A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition

GDCh

Chemie

www.angewandte.org

Accepted Article

Title: Acetonitrile Activation: An Effective C2 Cyclization Unit

Authors: Ning Jiao, Qixue Qin, Xiao Luo, Jialiang Wei, Yuchao Zhu, Xiaojin Wen, and Song Song

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201900947
Angew. Chem. 10.1002/ange.201900947

Link to VoR: http://dx.doi.org/10.1002/anie.201900947
http://dx.doi.org/10.1002/ange.201900947

WILEY-VCH

10.1002/anie.201900947

WILEY-VCH

COMMUNICATION

Acetonitrile Activation: An Effective C2 Cyclization Unit

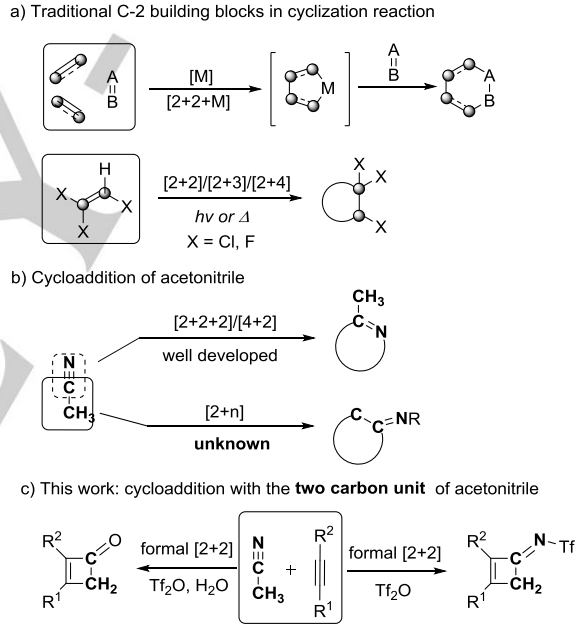
Qixue Qin, Xiao Luo, Jialiang Wei, Yuchao Zhu, Xiaojin Wen, Song Song, Ning Jiao*

Abstract: A novel acetonitrile activation for construction of cyclobutenones via [2+2] cyclization is developed. Acetonitrile is utilized for the first time as C2 cyclization building block. The present protocol successfully inhibits the competitive cycloaddition with the C≡N triple bond, but enables the *in situ* formation of unsaturated carbon-carbon bond and the subsequent cycloaddition as a C2 unit. This chemistry features simple reaction conditions, high chemoselectivities, wide substrate scopes, and offers a new and practical approach to cyclobutenones and cyclobuteneimines.

Of the various types of reactions, cyclization and cycloaddition reactions have been widely used in synthetic chemistry for the construction of (hetero)cyclic compounds.[1] C2 unit presents a versatile synthon for direct incorporation of two carbon chain in cyclization reactions. In the past decades, the simplest and abundant two-carbon molecules, ethylene,[2] acetylene[3] have been employed as C2 building blocks for the formation of small- and medium-sized cyclic compounds especially through cyclometallation reactions (Scheme 1a). Despite their significance, the direct incorporation of ethylene or acetylene into cyclic compounds is still very limited[4] due to the gas-phase reactants. Alternatively, trihaloethenes[5] were used as C2 building block in cycloaddition reactions, such as Diels-Alder reactions,[6] [2+2] cycloaddition[7] and 1,3-Dipolar cycloaddition[8] (Scheme 1a). However, the toxicity and the multiple-step preparation of trihaloethene substrates restrict their further application. For example, 1,1,2-trichloroethene has been classified as human carcinogen.[9] Furthermore, most of the cycloaddition processes still require harsh conditions or photo-irradiation with the generation of halogenated products. Therefore, it is highly attractive and very challenging to develop new reagents that could be used as a mild C2 building block in cycloaddition reactions.

Due to its abundance, low cost and low toxicity, acetonitrile has been widely used as common solvent in laboratory and industry. In addition, its inherent nitrile group and the relative active α-C(sp^3)-H bond enable it a valuable reactant used in a series of chemical transformations.[10] Among them, a variety of cycloaddition reactions including [4+2]/[2+2+2] cyclization with the nitrile group of the acetonitrile were developed to construct nitrogen-containing cyclic compounds (Scheme 1b).[11] To the best of our knowledge, however, the cycloaddition with the two carbons of acetonitrile serving as a new C2 building block is still unknown and very challenging (Scheme 1b), because there is no required unsaturated carbon-carbon bond. In addition, the potential competitive cycloaddition with the C≡N triple bond also restrict its possibility as a C2 cyclization unit.

Herein, we describe a novel metal-free triflic anhydride (Tf_2O) mediated [2+2] cycloaddition reaction using acetonitrile as C2 building block under mild reaction conditions (Scheme 1c). The unsaturated C=C bond was generated *in situ* by this metal-free strategy and selectively participated in this cycloaddition reaction for construction of four-membered carbon rings. Remarkably, through the reaction conditions selection, this chemistry can provide a general and highly efficient approach to cyclobutenones and cyclobuteneimines respectively (Scheme 1c), which are widely used as versatile synthon in organic synthesis including the total synthesis of naturally occurring or biologically target molecules.[12]



Scheme 1. Cyclizations with C2 Building Blocks.

For our continuous research interest in the construction of nitrogen- or oxygen-containing cyclic compounds,[13] we started the initial study towards the [2+2] cyclization by using **1a** and acetonitrile as the model reaction. We initially investigated this reaction by employing $(PPh_3)AuCl$ as catalyst to activate the alkyne in the mixed solvent of CH_3CN/Toluene under Ar atmosphere at 70 °C (entry 1). Unfortunately, no product was obtained even with other catalysts such as $Pd(OAc)_2$ and $Cu(OTf)_2$ (see Table S1, SI). To our delight, when triflic anhydride (Tf_2O) was used as an additive, the cycloaddition with the two carbons of acetonitrile serving as a new C2 building block occurred, and yielded the mixture of 4-membered carbon ring products cyclobutenone **2a** and cyclobuteneimine **3a** (entry 2). In contrast, no product was detected when Trifluoroacetic anhydride (TFAA) and Bis(trifluoromethanesulfonyl)imide (Tf_2NH) were used instead of Tf_2O (entry 3 and entry 4). Further investigation indicated that this transformation could proceed

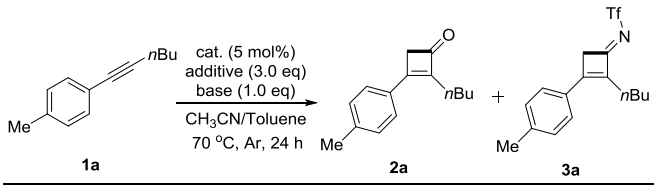
[*] Q. Qin, X. Luo, J. Wei, Y. Zhu, X. Wen, S. Song, and Prof. N. Jiao
State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University,
Xue Yuan Rd. 38, Beijing 100191, China
Prof. N. Jiao
Shanghai Key Laboratory of Green Chemistry and Chemical Processes, East China Normal University, Shanghai 200062, China
Fax: (+) 86-10-82805297
E-mail: jiaoning@pku.edu.cn
Homepage: http://sklnbd.bjmu.edu.cn/nj

Supporting information for this article is given via a link at the end of the document.

10.1002/anie.201900947

under metal free conditions, producing the mixture of **2a** and **3a** in 53% yield (**2a**:**3a** = 1:17, entry 5). Interestingly, 62% yield of **2a** and **3a** (**2a**:**3a** = 1:8) could be achieved with proton sponge (PS) as base (entry 6). Furthermore, when decreased the loading of PS to 25 mol%, the reaction produced cyclobuteneimine **3a** as the almost sole product in 66% yield (entry 7). It is noteworthy that the reaction did not work in the absence of Tf_2O (entry 8). Since the **2a** might be originated from **3a** by hydrolysis, 0.3 mL of H_2O was added in this reaction which afforded cyclobutenone **2a** as the sole product in 68% yield (entry 9). The efficiency and selectivity were not affected in dark reaction (entry 10).

Table 1. Reaction Conditions Investigation[a]

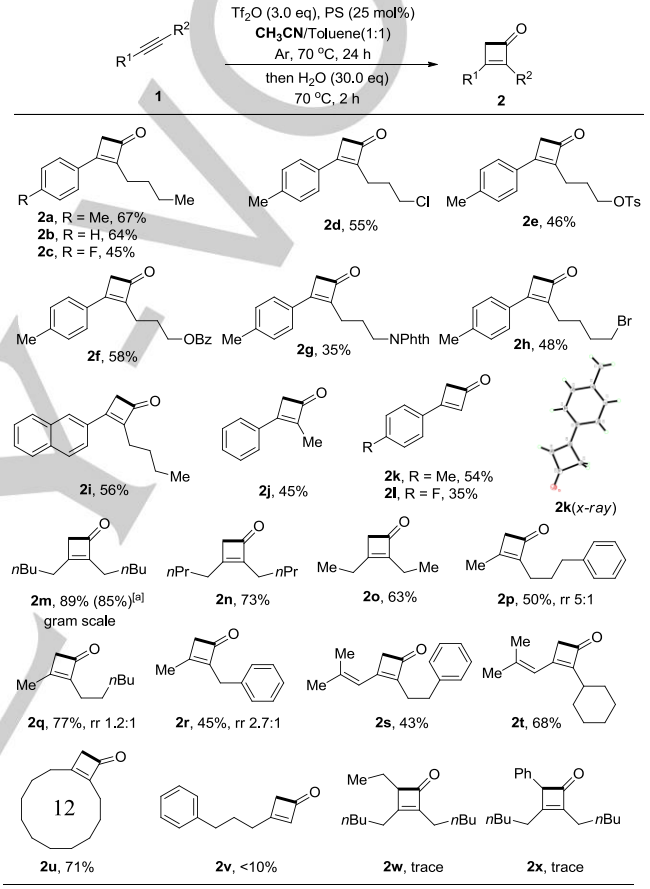


1a 2a 3a

Entry	Cat.	Additive	base	Yield(**2a**/**3a**)[b]
1	$(PPh_3)AuCl$	-	DBU	0
2	$(PPh_3)AuCl$	Tf_2O	DBU	57% (1:16)
3	$(PPh_3)AuCl$	TFAA	DBU	0
4	$(PPh_3)AuCl$	Tf_2NH	DBU	0
5	-	Tf_2O	DBU	53% (1:17)
6	-	Tf_2O	PS	62% (1:8)
7[c]	-	Tf_2O	PS	66% (1:20)
8[c]	-	-	PS	0
9[c,d]	-	Tf_2O	PS	68% (>20:1)[e]
10[c, d, f]	-	Tf_2O	PS	63% (>20:1)[e]

[a] Reaction conditions: **1a** (0.5 mmol), Tf_2O (3.0 equiv), base (1,0 equiv), CH_3CN/Toluene (2.5 mL/2.5 mL), stirred at 70 °C under Ar for 24 h. [b] Yields were determined by ^1H NMR using 1,1,2,2-Tetrachloroethane as an internal standard. [c] The loading of PS was decreased to 25 mol%. [d] When **1a** was consumed, H_2O (30.0 eq) was added for another 2 h reaction. [e] Isolated yields. [f] The reaction was conducted in dark.

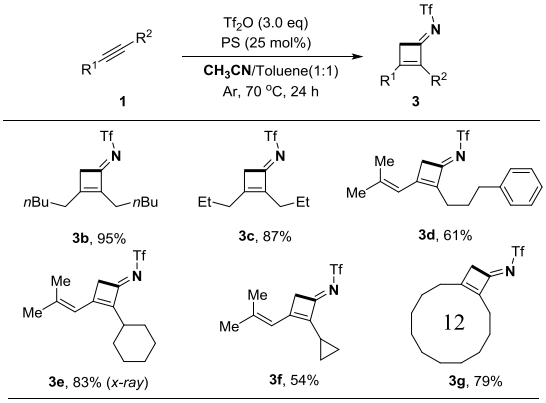
Under the optimized reaction conditions, we next studied the generality of this transformation for the preparation of cyclobutenones by exploring the scope of alkynes (Scheme 2). A variety of aryl and alkyl substituted alkynes were tolerated in this transformation. In addition, both terminal alkynes and internal alkynes performed well under these conditions. Notably, this transformation proceeded in good efficiency and high regioselectivity when aryl internal alkynes (**1a**-**1j**) were explored (**2a**-**2j**). Some functional groups, such as -Cl, -OTs, -OBz, -NPhth, -Br were tolerated in this transformation (**2d**-**2h**). The structure of **2k** was confirmed by *X-ray* analysis.[14] It was noteworthy that when enynes which could cause the competitive reactions with alkene or alkyne group were used as the substrates (**1s**, **1t**), the C=C bonds were not touched by this protocol, but producing the desired conjugated cyclobutenone products in moderate yields still with high regioselectivities (**2s**, **2t**). The cyclic alkyne also performed well under the standard conditions giving the corresponding cyclobutenone product **2u** in 71% yields. Unfortunately, the efficiency of the terminal alkyl alkyne (**1v**) was low under these conditions. Moreover, other nitriles, such as butyronitrile and benzeneacetonitrile were not suitable for this transformation, which gave only trace amount of desired products (**2w**, **2x**). It is noteworthy that these cyclobutenones could not be obtained by the protocols with amides as the precursor (see SI),[15] which demonstrate that the present approach would be complementary to the amide-based routes to cyclobutenones which could not be used in the preparation of α-unsubstituted cyclobutenones.



Scheme 2. Scope of Alkyne Partners for Cyclobutenones. Reaction conditions: **1** (0.5 mmol), Tf_2O (3.0 equiv), ProntonSponge (25 mol%), CH_3CN/Toluene (2.5 mL/2.5 mL), stirred at 70 °C under Ar for 24 h, followed by addition of H_2O (30.0 eq) at 70 °C for 2 h. Isolated yields. rr is regioisomeric ratio. [a] The reaction was conducted in 10.0 mmol.

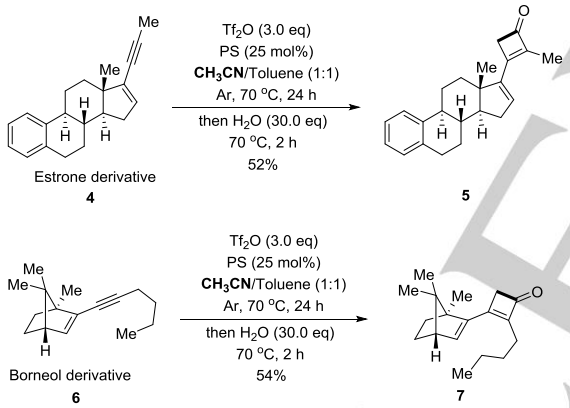
Notably, these transformations could be stopped at the stage of imine in the absence of H_2O. For some selected examples (Scheme 3), varies of cyclobuteneimines (**3b**-**3g**) were obtained with good yields and regioselectivities, which indicated the product diversity of this transformation. The structure of **3e** was also confirmed by *X-ray* analysis.[16]

10.1002/anie.201900947



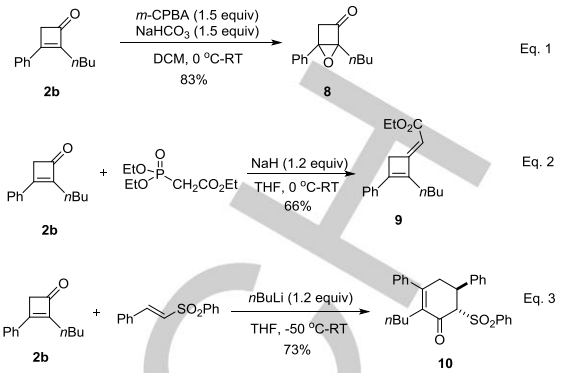
Scheme 3. Scope of Alkyne Partners for Cyclobuteneimines. Reaction conditions: **1** (0.5 mmol), Tf_2O (3.0 equiv), ProntonSponge (25 mol%), CH_3CN/Toluene (2.5 mL/2.5 mL), stirred at 70 °C under Ar for 24 h. Isolated yields.

Moreover, this reaction was applied to late stage modification of complex bioactive molecules containing alkyne group (Scheme 4). To be specific, **4** bearing a steroid scaffold was subjected to standard conditions and afforded the corresponding product **5** in 52% yield. Additionally, **6** derived from Borneol produced the desired product **7** in 54% yield under these mild conditions. These two products may present potential biological activity in medicinal chemistry.

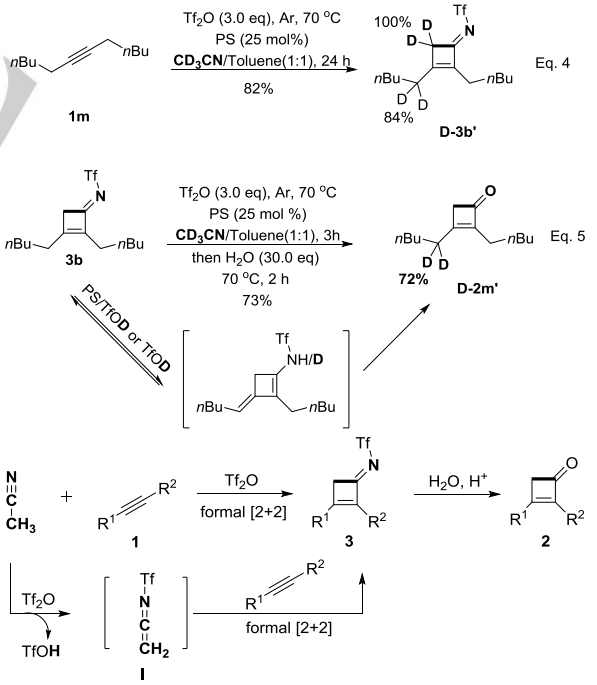


Scheme 4. Late-stage Modification of Estrone and Borneol Derivatives.

Due to their inherent ring strains and the great electrophilicity of carbonyl unit, cyclobutenones usually possess unique reactivity.[12] It was interesting that the epoxidized product **8** was produced in 83% yield from **2b** in the presence of *m*-CPBA (Eq. 1). **2b** also executed Horner–Wadsworth–Emmons reaction well to give four membered cyclic diene product **9** in 66% yield (Eq. 2). Furthermore, owing to their inherent high ring strain, **2b** readily underwent nucleophilic addition/4 π -ring opening/6 π -ring closing cascade reactions to give more versatile cyclohexenone **10** in 73% yield (Eq. 3).[17] These reactions demonstrate that cyclobutenones could serve as versatile synthons for the further synthesis of various structurally attractive and biologically important molecules.



To get insight into the mechanism, the reaction with CD_3CN was investigated, which afforded the desired deuterated product D-3b' in 82% yield (Eq. 4). This result demonstrates that the two carbons of cyclobutenones were derived from acetonitrile. Interestingly, we found the hydrogen atoms at one allyl position were also deuterated. Further deuterium exchange control experiments indicated that this process may occur after the [2+2] cyclization reaction through a keto-enol/imine-enamine tautomerism process (Eq. 5, also see SI). On the basis of the above results, a plausible reaction pathway was proposed in Scheme 5. As Tf_2O is a widely used in synthetic chemistry to generate triflate moieties with carbonyl substrates.[18] We believe that the acetonitrile is initially activated by Tf_2O to afford the key intermediate **I**, which subsequently undergoes formal [2+2] cyclization reaction with alkyne to produce the cyclobutene imine **3**. The further hydrolysis of **3** in the presence of H_2O yields the final cyclobutenone product **2**.



Scheme 5. Proposed Mechanism

In conclusion, we discovered a novel Tf_2O mediated acetonitrile activation for the construction of cyclobutenones via [2+2] cyclization. In contrast to the reported cycloaddition reaction with the nitrile group of acetonitrile, we realized the cycloaddition

reaction of acetonitrile as a C2 cyclization building block for the first time. This chemistry provides an efficient approach to cyclobutenones, which are versatile synthons for the rapid construction of complex molecules. Further investigation of this cyclization using acetonitrile as C2 unit is ongoing in our laboratory.

Acknowledgements

Financial support from the National Basic Research Program of China (973 Program) (No. 2015CB856600), the National Natural Science Foundation of China (21632001, 21772002, 81821004), and the Major changes in the central level support projects (2060302) are greatly appreciated. We thank Weijin Wang in this group for reproducing the results of **2s** and **2u**.

Keywords: Acetonitrile activation • C2 cyclization unit • [2+2] cyclization • cyclobutenones

[1] a) S. Kobayashi, K. A. Jorgensen, Eds. Cycloaddition Reactions in Organic Synthesis; Wiley-VCH: New York, **2002**. b) S.-M. Ma, Ed. Handbook of Cyclization Reactions; Wiley-VCH: New York, **2010**. h) X.-F. Wu, H. Neumann, M. Beller, *Chem. Rev*. **2013**, *113*, 1.

[2] a) S. J. McLain, C. D. Wood, R. R. Schrock, *J. Am. Chem. Soc*. **1979**, *101*, 4558. b) S. Tang, D. Wang, Y. Liu, L. Zeng, A. Lei, *Nat. Commun*. **2018**, *9*, 798. c) V. V. Pagar, T. V. RajanBabu, *Science* **2018**, *361*, 68.

[3] a) K. P. C. Vollhardt, *Acc. Chem. Res*. **1977**, *10*, 1. b) B. A. Trofimov, Y. M. Dvorko, D. A. Shabalin, E. Y. Schmidt, *Arkivoc*. **2016**, 161. Also see ref 2b.

[4] V. Saini, B. J. Stokes, M. S. Sigman, *Angew. Chem., Int. Ed*. **2013**, *52*, 11206; *Angew. Chem.* **2013**, *125*, 11414.

[5] A. S. Grossmann, T. Magauer, *Org. Biomol. Chem*. **2016**, *14*, 5377.

[6] a) R. D. Chambers, A. F. Gilbert, R. L. Powell, *J. Fluorine Chem*. **2000**, *104*, 233. b) G. Borsato, A. Linden, O. D. Lucchi, V. Lucchini, D. Wolstenholme, A. J. Zambon, *Org. Chem*. **2007**, *72*, 4272.

[7] Y. Tobe, T. Fujii, H. Matsumoto, K. Tsumuraya, D. Noguchi, N. Nakagawa, M. Sonoda, K. Naemura, Y. Achiba, T. Wakabayashi, *J. Am. Chem. Soc.* **2000**, *122*, 1762.

[8] Z. S. Sales, N. S. Mani, *J. Org. Chem*. **2009**, *74*, 891.

[9] TSCA Work Plan Chemical Risk Assessment Trichloroethylene: Degreasing, Spot Cleaning and Arts & Crafts Uses, U.S. Environmental Protection Agency, Washington, D.C., **2014**.

[10] a) J. W. Bruno, T. J. Marks, F. D. Lewis, *J. Am. Chem. Soc*. **1981**, *103*, 3608. b) H. R. Sonawane, N. S. Bellur, V. G. Shah, *J. Chem. Soc., Chem. Commun.* **1990**, 1603. c) Q. Michaudel, D. Thevenet, P.S. Baran, *J. Am. Chem. Soc*. **2012**, *134*, 2547. d) D. Prasad Hari, T. Hering, B. König, *Angew. Chem., Int. Ed*. **2014**, *53*, 725; *Angew. Chem.* **2014**, *126*, 743. e) X. Wu, J. Riedel, V. M. Dong, *Angew. Chem., Int. Ed*. **2017**, *56*, 11589; *Angew. Chem.* **2017**, *129*, 11747. f) Y.-Y. Liu, X.-H. Yang, R.-J. Song, S. Luo, J.-H. Li, *Nat. Commun*. **2017**, *8*, 14720. g) A. Bunescu, T. M. Ha, Q. Wang, J. Zhu, *Angew. Chem., Int. Ed*. **2017**, *56*, 10555; *Angew. Chem.* **2017**, *129*, 10691. h) Q. Qin, Y.-Y. Han, Y.-Y. Jiao, Y.-Y. He, S. Yu, *Org. Lett*. **2017**, *19*, 2909. i) X.–Q. Chu, D. Ge, Z.-L. Shen, T.-P. Loh, *ACS Catal*. **2018**, *8*, 258.

[11] For selected reviews, see: a) J. A. Varela, C. Sa, *Chem. Rev*. **2003**, *103*, 3787. b) B. Heller, M. Hapke, *Chem. Soc. Rev*. **2007**, *36*, 1085. c) G. Domínguez, J.´ Perez-Castells, *Chem. Soc. Rev*. **2011**, *40*, 3430. For selected example, see: d) J. J. Ritter, P. P. Minieri, *J. Am. Chem. Soc*. **1948**, *70*, 4045. e) J. J. Ritter, J. J. Kalish, *J. Am. Chem. Soc*. **1948**, *70*, 4048. f) M. M. McCormick, H. A. Duong, G. Zuo, J. Louie, *J. Am. Chem. Soc*. **2005**, *127*, 5030. g) C. Wang, X. Li, B. Wan, *Angew. Chem. Int. Ed*. **2011**, *50*, 7162; *Angew. Chem.* **2011**, *123*, 7300. h) W. He, C. Li, L. Zhang, *J. Am. Chem. Soc*. **2011**, *133*, 8482. i) G. Onodera, Y. Shimizu, J.-N. Kimura, J. Kobayashi, Y. Ebihara, K. Kondo, K. Sakata, R. Takeuchi, *J. Am. Chem. Soc*. **2012**, *134*, 10515. j) Y. Wang, C. Chen, J. Peng, M. Li, *Angew. Chem., Int. Ed*. **2013**, *52*, 5323; *Angew. Chem.* **2013**, *125*, 5431. k) Y. Wang, L.-J. Song, X. Zhang, J. Sun, *Angew. Chem. Int. Ed*. **2016**, *55*, 9704; *Angew. Chem.* **2016**, *128*, 9856.

[12] a) R. L. Danheiser, S. K. Gee, H. Sard, *J. Am. Chem. Soc*. **1982**, *104*, 7670. b) C. J. Kowalski, G. S. Lal, *J. Am. Chem. Soc*. **1988**, *110*, 3693. c) D. Bellus, B. Ernst, *Angew. Chem. Int. Ed. Engl*. **1988**, *27*, 797; *Angew. Chem.* **1988**, *100*, 820. d) R. Martin, Synthesis **2013**, 563. e) T. Kondo, T.-A. Mitsudo, *Chem. Lett*. **2005**, *34*, 1462. f) W. D. Jones, *Nature* **1993**, *364*, 676. g) B. Rybtchinski, D. Milstein, *Angew. Chem. Int. Ed*. **1999**, *38*, 870; *Angew. Chem.* **1999**, *111*, 918. h) F. Chen, T. Wang, N. Jiao, *Chem. Rev*. **2014**, *114*, 8613. i) L. Souillart, N. Cramer, *Chem. Rev*. **2015**, *115*, 9410. j) P.-H. Chen, G. Dong, *Chem. Eur. J.* **2016**, *22*, 18290.

[13] a) F. Chen, C. Qin, Y. Cui, N. Jiao, *Angew. Chem., Int. Ed*. **2011**, *50*, 11487; *Angew. Chem.* **2011**, *123*, 11698. b) C. Qin, W. Zhou, F. Chen, Y. Ou, N. Jiao, *Angew. Chem., Int. Ed*. **2011**, *50*, 12595; *Angew. Chem.* **2011**, *123*, 12803. c) Z. Xu, C. Zhang, N. Jiao, *Angew. Chem., Int. Ed*. **2012**, *51*, 11367; *Angew. Chem.* **2012**, *124*, 11529. d) X. Li, X. Li, N. Jiao, *J. Am. Chem. Soc*. **2015**, *137*, 9246. (e) T. Shen, Y. Zhang, Y.-F. Liang, N. Jiao, *J. Am. Chem. Soc*. **2016**, *138*, 13147. f) Y. Liang, N. Jiao, *Angew. Chem., Int. Ed*. **2016**, *55*, 4035; *Angew. Chem.* **2016**, *128*, 4103. g) J. Pan, X. Li, F. Lin, J. Liu, N. Jiao, *Chem* **2018**, *4*, 1427.

[14] CCDC 1864045. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[15] a) C. Schmidt, S. Sahraoui-Taleb, E. Differding, C. G. Dehasse-De Lombaert, L. Ghosez, *Tetrahedron Lett*. **1984**, *25*, 5043. b) J.-B. Falmagne, J. Escudero, S. Taleb-Sahraoui, L. Ghosez, *Angew. Chem., Int. Ed. Engl*. **1981**, *20*, 879; *Angew. Chem.* **1981**, *93*, 926. c) A. Kolleth, A. Lumbroso, G. Tanriver, S. Catak, S. Sulzer-Mosse, A. DeMesmaeker, *Tetrahedron Lett*. **2016**, *57*, 2697.

[16] CCDC 1863981. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[17] N. A. Magomedov, P. L. Ruggiero, Y. Tang, *J. Am. Chem. Soc*. **2004**, *126*, 1624.

[18] a) I. L. Baraznenok, V. G. Nenajdenko, E. S. Balenkova, *Tetrahedron*, **2000**, *56*, 3077. b) D. Kaiser, N. Maulide, *J. Org. Chem*. **2016**, *81*, 4421. c) H. Yorimitsu, *Chem. Rec*. **2017**, *17*, 1. For selected example, see: d) M. Movassaghi, M. D. Hill, *J. Am. Chem. Soc.* **2006**, *128*, 4592. e) E. Magnier, J. C. Blazejewski, M. Tordeux, C. Wakselman, *Angew. Chem., Int. Ed*. **2006**, *45*, 1279; *Angew. Chem.* **2006**, *118*, 1301. f) M. Movassaghi, M. D. Hill, O. K. Ahmad, *J. Am. Chem. Soc.* **2007**, *129*, 10096. g) G. Pelletier, W. S. Bechara, A. B. Charette, *J. Am. Chem. Soc*. **2010**, *132*, 12817. h) K.-J. Xiao, A.-E. Wang, P.-Q. Huang, *Angew. Chem. Int. Ed*. **2012**, *51*, 8314; *Angew. Chem.* **2012**, *124*, 8439. i) W. S. Bechara, G. Pelletier, A. B. Charette, *Nat. chem*. **2012**, *4*, 228. j) M. C. Hilton, R. D. Dolewski, A. J. McNally, *J. Am. Chem. Soc.* **2016**, *138*, 13806. k) J. A. Fernandez-Salas, A. J. Eberhart, D. J. Procter, *J. Am. Chem. Soc*. **2016**, *138*, 790. l) V. Tona, A. de la Torre, M. Padmanaban, S. Ruider, L. González, N. Maulide, *J. Am. Chem. Soc*. **2016**, *138*, 8348. m) L. Shang, Y. H. Chang, F. Luo, J. N. He, X. Huang, L. Zhang, L. C. Kong, K. X. Li, B. Peng, *J. Am. Chem. Soc*. **2017**, *139*, 4211. n) Y. Unoh, K. Hirano, M. Miura, *J. Am. Chem. Soc*. **2017**, *139*, 6106. o) A. de la Torre, D. Kaiser, N. Maulide, *J. Am. Chem. Soc*. **2017**, *139*, 6578. p) H. Huang, J. Denne, C.-H. Yang, H. Wang, J. Y. Kang, *Angew. Chem. Int. Ed*. **2018**, *57*, 6624; *Angew. Chem.* **2018**, *130*, 6734.

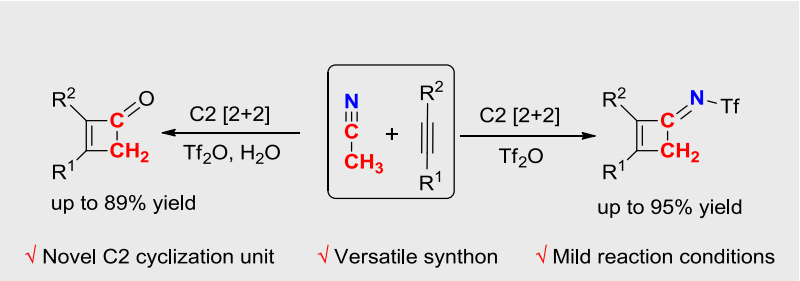
10.1002/anie.201900947

WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

Layout 2:

COMMUNICATION



*Qixue Qin, Xiao Luo, Jialiang Wei, Yuchao Zhu, Xiaojin Wen, Song Song and Ning Jiao**

Page No. – Page No.
Acetonitrile Activation: An Effective C2 Cyclization Unit

Text for Table of Contents

In contrast to the reported cycloaddition reaction with the nitrile group of acetonitrile, this work realized a novel [2+2] cycloaddition reaction for construction of cyclobutenones using acetonitrile as a C2 cyclization building block for the first time.