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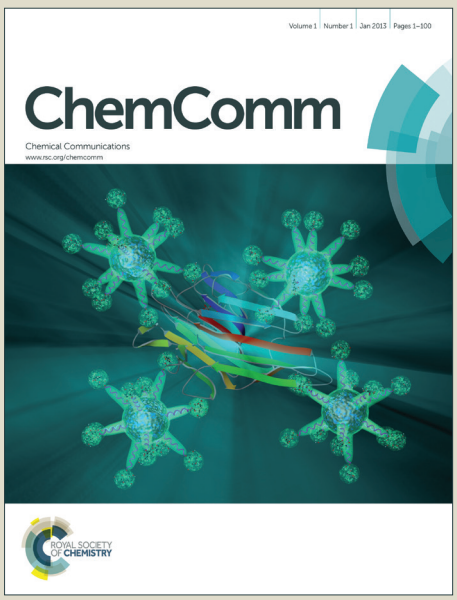

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Palladium-Catalyzed Oxidative 6-*exo*-trig Cyclization of 1,6-Enynes. Facile Synthesis of Bicyclo[4.1.0]heptan-5-ones

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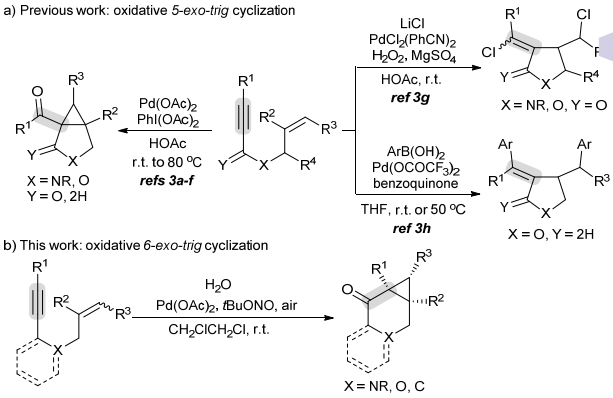
We here describe a new palladium-catalyzed oxidative *6-exo-trig* cyclization of 1,6-enynes at room temperature using *t*BuONO as oxidant for the synthesis of 3-bicyclo[4.1.0]heptan-5-ones. This cascade strategy achieves hydration, cyclization and cyclopropanation sequence, and represents a new transition-metal-catalyzed oxidative cyclization of 1,6-enynes through the *6-exo-trig* fashion.

Transition-metal-catalyzed cyclization of 1,n-enynes has become a powerful and atom-economical method for building diverse carbo- and hetero-cyclic frameworks.[1-6] Generally, the majority of these processes utilize three strategies, including cycloisomerization, skeletal rearrangement and metathesis.[1] However, these strategies deliver the carbo- and hetero-cyclic products with limited complex ring systems because within them the intermolecular incorporation of new functional groups into the ring systems from additional functional reagents is difficult. An alternative strategy includes transition-metal-catalyzed oxidative cyclization of 1,n-enynes,[2-5] which offers several advantages over the three classical strategies because various new functional groups are easily introduced into the ring systems and the functionalization of both positions of the π bond in the alkene and alkyne moieties occur. However, successful palladium-catalyzed oxidative cyclization of 1,n-enynes are quite rare and are limited to the *5-exo-trig* fashion (Scheme 1a) [2,3] despite the enormous recent advances enjoyed by Au catalysts.[4] The group of Tse[3a] and the Group of Sanford[3b,3c] have independently report a new palladium-catalyzed oxidative cyclization of 1,6-enynes by using $PhI(OAc)_2$ oxidant in HOAc medium for the synthesis of bicyclo[3.1.0]hexanes through the *5-exo-trig* cyclization and S_N2 C-O formation.[3d-f] The group of Liu[3g] have described another new palladium-catalyzed oxidative *5-exo-trig* cyclization/dichlorination of 1,6-enynes with LiCl in the presence of H_2O_2 oxidant leading to dichloro-contained five membered heterocyclic compounds. Recently, a mild and efficient Pd-catalyzed oxidative diarylating carbocyclization of enynes using arylboronic acids as additional reactants and benzoquinone as oxidant was illustrated by the group of Bäckvall[3h] to stereoselectively assemble tetrahydrofurans and tetrahydropyranes. There is a lack of a new strategy for the palladium-catalyzed oxidative cyclization of 1,n-enynes. Herein, we report a novel palladium-catalyzed oxidative *6-exo-trig* cyclization of 1,6-enynes (**1**) with the aid of *t*BuONO[7,8] at room temperature for the synthesis of bicyclo[4.1.0]heptan-5-one derivatives (Scheme 1b), which are important core structures in many natural products and pharmaceuticals.[9]



Scheme 1 Pd-Catalyzed Oxidative Cyclization of 1,6-Enynes.

Our studies began with the cyclization of 4-methyl-N-(2-methylallyl)-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (**1a**) for reaction condition optimization (Table 1). After a series of trials, we found that treatment of 1,6-enyne **1a** with 5 mol% $Pd(OAc)_2$ and 1.5 equiv *t*BuONO afforded the desired 3-azabicyclo[4.1.0]heptan-5-one **2a**[10] in 75% yield (entry 1). Screening of the amount of *t*BuONO revealed that the identical yield to that of 1.5 equiv *t*BuONO was achieved at a loading

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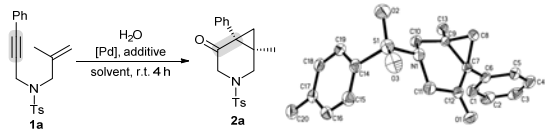
2 equiv *t*BuONO (entry 2), but the yield decreased from 75% to 58% by decreasing *t*BuONO to 1 equiv (entry 3). However, in the absence of *t*BuONO, the reaction did not deliver the detectable amounts of **2a** (entry 4). In light of these results, a number of oxidants, namely *n*AmONO, $AgNO_2$, $Fe(NO_3)_3$ and $PhI(OAc)_2$, were subsequently examined, and they were less effective than *t*BuONO (entry 1 versus entries 5-8). Two nitriles, *n*AmONO, and $Fe(NO_3)_3$, effected the reaction but decreased the yields of **2a** to 68% and 30%, respectively (entries 5 and 7). However, both $AgNO_2$ (entry 6) and $PhI(OAc)_2$ (entry 8) were inert for the cyclization reaction. Interestingly, the amount of water had a fundamental influence on the reaction, and 4 equiv H_2O was found to be the preferred choice (entry 1 versus entries 9 and 10). The results demonstrated that the Pd catalyst played an important role in the cyclization reaction, and its amount affected the reaction in terms of yields (entries 11-13). It should be noted that **2a** cannot be detected without Pd catalysts (entry 11), and 5 mol% $Pd(OAc)_2$ gave the best results (entry 1 versus entries 12 and 13). $Pd(TFA)_2$ had the same catalytic activity as $Pd(OAc)_2$ (entry 14), but $PdCl_2$ showed less activity (entry 15). Among the effect of the reaction temperatures (entry 16) and solvents (entries 17-1[illegible]) examined, it turned out that the use of CH_2ClCH_2Cl medium [illegible] room temperature was optimal for the reaction (entry 1). Th[illegible] results indicated that O_2 favoured the reaction (entries 1[illegible]2[illegible] and 21).The reaction under air or O_2 offered **2a** in good yie[illegible] (entries 1 and 20), but under argon the reactivity of 1,6-enyne **1a** was suppressed in a lower yield (entry 21).

Table 1. Screening of the Reaction Conditions.[a]

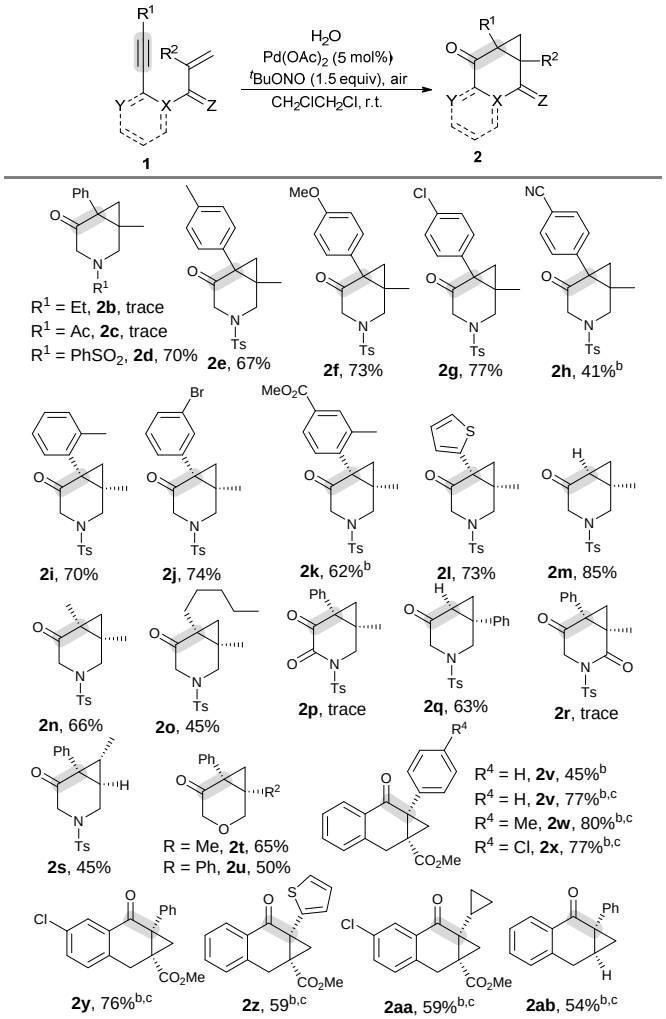


Entry	[M] [mol%]	Additive [equiv]	Solvent	Yield [%][b]
1	$Pd(OAc)_2$ (5)	*t*BuONO (1.5)	CH_2ClCH_2Cl	75
2	$Pd(OAc)_2$ (5)	*t*BuONO (2)	CH_2ClCH_2Cl	76
3	$Pd(OAc)_2$ (5)	*t*BuONO (1)	CH_2ClCH_2Cl	58
4	$Pd(OAc)_2$ (5)	—	CH_2ClCH_2Cl	0
5	$Pd(OAc)_2$ (5)	*n*AmONO (1.5)	CH_2ClCH_2Cl	68
6	$Pd(OAc)_2$ (5)	$AgNO_2$ (1.5)	CH_2ClCH_2Cl	trace
7	$Pd(OAc)_2$ (5)	$Fe(NO_3)_3$ (1.5)	CH_2ClCH_2Cl	30
8	$Pd(OAc)_2$ (5)	$PhI(OAc)_2$ (1.5)	CH_2ClCH_2Cl	trace
9[c]	$Pd(OAc)_2$ (5)	*t*BuONO (1.5)	CH_2ClCH_2Cl	67
10[d]	$Pd(OAc)_2$ (5)	*t*BuONO (1.5)	CH_2ClCH_2Cl	71
11	—	*t*BuONO (1.5)	CH_2ClCH_2Cl	0
12	$Pd(OAc)_2$ (10)	*t*BuONO (1.5)	CH_2ClCH_2Cl	76
13	$Pd(OAc)_2$ (2)	*t*BuONO (1.5)	CH_2ClCH_2Cl	64
14	$Pd(TFA)_2$ (5)	*t*BuONO (1.5)	CH_2ClCH_2Cl	73
15	$PdCl_2$ (5)	*t*BuONO (1.5)	CH_2ClCH_2Cl	34
16[e]	$Pd(OAc)_2$ (5)	*t*BuONO (1.5)	CH_2ClCH_2Cl	76
17	$Pd(OAc)_2$ (5)	*t*BuONO (1.5)	CH_2Cl_2	64
18	$Pd(OAc)_2$ (5)	*t*BuONO (1.5)	MeCN	62
19	$Pd(OAc)_2$ (5)	*t*BuONO (1.5)	HOAc	30
20[f]	$Pd(OAc)_2$ (5)	*t*BuONO (1.5)	CH_2ClCH_2Cl	74
21[g]	$Pd(OAc)_2$ (5)	*t*BuONO (1.5)	CH_2ClCH_2Cl	59

[a] Reaction conditions: **1a** (0.2 mmol), H_2O (4 equiv), [Pd] (5% mol), additive, and anhydrous solvent (1 mL) at room temperature under air atmosphere for 16 h. [b] Yield of isolated product. [c] H_2O (2 equiv). The coversion of **1a** is 89%. [d] H_2O (8 equiv). [e] At 40 °C. [f] Under O_2 atmosphere. [g] Under argon atmosphere.

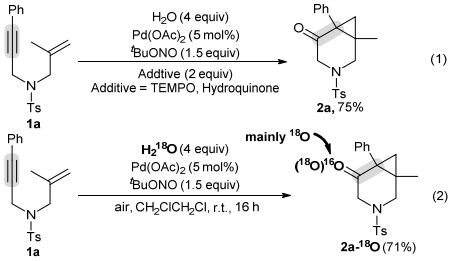
After establishing the optimal reaction conditions, we applied the palladium-catalyzed oxidative *6-exo*-trig cyclizatio[illegible] protocol to a variety of 1,6-enynes **1b-z**. As shown in Table 2, the substitution effect on the nitrogen atom had a crucial effect on the reactivity of substrates (**2b-d**). While substrates **1b** and **1c** with a Et group or an Ac group have no reactivity fo[illegible] the reaction (**2b** and **2c**), substrates **1d** with a $PhSO_2$ group wa[illegible] successfully converted into the corresponding 3[illegible] azabicyclo[4.1.0]heptan-5-one **2d** in 70% yield. In light of th[illegible] results, a wide range of *N*-Ts-substituted 1,6-enyens **1e-z** w[illegible] employed for the cyclization reaction under the optimal conditions (**2e-z**). To our delight, both electron-donating [illegible] **2f** and **2i**) and electron-withdrawing (**2g**, **2h**, **2j** and **2k**) aromatic substituents were well-tolerated at the termin[illegible] alkyne. For example, 1,6-enynes **1e** and **1i** with a *p*-MeC_6H_4 group or a *o*-MeC_6H_4 group were successfully converted into **2a** and **2i** in high yields. Moreover, halide substituents (Cl and Br) were compatible with the optimal conditions (**2g** and **2j**), thereby providing chances for further manipulation at the halogenated positions. 1,6-Enynes **1h** and **1k** having a strongly electron-withdrawing aromatic substituent (*p*-CNC_6H_4 or *p*-$CO_2MeC_6H_4$) were also viable substrates for assembling 3-azabicyclo[4.1.0]heptan-5-ones **2h** and **2k** in moderate yields, albeit with lower reactivity. Using heteroaryl alkyne [illegible] successfully reacted with H_2O, $Pd(OAc)_2$ and *t*BuONO, giving **2**[illegible] in 73% yield. It should be noted that terminal alkyne **1m** and aliphatic alkynes **1n-o** were consistent with the optimal conditions, and allowed the formation of **2m-2o** in moderate to good yields. However, electron-deficient alkyne **1p** or electron-deficient alkene **1r** were not suitable for the oxidative cyclization reaction (**1p** and **1r**). Gratifyingly, 1,6-enyne **1q**, bearing a Ph group at the 2 position of the allyl moiety, was found to smoothly deliver **2q** in 63% yield. An internal alkene **1s** was also viable substrate, stereoselectively giving **2**[illegible] according to 2D NMR analysis (see Supporting Information). The palladium-catalyzed oxidative *6-exo*-trig cyclization protocol could be applicable to the synthesis of 3-oxabicyclo[4.1.0]heptan-5-ones (**2t** and **2u**) and 1*H*-cyclopropa[*b*]naphthalen-2(1*aH*)-ones (**2v-aa**). 1,6-Enynes **1t** and **1u**, having a Me group or a Ph group at the 2 position of the allyl moiety, worked well with H_2O, $Pd(OAc)_2$ and *t*BuONO, offering **2t** and **2u** in moderate yields. For 1-allyl-2-ethynylbenzenes **1v-ab**, the corresponding 1*H*-cyclopropa[*b*]naphthalen-2(1*aH*)-ones **2v-ab** were successfully constructed in moderate to high yields, although 10 mol% $AgSbF_6$ was required to improve the cyclizaition process. For example, treatment of 1,6-enyne **1v** with H_2O, $Pd(OAc)_2$ and *t*BuONO for 24 h afforded **2v** in 45% yield, whereas with additional $AgSbF_6$ increased the yield to 77% yield.

Table 2. Substrate Scope.[a]



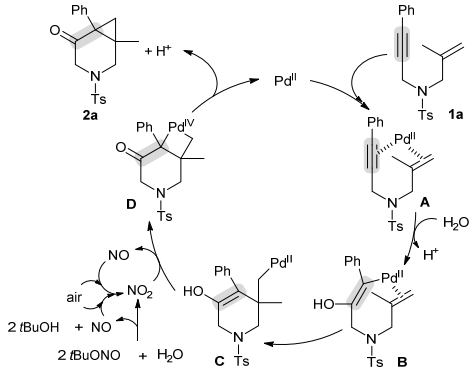
[a] Reaction conditions: **1** (0.2 mmol), H_2O (4 equiv), $Pd(OAc)_2$ (5 mol%), *t*BuONO (1.5 equiv), and anhydrous CH_2ClCH_2Cl (1 mL). [b] For 24 h. [c] $AgSbF_6$ (10 mol%) was added.

Some control experiments were performed to understand the mechanism (Scheme 2). We found that the radical inhibitors (TEMPO and hydroquinone) had no effect on the reaction of 1,6-enyne **1a**, ruling out a radical process [Eq (1)]. Subsequently, an ^{18}O-Labeled experiment by using $H_2{}^{18}O$ was investigated [Eq (2)]. The result showed that ^{18}O-containing product **2a-^{18}O** was isolated in 71% yield, suggesting that H_2O was the major resource of the oxygen atom in the new formed carbonyl group.



Scheme 2 Control Experiment.

The mechanism outlined in Scheme 3 for the oxidative cyclization reaction is proposed on the basis of the above results and previous reports.[2,3,7,8] Initially, complex of the active Pd^{II} species with the C-C double bond and the C-C triple bond of 1,6-enyne **1a** affords intermediate **A**, followed by hydration of the C-C triple bond with the active Pd^{II} species and H_2O gives intermediate **B**. Cyclization with the C-C double bond within intermediate **B** easily occurs to produce intermediate **C**. A Pd^{IV} intermediate **D**[8l-n] is formed from oxidative cyclization of intermediate **C** by NO_2 and air, [8] in-situ generated from *t*BuONO and H_2O.[7] Finally, reductive elimination of the Pd^{IV} intermediate **D** delivers product **2a** and regenerates the active Pd^{II} species.



Scheme 3. Possible Mechanism.

In summary, we have report a new strategy for the oxidative *6-exo*-trig cyclization by using $Pd(OAc)_2$ as the catalyst and *t*BuONO as the oxidant. This 1,6-enyne cyclization method proceeds through hydration, *6-exo*-trig cyclization and cyclopropanation cascade, and provides a mild and selective access to diverse bicyclo[4.1.0]heptan-5-one skeletons, including 3-azabicyclo[4.1.0]heptan-5-ones, 3-oxabicyclo[4.1.0]heptan-5-ones and 1′-cyclopropa[*b*]naphthalen-2(1*aH*)-ones, in moderate to good yields with excellent functional group tolerance and stereoselectivity. Further applications of this catalytic oxidative cyclization method in synthesis and detailed mechanistic studies are currently underway in our laboratory.

Notes and references

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1 (a) B. M. Trost, *Acc. Chem. Res.*, 1990, **23**, 34; (b) J. Tsuji, *Palladium Reagents and Catalysts*; John Wiley & Sons: Chichester, 1995; (c) I. Ojima, M. Tzamarioudaki, Z. Li and R. J. Donovan, *Chem. Rev.*, 1996, **96**, 635; (d) I. J. S. Fairlamb, *Angew. Chem. Int. Ed.*, 2004, **43**, 1048; (e) S. T. Diver and A. J. Giessert, *Chem. Rev.*, 2004, **104**, 1317; (f) H. Villar, M. Frings and C. Bolm, *Chem. Soc. Rev.*, 2007, **36**, 55; (g) C. Aubert, O. Buisine and M. Malacria, *Chem. Rev.*, 2002, **102**, 813; (h) C.

Bruneau, *Angew. Chem. Int. Ed.*, 2005, **44**, 2328; (i) K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, *Angew. Chem. Int. Ed.*, 2006, **45**, 7134; (j) J. Marco-Contelles and E. Soriano, *Chem. Eur. J.*, 2007, **13**, 1350; (k) A. Fürstner and P. W. Davies, *Angew. Chem. Int. Ed.*, 2007, **46**, 3410; (l) V. Michelet, P. Y. Toullec and J.-P. Genêt, *Angew. Chem. Int. Ed.*, 2008, **47**, 4268; (m) E. Jiménez-Núñez and A. M. Echavarren, *Chem. Rev.*, 2008, **108**, 3326; (n) S. I. Lee and N. Chatani, *Chem. Commun.*, 2009, 371; (o) I. D. G. Watson and F. D. Toste, *Chem. Sci.*, 2012, **3**, 2899;

2 For special reviews on the oxidative cyclization of 1,*n*-enynes: (a) L. N. S. Comprido and A. S. K. Hashmi, *Isr. J. Chem.* 2013, **53**, 883; (b) Y.-X Xie, R.-J. Song, J.-N. Xiang and J.-H. Li, *Chin. J. Org. Chem.* 2012, **32**, 1555.

3 Generally, palladium-catalyzed oxidative cyclization of 1,6-enyens via the *5-exo-trig* fashion: (a) X. Tong, M. Beller and M. K. Tse, *J. Am. Chem. Soc.* 2007, **129**, 4906; (b) L. L. Welbes, T. W. Lyons, K. A. Cychosz and M. S. Sanford, *J. Am. Chem. Soc.* 2007, **129**, 5836; (c) T. W. Lyons and M. S. Sanford, *Tetrahedron* 2009, **65**, 3211; (d) H. Liu, J. Yu, L. Wang and X. Tong, *Tetrahedron Lett.* 2008, **49**, 6924; (e) T. Tsujihara, K. Takenaka, K. Onitsuka, M. Hatanaka and H. Sasai, *J. Am. Chem. Soc.* 2009, **131**, 3452; (f) S. J. Welsch, M. Umkehrer, G. Ross, J. Kolb, C. Burdack and L. A. Wessjohann, *Tetrahedron Lett.* 2011, **52**, 6295; (g) G. Yin and G. Liu, *Angew. Chem. Int. Ed.* 2008, **47**, 5442; (h) M. Jiang, T. Jiang and J.-E. Bäckvall, *Org.*

4 Generally, gold-catalyzed oxidative cyclization of 1,*n*-enyens via the *dig* fashion: (a) C. A. Witham, P. Mauleón, N. D. Shapiro, B. D. Sherry and F. D. Toste, *J. Am. Chem. Soc.* 2007, **129**, 5838; (b) B. P. Taduri, S. M. Abu Sohel, H.-M. Cheng and R.-S. Liu, *Chem. Commun.* 2007, 2530; (c) D. Vasu, H.-H. Hung, S. Bhunia, S. A. Gawade, A. Das and R.-S. Liu, *Angew. Chem. Int. Ed.* 2011, **50**, 6911; (d) S. Bhunia, S. Ghorpade, D. B. Huple and R.-S. Liu, *Angew. Chem. Int. Ed.* 2012, **51**, 2939; (e) S. Ghorpade, M.-D. Su and R.-S. Liu, *Angew. Chem. Int. Ed.* 2013, **52**, 4229; (f) D. Qian and J. Zhang, *Chem. Commun.* 2011, **47**, 11152; (g) W. Wang, J. Yang, F. Wang and M. Shi, *Organometallics* 2011, **30**, 3859; (h) K. Ji and L. Zhang, *Org. Chem. Front.* 2014, **1**, 34; for selected special reviews on α-carbonyl gold carbenoids, see: (i) J. Xiao and X. Li, *Angew. Chem. Int. Ed.* 2011, **50**, 7226; (j) M. C. B. Jaimes and A. S. K. Hashmi, in *Modern Gold Catalyzed Synthesis* (Eds.: A. S. K. Hashmi, F. D. Toste), Wiley-VCH, Weinheim, 2012, pp. 273-296; (k) L. Zhang, *Acc. Chem. Res.* 2014, **47**, 877.

5 For papers on the other oxidative cyclization of 1,*n*-enynes under the Cu-catalyzed conditions: (a) Z.-Q. Wang, W.-W. Zhang, L.-B. Gong, R.-Y. Tang, X.-H. Yang, Y. Liu and J.-H. Li, *Angew. Chem. Int. Ed.* 2011, **50**, 8968; (b) J. Zhang, D. Wu, X. Chen, Y. Liu and Z. Xu, *J. Org. Chem.* 2014, **79**, 4799; (c) X.-F. Xia, L.-L. Zhang, X.-R. Song, X.-Y. Liu and Y.-M. Liang, *Org. Lett.* 2012, **14**, 2480; (d) P. Gao, X.-B. Yan, T. Tao, F. Yang, T. He, X.-R. Song, X.-Y. Liu and Y.-M. Liang, *Chem. Eur. J.* 2013, **19**, 14420; (e) Y.-T. He, L.-H. Li, Z.-Z. Zhou, H.-L. Hua, Y.-F. Qiu, X.-Y. Liu and Y.-M. Liang, *Org. Lett.* 2014, **16**, 3896; under metal-free conditions: (f) Y. Liu, J.-L. Zhang, R.-J. Song, P.-C. Qian and J.-H. Li, *Angew. Chem. Int. Ed.* 2014, **53**, 9017; (g) M. Hu, R.-J. Song and J.-H. Li, *Angew. Chem. Int. Ed.* 2014, **53**, 608; (h) J.-Y. Luo, H.-L. Hua, Z.-S. Chen, Z.-Z. Zhou, Y.-F. Yang, P.-X. Zhou, Y.-T. He, X.-Y. Liu and Y.-M, Liang, *Chem. Commun.* 2014, **50**, 1564.

6 For representative papers on the cyclopropanation via the *6-endo-dig* cycloisomerization of 1,6-enynes catalyzed by Pd: (a) R. Grigg, R. Rasul, J. Redpath and D. Wilson, *Tetrahedron Lett.* 1996, **37**, 4609; (b) J. Bohmer, R. Grigg and J. D. Marchbank, *Chem. Commun.* 2002, 768; Au: (c) C. Nieto-Oberhuber, M. P. Muñoz, E. Buñuel, C. Nevado, D. J. Cárdenas and A. M. Echavarren, *Angew. Chem. Int. Ed.* 2004, **43**, 2402; (d) C.-M. Chao, D. Beltrami, P. Y. Toullec and V. Michelet, *Chem. Commun.* 2009, 6988; Pt: (e) J. Blum, H. Beer-Kraft and Y. Badrieh, *J. Org. Chem.* 1995, **60**, 5567; (f) A. Fürstner, H. Szillat and F. Stelzer, *J. Am. Chem. Soc.* 2000, **122**, 6785; (g) M. Méndez, M. P. Muñoz, C. Nevado, D. J. Cárdenas and A. M. Echavarren, *J. Am. Chem. Soc.* 2001, **123**, 10511; (h) A. Fürstner, F. Stelzer and H. Szillat, *J. Am. Chem. Soc.* 2001, **123**, 11863; Rh: (i) P. Costes, J. Weckesser, O. Dechy-Cabaret, M. Urrutigoïty and P. Kalck, *Appl. Organomet. Chem.* 2008, **22**, 211; (j) T. Nishimura, T. Kawamoto, M. Nagaosa, H. Kumamoto and T. Hayashi, *Angew. Chem. Int. Ed.* 2010, **49**, 1638; (k) T. Nishimura, Y. Takiguchi, Y. Maeda and T. Hayashi, Adv. Synth. Catal. 2013, **355**, 1374, and references cited therein; Ru: (l) F. Monnier, C. Vovard-Le Bray, D. Castillo, V. Aubert, S. Dérien, P. H. Dixneuf, L. Toupet, A. Ienco and C. Mealli, *J. Am. Chem. Soc.* 2007, **129**, 6037; (m) M. Eckert, V. Moulin, F. Monnier, I. D. Titanyuk, S. N. Osipov, T. Roisnel, S. Dérien and P. H. Dixneuf, *Chem. Eur. J.* 2011, **17**, 9456; Ir: (n) T. Shibata, Y. Kobayashi, S. Maekawa, N. Toshida and K. Takagi, *Tetrahedron* 2005, **61**, 9018; (o) S. H. Sim, S. I. Lee, J. H. Park and Y. K. Chung, *Adv. Synth. Catal.* 2010, **352**, 317, (p) M. Barbazanges, M. Augé, J. Moussa, H. Amouri, C. Aubert, C. Desmarets, L. Fensterbank, V. Gandon, M. Malacria and J. Ollivier, *Chem. Eur. J.* 2011, **17**, 13789; Cu: (q) C. Fehr, I. Farris and H. Sommer, *Org. Lett.* 2006, **8**, 1839.

7 For selected reviews and recent papers on the use of *t*BuONO in synthesis: (a) D. Koley, O. C. Colón and S. N. Savinov, *Org. Lett.* 2009, **11**, 4172; (b) T. Taniguchi, A. Yajima and H. Ishibashi, *Adv. Synth. Catal.* 2011, **353**, 2643; (c) C. Kilpatrick, M. Heller and S. Arns, *Chem. Commun.* 2013, **49**, 514; (d) S. Manna, S. Jana, T. Saboo, A. Maji and D. Maiti, *Chem. Commun.* 2013, **49**, 5286; (e) S. Maity, T. Naveen, U. Sharma and D. Maiti, *Org. Lett.* 2013, **15**, 3384; (f) B. Majhi, P. Kundu, S. Ahammed and B. C. Ranu, *Chem. Eur. J.* 2014, **20**, 9862; (g) T. Shen, Y. Yuan and N. Jiao, *Chem. Commun.* 2014, **50**, 554; (h) F. Chen, X. Huang, X. Li, T. Shen, M. Zou and N. Jiao, *Angew. Chem. Int. Ed.* 2014, **53**, 10495;

8 For papers on the use of *t*BuONO as oxidant: (a) H. Zhang and G. Wang, *Tetrahedron Lett.* 2014, **55**, 56; (b) B. Yu, Z.-F. Diao, A.-H. Liu, X. Han, B. Li, L.-N. He and X.-M. Liu, *Curr. Org. Synth.* 2014, **11**, 156; (c) L. Li, R. Matsuda, I. Tanaka, H. Sato, P. Kanoo, H. J. Jeon, M. L. Foo, A. Wakamiya, Y. Murata and S. Kitagawa, *J. Am. Chem. Soc.* 2014, **136**, 7543; For selected papers on the use of nitrites or NO_x within the Pd-catalyzed reactions: (d) M. A. Andrews and K. P. Kelly, *J. Am. Chem. Soc.* 1981, **103**, 2894; (e) M. A. Andrews and C.W. F. Cheng, *J. Am. Chem. Soc.* 1982, **104**, 4268; (f) F. Mares, S. E. Diamond and J. J. Regina, *J. Am. Chem. Soc.* 1985, **107**, 3545; (g) J. Dong, L. Jin and P. Sun, *Org. Lett.* 2014, **16**, 4540; (h) Z. K. Wickens, B. Morandi and R. H. Grubbs, *Angew. Chem. Int. Ed.* 2013, **52**, 11257; (i) Z. K.Wickens, K. Skakuj, B. Morandi and R. H. Grubbs, *J. Am. Chem. Soc.* 2014, **136**, 890; (j) Z. K. Wickens, E. E. Guzmán and R. H. Grubbs, *Angew. Chem. Int. Ed.* 2014, **53**, 236.

9 For selected papers: (a) P. Bissel, A. Khalil, J. M. Rimoldi, J. Igarashi, D. Edmondson, A. Miller and N. Castagnoli Jr, *Bioorg. Med. Chem.* 2008, **16**, 3557; (b) R. H. Belmaker and G. Agam, *N. Engl. J. Med.* 2008, **358**, 55; (c) T. M. Bridges, A. E. Brady, J. Phillip Kennedy, R. Nathan Daniels, N. R. Miller, K. Kim, M. J. Breininger, P. R. Gentry, J. T. Brogan, C. K. Jones, P. Jeffrey Conn and C. W. Lindsley, *Bioorg. Med. Chem. Lett.* 2008, **18**, 5439; (d) H. Xiong, B. Chen, T. F. Durand-Réville, C. Joubran, Y. W. Alelyunas, D. Wu and H. Huynh, *ACS Med. Chem. Lett.* 2014, **5**, 1143.

10 CCDC 1029834 (**2a**) contains the supplemental crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.