield based on recovered starting materials.

We next examined the scope of various propiolamides **1** for this oxidative C(sp^3)-H functionalization/*ispo*-carbocyclization tandem reaction under the standard reaction conditions. As shown in Table 3, we are pleased to find amides with *N*-Bn or *N*-allyl were viable substrates for the reaction (Products **3ba-ca**), but a *N*-H group resulted in no reaction. Subsequently, the substitutes effect of the *N*-aryl moiety was investigated. *N*-Arylpropiolamideswith Me, Ph or OMe groups were well-tolerated, affording the corresponding 3-alkyl spiro[4,5]trienonesin moderate yields (Products **3ea-ha**). For example, amides **1e** and **1g** with a Me group at the *ortho* or *meta*

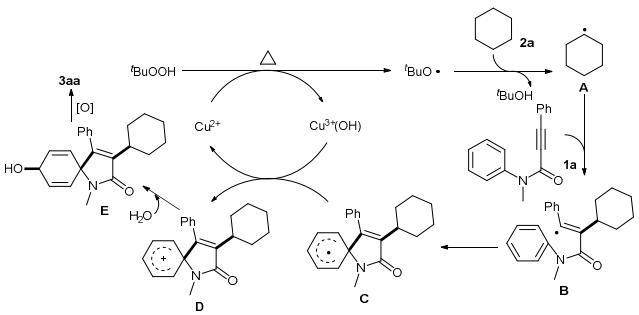
position successfully underwent the tandem transformation, furnishing the desired products **3ea** and **3ga** in 48% and 40% yield, respectively. Using naphthalene-derived substrate **1i**, 43% yield of 4'-cyclohexyl-1'-methyl-3'-phenyl-4*H*-spiro[naphthalene-1,2'-pyrrole]-4,5'(1'*H*)-dione **3ia** was isolated. Extensive screening revealed that electron-deficient or electron-rich substitutes gropus, including CN, Me, and OMe, on the aromatic ring at the terminal alkyne were tolerated well (Products **3ja-la**). Notably, the amides heteroaryl alkyne **1m** and **1n** reacted with cyclohexane **2a**, giving the desired products **3ma** and **3na** in 65% and 38% yield, respectively. Unfortunately, *N*-methyl-*N*-phenylbut-2-ynamide **1o** was not suitable substrate for the reaction.

To understand mechanism of the current reaction, a radical inhibitor, TEMPO (2,2,6,6-tetramethylpiperidinyloxyl), was added to the oxidative C(sp^3)-H functionalization/*ispo*-carbocyclization reaction (Scheme 2): Adding 2 equiv of TEMPO completely inhibited the conversion of *N*-arylpropiolamides **1a**; However, substrate **2a** was treated with TEMPO to form 1-(cyclohexyloxy)-2,2,6,6-tetramethylpiperidine (**4**) in 89% yield (Eq 5 in Scheme 2). It is indicated that the radical process might be involved in this reaction. In addition, treatment of substrate **1a** with cyclohexane **2a**, $H_2{}^{18}O$, $Cu(OAc)_2$ and TBHP afforded 79.2% ^{18}O-containing product, which were determined by GC-MS analysis, suggesting that the newly-formed oxygen atom is from water (Eq 6 in Scheme 2).



Scheme 2 Control Experiment.

Based on the above results and previous reports, we proposed a possible mechanism for this system (Scheme 3).[7-9] Initially, TBHP readily split into *tert*-butoxy radicals in the presence of $Cu(OAc)_2$ under heating conditions. Abstraction of a C-H bond in cyclohexane **2a** was subsequently by the *tert*-butoxy radical to yield alkyl radical **A**. Addition of the radical **A** to the C≡C bond of *N*-arylpropiolamide **1a** results in the formation of radical intermediate **B**, which upon intramolecular *ipso*-cyclization gives radical intermediate **C**. oxidation of intermediate **C** by the Cu^{III} species forms cation intermediate **D**. Finally, nucleophilic addition and oxidation of intermediate **D** with H_2O and TBHP takes place to afford 3-alkyl spiro[4,5]trienones **3aa**.



Scheme 3 Possible Mechanism.

Conclusions

In summary, we have illustrated the first copper-catalyzed C-H oxidative coupling and *ispo*-cyclization of *N*-arylpropiolamides with unactivated alkanes for the synthesis of 3-alkyl spiro[4,5]trienones using TBHP oxidant. This method achieves alkyne difunctionalization through a sequence of C-H oxidative coupling, *ispo*-carbocyclization and dearomatization, and represents a new shortcut to one-step formation of two C-C bonds and one C-O double bond. Applications of this method in organic synthesis are currently underway in our laboratory.

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Notes and references

[a] *State Key Laboratory of Chemo/Biosensing and Chemometrics, College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, China; E-mail: srj0731@hnu.edu.cn and jhli@hnu.edu.cn*

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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