Organic LETTERS

Letter

pubs.acs.org/OrgLett

Highly Selective Construction of Medium-Sized Lactams by Palladium-Catalyzed Intramolecular Hydroaminocarbonylation of Aminoalkynes

Yue Hu[†,§] and Hanmin Huang*[,†,‡]

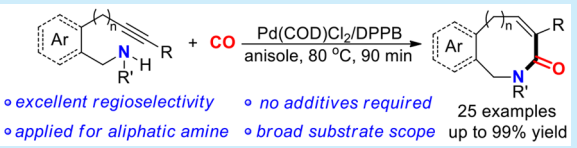
[†]State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, P. R. China

[‡]Department of Chemistry, University of Science and Technology of China, Hefei 230026, P. R. China

[§]University of Chinese Academy of Sciences, Beijing 100049, P. R. China

Supporting Information

ABSTRACT: A novel palladium-catalyzed intramolecular hydroaminocarbonylation of aminoalkynes has been developed. This direct and operationally simple protocol provides a rapid and reliable approach to a diverse array of valuable seven- and eight-membered lactams with high chemoselectivity and regioselectivity. The high selectivity might be attributed to rational tuning the electronic nature of the amine moiety and the palladium catalyst, which enabled this transformation to proceed in the absence of acidic or any other additives under fairly mild reaction conditions. This method paves the way for the synthesis of medium-sized lactams.



Medium-sized heterocycles are a significantly important class of compounds, which are extensively present in various biologically active molecules.[1] Specifically, seven- and eight-membered lactams represent prominent structural motifs widely found in many natural products and pharmaceuticals (Figure 1).[2] The efficient synthetic methods to these units still remain a big challenge due to their unfavorable transannular interactions and entropic factors.[3] Although several methods, such as intramolecular carbonylation,[4] ring-closing metathesis,[5] and cyclization reaction,[6] have been exploited and developed for preparing medium-sized lactams, the search for new environmentally friendly, atom-efficient methods which avoid the use of the finely prefunctionalized starting materials is still in great demand.

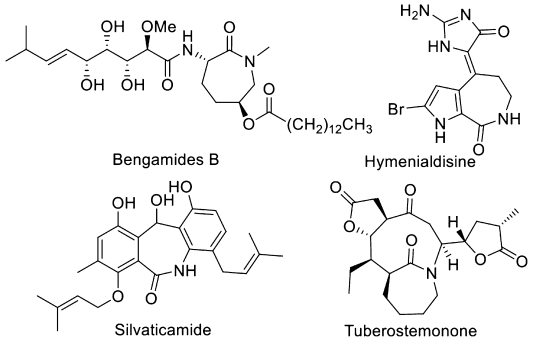


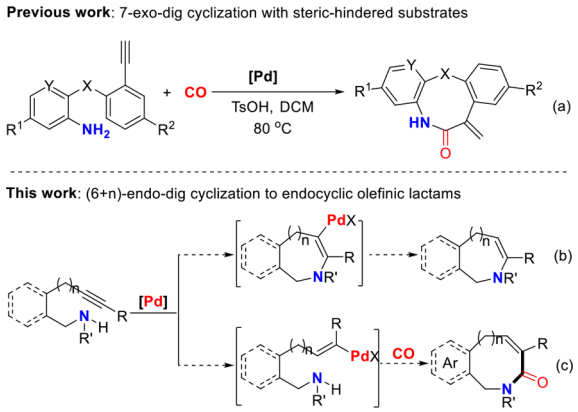
Figure 1. Selected natural products containing seven-membered lactam derivatives.

The intramolecular hydroaminocarbonylation of aminoalkynes in the presence of CO is one of the most direct and atom-economic methodologies to produce lactams, which constitute an extremely important class of compounds in a wide range of natural alkaloids and synthetic materials.[7] Although tremendous effort has been made in this area, such a process, however, is often limited to the synthesis of six-membered ring or smaller lactams.[8] In this context, Alper and coworkers developed a intramolecular hydroaminocarbonylation of terminal alkynes for the synthesis of eight-membered exocyclic olefinic lactams under the catalysis of a special palladium catalyst, in which a catalytic amount of acid was utilized to generate the postulated palladium hydride species for initiating the reaction (Scheme 1a).[4b] Moreover, steric-hindered substrates are required to avoid the potential intramolecular hydroamination reaction, which significantly restricts the practicality of this process. Recently, our group has successfully established a palladium-catalyzed intramolecular hydroaminocarbonylation of 2-vinylbenzylamines in the absence of acidic or any other additives, which allowed for the synthesis of a variety of branched six-membered lactams in good to excellent yields with high regioselectivity. Moreover, detail mechanistic studies disclosed that palladium hydride was indeed involved as a key reactive species to initiate the reaction and the fast intramolecular aminolysis of the acylpalladium intermediate could overcome the basicity barrier imparted by the aliphatic amines.[9] On the basis of these results, we envisioned that the palladium-catalyed intramolecular hydroaminocarbonylation of 2-phenylethynyl benzylamines would be an appealing approach to medium-sized lactams (Scheme 1c). However, the realization of such a process is challenging, since the intramolecular hydroamination reaction may take place to compete with the

Received: July 25, 2017

DOI: 10.1021/acs.orglett.7b02284
Org. Lett. XXXX, XXX, XXX−XXX

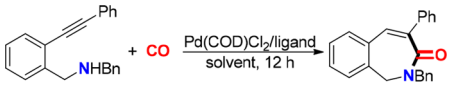
Scheme 1. Pd-Catalyzed Hydroaminocarbonylation of Aminoalkynes to Medium-Sized Lactams with Completely Regioselective Cyclization



desired carbonylation reaction (Scheme 1b). We believe that the competition would be controlled by tuning the electronic nature of the amine moiety and the palladium catalyst to affect the rate of the processes of aminopalladation and aminolysis of acylpalladium species. Herein, we describe the first palladium-catalyzed intramolecular hydroaminocarbonylation of 2-phenylethynyl benzylamines in the absence of any additives, which provides efficient access to various valuable seven- and eight-membered lactams in excellent yields under mild reaction conditions. Notably, our catalytic system was highly regioselective to give endocyclic unsaturated lactams, which is complementary to our previous reactions.[9]

Initially, we began our investigation by examining the intramolecular hydroaminocarbonylation with *N*-benzyl-1-(2-(phenylethynyl)phenyl)methanamine (**1a**) as the model substrate. The reaction was carried out in the presence of 30 atm of CO with palladium as the catalyst. Delightfully, the seven-membered unsaturated lactam **2a** was obtained in 36% yield, and hydroamination product was detected when the reaction was conducted at 120 °C in THF with $Pd(COD)Cl_2/PPh_3$ as the catalytic system (Table 1, entry 1). The solid structure of **2a** was unambiguously determined by single-crystal X-ray diffraction analysis.[10] It is worth mentioning that the cyclocarbonylation reaction was highly regioselective to give only endocyclization product, and no six-membered isomer was detected under the current catalytic system. Encourged by this result, we attempted to optimize the reaction conditions by screening of the solvents. Apart from THF, the reaction could also proceed well in other solvents, such as CH_3CN, DCE, $PhCF_3$, DMA, and anisole, to deliver the desired product **2a** in moderate to good yields (Table 1, entries 2−6). Among the solvents tested, anisole was found to be the most effective (see the Supporting Information). Subsequently, further experiments were carried out to test various bidentate phosphines with $Pd(COD)Cl_2$ as the catalyst precursor. Only poor yield was obtained when Xantphos, DPPM, or DPEphos was employed as the ligand (Table 1, entries 7 and 8). Other ligands, including DPPE, DPPP, DPPB, and DPPF, could also promote the reaction to afford the desired product **2a** in moderate to excellent yields (Table 1, entries 9−12), and DPPB was the ideal choice (Table 1, entry 11). We then turned our attention to explore the precatalyst using DPPB as the ligand and found that $Pd(COD)Cl_2$ was far superior (see the SI). It is worth noting that the reaction also proceeded well when we reduced the CO pressure to 5 atm (Table 1, entry 13). Next, the

Table 1. Screening of Reaction Conditions[a]



1a 2a

entry	ligand	solvent	temp (°C)	yield[b] (%)
1	PPh_3	THF	120	36
2	PPh_3	CH_3CN	120	53
3	PPh_3	DCE	120	59
4	PPh_3	$PhCF_3$	120	54
5	PPh_3	anisole	120	62
6	PPh_3	DMA	120	47
7	Xantphos	anisole	120	19
8	DPPM	anisole	120	30
9	DPPE	anisole	120	62
10	DPPP	anisole	120	84
11	DPPB	anisole	120	92
12	DPPF	anisole	120	72
13[c]	DPPB	anisole	120	90
14[c]	DPPB	anisole	100	90
15[c]	DPPB	anisole	80	90
16[c]	DPPB	anisole	60	72
17[c,d]	DPPB	anisole	80	90

[a]Reaction conditions: **1a** (0.4 mmol), $Pd(COD)Cl_2$ (0.02 mmol), PPh_3 (0.044 mmol), bidentate ligand (0.022 mmol), solvent (1.0 mL), CO (30 atm), 12 h. [b]Isolated yield. [c]CO (5 atm). [d]90 min.

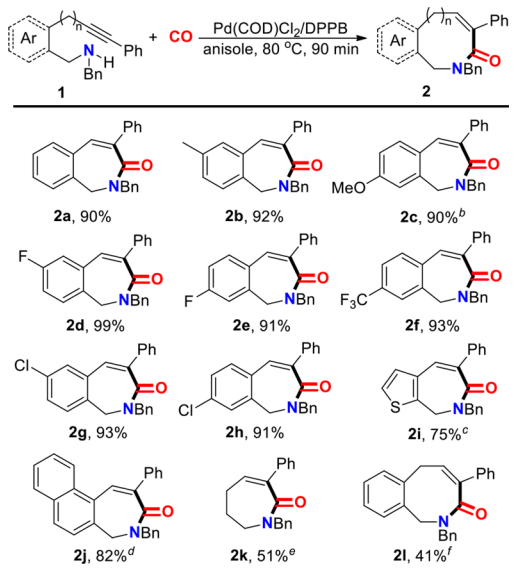
effect of temperature was also investigated, and it was found that almost the same yield of product **2a** was achieved when the reaction temperature was decreased to 80 °C (Table 1, entry 15). However, further decreasing the temperature to 60 °C resulted in relatively lower conversion (Table 1, entry 16). Notably, the desired product **2a** could be obtained in 90% yield even the reaction time was shortened to 90 min (Table 1, entry 17).

With the optimized conditions in hand, we next examined the substrate scope. As shown in Scheme 2, the electronic properties of the substituents on the aromatic ring of the substrate did not have a strong influence on the reactivity. For instance, the substrates with electron-donating groups (**1b** and **1c**) and electron-withdrawing groups (**1d−h**) were all tolerated under the current conditions, and the reactions could proceed smoothly to afford the corresponding products in excellent yields (**2b−h**), providing ample opportunities for further elaboration of the products. Furthermore, the heterocyclic substrate **1i** was also suitable for this transformation to provide the desired product **2i** in 75% yield. In addition, when DPPB was replaced with DPPHex as ligand, the naphthyl-derived substrate **1j** was also compatible with this process to afford the corresponding product **2j** in 82% yield, although longer reaction time and higher temperature were required. It should be noted that, apart from the benzolactams, the unsaturated aliphatic lactam **2k** could also be obtained in 51% yield. Gratifyingly, substrate **1l** was successfully transformed into the corresponding eight-membered lactam in moderate yield (**2l**). The structures of products **2c**, **2e**, **2j**, **2k**, and **2l** were further validated by X-ray single-crystal diffraction analysis.[10]

Subsequently, substrates bearing different substituents at the *β*-position of the alkyne moiety have been evaluated (Table 2). A variety of aryl-substituted alkynes were well tolerated under the current reaction conditions, affording the corresponding lactams in good to excellent yields (**2m−r**). No significant rate difference was observed between these substituted substrates. Interestingly,

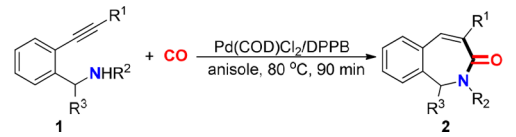
DOI: 10.1021/acs.orglett.7b02284
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Substrate Scope of 2-Alkynylbenzylamine[a]



[a]Reaction conditions: **1** (0.4 mmol), $Pd(COD)Cl_2$ (0.02 mmol), DPPB (0.022 mmol), anisole (1.0 mL), CO (5 atm), 90 min. Isolated yield are shown. Unless otherwise noted. [b]6 h. [c]4 h. [d]DPPHex was used as the ligand, 120 °C for 12 h. [e]120 °C for 6 h. [f]100 °C for 48 h.

Table 2. Substrate Scope of 2-Alkynylbenzylamine[a]



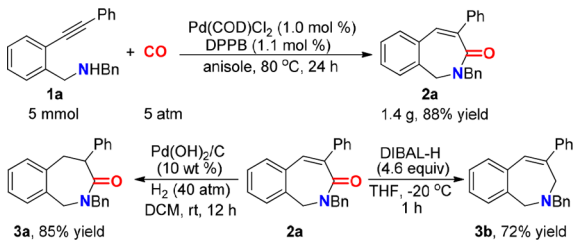
entry	R^1	R^2	R^3	yield[b] (%)
1	4-$CH_3C_6H_4$	$C_6H_5CH_2$	H	**2m**, 88
2	3-$CH_3C_6H_4$	$C_6H_5CH_2$	H	**2n**, 86
3	4-*t*-BuC_6H_4	$C_6H_5CH_2$	H	**2o**, 90
4[c]	4-$CH_3OC_6H_4$	$C_6H_5CH_2$	H	**2p**, 84
5	4-ClC_6H_4	$C_6H_5CH_2$	H	**2q**, 85
6[d]	4-FC_6H_4	$C_6H_5CH_2$	H	**2r**, 88
7[e]	4-BrC_6H_4	$C_6H_5CH_2$	H	**2s**, 59
8[f]	$CH_3(CH_2)_3$	$C_6H_5CH_2$	H	**2t**, 48
9[g]	*c*-$C_6H_{11}CH_2$	$C_6H_5CH_2$	H	**2u**, 50
10[h]	$C_6H_5CH_2$	$C_6H_5CH_2$	H	**2v**, 54
11	C_6H_5	*n*-Pr	H	**2w**, 96
12	C_6H_5	*c*-C_6H_{11}	H	**2x**, 83
13[i]	C_6H_5	$C_6H_5CH_2$	CH_3	**2y**, 97

[a]Reaction conditions: **1** (0.4 mmol), $Pd(COD)Cl_2$ (0.02 mmol), DPPB (0.022 mmol), anisole (1.0 mL), CO (5 atm), 90 min. [b]Isolated yield. [c]100 °C for 6 h. [d]3 h. [e]6 h. [f]48 h. [g]100 °C for 24 h. [h]24 h. [i]120 °C for 6 h (isomer ratio = 1.4:1), combined yield of exo- and endocyclic products.

a labile substituent, such as a chloro group in **1q** and a bromo group in **1s** at the 4-position of the aromatic ring, was tolerated under the present reaction conditions. To our delight, the substrates with aliphatic groups, including *n*-butyl, *c*-hexyl, and benzyl, were also applicable to the present transformation, although only moderate yields were achieved (**2t**–**v**). The reactions proceeded smoothly for substrates with electron-rich groups located on the nitrogen atom, affording the desired products **2w** and **2x** in 96% and 83% yields, respectively. However, no reaction occurred when phenyl and electron-withdrawing groups including acetyl were installed into the nitrogen atom, which might be attributed to the much lower nucleophilicity of the nitrogen to aminolysis of the acylpalladium intermediate. Substrate with free amine (NH_2) was also evaluated, but no desired product was detected (see the SI). Encouragingly, substrate with a methyl group at the benzyl position of amine could be easily converted into the product in 97% yield, although higher temperature was required and the isomers of both exo- and endo-cyclization products were obtained (isomer ratio = 1.4:1). The structure of product **2q** was also confirmed by X-ray single-crystal diffraction analysis.[10]

The practicality of the present catalytic system was illustrated through a gram-scale preparation of **2a** and transformation (Scheme 3). The hydroaminocarbonylation on a 5 mmol scale

Scheme 3. Synthetic Versatility of the Present Catalytic System



was found to be completed in 24 h, even in the presence of 1.0 mol % catalyst, providing 1.4 g of the corresponding product **2a** in 88% yield. The hydrogenation of the unsaturated carbon–carbon double bond in **2a** was realized under the catalysis of $Pd(OH)_2/C$, affording 2-benzyl-4-phenyl-4,5-dihydro-1*H*-benzo[*c*]azepin-3(2*H*)-one **3a** in 85% isolated yield. Reduction of the amide moiety in **2a** with excess DIBAL-H proceeded smoothly in THF to deliver the corressponding product **3b** containing allylamine functionality in 72% yield.[11]

Although comprehensive studies are required to elucidate the mechanistic details of the present reaction, a tentative proposal is presented in Figure 2.[12] Initially, the catalytic active palladium

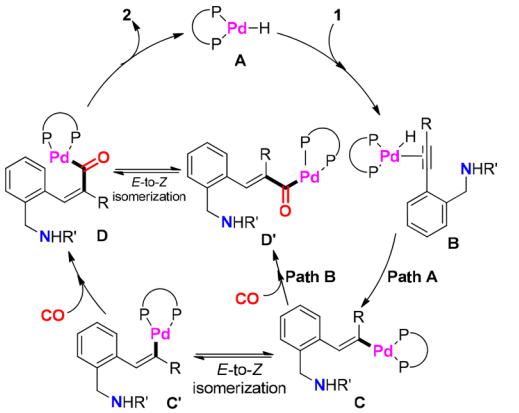


Figure 2. Plausible reaction mechanism.

hydride species **A** is formed, which coordinated to the C–C triple bond and followed by migratory insertion to generate the unique linear alkenyl palladium species **C**. The fast hydropalladation would suppress the competitive intramolecular hydroamination. The subsequent *E*-to-*Z* isomerization of this double bond affords alkenyl–Pd(II) intermediate **C′**.[13] Then insertion of CO into the

DOI: 10.1021/acs.orglett.7b02284
Org. Lett. XXXX, XXX, XXX–XXX

palladium−alkenyl bond of **C′** leads to the formation of acyl palladium complex **D**. Intramolecular aminolysis eventually furnishes the observed product along with regeneration of the active palladium hydride species for the next catalytic cycle. Alternatively, CO insertion to the hydropalladation intermediate **C** followed by *E*-to-*Z* isomerization and intramolecular aminolysis could also give the final product (path B).

In summary, we have successfully developed an efficient palladium-catalyzed intramolecular hydroaminocarbonylation of 2-alkynyl benzylamines in the absence of acidic additive, which allows for the synthesis of a wide range of biologically active seven- and eight-membered lactams with high chemoselectivity and regioselectivity under mild reaction conditions. The catalytic system presents broad functional group tolerance and substrate scope. More importantly, this novel strategy provides effective access to medium-sized heterocycles and shows great potential in synthetic chemistry. Further investigations aimed at gaining a detailed mechanistic understanding of this reaction and developing more synthetically useful transformations are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02284.

Experimental details and full spectroscopic data for all new compounds (PDF)
X-ray structure of **2a** (CIF)
X-ray structure of **2c** (CIF)
X-ray structure of **2e** (CIF)
X-ray structure of **2j** (CIF)
X-ray structure of **2k** (CIF)
X-ray structure of **2l** (CIF)
X-ray structure of **2q** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: hanmin@ustc.edu.cn.

ORCID

Hanmin Huang: 0000-0002-0108-6542

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the CAS Interdisciplinary Innovation Team an the National Natural Science Foundation of China (21672199).

■ REFERENCES

(1) For reviews, see: (a) Evans, P. A.; Holmes, A. B. *Tetrahedron* **1991**, *47*, 9131. (b) Faulkner, J. D. *Nat. Prod. Rep.* **1999**, *16*, 155. (c) Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 44. (d) Kantorowski, E. J.; Kurth, M. J. *Tetrahedron* **2000**, *56*, 4317. (e) Fraga, B. M. *Nat. Prod. Rep.* **2003**, *20*, 392. For selected examples, see: (f) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.

(2) For leading references, see: (a) *Heterocycles in Natural Product Synthesis*; Majumdar, K. C., Chattopadhyay, S. K., Eds.; Wiley-VCH: Weinheim, 2011. (b) Grunewald, G. L.; Dahanukar, V. H.; Ching, P.; Criscione, K. R. *J. Med. Chem.* **1996**, *39*, 3539. (c) Sun, H.; Nikolovska-Coleska, Z.; Lu, J.; Meagher, J. L.; Yang, C.-Y.; Qiu, S.; Tomita, Y.; Ueda, Y.; Jiang, S.; Krajewski, K.; Roller, P. P.; Stuckey, J. A.; Wang, S. *J. Am. Chem. Soc.* **2007**, *129*, 15279.

(3) (a) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95. (b) Molander, G. A. *Acc. Chem. Res.* **1998**, *31*, 603. (c) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881. (d) Yet, L. *Chem. Rev.* **2000**, *100*, 2963. (e) Nubbemeyer, U. *Top. Curr. Chem.* **2001**, *216*, 125.

(4) (a) Lu, S.-M.; Alper, H. *J. Am. Chem. Soc.* **2005**, *127*, 14776. (b) Lu, S.-M.; Alper, H. *J. Am. Chem. Soc.* **2008**, *130*, 6451. (c) Mancuso, R.; Raut, D. S.; Marino, N.; De Luca, G.; Giordano, C.; Catalano, S.; Barone, I.; Andò, S.; Gabriele, B. *Chem. - Eur. J.* **2016**, *22*, 3053.

(5) (a) Creighton, C. J.; Leo, G. C.; Du, Y.; Reitz, A. B. *Bioorg. Med. Chem.* **2004**, *12*, 4375. (b) Kaul, R.; Surprenant, S.; Lubell, W. D. *J. Org. Chem.* **2005**, *70*, 3838.

(6) (a) David, O.; Meester, W. J. N.; Bieräugel, H.; Schoemaker, H. E.; Hiemstra, H.; van Maarseveen, J. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4373. (b) Zhao, Q.; Li, C. *Org. Lett.* **2008**, *10*, 4037. (c) Wu, S.; Zeng, R.; Fu, C.; Yu, Y.; Zhang, X.; Ma, S. *Chem. Sci.* **2015**, *6*, 2275. (d) Zhao, W.; Qian, H.; Li, Z.; Sun, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 10005. (e) Zhou, B.; Li, L.; Zhu, X.-Q.; Yan, J.-Z.; Guo, Y.-L.; Ye, L.-W. *Angew. Chem., Int. Ed.* **2017**, *56*, 4015.

(7) (a) Sammes, P. G. *Chem. Rev.* **1976**, *76*, 113. (b) Kametani, T.; Nagahara, T. *Heterocycles* **1987**, *25*, 729. (c) Tsang, W. Y.; Ahmed, N.; Hinchliffe, P. S.; Wood, J. M.; Harding, L. P.; Laws, A. P.; Page, M. I. *J. Am. Chem. Soc.* **2005**, *127*, 17556. (d) Albrecht, S.; Defoin, A.; Salomon, E.; Tarnus, C.; Wetterholm, A.; Haeggström, J. Z. *Bioorg. Med. Chem.* **2006**, *14*, 7241. (e) Billamboz, M.; Bailly, F.; Lion, C.; Touati, N.; Vezin, H.; Calmels, C.; Andréola, M.-L.; Christ, F.; Debyser, Z.; Cotelle, P. *J. Med. Chem.* **2011**, *54*, 1812. (f) Yada, A.; Okajima, S.; Murakami, M. *J. Am. Chem. Soc.* **2015**, *137*, 8708.

(8) For selected examples, see: (a) Tang, S.; Yu, Q.-F.; Peng, P.; Li, J.-H.; Zhong, P.; Tang, R.-Y. *Org. Lett.* **2007**, *9*, 3413. (b) Park, J.; Kim, E.; Chung, Y. *Org. Lett.* **2008**, *10*, 4719.

(9) Hu, Y.; Shen, Z.; Huang, H. *ACS Catal.* **2016**, *6*, 6785.

(10) CCDC 1561014 (**2a**), 1561015 (**2c**), 1561016 (**2e**), 1561017 (**2j**), 1561018 (**2k**), 1561019 (**2l**) and 1561022 (**2q**) contain the supplementary crystallographic data for this paper. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(11) Hickin, J. A.; Ahmed, A.; Fucke, K.; Ashcroft, M.; Jones, K. *Chem. Commun.* **2014**, *50*, 1238.

(12) For reviews, see: (a) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 4986. (b) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Rev.* **2013**, *113*, 1. (c) Wu, X.-F.; Fang, X.; Wu, L.; Jackstell, R.; Neumann, H.; Beller, M. *Acc. Chem. Res.* **2014**, *47*, 1041. For selected examples, see: (d) Fang, X.; Jackstell, R.; Beller, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 14089. (e) Liu, H.; Yan, N.; Dyson, P. J. *Chem. Commun.* **2014**, *50*, 7848. (f) Fang, X.; Li, H.; Jackstell, R.; Beller, M. *J. Am. Chem. Soc.* **2014**, *136*, 16039. (g) Zhang, G.; Gao, B.; Huang, H. *Angew. Chem., Int. Ed.* **2015**, *54*, 7657. (h) Cheng, J.; Qi, X.; Li, M.; Chen, P.; Liu, G. *J. Am. Chem. Soc.* **2015**, *137*, 2480. (i) Sha, F.; Alper, H. *ACS Catal.* **2017**, *7*, 2220.

(13) For the selected examples of *E*−*Z* isomerization of alkenyl-Pd species, see: (a) Chernyak, N.; Gorelsky, S. I.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2011**, *50*, 2342. (b) Le, C. M.; Hou, X.; Sperger, T.; Schoenebeck, F.; Lautens, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 15897. (c) Le, C. M.; Menzies, P. J. C.; Petrone, D. A.; Lautens, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 254. (d) Petrone, D. A.; Franzoni, I.; Ye, J.; Rodríguez, J. F.; Poblador-Bahamonde, A. I.; Lautens, M. *J. Am. Chem. Soc.* **2017**, *139*, 3546.

DOI: 10.1021/acs.orglett.7b02284
Org. Lett. XXXX, XXX, XXX−XXX