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Access to 3-(2-Oxoalkyl)-azaspiro[4.5]trienones *via* Acid-Triggered Oxidative Cascade Reaction through Alkenyl Peroxide Radical Intermediate

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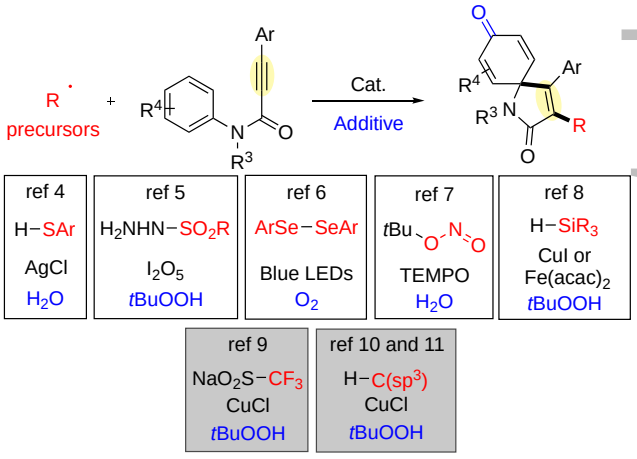
Abstract. Azaspiro[4.5]trienones bearing ketone side chains at the 3-position are prepared from *N*-alkyl-arylpropiolamides and ketones *via* oxidative 1,2-difunctionalization of alkynes. The cascade sequence starts with the generation of alkenyl peroxide intermediates, which are obtained by addition of *tert*-butyl hydroperoxide to ketones in presence of a catalytic amount of a strong acid. Then, the ketone radical adds to alkynes, followed by spirocyclization and dearomatization process. This method represents a new example of difunctionalization of alkynes with simultaneous formation of two carbon–carbon single bonds and one carbon–oxygen double bond in one step.

Keywords: Radical reaction; Cascade; Heterocycles; Ketones; Peroxides

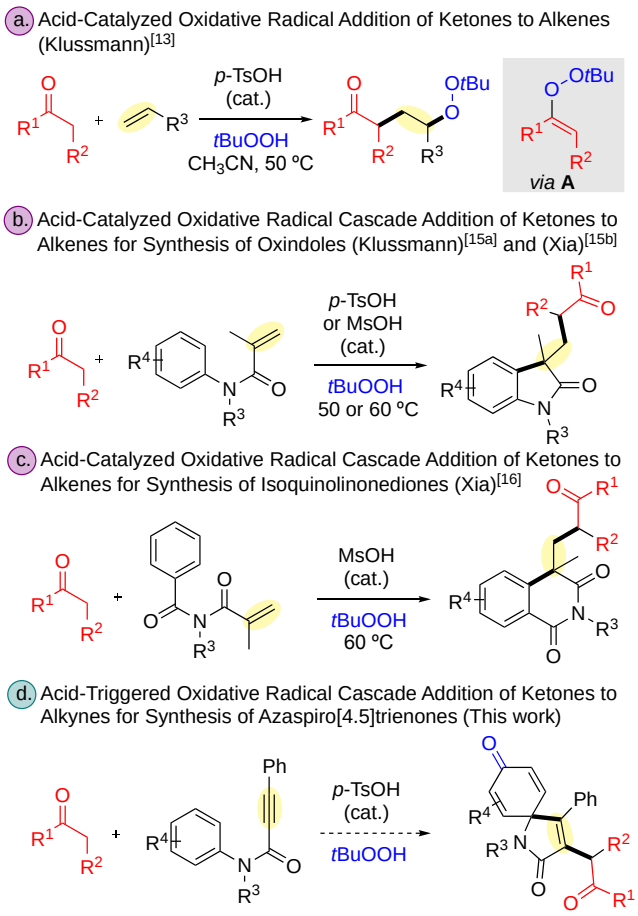
Spirocyclic compounds are important motifs embedded in many natural products, bioactive compounds and functional molecules.[1] Spiro[4.5]trienones, which are also valuable intermediates in organic synthesis, are often prepared *via* multi-steps synthesis.[2] One of the most efficient strategy for the construction of multiple bonds in a single operation involves 1,2-difunctionalization of unsaturated molecules,[3] including photoredox radical process.[4] Among them oxidative radical-mediated spirocyclization of *N*-arylpropiolamides has proven to be an attractive and straightforward method to access spiro[4.5]trienones in a single step (Scheme 1). For example, radical oxidation of thiols,[5] sulfonylhydrazides,[6] diaryl diselenide,[7] nitrite,[8] or silanes[9] gave formation of heteroatom-centered radicals, which added to alkynes followed by spirocyclization and dearomatization (Scheme 1). This procedure allowed the 1,2-difunctionalization of activated alkynes through the one-pot formation of C–heteroatom and C–C single bonds. However, there are only few reports focusing on the use of carbon-centered radicals, albeit it offers a direct synthesis of polycyclic compounds with the construction of two C–C single bonds. As examples, Liu and Liang have successfully employed Langlois' reagent (CF_3SO_2Na) as trifluoromethyl radical precursor in the synthesis of 3-trifluoromethylated azaspiro[4.5]trienones.[10] Alkyl radicals –generated by hydrogen abstraction process of ether[11] or cycloalkane C(sp^3)–H bonds[12] using Cu catalyst with *tert*-butyl hydroperoxide (*t*BuOOH)– have been also employed in those cascade reactions (Scheme 1).



Scheme 1. Previous Syntheses of Functionalized spiro[4.5]trienones *via* Oxidative Radical-Mediated Spirocyclization of *N*-Arylpropiolamides.

In 2014, Klussmann and co-workers reported acid-mediated 1,2-difunctionalization of alkenes with ketones and *tert*-butyl hydroperoxide (*t*BuOOH) (Scheme 2a).[13] The reaction involves the generation of ketone radical *via* the decomposition of alkenyl peroxide **A** –generated by the addition of *t*BuOOH to

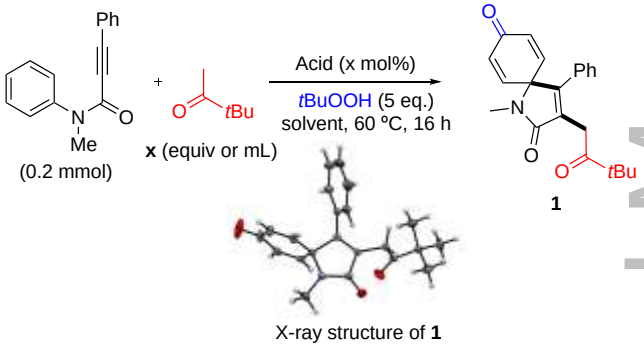
ketone catalyzed by acid– through homolytic bond O–O cleavage.[14] Independently, Klussmann's and Xia's groups have employed ketone radicals in cascade reaction. Indeed, after addition of ketone radical to alkene unit of *N*-aryl acrylamides, a radical cyclization affords oxindoles in good yields (Scheme 2b).[15] Xia and coworkers also reported a similar procedure for the preparation of isoquinolinonediones (Scheme 2c).[16] To the best of our knowledge, alkenyl peroxide intermediates have never been employed in addition of ketone radicals into alkynes, yet. In our continuous efforts to employ carbon-centered radicals in C–H bond functionalizations,[17] we decided to investigate the reactivity of ketones in presence of *t*BuOOH and activated alkynes such as *N*-arylpropiolamides in order to introduce at least two different functional groups into unsaturated molecules (Scheme 2d).



Scheme 2. Application of Alkenyl Peroxide Intermediates in Organic Synthesis.

We selected *N*-methyl-*N*,3-diphenylpropiolamide and pinacolone as model substrates (Table 1). In the presence of 10 mol% *p*-TsOH and *t*BuOOH (in decane solution) in acetonitrile at 60 °C, 3-(3,3-dimethyl-2-oxobutyl)-1-methyl-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (**1**) is obtained in a poor yield (entry 1). When the reaction is carried out without acid catalyst or peroxide, no reactions occurred (entries 2 and 3). The presence of oxygen has a deleterious effect on this cascade reaction (entry 4). The use of a larger amount of ketone (10 equiv.) allowed to improve the yield in **1** to 23% (entry 5). A better yield of 52% in **1** is obtained using pinacolone as reactant and solvent (0.2 mol/L) (entry 6). Aqueous solution of *t*BuOOH and other oxidants such as $(tBuO)_2$ or $PhI(OAc)_2$ are not successful (entries 7-9). *p*-TsOH outperformed other catalyst such as H_2SO_4, AcOH and Cu(OTf) (entries 10-12). A lower catalyst loading resulted in a lower yield, whereas a higher loading of 20 mol% failed to improve the yield (entries 13 and 14). Finally, a prolonged reaction time allowed to improve the yield up to 76% after 48 h (entries 14-16). The structure of **1** has been confirmed by X-ray analysis.[18] Interestingly, previous method to access azaspiro[4.5]trienones bearing ketone side chains at the 3-position involves oxidative ipso-annulation of specific substrates (i.e. *N*-(p-methoxyaryl)propiolamides with α-carbonyl alkyl bromides).[19]

Table 1. Optimization of the Reaction Conditions



X-ray structure of **1**

Entry	**x**	Acid (x)	Solvent	Yield in **1** (%)[a]
1	5 eq	*p*-TsOH (10)	CH_3CN	16
2	5 eq	–	CH_3CN	NR
3[b]	5 eq	*p*-TsOH (10)	CH_3CN	NR
4[c]	5 eq	*p*-TsOH (10)	CH_3CN	NR
5	10 eq	*p*-TsOH (10)	CH_3CN	23
6	1 mL	*p*-TsOH (10)	–	52
7[d]	1 mL	*p*-TsOH (10)	–	8
8[e]	1 mL	*p*-TsOH (10)	–	NR
9[f]	1 mL	*p*-TsOH (10)	–	NR
10	1 mL	H_2SO_4 (10)	–	40
11	1 mL	AcOH (10)	–	NR
12	1 mL	$Cu(OTf)_2$	–	6
13	1 mL	*p*-TsOH (5)	–	44
14	1 mL	*p*-TsOH (20)	–	52
15[g]	1 mL	*p*-TsOH (10)	–	68
16[h]	1 mL	*p*-TsOH (10)	–	82 (76)

[a] Determined by GC-analysis using *n*-dodecane as internal standard and isolated yield was shown in parentheses. [b] Reaction carried out without *t*BuOOH. [c] Reaction carried out under air atmosphere. [d] *t*BuOOH in water solution used instead of *t*BuOOH in decane. [e] $(tBuO)_2$ used instead

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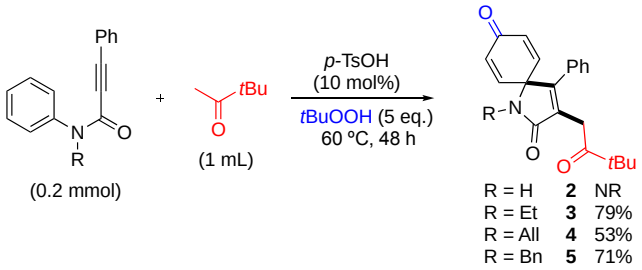
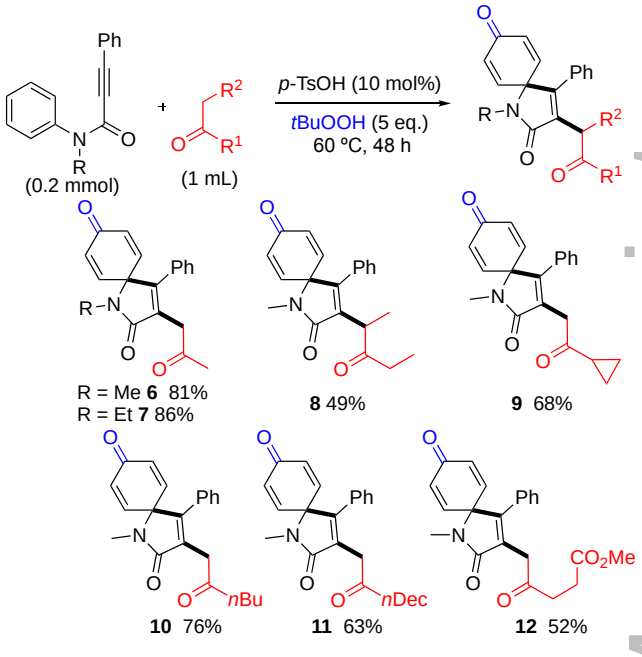
of *t*BuOOH in decane. [f] $PhI(OAc)_2$ used instead of *t*BuOOH in decane. [g] 24 h. [h] 48 h.

With the best conditions in hand, we then studied the effect of the nitrogen substituent on this acid-mediated oxidative radical cascade reaction (Scheme 3). From, non-substituted *N*,3-diphenylpropiolamide, no reaction occurred. The replacement of *N*-methyl by *N*-ethyl substituent has almost no effect as the azaspiro[4.5]trienones **3** is isolated in 79% yield. *N*,3-diphenylpropiolamide bearing a removal *N*-protecting group, e. g., *N*-allyl or *N*-benzyl, also reacted with pinacolone to give the corresponding 3-(3,3-dimethyl-2-oxobutyl)-azaspiro[4.5]trienones **4** and **5** in 53% and 71% yield, respectively without the cleavage of the *N*-protecting group.



Scheme 3. Effect of the *N*-Substituent of *N*-arylpropiolamides in Acid-Triggered Oxidative Cascade Addition – Spirocyclization – Dearomatization Process

Then, we investigated the reactivity of other ketones in this acid-mediated oxidative radical cascade reaction (Scheme 4). Acetone underwent cascade reaction with *N*-methyl-*N*,3-diphenylpropiolamide or *N*-ethyl-*N*,3-diphenylpropiolamide to afford the azaspiro[4.5]trienones **6** and **7** in good yields. Going from primary to secondary ketones, a decrease of reactivity is observed as the spirocyclization with diethyl ketone afforded the product **8** in only 49% yield. This lack of reactivity could be attributed to steric factors. Unsymmetrical 1-cyclopropylethan-1-one showed a preference for radical formation at the primary carbon, giving the corresponding cyclized product **9** in 68% yield. It is important to note that even under these radical conditions the cyclopropyl group remains intact at the end of the reaction. This observation, suggested that the formation of carbon-centered radical *via* the decomposition of alkenyl peroxide is faster at primary carbon than tertiary carbon. Other unsymmetrical ketones such as hexan-2-one or dodecan-2-one displayed the same trend of reactivity and selectively reacted at the primary carbon yielding the targeted compounds **10** and **11** in 76% and 63% yield, respectively. This spirocyclization cascade reaction is tolerant to ester group as from *N*-methyl-*N*,3-diphenylpropiolamide and methyl levulinate, a bio-sourced ketone, the cyclized product **12** is isolated in 52% yield. However, no reaction occurred when (substituted) acetophenones are employed as reactants owing such ketones have more pronounced radical cation characters (see supporting information for more details).[20]



Scheme 4. Scope of the Ketones in Acid-Triggered Oxidative Radical Cascade Addition – Spirocyclization – Dearomatization Process.

To further explore the scope of this radical cascade spirocyclization reaction, various substituted *N*-arylpropiolamides are investigated under the optimized reaction conditions with pinacolone as radical precursor (Scheme 5). Firstly, the impact of *ortho*-substituents on aniline unit of *N*-arylpropiolamide is investigated. When the cascade reaction is performed with *ortho*-C–halo (halo = F, Cl, Br) substituted substrates, the azaspiro[4.5]trienones **13-15** are obtained in moderate to good yields without cleavage of the C–halo bonds allowing further transformations. From *ortho*-phenyl substituted *N*-phenylpropiolamide the cascade reaction, **16** is obtained in 77% yield. The reaction is slightly sensitive to the steric effect. Indeed, from *N*-arylpropiolamides, in which the aniline moiety bears two electron-donating groups (e. g., Et or *i*Pr) at both *ortho*-positions, the corresponding cyclized products **17** and **18** are obtained in 42% and 54% yield, respectively. Bromo or even iodo atom at the *meta*-position of the aniline unit are also tolerated affording the desired products **19** and **20** in good yields. Notably, when the reaction is performed using a substrate with a methyl group attached to the triple bond, *N*-methyl-*N*-phenylbut-2-ynamide, the acid-

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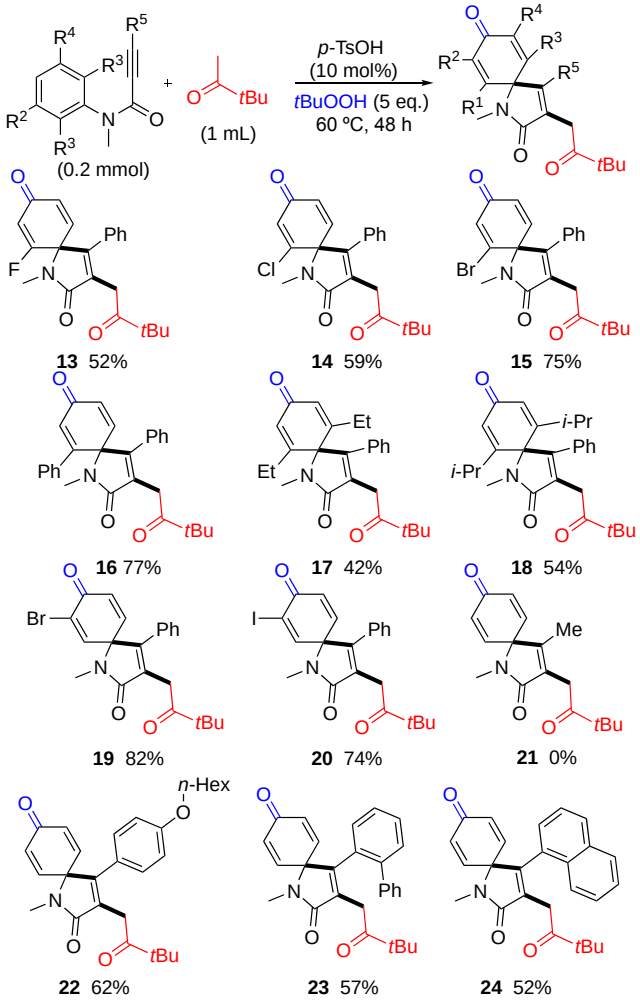
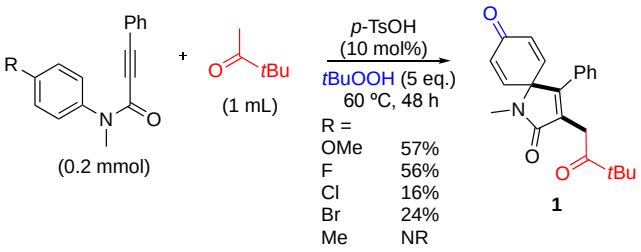
mediated radical cascade spirocyclization with pinacolone failed to deliver the corresponding azaspiro[4.5]trienone **21**. However, substituent on the aryl group attached to the triple bond are well-tolerated. As example *p*-hexyloxy substituted aryl alkyne delivered **22** in 62% yield, and *o*-phenyl-substituted aryl alkynes gave the corresponding product **23** in 57% yield. Naphthalen-1-yl alkyne was also viable to furnish **24**.



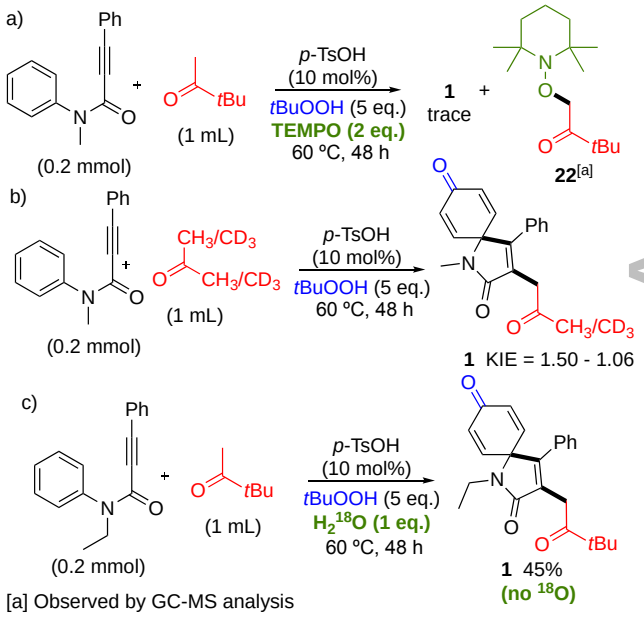
Scheme 5. Scope of the *N*-arylpropiolamides in Acid-Triggered Oxidative Radical Addition – Spirocyclization – Dearomatization Process

Interestingly, the reaction with *N*-arylpropiolamides containing an aniline unit substituted by a *para*-methoxy or a *para*-fluoro group afforded **1** in moderate yields (Scheme 6). Moreover, the reaction with substrates bearing a *para*-chloro or *para*-bromo substituent to the amide moiety also give **1**, albeit in a poor yield (16-24%). Whereas, no reaction occurred with substrates bearing a *para*-methyl substituent. We attributed these results to the addition of the *tert*-butylperoxy radical to the *para*-position of the phenyl group, forming a C–O bond and leading to cleavage of the C–OMe, or C–X (X = F, Cl, Br) bonds to yield MeOH, and HX, respectively, prior to final elimination of *t*BuOH to afford the desired products (Scheme 8).



Scheme 6. Reactivity of *N*-Arylpropiolamides Bearing a *para*-Substituent on the Aniline Unit in Acid-Triggered Oxidative Radical Cascade Addition – Spirocyclization – Dearomatization Proces.

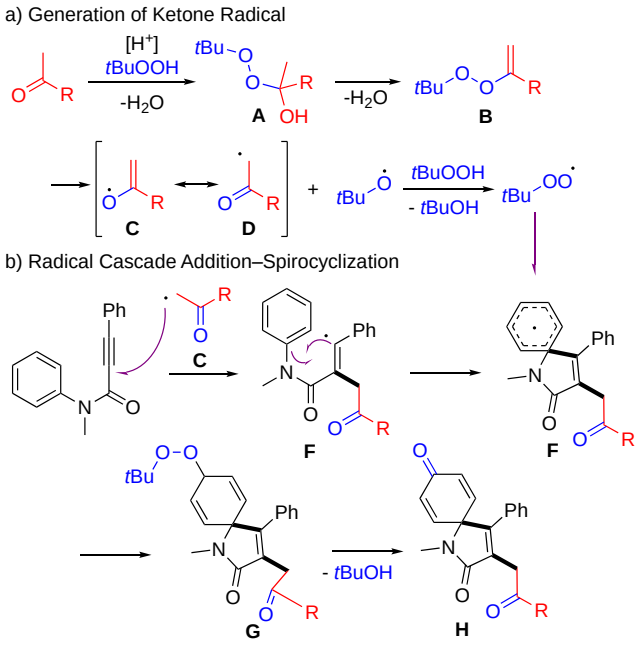
Several control experiments are carefully carried out to gain deep insight into the reaction pathway. Firstly, azaspiro-[4.5]trienone (**1**) is not observed when 2 equivalents of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), a radical scavenger, is added into the reaction system. However, the ketone-TEMPO adduct **22** is detected by GC-MS analysis. This observation confirms that the cascade spirocyclization involves ketone radical species (Scheme 7a). From (d_6)-acetone KIE values of 1.50-1.06 are determined from intermolecular competition reaction and from two parallel reactions.[21] These results indicate that the formation of carbon-centered radical *via* the decomposition of alkenyl peroxide is not the rate-determining step (Scheme 7b). Finally in the presence of 1 equivalent of water-^{18}O, the azaspiro-[4.5]trienone (**1**) is obtained in only 45% yield an no ^{18}*O*-labeled product was detected by GC-MS analysis (Scheme 7c). This labeling experiment indicated that the oxidation of aniline moiety mostly occurred *via* the action of *tert*-butylperoxy radical (*t*BuOO•) rather than a water attack.[10]



[a] Observed by GC-MS analysis

Scheme 7. Control Experiments

On the basis of this study and previous reports,[4-11] a plausible mechanism is proposed (Scheme 8). Firstly, in the presence of a strong acid (*p*-TsOH), alkenyl peroxide intermediate **B,** is formed after addition of *t*BuOOH to the ketone and dehydration. Then, the decomposition of alkenyl peroxide **B** through homolytic bond cleavage leads to ketone radical **D** and *t*BuO•, which latter reacts with *t*BuOOH to give *t*-BuOO• and *t*BuOH.[13a] A subsequent radical addition of **C** into the alkyne at the α-position of the C=O bond of *N*-arylpropiolamide generates vinyl radical **E**, which undergoes an intramolecular radical cyclization at the *ipso*-position to give **F.** **F** is then trapped by the *tert*-butylperoxy radical (*t*BuOO•) to afford **G**. Finally, **H** undergoes deprotonation and the elimination of *t*BuOH to afford the desired azaspiro-[4.5]trienone derivative and *t*BuOH.



Scheme 8. Proposed Mechanism for Acid-Triggered Oxidative Radical Addition – Spirocyclization – Dearomatization Process

In summary, we have developed metal-free conditions for the diflunctionalization of activated alkynes with ketones. The reaction enables radical cascade addition – spirocyclization – dearomatization process initiated by the formation of ketone radicals formation from ketones and *tert*-butyl hydroperoxide under acidic conditions. This one-pot cascade reaction give a straightforward access to 3-(2-oxoalkyl)azaspiro-[4.5]trienones, incorporating a spirocycle unit that is a common structural motif in many natural products and pharmaceuticals.

Experimental Section

General Procedure for Acid-Triggered Oxidative Radical Addition – Spirocyclization – Dearomatization Process: In an oven-dried 15 mL Schlenk tube, *N*, 3-diarylpropiolamide (0.2 mmol, 1.0 equiv.) and TBHP (1 mmol, 5.0 equiv.) (TBHP: 5.5M in the dodecane solution) were dissolved in degassed ketone (1 mL). Then, 4-methylbenzenesulfonic acid (0.02 mmol, 0.1 equiv.) was added under a stream of argon, and the reaction mixture was stirred at 60 ºC over 48 h. After evaporation of solvent, the product was purified using flash column chromatography on silica gel to afford desired azaspiro[4.5]trienone products.

Acknowledgements

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References

[1] a) A. S. Chawla, A. H. Jackson, *Nat. Prod. Rep.* **1989**, *6*, 55-66; b) D. Yugandhar, A. K. Srivastava, *ACS Comb. Sci.* **2015**, *17*, 474-481; c) Z. Jin, *Nat. Prod. Rep.* **2005**, *22*, 111-126; d) E. M. Antunes, B. R. Copp, M. T. Davies-Coleman, T. Samaai, *Nat. Prod. Rep.* **2005**, *22*, 62-72; e) Q. Arianna, *Curr. Med. Chem.* **2018**, *25*, 917-962.

[2] a) For reviews on the synthesis of spiro[4,5]decatrienones and related spirocyclic compounds, see: S. Rodríguez, P. Wipf, *Synthesis* **2004**, 2767-2783; b) S. Kotha, A. C. Deb, K. Lahiri, E. Manivannan, *Synthesis* **2009**, 165-193; c) S. P. Roche, J. A. Porco, *Angew. Chem. Int. Ed.* **2011**, *50*, 4068-4093; d) C.-X. Zhuo, W. Zhang, S.-L. You, *Angew. Chem. Int. Ed.* **2012**, *51*, 12662-12686.

[3] a) For reviews on 1,2-difunctionalization of unsaturated molecules, see: J. P. Wolfe, *Synlett* **2008**, 2913-2937; b) Y. Zhu, R. G. Cornwall, H. Du, B. Zhao, Y. Shi, *Acc. Chem. Res.* **2014**, *47*, 3665-3678; c) Y. Shimizu, M. Kanai, *Tetrahedron Lett.* **2014**, *55*, 3727-3737.

[4] a) For reviews on radical 1,2-difuntionalization of unsaturated compounds using photoredox systems, see: T. Courant, G. Masson, *J. Org. Chem.* **2016**, *81*, 6945-6952; b) T. Koike, M. Akita, *Chem* **2018**, *4*, 409-437; c) C.-S. Wang, P. H. Dixneuf, J.-F. Soulé, *Chem. Rev.* **2018**, *118*, 7532-7585.

[5] a) H. Cui, W. Wei, D. Yang, J. Zhang, Z. Xu, J. Wen, H. Wang, *RSC Adv.* **2015**, *5*, 84657-84661; b) P.-C. Qian, Y. Liu, R.-J. Song, J.-N. Xiang, J.-H. Li, *Synlett* **2015**, *26*, 1213-1216.

[6] J. Wen, W. Wei, S. Xue, D. Yang, Y. Lou, C. Gao, H. Wang, *J. Org. Chem.* **2015**, *80*, 4966-4972.

[7] H. Sahoo, A. Mandal, S. Dana, M. Baidya, *Adv. Synth. Catal.* **2018**, *360*, 1099-1103.

[8] X.-H. Yang, X.-H. Ouyang, W.-T. Wei, R.-J. Song, J.-H. Li, *Adv. Synth. Catal.* **2015**, *357*, 1161-1166.
[9] a) P. Gao, W. Zhang, Z. Zhang, *Org. Lett.* **2016**, *18*, 5820-5823; b) L.-J. Wu, F.-L. Tan, M. Li, R.-J. Song, J.-H. Li, *Org. Chem. Front.* **2017**, *4*, 350-353.
[10] H.-L. Hua, Y.-T. He, Y.-F. Qiu, Y.-X. Li, B. Song, P. Gao, X.-R. Song, D.-H. Guo, X.-Y. Liu, Y.-M. Liang, *Chem. Eur. J.* **2015**, *21*, 1468-1473.
[11] W.-T. Wei, R.-J. Song, X.-H. Ouyang, Y. Li, H.-B. Li, J.-H. Li, *Org. Chem. Front.* **2014**, *1*, 484-489.
[12] X.-H. Ouyang, R.-J. Song, B. Liu, J.-H. Li, *Chem. Commun.* **2016**, *52*, 2573-2576.
[13] a) B. Schweitzer-Chaput, J. Demaerel, H. Engler, M. Klussmann, *Angew. Chem. Int. Ed.* **2014**, *53*, 8737-8740; b) B. Schweitzer-Chaput, T. Kurtén, M. Klussmann, *Angew. Chem. Int. Ed.* **2015**, *54*, 11848-11851.
[14] For a review on alkenyl peroxide chemistry, see: M. Klussmann, *Chem. Eur. J.* **2018**, *24*, 4480-4496.
[15] a) E. Boess, S. Karanestora, A.-E. Bosnidou, B. Schweitzer-Chaput, M. Hasenbeck, M. Klussmann, *Synlett* **2015**, *26*, 1973-1976; b) X.-F. Xia, S.-L. Zhu, M. Zeng, Z. Gu, H. Wang, W. Li, *Tetrahedron* **2015**, *71*, 6099-6103.
[16] S.-L. Zhu, P.-X. Zhou, X.-F. Xia, *RSC Adv.* **2016**, *6*, 63325-63330.
[17] a) Y. Li, C. Wang, F. Zhu, Z. Wang, J.-F. Soulé, P. H. Dixneuf, X.-F. Wu, *Chem. Commun.* **2017**, *53*, 142-144; b) C.-S. Wang, T. Roisnel, P. H. Dixneuf, J.-F. Soulé, *Org. Lett.* **2017**, *19*, 6720-6723; c) C.-S. Wang, X.-F. Wu, P. H. Dixneuf, J.-F. Soulé, *ChemSusChem* **2017**, *10*, 3075-3082.
[18] CCDC 1859585; Cambridge Crystallographic Data Centre.
[19] M. Li, R.-J. Song, J.-H. Li, *Chin. J. Chem.* **2017**, *35*, 299-302.
[20] M. Sena, J. M. Riveros, *Chem. Eur. J.* **2000**, *6*, 785-793.
[21] E. M. Simmons, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2012**, *51*, 3066-3072.

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