EurJOC
European Journal of Organic Chemistry

Chemistry Europe
European Chemical Societies Publishing

Accepted Article

Title: Iron-Catalyzed [2+2+2] Annulation of Aliphatic Bridged 1,n-Enynes with Aldehydes for Synthesis of Fused Pyrans

Authors: Tian Tian, Xin Wang, Leiyang Lv, and Zhiping Li

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.202000653

Link to VoR: https://doi.org/10.1002/ejoc.202000653

WILEY-VCH

10.1002/ejoc.202000653

WILEY-VCH

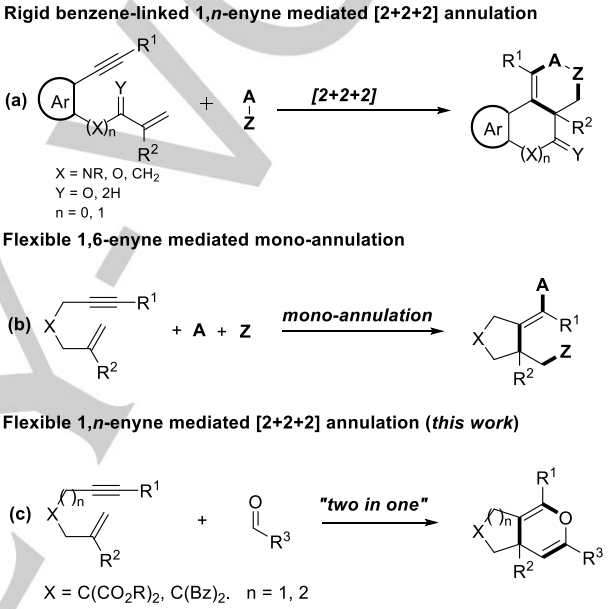
Iron-Catalyzed [2+2+2] Annulation of Aliphatic Bridged 1,*n*-Enynes with Aldehydes for Synthesis of Fused Pyrans

Tian Tian, Xin Wang, Leiyang Lv, Zhiping Li*

Abstract: Iron-catalyzed [2+2+2] annulation of aliphatic bridged 1,*n*-enynes with aldehydes was developed. Aldehydes play dual roles that not only as the precursors of acyl radicals to trigger the cascade cyclization but also as the radical accepters to terminate the annulation. This two in one strategy overcomes the limitation in [2+2+m] cyclization that requires rigid benzene skeleton as the essential linker, thus enabling the efficient synthesis of functionalized fused [5.6] and [6.6] pyran skeletons.

Transition metal-catalyzed [2+2+2] cycloaddition plays an important role in six-membered ring synthesis, by which the researchers can realize selective transformations that would either be difficult or impossible by conventional organic chemistry.[1] Tandem radical cyclization of 1,*n*-enynes is growing rapidly as a useful method for the construction of carbocyclic and heterocyclic skeletons.[2] The radical [2+2+2] annulation of 1,*n*-enynes is particularly interesting due to the one step access to polycyclic skeletons[3], which are core structures of various natural products, agrochemicals and pharmaceuticals. In 2013, Li and co-workers reported the first tandem radical [2+2+2] annulation by tactfully using benzene-linked 1,*n*-enynes as the all-purpose substrates.[4] The key to the success is that the linker benzene provides a rigid planar conformation that favors the spatial interaction of radical intermediate with unsaturated C=C and/or C ≡ C moiety (Scheme 1a).[5] By contrast, the analogue cyclization involving flexible 1,*n*-enynes is mostly restricted to the mono-annulation (Scheme 1b)[6], probably because its relaxed configuration fails to the second cyclization. Accordingly, radical [2+2+2] annulation of flexible aliphatic bridged 1,*n*-enynes is a largely unexplored research area and remains a big challenge.[7]

Fused [n.6] pyran compounds have superior antibacterial, antiviral and antitumor activities.[8] However, the method for synthesis of pyran skeleton mainly depends on [4+2] Hetero-Diels-Alder reactions,[9] which is difficult to apply to synthesize fused [n.6] pyrans. In 2016, we disclosed that aldehydes were identified as ideal two-atom units to undergo regioselective cascade radical [2+2+2] cyclization with benzene-linked 1,7-enynes under $FeCl_2$/di-*tert*-butyl peroxide (DTBP) catalytic system.[5d] Aldehydes play dual roles in this transformation, namely as both the precursors of acyl radicals to trigger the cascade cyclization and the radical accepters to terminate the annulation. Motivated by this finding, we became interested in further probing the reactivity of acyl radicals with flexible aliphatic bridged 1,*n*-enynes, presuming that the two in one strategy might help to overcome the adverse spatial interaction in radical [2+2+2] annulation. Herein we report the preliminary results of this hypothesis (Scheme 1c).



Scheme 1. Radical-mediated 1,*n*-enynes cascade cyclizations.

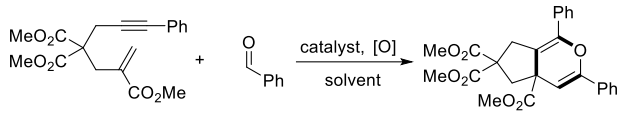
We started the investigation using dimethyl malonate tethered 1,6-enyne **1a** and benzaldehyde **2a** as the model substrates to optimize the reaction conditions (Table 1). Initially, a yield of 20% of desired fused [5.6] pyran **3aa** was obtained when $FeCl_2$ was selected as catalyst and $(t\text{-BuO})_2$ was used as the oxidant in PhCl at 105 °C (entry 1). Screening ferrous salts with different types of anions (entries 2-7), we found that the yield of **3aa** was achieved in 53% when acetylacetonato ($acac^-$) was used as the anion of the ferrous salt (entry 7). It should be noted that the reaction gave a yield of 38% **3aa** in the absence of a metal catalyst (entry 8), indicating that the iron catalyst increased the efficiency of the reaction. The solvent had a prominent effect on the reaction efficiency (entries 9-13). For example, when PhCl was replaced by PhMe, a decreased yield (42%) was obtained (entry 9). Other solvents such as MeCN, EtOAc, DCE and DMF turned out to be less effective for this transformation (entries 10-13). Subsequently, we tested other oxidants such as *tert*-butyl hydroperoxide (TBHP), *tert*-butyl peroxybenzoate (TBPB) and benzoyl peroxide (BPO), while no improved result was observed (entries 14-16). When half amount of $Fe(acac)_2$ was used, it was found that the yield remained almost the same (entry 17 *vs* 7). Furthermore, the increased product yield (67%) was obtained upon increasing the $(t\text{-BuO})_2$ to 5.0 equivalents (entry 18).

[*] T. Tian, X. Wang, L. Lv, Prof. Dr. Z. Li
Department of Chemistry
Renmin University of China
Beijing 100872 (P.R. China)
E-mail: zhipingli@ruc.edu.cn
Homepage: http://chem.ruc.edu.cn/ligroup/index.html

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

Control experiment revealed that no **3aa** was detected in the absence of oxidant (entry 19). Upon these screenings, we established the optimized reaction conditions using $Fe(acac)_2$ as the catalyst and $(t\text{-BuO})_2$ as the oxidant in PhCl at 105 °C for 3 h (entry 18).

Table 1. Optimization of the reaction conditions[a]



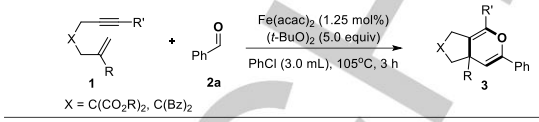
1a **2a** **3aa**

Entry	Catalyst	[O]	Sovent	Yield (%)[b]
1	$FeCl_2$	$(t\text{-BuO})_2$	PhCl	20
2	$FeBr_2$	$(t\text{-BuO})_2$	PhCl	29
3	$Fe(OAc)_2$	$(t\text{-BuO})_2$	PhCl	31
4	$FeCl_3$	$(t\text{-BuO})_2$	PhCl	49
5	$Fe_2(CO)_9$	$(t\text{-BuO})_2$	PhCl	50
6	$Fe(Cp)_2(Bz)_2$	$(t\text{-BuO})_2$	PhCl	52
7	$Fe(acac)_2$	$(t\text{-BuO})_2$	PhCl	53
8	—	$(t\text{-BuO})_2$	PhCl	38
9	$Fe(acac)_2$	$(t\text{-BuO})_2$	PhMe	42
10	$Fe(acac)_2$	$(t\text{-BuO})_2$	MeCN	8
11	$Fe(acac)_2$	$(t\text{-BuO})_2$	EA	6
12	$Fe(acac)_2$	$(t\text{-BuO})_2$	DCE	trace
13	$Fe(acac)_2$	$(t\text{-BuO})_2$	DMF	trace
14	$Fe(acac)_2$	TBHP	PhCl	9
15	$Fe(acac)_2$	TBPB	PhCl	34
16	$Fe(acac)_2$	BPO	PhCl	11
17[c]	$Fe(acac)_2$	$(t\text{-BuO})_2$	PhCl	55
18[c] [d]	**$Fe(acac)_2$**	**$(t\text{-BuO})_2$**	**PhCl**	**67**
19[c]	$Fe(acac)_2$	—	PhCl	0

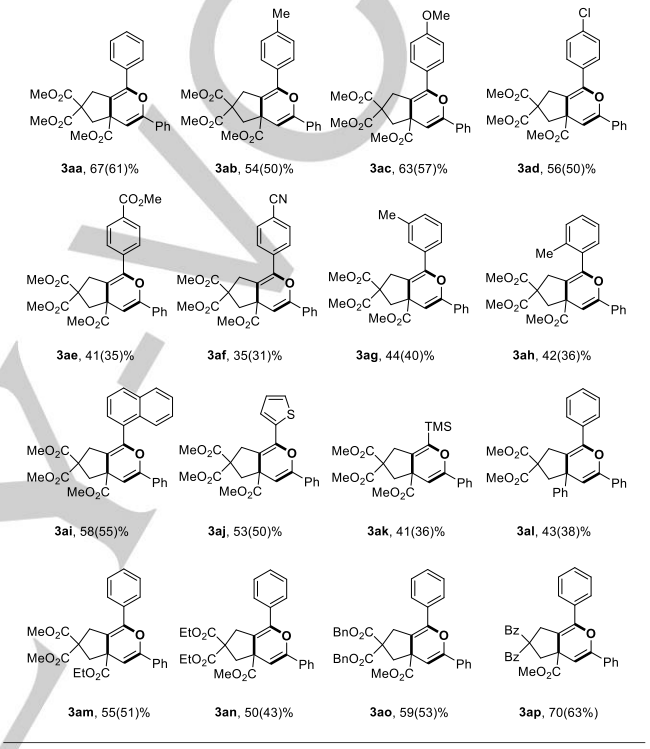
[a] Reaction conditions: **1a** (0.3 mmol), **2a** (1.5 mmol), catalyst (2.5 mol%), oxidant (0.75 mmol), solvent (3.0 mL), 105 °C, 3 h, under N_2 unless otherwise noted. [b] NMR yields were determined by ^{1}H NMR using an internal standard. [c] Catalyst is 1.25 mol%. [d] Oxidant (1.5 mmol).

With the optimal reaction conditions established, the scope of 1,6-enynes was investigated by the reactions with benzaldehyde **2a** (Table 2). This [2+2+2] annulation was applicable to a series of flexible 1,6-enynes. Both electron-donating (Me, OMe) and electron-withdrawing groups (Cl, CO_2Me, CN) at the *para*-position of the alkyne components were viable in the reaction (**3ab-3af**). The reduced yields were obtained for alkynes bearing substituents at the *meta*- and *ortho*-positions (**3ag** and **3ah**), probably for the steric hindrance. 2-Naphthyl and 2-thiophyl substituted alkynes were well tolerated under the standard conditions, giving the corresponding products **3ai** and **3aj** in 58% and 53% yields, respectively. Notably, 1,6-enyne containing trimethylsilyl (TMS) was also compatible with the reaction conditions (**3ak**). Importantly, when the CO_2Me substituent at the acrylate moiety was replaced by a Ph group or CO_2Et group, the corresponding products **3al** and **3am** could be obtained in 43% and 55% yield, respectively. However, when this position is replaced by H atom, this reaction failed to give the desired product. The result suggested that a stable tertiary radical is essential for the desired cycloaddition. In addition, the skeletons of 1,6-enynes including other malonates and 1,3-dione were applied smoothly and delivered the desired products (**3an**, **3ao** and **3ap**).

Table 2. Scope of 1, 6-enynes (**1**) [a] [b]



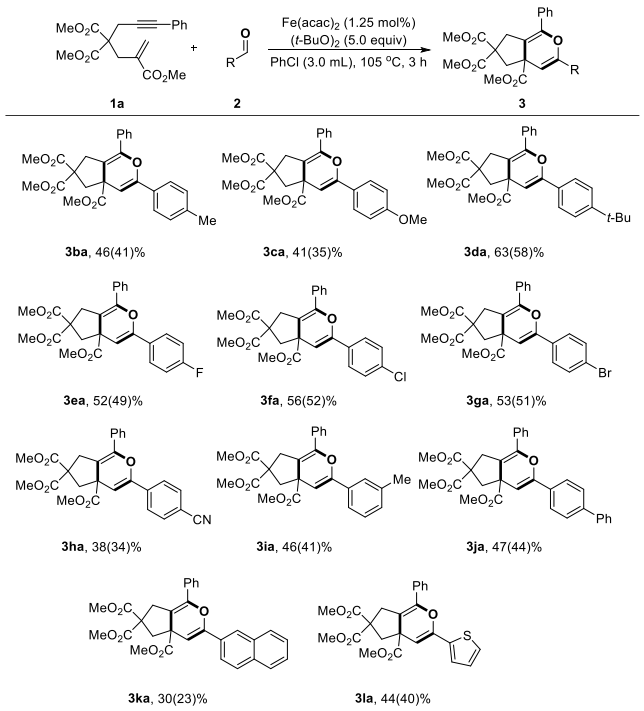
1 2a 3



[a] Reaction conditions: **1** (0.3 mmol),**2a** (1.5 mmol), $Fe(acac)_2$ (1.25 mol %), $(t\text{-BuO})_2$ (1.5 mmol), PhCl (3.0 mL), 105 °C, 3 h, under N_2 unless otherwise noted. [b] Reported yield were based on **1** and determined by ^{1}H NMR using an internal standard; isolated yields are given in parentheses.

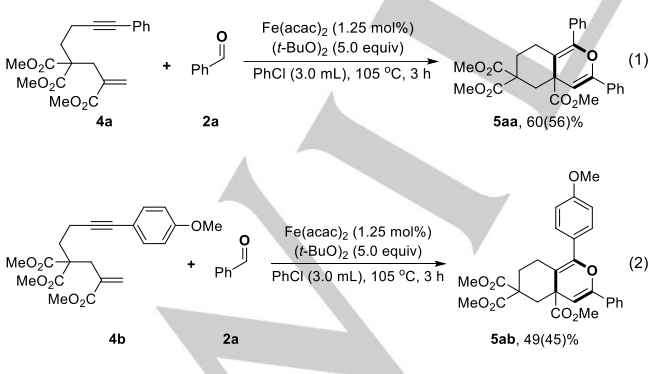
Next, the scope of the annulation was examined with respect to the aldehydes (Table 3). The electron-rich aldehydes, such as *p*-anisyl aldehyde, *p*-tolualdehyde, and *p*-*tert*-butyl benzaldehyde, reacted smoothly with 1,6-enyne **1a** to afford the target products **3ba-3da** in 41-63% yields. The aldehydes with a halogen atom (-F, -Cl, -Br) underwent the radical [2 + 2 + 2] annulation to give the fused pyrans **3ea-3ga** efficiently. The cyano group (-CN) on the ring of benzaldehyde was also tolerated and **3ha** was obtained in 38% yield. Steric hindrance on the meta-position of the aldehyde eroded the efficiency of this transformation (**3ia**). Biphenyl formaldehyde (**3ja**), 2-naphthaldehyde (**3ka**) and thiophene-2-carbaldehyde (**3la**) were tested as suitable substrates for the current annulation. However, aliphatic aldehydes were not applicable under the standard conditions due to the competitive decarbonylation reaction.

Table 3. Scope of aldehydes (**2**) [a] [b]

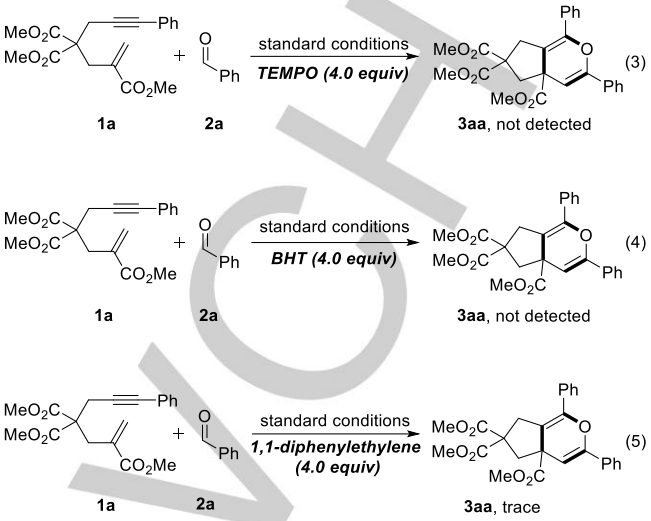


[a] Reaction conditions: **1a** (0.3 mmol),**2** (1.5 mmol), $Fe(acac)_2$ (1.25 mol %), $(t\text{-}BuO)_2$ (1.5 mmol), PhCl (3.0 mL), 105 °C, 3 h, under N_2 unless otherwise noted. [b] Reported yield were based on **1a** and determined by ^1H NMR using an internal standard; isolated yields are given in parentheses.

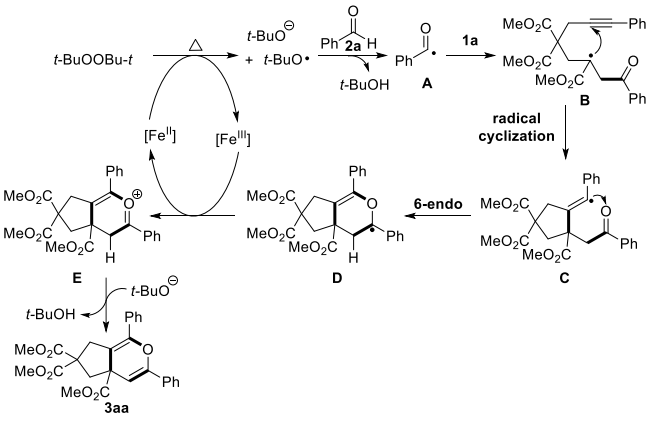
To expand the scope of the substrates, we found that malonate-bridged 1,7-enynes (**4a** and **4b**) could also be applied under the standard reaction conditions (eqs 1 and 2). The desired isochromene derivatives (**5aa** and **5ab**) were obtained in 60% and 49% yields,respectively. This is the first report on the synthesis of fused [6.6] pyran skeleton starting from a flexible aliphatic enynes.



In order to investigate the possible reaction pathways, some control experiments were carried out (eqs 3-5). The results showed that the reactions of 1,6-enyne **1a** with benzaldehyde **2a** were completely suppressed in the presence of radical inhibitors including (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO), butylated hydroxytoluene (BHT) and 1,1-diphenylethylene. In addition, the TEMPO-acyl radical adduct was obtained in the case of TEMPO applied (see S19 in Supporting Information). These outcomes indicated that the [2+2+2] annulation was most likely initiated by the formation of acyl radical from aldehyde.



On the basis of the results and previous reports,[2-6] a possible reaction mechanism for this [2+2+2] annulation is illustrated in Scheme 2. Initially, di-*tert*-butyl peroxide oxidizes Fe^{II} to Fe^{III} under heating conditions and decomposes into *t*-BuO^- and *t*-BuO•, which abstracts H of aldehyde (**2a**) C-H bond delivers the acyl radical **A** and *t*-BuOH. The regioselective addition of **A** across the C=C bond of the enyne **1a** affords the radical intermediate **B**, which further undergoes cyclization with the C ≡ C bond to give the vinyl radical intermediate **C**. The newly introduced carbonyl as an inner-sphere radical acceptor that enables the efficient 6-endo-trig addition of vinyl radical to give intermediate **D**.[10,11] Irreversible oxidation of **D** to **E** by Fe^{III} and final deprotonation by *t*-BuO^- delivers the annulation product **3aa**.



Scheme 2. Proposed mechanism

In summary, we have discovered an iron-catalyzed radical [2+2+2] annulation of aliphatic bridged 1,*n*-enynes with aldehydes. In this transformation, aldehydes play dual roles that not only as the precursors of acyl radicals to trigger the cascade

cyclization but also as the radical accepters to terminate the annulation. With this two in one strategy in hand, we have overcome the limitation in radical [2+2+m] cyclization that requires rigid benzene skeleton as the essential linker and enabled the one-step, efficient synthesis of various fused [5.6] and [6.6] pyran molecules. Further studies on the mechanism and applications of aldehydes as two-atom units in cascade radical annulations are in progress.

Acknowledgements

Financial support from the National Science Foundation of China (21672259).

Keywords: Iron catalysis • [2+2+2] Cycloaddition • 1,n-Enyne • Aldehyde • Fused pyran

[1] For various reviews on transition metal-catalyzed [2+2+2] cycloaddition, see: a) M. Lautens, W. Klute, W. Tam, *Chem. Rev.* **1996**, *96*, 49–92; b) S. Kotha, E. Brahmachary, K. Lahiri, *Eur. J. Org. Chem.* **2005**, *2005*, 4741–4767; c) T. Shibata, K. Tsuchikama, *Org. Biomol. Chem.* **2008**, *6*, 1317–1323; d) K. Tanaka, *Chem. Asian J.* **2009**, *4*, 508–518; e) G. Dominguez, J. Perez-Castells, *Chem. Soc. Rev.* **2011**, *40*, 3430–3444; f) P. A. Inglesby, P. A. Evans, *Chem. Soc. Rev.* **2010**, *39*, 2791–2805.

[2] For selected reviews on tandem radical cyclization of 1,*n*-enynes, see: a) V. Michelet, P. Y. Toullec, J.-P. Genet, *Angew. Chem. Int. Ed.* **2008**, *47*, 4268–4315; b) C. M. R. Volla, I. Atodiresei, M. Rueping, *Chem. Rev.* **2014**, *114*, 2390–2431; c) J. Xuan, A. Studer, *Chem. Soc. Rev.* **2017**, *46*, 4329—4346; d) C. Aubert, O. Buisine, M. Malacria, *Chem. Rev.* **2002**, *102*, 813−834.

[3] For a recent review on radical [2+2+2] annulation of 1,*n*-enynes, see: C.-H. Xu, Y. Li, J.-H. Li, J.-N. Xiang, W. Deng, *Sci. China Chem.* **2019**, *62*, 1463–1475.

[4] G.-B. Deng, Z.-Q. Wang, J.-D. Xia, P.-C. Qian, R.-J. Song, M. Hu, L.-B. Gong, J.-H. Li, *Angew. Chem., Int. Ed.* **2013**, *52*, 1535–1538.

[5] For selected examples, see: a) Y. Li, G.-H. Pan, M. Hu, B. Liu, R.-J. Song, J.-H. Li, *Chem. Sci.* **2016**, *7*, 7050-7054; b) Y. Liu, J.-L. Zhang, M.-B. Zhou, R.-J. Song, J.-H. Li, *Chem. Commun.* **2014**, *50*, 14412-14414; c) B. Liu, C.-Y. Wang, M. Hu, R.-J. Song, F. Chen, J.-H. Li, *Chem. Commun.* **2017**, *53*, 1265-1268; d) L. Lv, Z. Li, *Org. Lett.* **2016**, *18*, 2264-2267; e) L. Lv, X. Bai, X. Yan, Z. Li, *Org. Chem. Front.* **2016**, *3*, 1509-1513; f) J. Xuan, D. Gonzalez-Abradelo, C. A. Strassert, C.-G. Daniliuc, A. Studer, *Eur. J. Org. Chem.* **2016**, *2016*, 4961-4964; g) Y. An, J. Zhang, H. Xia, J. Wu, *Org. Chem. Front.* **2017**, *4*, 1318-1321.

[6] a) P. Gao, X.-B. Yan, T. Tao, F. Yang, T. He, X.-R. Song, X.-Y. Liu, Y.-M. Liang, *Chem. Eur. J.* **2013**, *19*, 14420–14424; b) Y.-T. He, L.-H. Li, Z.-Z. Zhou, H.-L. Hua, Y.-F. Qiu, X.-Y. Liu, Y.-M. Liang, *Org. Lett.* **2014**, *16*, 3896–3899; c) Y.-Q. Wang, Y.-T. He, L.-L. Zhang, X.-X. Wu, X.-Y. Liu, Y.-M. Liang, *Org. Lett.* **2015**, *17*, 4280–4283; d) L. Zhang, Z. Li, Z.-Q. Liu, *Org. Lett.* **2014**, *16*, 3688–3691; e) W. Wu, S. Yi, Y. Yu, W. Huang, H. Jiang, *J. Org. Chem.* **2017**, *82*, 1224–1230; f) W.-T. Wei, W.-W. Ying, W.-H. Bao, L.-H. Gao, X.-D. Xu, Y.-N. Wang, X.-X. Meng, G.-P. Chen, Q. Li, *ACS Sustainable Chem. Eng.* **2018**, *6*, 15301-15306; g) L.-H. Gao, X.-X. Meng, Y.-N. Wang, S.-Z. Song, G.-P. Ge, Y. Dong, W.-T. Wei, Y.-Y. Liu, Q. Li, *Asian J. Org. Chem.* **2019**, *8*, 348-352; h) M. Li, C.-T. Wang, Y.-F. Qiu, X.-Y. Zhu, Y.-P. Han, Y. Xia, X.-S. Li, Y.-M. Liang, *Chem. Commun.* **2018**, *54*, 5334−5337; i) X. Cao, X. Cheng, J. Xuan, *Org. Lett.* **2018**, *20*, 449−452; j) W.-W. Ying, W.-T. Chen, W.-H. Bao, L.-H. Gao, X.-Y. Wang, G.-P. Chen, G.-P. Ge, W.-T. Wei, *Synlett* **2018**, *29*, 1664–1668; k) L.-H. Gao, J.-Y. Zhang, S.-Z. Song, T.-T. Cao, G.-P. Ge, Q. Li, W.-T. Wei, *Org. Biomol. Chem.* **2019**, *17*, 7674–7678; l) Y. Gu, L. Dai, K. Mao, J. Zhang, C. Wang, L. Zhao, L. Rong, *Org. Lett.* **2020**, *22*, 2956-2960.

[7] J. Xuan, C. Daniliuc, A. Studer, *Org. Lett.* **2016**, *18*, 6372-6375.

[8] For a selected review, see: a) J.-M. Gao, S.-X. Yang and J.-C. Qin, *Chem. Rev.* **2013**, *113*, 4755-4811; For several selected examples, see: b) Y. Takenaka, T. Tanahashi, N. Nagakura, N. Z. Hamada, *Naturforsch*. **2000**, *55*, 910-914; c) A. A. Stierle, D. B. Stierle, T. Bugni, *J. Nat. Prod.* **2001**, *64*, 1350-1353; d) M. Katayama, M. Yanagi, S. Marumo, *Agric. Biol. Chem.* **1989**, *53*, 3379; e) Z. Lin, T. Zhu, Y. Fang, Q. Gu, W. Zhu, *Phytochemistry* **2008**, *69*, 1273-1278; f) A. A. Stierle, D. B. Stierle, T. Girtsman, T. C. Mou, C. Antczak, H. *J. Nat. Prod.* **2015**, *78*, 2917-2923; g) H. Huang, X. Feng, Z. Xiao, L. Liu, H. Li, L. Ma, Y. Lu, J. Ju, Z. She, Y. Lin, *J. Nat. Prod.* **2011**, *74*, 997-1002.

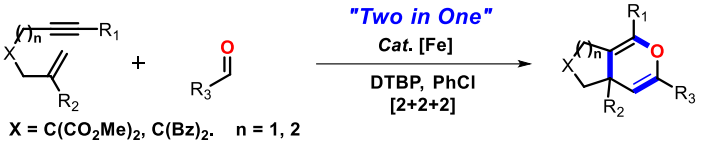
[9] For selected examples, see: a) B. M. Trost, R. E. Brown, F. D. Toste, *J. Am. Chem. Soc.* **2000**, *122*, 5877-5878; b) I. Koyama, T. Kurahashi, S. Matsubara, *J. Am. Chem. Soc.* **2009**, *131*, 1350–1351; c) D. Kossler, N. Cramer, *J. Am. Chem. Soc.* **2015**, *137*, 12478−12481; d) Y. Hu, S. Li, Z. Wang, Y. Yao, T. Li, C. Yu, C. Yao, *J. Org. Chem.* **2018**, *83*, 6, 3361-3366.

[10] For selected reviews, see: a) D. Liu, C. Liu, A. Lei, *Chem. Asian J.* **2015**, *10*, 2040-2054; b) C. Liu, A. Lei, *Chem. Eur. J.* **2019**, *25*, 7768–7770.

[11] For selected examples, see: c) D. Liu, S. Tang, H. Yi, C. Liu, X. Qi, Y. Lan, A. Lei, *Chem. Eur. J.* **2014**, *20*, 15605-15610; d) X. Cui, X. Xu, L. Wojtas, M. M. Kim, X. P. Zhang, *J. Am. Chem. Soc.* **2012**, *134*, 19981-19984. e) H. Jiang, Y. Cheng, Y. Zhang. S. Yu, *Org. Lett.* **2013**, *15*, 4884–4887; f) S. Tang, K. Liu, Y. Long, X. Qi, Y. Lan, A. Lei, *Chem. Commun.* **2015**, *51*, 8769–8772; h) L. Lv, H, Xi, X. Bai, Z. Li, *Org. Lett.* **2015**, *17*, 4324–4327; i) X. Bai, L. Lv, Z. Li, *Org. Chem. Front.* **2016**, *3*, 804-808; j) L. Lv, Z. Li, *Chin. J. Chem.* **2017**, *35*, 303-306.

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

COMMUNICATION



Aliphatic Flexible Chain 1, *n*-Enynes Radical [2+2+2] Annulation

*Tian Tian, Xin Wang, Leiyang Lv, Zhiping Li**

Page No. – Page No.

Iron-Catalyzed [2+2+2] Annulation of Aliphatic Bridged 1,n-Enynes with Aldehydes for Synthesis of Fused Pyrans

Two-in-One: Iron-catalyzed [2+2+2] annulation of aliphatic bridged 1,*n*-enynes with aldehydes was developed. Aldehydes play dual roles that not only as the precursors of acyl radicals to trigger the cascade cyclization but also as the radical accepters to terminate the annulation. This two in one strategy overcomes the limitation in [2+2+m] cyclization that requires rigid benzene skeleton as the essential linker, thus enabling the efficient synthesis of functionalized fused [5.6] and [6.6] pyran skeletons.