JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Catalytic Dual 1,1-H-Abstraction/Insertion for Domino Spirocyclizations

Jiang-Kai Qiu,[†,‡] Bo Jiang,*[,†] Yi-Long Zhu,[†,‡] Wen-Juan Hao,[†] De-Cai Wang,[‡] Jun Sun,[†,‡] Ping Wei,[‡] Shu-Jiang Tu,*[,†] and Guigen Li*[,§,∥]

[†]School of Chemistry and Chemical Engineering, Jiangsu Key Laboratory of Green Synthetic Chemistry for Functional Materials, Jiangsu Normal University, Xuzhou, 221116, P. R. China

[‡]Biotechnology and Pharmaceutical Engineering, Nanjing Tech University, Nanjing, 210009, Jiangsu, P. R. China

[§]Institute of Chemistry & BioMedical Sciences, Collaborative Innovation Center of Chemistry for Life Sciences, Nanjing University, Nanjing, 210093, P. R. China

[∥]Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79409−1061, United States

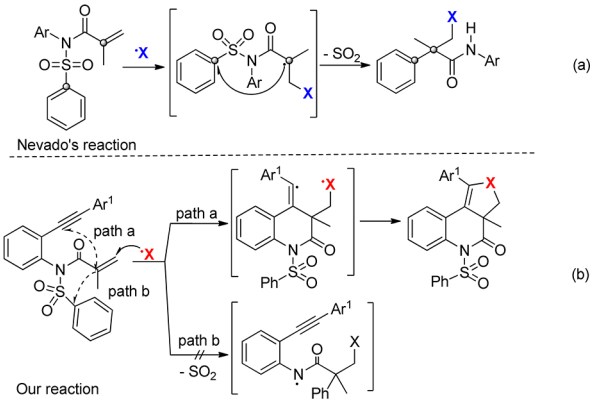
Supporting Information

ABSTRACT: A catalytic domino spirocyclization of 1,7-enynes with simple cycloalkanes and cyclo-1,3-dicarbonyls has been established via multiple C−C bond formations from alkynyl/alkenyl functions and dual α,α-C(sp^3)-H abstraction/insertion. The reaction involves addition, 6-*exo*-*dig* cyclization and radical coupling sequences under convenient catalytic conditions and provides a concise access to spiro cyclopenta[*c*]quinolines in good to excellent yields.

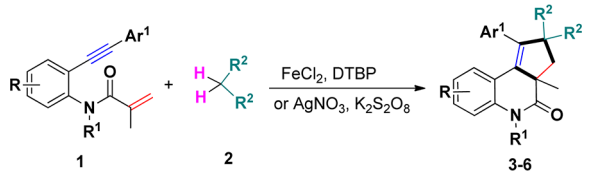
Widely utilized for numerous challenging and intriguing syntheses, 1,*n*-enynes are privileged building blocks for substrate-specific domino cyclizations.[1,2] They can readily result in multiple functionalities via synergistic cascade processes across C═C and C≡C bonds of various substrates in one-pot fashions.[3] So far, considerable efforts have been devoted to the use of 1,*n*-enynes for assembling highly complex structures of chemically and biomedically importance.[4] Meanwhile, a transition-metal-catalyzed radical process for sp^3 C−H bond functionalization has emerged as powerful tool for domino C−C/C−X bond formations due to its remarkable atom-economy potential.[5,6] An extensive literature survey revealed that a single C−H bond functionalization on sp^3 carbon atom has been widely studied.[7] However, to the best of our knowledge, a dual α,α-C(sp^3)-H activation/bifunctionalization on the same carbon atom has not be documented yet.

In recent years, our laboratories have been heavily involved in the development of domino bicyclization reactions for multiple ring formations.[8] For this purpose, we planned the synthesis of arylalkynyl-anchored starting materials by taking advantage of a methodology invented by Nevado et al. in which the radical adds to the double bond of *N*-(arylsulfonyl)acrylamides, leading to the formation of aza-heterocycles through radical addition/arylmigration/desulfonylation sequence (Scheme 1a).[9] Surprisingly, we found the expected products cannot be generated. Instead, the reaction occurred in a completely unexpected direction (Scheme 1b). Here, we would like to report this discovery (Scheme 2).

Scheme 1. Design of Radical Cyclization of 1,7-Enynes



Scheme 2. Cascade Spirocyclization of 1,7-Enynes



As shown in Scheme 2, it is particularly interesting and rare that dual radicals can be readily generated via α,α-C(sp^3)-H activation under a one-pot catalytic condition, and they can participate in domino reaction consisting of the sequence of intermolecular α,β-conjugated addition, intramolecular radical addition onto 1,7-conjugated enynes **1** and radical cyclization. The present radical spirocyclization between 1,7-enynes and simple alkanes provides an easy access to a series of spiro-substituted cyclopenta[*c*]quinolines with two quaternary stereocenters serving for organic and medicinal research.

Initially, we chose methacrylamides **1a** and cyclohexane (**2a**)[10] as the model substrates to optimize the reaction conditions (Table S1, see Supporting Information, SI). We found that the

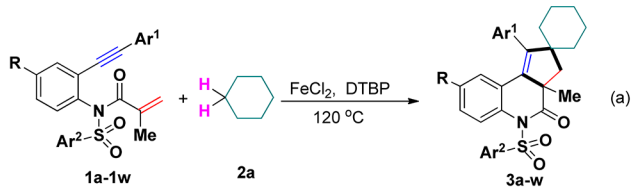
Received: June 3, 2015
Published: July 1, 2015

DOI: 10.1021/jacs.5b05735
J. Am. Chem. Soc. 2015, 137, 8928−8931

catalyst and radical initiator showed a significant impact on the reaction. The desired product was obtained in only 12% yield in the absence of any catalyst using TBHP (70% in water) as the oxidant (entry s1, SI). Raising the temperature did not enhance the chemical yield of **3a** (entry s2, SI). Pleasingly, the use of anhydrous TBHP afforded a higher yield of 42%, which indicates that the presence of water severely hampered the domino process. Subsequently, other anhydrous oxidants, such as benzoyl peroxide (BPO), *tert*-butyl peroxybenzoate (TBPB), $K_2S_2O_8$, dicumylperoxide (DCP), and di-*tert*-butyl peroxide (DTBP), were investigated, and it was found that DCP and DTBP are more efficient than other oxidants (entries s4−s8, SI). Among the latter two, DTBP was superior to DCP (entry s8, SI) as the oxidant. Encouraged by these results, a series of metal catalysts including CuI, CuO, Cu_2O, $FeCl_2$, and $FeCl_3$ were employed for the system; $FeCl_2$ proved to give the highest catalytic activity (entry 12 vs entries s9-s11 and s13, SI). Accordingly, the amounts of both $FeCl_2$ and DTBP were examined (entries s14 and s15, SI); it turned out that 10 mol % of $FeCl_2$ and 4.0 equiv of DTBP gave the highest yield of 89%.

With the above conditions in hand, the scope of 1,7-enynes **1** was examined by reacting them with various simple cyclohexane **2a** (Scheme 3). With the benzenesulfonyl protection group (Ar^2) on the amine anchor, the variant of substituents on the arylalkynyl moiety including, Me, MeO, F, and Cl can tolerate the catalytic conditions well. Electronic effect of substituents on the arylalkynyl moiety showed an obvious impact on the reaction

Scheme 3. Substrate Scope for Synthesis of 3[a]

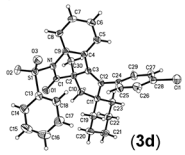


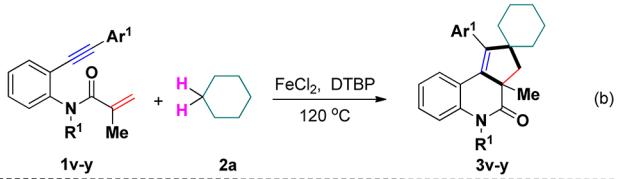
R = H
3a, Ar^1 = C_6H_5/Ar^2 = Ph (89%)
3b, Ar^1 = 4-MePh/Ar^2 = Ph (75%)
3c, Ar^1 = 4-MeOPh/Ar^2 = Ph (84%)
3d, Ar^1 = 4-ClPh/Ar^2 = Ph (62%)
3e, Ar^1 = 4-FPh/Ar^2 = Ph (74%)
3f, Ar^1 = 4-MePh/Ar^2 = 4-MeOPh (86%)
3g, Ar^1 = 4-MePh/Ar^2 = 4-ClPh (63%)
3h, Ar^1 = 4-MeOPh/Ar^2 = 4-MePh (82%)
3i, Ar^1 = 4-MeOPh/Ar^2 = 4-MeOPh (85%)
3j, Ar^1 = 4-MeOPh/Ar^2 = 4-BrPh (57%)
3k, Ar^1 = 4-ClPh/Ar^2 = 4-ClPh (52%)
3l, Ar^1 = 4-ClPh/Ar^2 = 4-MeOPh (66%)

R = F
3u, Ar^1 = Ph/Ar^2 = Ph (66%)

R = Me
3m, Ar^1 = Ph/Ar^2 = 4-*t*-BuPh (83%)
3n, Ar^1 = Ph/Ar^2 = 2-ClPh (70%)
3o, Ar^1 = Ph/Ar^2 = 3-BrPh (60%)
3p, Ar^1 = 4-MePh/Ar^2 = Ph (88%)
3q, Ar^1 = 4-MePh/Ar^2 = 2-Np (82%)

R = Cl
3r, Ar^1 = Ph/Ar^2 = Ph (63%)
3s, Ar^1 = 4-MePh/Ar^2 = Ph (60%)
3t, Ar^1 = 4-MePh/Ar^2 = 4-MeOPh (57%)


(3d)



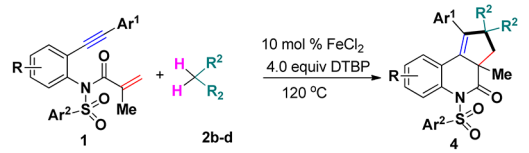
3v, Ar^1 = 4-FPh/R^1 = Me (50%)
3w, Ar^1 = 4-MeOPh/R^1 = Me (62%)
3x, Ar^1 = 4-FPh/R^1 = Et (70%)
3y, Ar^1 = 4-FPh/R^1 = H (trace)

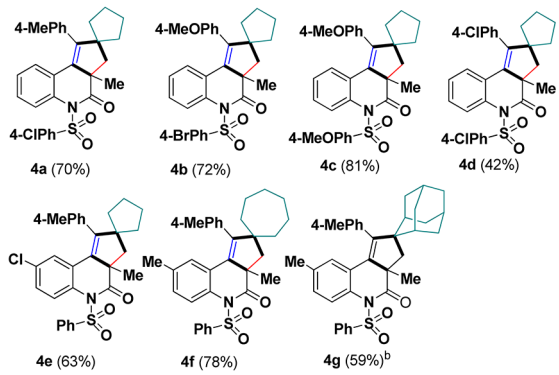
[a]Reaction conditions: 1,7-conjugated enynes (0.25 mmol), $FeCl_2$ (0.025 mmol), DTBP (1.0 mmol), 2.0 mL of cyclohexane as solvent, 120 °C, 12 h. Isolated yields based on **1**.

efficiency. Upon the treatment with substrate **1a**, the desired product **3a** was obtained in 89% yield. Interestingly, substrate **1a** carrying electron-donating groups showed higher reactivity than those with electron-withdrawing counterparts (**3b**, **3c** and **3f** vs **3d** and **3e**). Electronic nature of substituents on both *N*-arylsulfonyl (Ar^2) and arylalkynyl (Ar^1) moieties was also probed. The reaction occurred smoothly with a variety of functional groups on both *N*-arylsulfonyl and arylalkynyl moieties of substrates **1**. Reactions of substrates **1** involving both *N*-arylsulfonyl and arylalkynyl moieties attached by electron-donating groups all worked efficiently to give the spirocyclic cyclopenta[*c*]quinolines in 82% to 86% yields (**3f**, **3h**, and **3i**). The substrates **1** bearing -Cl and -F on *N*-phenyl moiety can also lead to the formation of cyclopenta[*c*]quinolines **3r**−**3u** ranging from 57%−66% yields. *N*-2-naphthalenylsulfonyl (2-Npsulfonyl) 1,7-enynes were successfully engaged in this radical cyclization cascades. Alternatively, *N*-methyl and *N*-ethyl 1,7-enynes **1v**−**1x** were successfully converted into the corresponding *N*-methyl and *N*-ethyl spirocyclic cyclopenta[*c*]quinolines **3v**−**3x** in 50−70% yields (Scheme 3b). As expected, 1,7-enynes with a free amino group (**1y**) gave a complex mixture (Scheme 3b, **3y**). Unfortunately, replacing methyl group with hydrogen on the terminal olefin unit, 1,7-conjugated enynes did not occur under the standard conditions, which indicates that the methyl group linked to terminal olefin unit plays a key role in the success of this reaction.

To expand the synthetic utility of this reaction, several cycloalkanes were employed to react with 1,7-enynes (Scheme 4). Using cyclopentane **2b** as replacement for cyclohexane **2a**,

Scheme 4. Substrate Scope for Synthesis of 4[a]





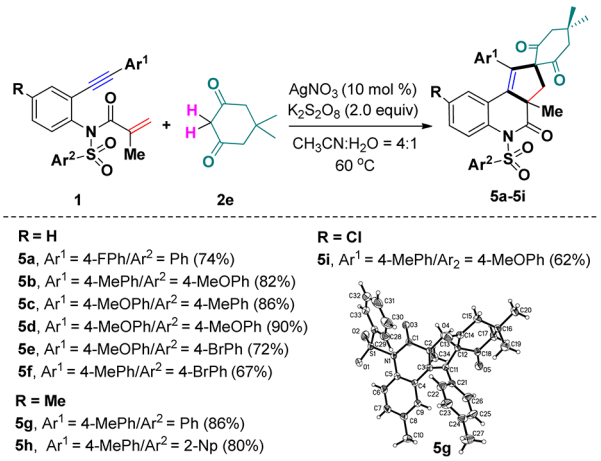
[a]Reaction conditions: 1,7-conjugated enynes (0.25 mmol), $FeCl_2$ (0.025 mmol), DTBP (1.0 mmol), 2.0 mL of cycloalkane as solvent, 120 °C, 12 h. Isolated yields based on **1**. [b]1,7-conjugated enynes (0.25 mmol), adamantine (1.25 mmol), DTBP (1.0 mmol), 2.0 mL of chlorobenzene as a solvent, 120 °C, 12 h.

different groups on 1,7-enynes were proven to be suitable for this domino process, providing the desired products **4a**−**4e** in moderate to good yields (Scheme 4). In addition, cycloheptane **2c** and adamantine **2d** were also found to be suitable for this reaction. Our next efforts were on studying the feasibility of the radical spirocyclization using difunctional C-centered radicals, such as cyclo-1,3-dicarbonyls,[11] to replace cycloalkanes. The

DOI: 10.1021/jacs.5b05735
J. Am. Chem. Soc. 2015, 137, 8928−8931

reaction between 1,7-enynes **1e** and 5,5-dimethylcyclohexane-1,3-dione **2e** was conducted. Surprisingly, the reaction cannot proceed under the above conditions, which forced us to search for a new condition with regard to catalysis, oxidants, and solvents. We found that the use of $AgNO_3$ (10 mol %) and $K_2S_2O_8$ (2.0 equiv) in the mixed solvent of CH_3CN and H_2O (v/v: 4:1)[9b] can drive the reaction to give product **5a** in 74% yield (Scheme 5). A great scope is shown by various substituents,

Scheme 5. Substrate Scope for Synthesis of 5[a]



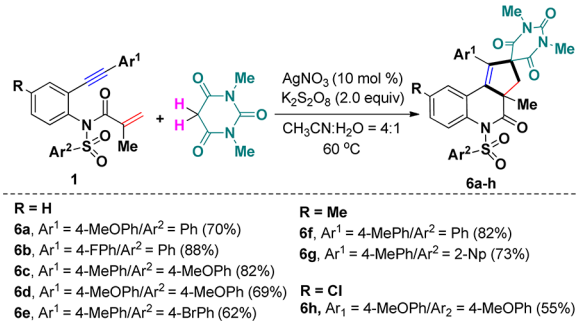
[a]Reaction conditions: 1,7-conjugated enynes (0.25 mmol), 5,5-dimethylcyclohexane-1,3-dione (0.50 mmol), $AgNO_3$ (0.025 mmol), $K_2S_2O_8$ (0.5 mmol), 2.0 mL of CH_3CN:H_2O = 4:1 as solvent, 60 °C, 20 h. Isolated yields based on **1**.

including methoxyl, methyl, fluoro, and bromo on the arylalkyne moieties or on the sulfonyl-attached aryl rings of the substrates, affording spiro-cyclo-1,3-dicarbonyl-substituted cyclopenta[*c*]-quinolines **5a**−**5f** in 67%−90% chemical yields. Similarly, acrylamides attached with either electron-donating or -with-drawing moieties at the 4-position of *N*-sulfonyl aromatic rings were converted into the corresponding spiro-substituted cyclopenta[*c*]quinolines **5g**−**5i** in good yields as well.

It is well-known that barbituric acids loaded with pyrimidine motifs widely exist in natural compounds, and their derivatives can serve as anxiolytics, sleeping pills, antispasmodic, and central nervous system sedatives,[12,13] and we thus explored the synthesis of these compounds by using 1,3-dimethylpyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (1,3-dimethyl barbituric acid) as biradical donors. To our delight, the reactions using various 1,7-conjugated enynes **1** in the presence of 10 mol % of $AgNO_3$ and 2.0 equiv of $K_2S_2O_8$ in a 4:1 ratio of MeCN-H_2O mixture at 60 °C led to the formation of products **6a**−**6h** in modest to good yields (Scheme 6). Substrates with different substitution patterns on the aromatic rings of both the alkynyl (Ar^1) and sulfonyl (Ar^2) moieties in **1** can be efficiently converted into the corresponding tetracyclic spiro[cyclopenta[*c*]quinoline-2,5′-pyrimidine]-2′,4,4′,6′(3′*H*, 5*H*)-tetraones **6a**−**6e** in good yields.

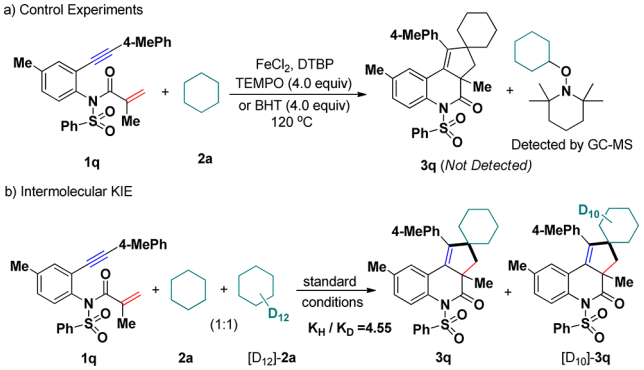
To understand the mechanism, the substrate **1q** was subjected to reaction with 2 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or butylhydroxytoluene (BHT) (Scheme 7a), but no expected product **3q** was observed with the starting material **1q** remaining. For the former reaction, the TEMPO-Cy adduct was detected by GC-MS (MS = 239.2) analysis, which indicates the possible radical mechanism. Subsequently, the deuterium labeling experiment was performed to show a significant kinetic

Scheme 6. Substrate Scope for Synthesis of 6[a]



[a]Reaction conditions: 1,7-conjugated enynes (0.25 mmol), 1,3-dimethylbarbituric acid (0.50 mmol), $AgNO_3$ (0.025 mmol), $K_2S_2O_8$ (0.5 mmol), 2.0 mL of CH_3CN:H_2O = 4:1 as solvent, 60 °C, 20 h. Isolated yields based on **1**.

Scheme 7. Mechanistic Study[a]



[a]Reaction conditions: 1,7-conjugated enynes (0.25 mmol), $FeCl_2$ (0.025 mmol), DTBP (1.0 mmol), 2.0 mL of cyclohexane as solvent, 120 °C, 12 h.

isotope effect (KIE, KIE = 4.55) in an intermolecular competing reaction of **2a** and [D_{12}]-**2a** (Scheme 7b), which confirmed that the rupture of C(sp^3)-H bonds on the cyclohexane ring occurs at the rate-determining step.

On the basis of the above analysis and literature survey,[2a,b,9b,11] the mechanisms were proposed and represented by the formation of spiro products **3**−**6**, (see Supporting Information). In the former, the first step is to abstract H from the cycloalkanes by *tert*-butoxy radical generated *in situ* from the Fe(II))-assisted homolysis of DTBP. The resulting cycloalkyl radical undergoes an *α*,*β*-conjugated addition followed by intramolecular radical addition onto 1,7-conjugated enynes **1** to give radical intermediate **A**, which undergoes 6-*exo*-*dig* cyclization to afford vinyl radical intermediate **B**. The intramolecular radical coupling between vinyl radical **B** and the cycloalkyl radical leads to the formation of spiro product **3**. The latter undergoes similar radical addition (**1** to **C**), 6-*exo*-*dig* cyclization (**C** to **D**), and radical coupling (**D** to **5** and **6**) sequences mediated by $AgNO_3$ and $K_2S_2O_8$ (Scheme 7). Although the generation of alkyl radicals triggered by various oxidants has been achieved well, the *α*,*α*-C(sp^3)-H bifunctionalization toward sprio-heterocycles via dual radical H-abstractions is very rare in organic chemistry as mentioned earlier.

In summary, we have discovered a new cascade spirocyclization reaction of 1,7-conjugated enynes with cycloalkanes and cyclo-1,3-dicarbonyls through a unpresented *α*,*α*-C(sp^3)-H bifunctionalization activation under mild catalytic conditions.

DOI: 10.1021/jacs.5b05735
J. Am. Chem. Soc. 2015, 137, 8928−8931

This reaction provides an easy access to a series of spiro cyclopenta[*c*]quinolines of chemical and biomedical importance. The bond-forming efficiency, accessibility of starting materials, functional group tolerance, and the scalable potential makes this reaction a powerful synthetic tool with a great substrate scope. Further investigation on the scope extension and asymmetric version of this reaction is currently underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details including product characterization and NMR-experiments. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b05735.

■ AUTHOR INFORMATION

Corresponding Authors

*jiangchem@jsnu.edu.cn
*laotu@jsnu.edu.cn
*guigen.li@ttu.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from the NSFC (nos. 21332005, 21232004, 21272095, and 21472071), PAPD of Jiangsu Higher Education Institutions, the Qing Lan Project (12QLG006), the Outstanding Youth Fund of JSNU (YQ2015003), Robert A. Welch Foundation (D-1361, USA), and NIH (R33DA031860, USA), and NSF of JSNU (14XLR005).

■ REFERENCES

(1) For selected reviews: (a) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34. (b) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813. (c) Bruneau, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2328. (d) Zhang, L.; Sun, J.; Kozmin, S. *Adv. Synth. Catal.* **2006**, *348*, 2271. (e) Marco-Contelles, J.; Soriano, E. *Chem. - Eur. J.* **2007**, *13*, 1350. (f) Fuerstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (g) Lee, S. I.; Chatani, N. *Chem. Commun.* **2009**, *4*, 371−384. (h) Watson, I. D. G.; Toste, F. D. *Chem. Sci.* **2012**, *3*, 2899. (i) Wille, U. *Chem. Rev.* **2013**, *113*, 813.

(2) For selected examples of 1,*n*-enyne cyclization, see: (a) Liu, Y.; Zhang, J.-L.; Song, R.-J.; Qian, P.-C.; Li, J.-H. *Angew. Chem., Int. Ed.* **2014**, *53*, 9017. (b) Wang, Z.-Q.; Zhang, W.-W.; Gong, L.-B.; Tang, R.-Y.; Yang, X.-H.; Liu, Y.; Li, J.-H. *Angew. Chem., Int. Ed.* **2011**, *50*, 8968. (c) Liu, P.; Fukui, Y.; Tian, P.; He, Z.-T.; Sun, C.-Y.; Wu, N.-Y.; Lin, G.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 11700. (d) Fehr, C.; Galindo, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2901.

(3) For representative examples of the 1,*n*-enyne cyclization using other low-cost metals, see: (a) Fuerstner, A.; Martin, R.; Majima, K. *J. Am. Chem. Soc.* **2005**, *127*, 12236. (b) O'Conner, J. M.; Friese, S. J.; Rodgers, B. L. *J. Am. Chem. Soc.* **2005**, *127*, 16342. (c) Sylvester, K. T.; Chirik, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 8772. (d) Trost, B. M.; Tour, J. M. *J. Am. Chem. Soc.* **1987**, *109*, 5268. (e) Chen, M.; Weng, Y.; Guo, M.; Zhang, H.; Lei, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2279.

(4) For selected reviews, see: (a) *Domino Reactions in Organic Synthesis*; Tietze, L. F., Brasche, G., Gericke, K. M., Eds.; Wiley-VCH: Weinheim, 2006. (b) Michelet, V.; Toullec, P. Y.; Genet, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268. (c) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (d) Aubert, C.; Fensterbank, L.; Garcia, P.; Malacria, M.; Simonneau, A. *Chem. Rev.* **2011**, *111*, 1954. (e) *Domino Reactions*; Tietze, L. F., Ed.; Wiley-VCH, Weinheim, 2014. (f) Jiang, B.; Rajale, T.; Wever, W.; Tu, S.-J.; Li, G. *Chem. - Asian J.* **2010**, *5*, 2318.

(5) For selected transition-metal-initiated radical reaction for sp^3 C−H bond functionalization: (a) Iqbal, J. B.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519. For selected examples, see: (b) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 56. (c) Zhang, Y.; Li, C.-J. *Angew. Chem., Int. Ed.* **2006**, *45*, 1949. (d) Li, Z.; Cao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2007**, *46*, 6505. (e) Li, Z.; Yu, R.; Li, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7497. (f) He, C.; Guo, S.; Ke, J.; Hao, J.; Xu, H.; Chen, H.; Lei, A. *J. Am. Chem. Soc.* **2012**, *134*, 5766.

(6) For selected examples of sp^3 C−X (X = O, N) bond formation via sp^3 C−H bond activation, see: (a) Kamata, K.; Yonehara, K.; Nakagawa, Y.; Uehara, K.; Mizuno, N. *Nat. Chem.* **2010**, *2*, 478. (b) Chen, M. S.; White, M. C. *Science* **2010**, *327*, 566. (c) Harvey, M. E.; Musaev, D. G.; Du Bois, J. *J. Am. Chem. Soc.* **2011**, *133*, 17207. (d) Nadres, E. T.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 7. (e) Michaudel, Q.; Thevenet, D.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 2547. (f) Zhang, S. Y.; He, G.; Zhao, Y. S.; Wright, K.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 7313. (g) Simmons, E. M.; Hartwig, J. F. *Nature* **2012**, *483*, 70. (h) Hennessy, E. T.; Betley, T. A. *Science* **2013**, *340*, 591. (i) Gormisky, P. E.; White, M. C. *J. Am. Chem. Soc.* **2013**, *135*, 14052.

(7) For selected reviews on C(sp^3)−H bond activation, see: (a) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069. (b) Li, C. *Acc. Chem. Res.* **2009**, *42*, 335. (c) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (d) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (e) Roizen, J. L.; Harvey, M. E.; Du Bois, J. *Acc. Chem. Res.* **2012**, *45*, 911. (f) White, M. C. *Science* **2012**, *335*, 807. (g) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726.

(8) (a) Jiang, B.; Tu, S.-J.; Kaur, P.; Wever, W.; Li, G. *J. Am. Chem. Soc.* **2009**, *131*, 11660. (b) Li, T.-J.; Yin, H.-M.; Yao, C.-S.; Wang, X.-S.; Jiang, B.; Tu, S.-J.; Li, G. *Chem. Commun.* **2012**, *48*, 11966. (c) Jiang, B.; Li, Q.-Y.; Zhang, H.; Tu, S.-J.; Pindi, S.; Li, G. *Org. Lett.* **2012**, *14*, 700. (d) Fan, W.; Ye, Q.; Xu, H.-W.; Jiang, B.; Wang, S.-L.; Tu, S.-J. *Org. Lett.* **2013**, *15*, 2258. (e) Jiang, B.; Ye, Q.; Fan, W.; Wang, S.-L.; Tu, S.-J.; Li, G. *Chem. Commun.* **2014**, *50*, 6108.

(9) (a) Kong, W.; Fuentes, N.; Garcia-Dominguez, A.; Merino, E.; Nevado, C. *Angew. Chem., Int. Ed.* **2015**, *54*, 2487. (b) Fuentes, N.; Kong, W.; Fernandez-Sanchez, L.; Merino, E.; Nevado, C. *J. Am. Chem. Soc.* **2015**, *137*, 964. (c) Kong, W.; Merino, E.; Nevado, C. *Angew. Chem., Int. Ed.* **2014**, *53*, 5078. (d) Kong, W.; Casimiro, M.; Fuentes, N.; Merino, E.; Nevado, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 13086.

(10) For selected examples of C(sp^3)−H bond functionalization of cyclohexane, see: (a) Guo, L.-N.; Wang, S.; Duan, X.-H.; Zhou, S.-L. *Chem. Commun.* **2015**, *51*, 4803. (b) Zhang, H.-L.; Pan, C.-D.; Jin, N.; Gu, Z. X.; Hu, H.-W.; Zhu, C.-J. *Chem. Commun.* **2015**, *51*, 1320. (c) Liu, Y.-G; Guan, X.-G.; Wong, E. L.-M.; Liu, P.; Huang, J.-S.; Che, C.-M. *J. Am. Chem. Soc.* **2013**, *135*, 7194. (d) Xia, J.-B.; Zhu, C.; Chen, C. *Chem. Commun.* **2014**, *50*, 11701. (e) Michaudel, Q.; Thevenet, D.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 2547. (f) Jang, E. S.; McMullin, C. L.; Kass, M.; Meyer, K.; Cundari, T.-R.; Warren, T. H. *J. Am. Chem. Soc.* **2014**, *136*, 10930. (g) Ohmura, T.; Torigoe, T.; Suginome, M. *Chem. Commun.* **2014**, *50*, 6333. (h) Oohora, K.; Kihira, Y.; Mizohata, E.; Inoue, T.; Hayashi, T. *J. Am. Chem. Soc.* **2013**, *135*, 17282.

(11) (a) Wang, H.; Guo, L.-N.; Duan, X.-H. *Chem. Commun.* **2013**, *49*, 10370. (b) Wang, H.; Guo, L.-N.; Duan, X.-H. *Org. Lett.* **2013**, *15*, 5254.

(12) (a) Szostak, M.; Spain, M.; Sautier, B.; Procter, D. J. *Org. Lett.* **2014**, *16*, 5694. (b) Young, M. C.; Liew, E.; Hooley, R. J. *Chem. Commun.* **2014**, *50*, 5043. (c) Szostak, M.; Sautier, B.; Procter, D. J. *Chem. Commun.* **2014**, *50*, 2518. (d) Szostak, M.; Sautier, B.; Spain, M.; Behlendorf, M.; Procter, D. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 12559. (e) Ballard, P.; Rowland, M. *Drug Metab. Dispos.* **2011**, *39*, 2165. (f) Singh, P.; Kaur, J.; Bhardwaj, A. *Eur. J. Med. Chem.* **2010**, *45*, 1256.

(13) (a) Dhokale, R. A.; Thakare, P. R.; Mhaske, S. B. *Org. Lett.* **2012**, *14*, 3994. (b) Reddy, L. S.; Babu, N. J.; Nangia, A. *Chem. Commun.* **2006**, *13*, 1369. (c) Rencurel, F.; Stenhouse, A.; Hawley, S. A.; Friedberg, T.; Hardie, D. G.; Sutherland, C.; Wolf, C. R. *J. Biol. Chem.* **2005**, *280*, 4367. (d) Woisetschlager, O. E.; Sunkel, K.; Weigand, W.; Beck, W. *J. Organomet. Chem.* **1999**, *584*, 122. (e) Dudley, K. H.; Davis, I. J.; Kim, D. K.; Ross, F. T. *J. Org. Chem.* **1970**, *35*, 147.

DOI: 10.1021/jacs.5b05735
J. Am. Chem. Soc. 2015, 137, 8928−8931