Organic LETTERS

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Iron-Catalyzed Radical [2 + 2 + 2] Annulation of Benzene-Linked 1,7-Enynes with Aldehydes: Fused Pyran Compounds

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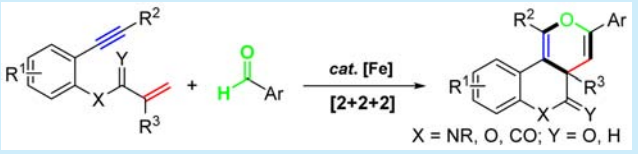
Supporting Information

ABSTRACT: An iron-catalyzed radical [2 + 2 + 2] annulation of benzene-linked 1,7-enynes with aldehydes has been developed. With this method, a variety of fused [6.6.6] pyran molecules are built in an efficient and selective manner. The aldehydic radical-mediated strategy exhibits a particularly attractive dual role, which triggers and terminates the domino cyclization.



Fused heteroarene compounds have attracted the attention of chemists due to their unique intrinsic characteristics and wide applications in drug discovery and material sciences.[1] For example, fused pyran compounds are prevalent structural motifs in a variety of natural products, pharmaceuticals, and marine organisms (Figure 1).[2] Despite their significance, the established

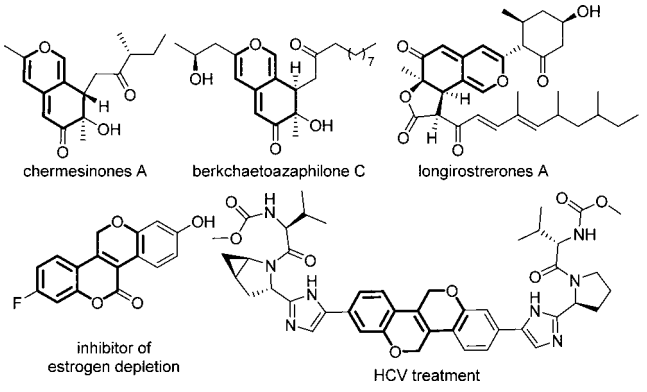
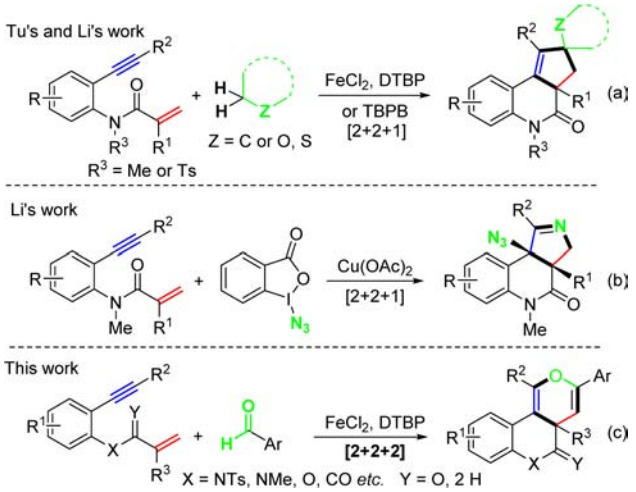


Figure 1. Representative bioactive examples of oxygen-containing six-membered fused heterocycles.

methods to construct these fused pyran scaffolds continue to use commercially unavailable starting materials or require quite a few synthetic steps with low overall yields. Therefore, alternative atom- and step-economic access to assemble these skeletons is urgently in demand. However, selectivity control and functional group compatibility make this straightforward approach extremely challenging.

The [2 + 2 + *m*] annulation reaction has emerged as one of the most straightforward and atom-economic protocols to construct five- and/or six-membered cyclic systems.[3] There have been remarkable and instructive advances on the transition-metal-catalyzed construction of molecular complexity with this powerful method.[4] Recently, Tu's group[5] and Li's group[6] reported an unprecedented radical [2 + 2 + 1] carbocyclization of 1,7-enynes with simple cycloalkanes or heterocyclic compounds, respectively (Scheme 1, eq a). This dual α,α-C(sp^3)−H abstraction/insertion bifunctionalization activation

Scheme 1. [2 + 2 + *m*] Annulation of Benzene-Linked 1,7-Enynes



strategy is extremely fascinating. Besides, this radical triggered cascade spirocyclization also presents a new synthetic method to build a fused [6.6.5] polycyclic architecture. Very recently, Li's group also realized a copper-catalyzed radical [2 + 2 + 1] annulation of benzene-linked 1,*n*-enynes (*n* = 6,7) with azidobenziodoxolone to prepare fused pyrrolines (Scheme 1, eq b).[7]

To the best of our knowledge, there have been no reported examples of catalytic 1,7-enyne [2 + 2 + 2] annulation for the construction of fused pyran scaffolds.[8] Aldehydes are commonly recognized as the carbonyl resources for the synthesis of alcohols or asymmetric ketones,[9] including β-peroxy ketones,[10] α,β-

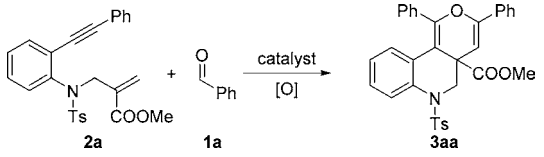
Received: March 29, 2016
Published: April 13, 2016

DOI: 10.1021/acs.orglett.6b00902
Org. Lett. 2016, 18, 2264−2267

unsaturated ketones,[11] and carbonyl-containing oxindoles[12] or indolines.[13] In this work, the aldehydic radical-mediated strategy exhibits a particularly attractive dual role, which triggers and also terminates the domino cyclization in a one-pot procedure. Herein, we report the first iron-catalyzed, radical-mediated [2 + 2 + 2] annulation of benzene-linked 1,7-enynes with aldehydes (Scheme 1, eq c), which enables the one-step, efficient synthesis of various fused [6.6.6] pyran molecules, including 6*H*-pyrano[4,3-*c*]quinolin-5(4a*H*)-one, 4a,5-dihydro-6*H*-pyrano-[4,3-*c*]quinolone, pyrano[4,3-*c*]chromen-5(4a*H*)-one, and pyrano[4,3-*c*]chromen-5(4a*H*)-one.

We started our investigation with the tandem cyclization of benzaldehyde **1a** and benzene-linked 1,7-enyne **2a** as a model to optimize the reaction conditions (Table 1). 1,7-Enyne **2a** was

Table 1. Optimization of the Reaction Conditions[a]



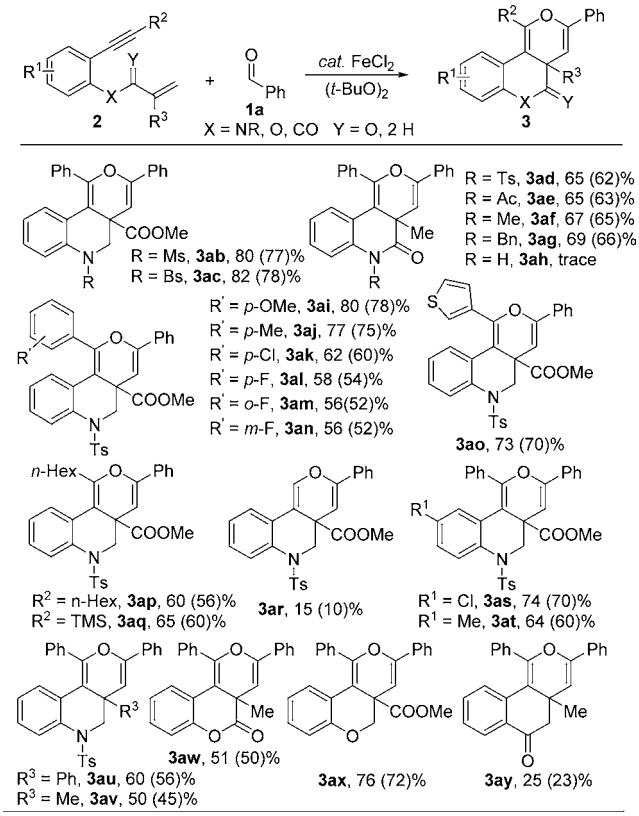
entry	catalyst	[O]	solvent	3aa (%)[b]
1	**$FeCl_2$**	**$(t\text{-BuO})_2$**	**PhCl**	**70(67)**
2	$FeCl_2$	$(t\text{-BuO})_2$	EA	69
3	$FeCl_2$	$(t\text{-BuO})_2$	$CHCl_3$	40
4	$FeCl_2$	$(t\text{-BuO})_2$	THF	23
5	$FeCl_2$	$(t\text{-BuO})_2$	DMF	39
6	$FeCl_2$	$(t\text{-BuO})_2$	DMSO	22
7	$FeCl_2{\cdot}4H_2O$	$(t\text{-BuO})_2$	PhCl	67
8	$FeCl_3$	$(t\text{-BuO})_2$	PhCl	70
9	$FeBr_2$	$(t\text{-BuO})_2$	PhCl	68
10	$Fe(OAc)_2$	$(t\text{-BuO})_2$	PhCl	64
11	$Fe(acac)_2$	$(t\text{-BuO})_2$	PhCl	68
12	$CuCl_2$	$(t\text{-BuO})_2$	PhCl	68
13	$CuBr_2$	$(t\text{-BuO})_2$	PhCl	66
14	$MnBr_2$	$(t\text{-BuO})_2$	PhCl	67
15	$CoCl_2$	$(t\text{-BuO})_2$	PhCl	52
16	$FeCl_2$	*t*-BuOOH	PhCl	48
17	$FeCl_2$	PhCOOO*t*Bu	PhCl	52
18	$FeCl_2$	$(PhCOO)_2$	PhCl	23
19		$(t\text{-BuO})_2$	PhCl	40
20	$FeCl_2$		PhCl	ND

[a]Reaction conditions: **1a** (1.5 mmol), **2a** (0.3 mmol), catalyst (2.5 mol %), [O] (0.75 mmol), PhCl (1.0 mL), 120 °C, 2 h, under N_2. [b]Reported yields were based on **2a** and determined by ^{1}H NMR using an internal standard; the isolated yield is given in parentheses.

treated with **1a**, $FeCl_2$, and di-*tert*-butyl peroxide (DTBP) and led to formation of the desired [2 + 2 + 2] annulation product **3aa** in 70% yield in the presence of chlorobenzene (entry 1). Solvent screening revealed that ethyl acetate also gave a comparable yield (69%) (entry 2), while other tested solvents such as $CHCl_3$, THF, DMF, and DMSO were all inferior in terms of reaction yields (entries 3−6). Subsequently, a number of metal catalysts were investigated; it was found that the other iron ($FeCl_3$, $FeBr_2$, etc.), copper ($CuCl_2$, $CuBr_2$), and manganese ($MnBr_2$) catalysts all worked efficiently and delivered **3aa** in good yields (entries 7−14), while cobalt catalyst ($CoCl_2$) gave a 52% yield (entry 15). Afterward, screening of other oxidants revealed that TBHP, *tert*-butyl peroxybenzoate (TBPB), and benzoyl peroxide (BPO) all met little success in this radical [2 + 2 + 2] annulation (entries 16−18). Notably, the reaction could also furnish product **3aa** in 40% yield in the absence of $FeCl_2$ (entry 19). However, no desired product was detected without loading an oxidant (entry 20).

With the optimal reaction conditions in hand, the scope of 1,7-enynes was investigated (Scheme 2). The [2 + 2 + 2] annulation

Scheme 2. Scope of the 1,7-Enynes[a]



[a]Reaction conditions: **1a** (1.5 mmol), **2** (0.3 mmol), $FeCl_2$ (2.5 mol %), $(t\text{-BuO})_2$ (0.75 mmol), PhCl (1.0 mL), 120 °C, 2 h, under N_2. Reported yields were based on **2** and determined by ^{1}H NMR using an internal standard; the isolated yields are given in parentheses.

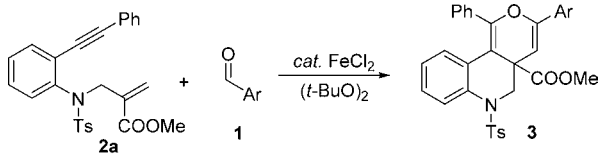
protocol was applicable to various benzene-linked 1,7-enynes, namely, aniline-linked 1,7-enynes, phenol-linked 1,7-enynes, and carbon-linked 1,7-enynes. Initially, the substitution effect of the nitrogen atom was investigated. The *N*-sulfonyl-substituted anilines (**2b** and **2c**) reacted smoothly to give the desired products **3ab** and **3ac** in good yields. With 1,7-enynes **2d**−**2g**, bearing a tosyl group, an acetyl group, a methyl group, or a benzyl group on the amidic nitrogen atom, 6*H*-pyrano[4,3-*c*]quinolin-5(4a*H*)-ones **3ad**−**3ag** were easy to construct in moderate to good yields, while 1,7-enyne **2h** with a free N−H group was inert and resulted in no formation of **3ah**. Several substituents, namely, MeO, Me, Cl, and F on the aromatic ring at the terminal alkyne, were well-tolerated (**3ai**−**3an**). The electron-withdrawing halogen groups, such as Cl and *p*-, *m*-, and *o*-F, were also compatible with the optimal conditions, albeit in moderate yields (56−62%), which can be further manipulated at the halogenated positions. Aliphatic alkyne **2p** and trimethylsilyl alkyne **2q** were also applicable for the transformation to give desired products **3ap** and **3aq** in good yields. Moreover, **3ar** was obtained in 15% yield when terminal alkyne **2r** was applied under the optimized conditions. The 4-Me- and 4-Cl-substituted 1,7-enynes on the aromatic ring of the aniline moiety were well-tolerated under the

DOI: 10.1021/acs.orglett.6b00902
Org. Lett. 2016, 18, 2264−2267

standard conditions and gave desired products **3as** and **3at** in 74 and 64% yields, respectively. Additionally, screening revealed that the 1,7-enynes **2u** and **2v**, with a Ph group and a Me group, respectively, at the 2-position of the acrylamide moiety were smoothly converted into the corresponding **3au** and **3av** in good yields. In the case of the phenol-linked 1,7-enynes **2w** and **2x**, the fused [6.6.6] oxygen-containing skeletons **3aw** and **3ax** were constructed in 51 and 76% yields, respectively. In addition, 4a,5-dihydro-6*H*-benzo[*h*]isochromen-6-one (**3ay**) could also be formed using the carbon-linked 1,7-enyne **2y** in 25% yield. Unfortunately, the 1,7-enyne with an internal olefin moiety failed to give the desired product.

Next, the scope of the aldehydes was examined (Scheme 3). The electron-rich aldehydes, such as anisyl aldehyde and *p*-tolualdehyde, reacted smoothly with **2a** to afford desired products **3ba** and **3ca** in good yields. The aldehydes with a halogen atom also underwent the [2 + 2 + 2] annulation to give the fused pyrans **3da**−**3fa** in moderate yields. Moreover, the absolute configuration of **3da** was confirmed by X-ray diffraction analysis (Figure 2). As expected, the strongly electron-withdrawing group (CN) on the phenyl ring of benzaldehyde eroded the efficiency of this transformation, and **3ga** was obtained in 48% yield. Furthermore, other aromatic aldehydes such as 2-naphthaldehyde (**1h**) and thiophene-2-carbaldehyde (**1i**) were also applicable for the present transformation. Unfortunately, the decarbonylation reaction occurred when aliphatic aldehydes were applied and did not give the bifunctionalization products under the same reaction conditions.

Scheme 3. Scope of the Aldehydes[a]



Ar = C_6H_4-4-OMe,	**3ba**, 73 (70)%
Ar = C_6H_4-4-Me,	**3ca**, 69 (65)%
Ar = C_6H_4-4-Cl,	**3da**, 67 (63)%
Ar = C_6H_4-4-Br,	**3ea**, 65 (60)%
Ar = C_6H_4-4-F,	**3fa**, 68 (65)%
Ar = C_6H_4-4-CN,	**3ga**, 50 (48)%
Ar = 2-naphyl,	**3ha**, 73 (70)%
Ar = 1-thiophyl,	**3ia**, 75 (72)%

[a]Reaction conditions: **1** (1.5 mmol), **2a** (0.3 mmol), $FeCl_2$ (2.5 mol %), $(t\text{-BuO})_2$ (0.75 mmol), PhCl (1.0 mL), 120 °C, 2 h, under N_2. Reported yields were based on **2a** and determined by ^1H NMR using an internal standard; the isolated yields are given in parentheses.

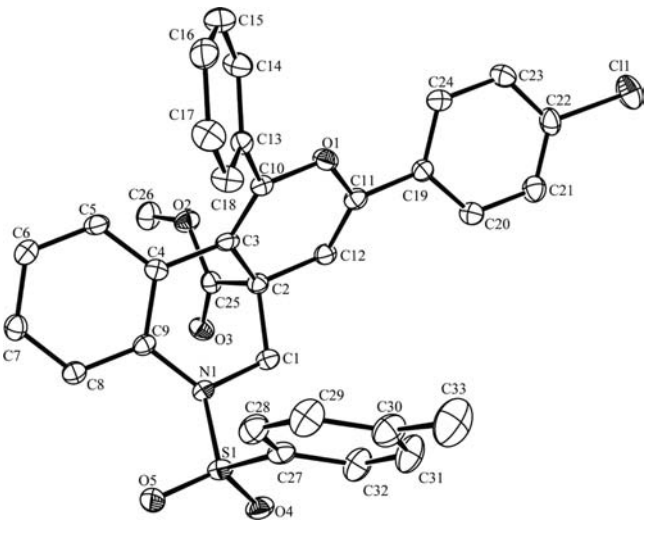
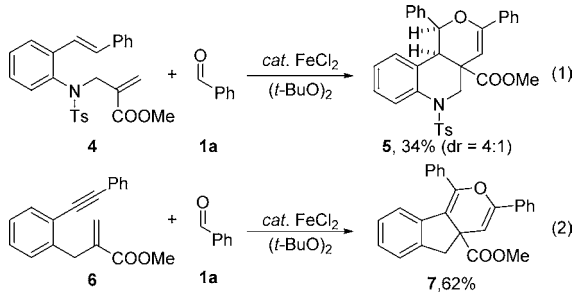
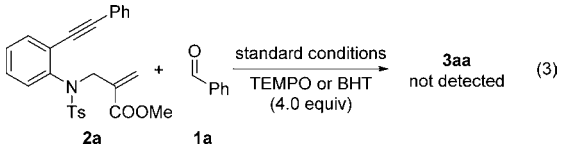


Figure 2. X-ray diffraction of **3da**.

Notably, when 1,7-diene **4** and benzaldehyde **2a** were applied under the standard conditions, the desired [2 + 2 + 2] annulation product **5** was obtained, though in 34% yield with 4:1 diastereoselectivity (eq 1). Gratifyingly, when 1,6-enyne **6** was used as the substrate,[14] the reaction also proceeded efficiently and furnished the corresponding methyl 1,3-diphenylindeno-[1,2-*c*]pyran-4a(5*H*)-carboxylate **7** in good yields (eq 2), thus demonstrating the generality of this method.

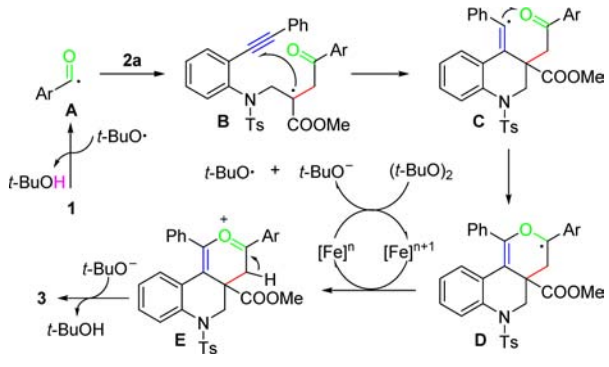


Control experiments showed that the reaction of **1a** with **2a** and DTBP was completely suppressed when a stoichiometric amount of radical inhibitors, including TEMPO or butylated hydroxytoluene (BHT), was added (eq 3). Notably, the TEMPO adduct aldehyde was obtained in the presence of TEMPO (see Supporting Information), which suggested that this [2 + 2 + 2] annulation was initiated by the formation of aldehydic radicals from aldehydes **1a**.



On the basis of the present results and previous reports,[15] a possible reaction mechanism for this [2 + 2 + 2] annulation is proposed in Scheme 4. Initially, the C(sp^2)−H bond in aldehyde **1** is cleaved to deliver the acyl radical **A** by DTBP under heating. Subsequently, the addition of **A** across a C−C double bond in the enyne **2** produces the radical intermediate **B**, followed by

Scheme 4. Proposed Reaction Mechanism



DOI: 10.1021/acs.orglett.6b00902
Org. Lett. 2016, 18, 2264−2267

cyclization with a C−C triple bond to afford the vinyl radical intermediate **C**. The intermediate **C** then undergoes 6-*endo*-*trig* addition to the carbonyl to give intermediate **D**.[16] Irreversible oxidation of **D** by an iron catalyst gives oxonium cation **E**. Final deprotonation delivers annulation product **3**.

In summary, we have discovered a novel iron-catalyzed radical [2 + 2 + 2] annulation of benzene-linked 1,7-enynes with aldehydes. With this method, a variety of fused [6.6.6] pyran molecules are prepared efficiently and selectively. The aldehydic radical-mediated strategy exhibits a particularly attractive dual role, which triggers and also terminates the domino cyclization in a one-pot procedure. Further studies on the mechanism and applications of this radical bifunctionalization strategy in natural product synthesis are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00902.

Experimental procedures and spectral data for all new compounds (PDF)

X-ray crystal structure data for **3da** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support is from the National Science Foundation of China (21272267), State Key Laboratory of Heavy Oil Processing (SKLOP201401001), and Beijing National Laboratory for Molecular Sciences (BNLMS).

■ REFERENCES

(1) (a) Pratap, R.; Ram, V. J. *Chem. Rev.* **2014**, *114*, 10476. (b) Thompson, B. C.; Fréchet, J. M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 58. (c) Larrosa, I.; Romea, P.; Urpí, F. *Tetrahedron* **2008**, *64*, 2683. (d) Wu, J.; Pisula, W.; Müllen, K. *Chem. Rev.* **2007**, *107*, 718. (e) Gunatilaka, A. A. L. *J. Nat. Prod.* **2006**, *69*, 509.

(2) (a) Stierle, A. A.; Stierle, D. B.; Girtsman, T.; Mou, T. C.; Antczak, C.; Djaballah, H. *J. Nat. Prod.* **2015**, *78*, 2917. (b) Kozlowski, J.; Coburn, C.; Yu, W.; Tong, L.; Hu, B.; Zhong, B.; Hao, J.; Wang, D.; Ji, T. WO Patent Appl. 2015094998 A1, 2015. (c) Huang, H.; Feng, X.; Xiao, Z.; Liu, L.; Li, H.; Ma, L.; Lu, Y.; Ju, J.; She, Z.; Lin, Y. *J. Nat. Prod.* **2011**, *74*, 997. (d) Sui, Z.; Zhang, X.; Li, X. WO Patent Appl. 2006047017 A1, 2006. (e) Panthama, N.; Kanokmedhakul, S.; Kanokmedhakul, K.; Soytong, K. *J. Nat. Prod.* **2011**, *74*, 2395. For a review, see: (f) Gao, J.-M.; Yang, S.-X.; Qin, J.-C. *Chem. Rev.* **2013**, *113*, 4755.

(3) For the [2 + 2 + *m*] annulation involving a radical process, see: (a) Fukuyama, T.; Nakashima, N.; Okada, T.; Ryu, I. *J. Am. Chem. Soc.* **2013**, *135*, 1006. (b) Deng, G.-B.; Wang, Z.-Q.; Xia, J.-D.; Qian, P.-C.; Song, R.-J.; Hu, M.; Gong, L.-B.; Li, J.-H. *Angew. Chem., Int. Ed.* **2013**, *52*, 1535. (c) Godineau, E.; Landais, Y. *J. Am. Chem. Soc.* **2007**, *129*, 12662.

(4) For selected reviews on [2 + 2 + *m*] cycloaddition, see: (a) Domínguez, G.; Pérez-Castells. *Chem. Soc. Rev.* **2011**, *40*, 3430. (b) Galan, B. R.; Rovis, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 2830. (c) Chopade, P. R.; Louie, J. *Adv. Synth. Catal.* **2006**, *348*, 2307. (d) Blanco-Urgoiti, J.; Añorbe, L.; Pérez-Serrano, L.; Domínguez, G.; Pérez-Castells, J. *Chem. Soc. Rev.* **2004**, *33*, 32. (e) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.

(5) Qiu, J.-K.; Jiang, B.; Zhu, Y.-L.; Hao, W.-J.; Wang, D.-C.; Sun, J.; Wei, P.; Tu, S.-J.; Li, G. *J. Am. Chem. Soc.* **2015**, *137*, 8928.

(6) Hu, M.; Fan, J.-H.; Liu, Y.; Ouyang, X.-H.; Song, R.-J.; Li, J.-H. *Angew. Chem., Int. Ed.* **2015**, *54*, 9577.

(7) Ouyang, X.-H.; Song, R.-J.; Liu, Y.; Hu, M.; Li, J.-H. *Org. Lett.* **2015**, *17*, 6038.

(8) For recent examples of 1,7-enyne annulation, see: (a) Gao, F.; Yang, C.; Ma, N.; Gao, L.-G.; Li, D.; Xia, W. *Org. Lett.* **2016**, *18*, 600. (b) Zhu, Y.-L.; Jiang, B.; Hao, W.-J.; Wang, A.-F.; Qiu, J.-K.; Wei, P.; Wang, D.-C.; Li, G.; Tu, S.-J. *Chem. Commun.* **2016**, *52*, 1907. (c) Wang, A.-F.; Zhu, Y.-R.; Wang, S.-L.; Hao, W.-J.; Li, G.; Tu, S.-J.; Jiang, B. *J. Org. Chem.* **2016**, *81*, 1099. (d) Hu, M.; Song, R.-J.; Ouyang, X.-H.; Tan, F.-L.; Wei, W.-T.; Li, J.-H. *Chem. Commun.* **2016**, *52*, 3328. (e) Zhu, Y.-L.; Jiang, B.; Hao, W.-J.; Qiu, J.-K.; Sun, J.; Wang, D.-C.; Wei, P.; Wang, A.-F.; Li, G.; Tu, S.-J. *Org. Lett.* **2015**, *17*, 6078. (f) Liu, Y.; Zhang, J.-L.; Song, R.-J.; Li, J.-H. *Org. Lett.* **2014**, *16*, 5838. (g) Liu, Y.; Zhang, J.-L.; Song, R.-J.; Qian, P.-C.; Li, J.-H. *Angew. Chem., Int. Ed.* **2014**, *53*, 9017. For a review, see: (h) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268.

(9) (a) Xiao, L.-J.; Fu, X.-N.; Zhou, M.-J.; Xie, J.-H.; Wang, L.-X.; Xu, X.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2016**, *138*, 2957. (b) Chudasama, V.; Fitzmaurice, R. J.; Caddick, S. *Nat. Chem.* **2010**, *2*, 592.

(10) (a) Lv, L.; Shen, B.; Li, Z. *Angew. Chem., Int. Ed.* **2014**, *53*, 4164. (b) Liu, W.; Li, Y.; Liu, K.; Li, Z. *J. Am. Chem. Soc.* **2011**, *133*, 10756.

(11) Wang, J.; Liu, C.; Yuan, J.; Lei, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 2256.

(12) Zhou, M.-B.; Song, R.-J.; Ouyang, X.-H.; Liu, Y.; Wei, W.-T.; Deng, G.-B.; Li, J.-H. *Chem. Sci.* **2013**, *4*, 2690.

(13) Lv, L.; Qi, L.; Guo, Q.; Shen, B.; Li, Z. *J. Org. Chem.* **2015**, *80*, 12562.

(14) For recent examples of 1,6-enyne annulation, see: (a) Undeela, S.; Ravikumar, G.; Nanubolu, J. B.; Singarapu, K. K.; Menon, R. S. *Chem. Commun.* **2016**, *52*, 4824. (b) Hu, M.; Song, R.-J.; Li, J.-H. *Angew. Chem., Int. Ed.* **2015**, *54*, 608. (c) Deng, G.-B.; Wang, Z.-Q.; Xia, J.-D.; Qian, P.-C.; Song, R.-J.; Hu, M.; Gong, L.-B.; Li, J.-H. *Angew. Chem., Int. Ed.* **2013**, *52*, 1535. (d) Luo, J.-Y.; Hua, H.-L.; Chen, Z.-S.; Zhou, Z.-Z.; Yang, Y.-F.; Zhou, P.-X.; He, Y.-T.; Liu, X.-Y.; Liang, Y.-M. *Chem. Commun.* **2014**, *50*, 1564.

(15) (a) Lv, L.; Xi, H.; Bai, X.; Li, Z. *Org. Lett.* **2015**, *17*, 4324. (b) Lv, L.; Lu, S.; Guo, Q.; Shen, B.; Li, Z. *J. Org. Chem.* **2015**, *80*, 698. (c) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991.

(16) (a) Liu, D.; Tang, S.; Yi, H.; Liu, C.; Qi, X.; Lan, Y.; Lei, A. *Chem. - Eur. J.* **2014**, *20*, 15605. (b) Cui, X.; Xu, X.; Wojtas, L.; Kim, M. M.; Zhang, X. P. *J. Am. Chem. Soc.* **2012**, *134*, 19981. For a recent review, see: (c) Liu, D.; Liu, C.; Lei, A. *Chem. - Asian J.* **2015**, *10*, 2040.

DOI: 10.1021/acs.orglett.6b00902
Org. Lett. 2016, 18, 2264−2267