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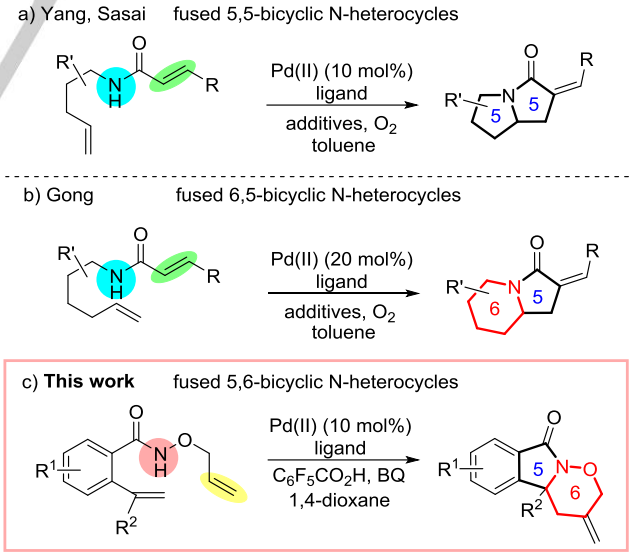
Pd(II)-Catalyzed Oxidative Tandem aza-Wacker/Heck Cyclization for the Construction of Fused 5,6-Bicyclic N,O-Heterocycles

Chenghao Ye,[a] Xuezhen Kou,[a] Jingzhao Xia,[a] Guoqiang Yang,[a] Li Kong,*[b] Quhao Wei,*[b] and Wanbin Zhang*[a]

Abstract: A Pd(II)-catalyzed oxidative tandem cyclization was developed for the construction of fused 5,6-bicyclic N, O-heterocycles. This reaction was enabled by the combined use of a 3-methylpyridine ligand and pentafluorobenzoic acid additive. A range of heterocyclic products with different substituents could be prepared in moderate to good yields via this methodology. Several transformations, including a scaled up preparation of product **2a**, were also carried out showing the good applicability of our methodology.

Nitrogen-containing heterocycles are basic skeletons of natural and pharmaceutical products, and also important building blocks for organic synthesis, thus the development of methods for the synthesis of such compounds are at the center of organic chemistry.[1] The preparation of fused nitrogen-containing heterocycles is one of the important areas of this field; the complexity and rigidity of fused nitrogen-containing heterocycles make them good candidates for drug backbones.[2] Transition-metal-catalyzed tandem cyclizations are recognized as a class of efficient reactions for the construction of polycyclic compounds, including heterocycles.[3] Oxidative tandem cyclizations possess several advantages: They are simple to operate, are not air sensitive, and exhibit good compatibility with various halogen-substituents. However, transition-metal-catalyzed oxidative tandem cyclizations have not been widely studied, possibly due to the catalytic efficiency being highly dependent on the structure of the substrates.[4-8]

The development of Wacker-type reactions has been a long-standing research topic for organic chemists.[9] From a mechanistic aspect, after nucleopalladation of the olefin bond, a carbon-bonded Pd(II) intermediate is generated, which can partake in subsequent reaction steps. This is an ideal reaction for triggering oxidative tandem cyclizations for the construction of polycyclic heterocycles. Sasai reported the first oxy-Wacker/Heck tandem cyclization.[5] Yang developed two catalytic systems for aza-Wacker/Heck tandem cyclizations, with construction of chiral fused 5,5-bicyclic N-heterocycles, a significant achievement in the area of asymmetric aza-Wacker-type reactions.(Scheme 1, a)[6] Sasai has also developed a similar reaction employing his SPRIX ligand.[7] However, these reactions remain limited to the construction of five-membered rings, possibly due to the nucleopalladation step entropically favoring the formation of smaller ring systems. Very recently, Gong divulged a Pd(II)-catalyzed aza-Wacker/Heck tandem cyclization for the generation of fused 6,5-bicyclic N-heterocycles but only moderate yields were obtained and high catalyst loadings were required (Scheme 1, b). [8] In a continuation of our research concerning Wacker-type reactions,[10] herein, we report a Pd(II)-catalyzed oxidative tandem cyclization for the preparation of 5,6-bicyclic N,O-heterocycles. The aforementioned reports utilize the amide group of acrylamides as the nitrogen-nucleophile and the electron-deficient C=C bond of the acrylamide as the second olefin-electrophile. In this study, we employ *N*-alkoxy amides as a nitrogen-nucleophile and the electron-rich C=C bond as the second olefin-electrophile.[11]



Scheme 1. Pd(II)-catalyzed oxidative tandem cyclizations for construction of polycyclic N-heterocycles.

Previously, we realized a Pd(II)-catalyzed aerobic aza-Wacker-type reaction and a Pd(II)-catalzyed aerobic aminoxygenation of olefins for the construction of isoindolinones.[10f,12] We next turned our attention to the construction of polycyclic compounds bearing

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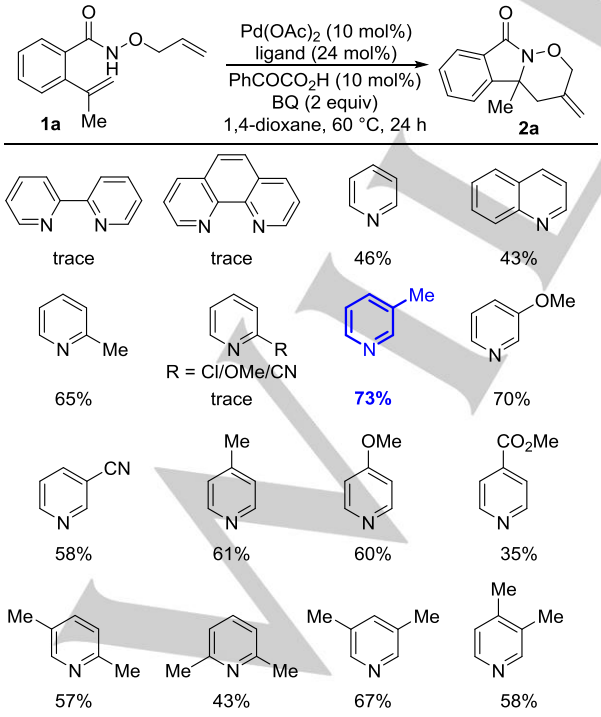
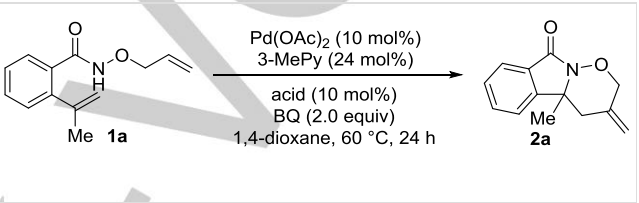
an isoindolinone skeleton. We designed substrate **1,** which contains an *O*-allyl group, to trap the carbon-palladation intermediate thus allowing for the construction of an additional 6-membered ring. After preliminary screening of the reaction conditions (See SI), we found that only BQ was able to promote the reaction as an oxidant. Since this type of substrate is unstable under basic oxidative conditions, we propose that an acid additive may inhibit the decompose of substrate, thus increasing the yield.[13] In addition, acid additive may also supply counterion to exchange with OAc, thus affecting the catalytic ability of Pd(II) center. It was found that 2-oxo-2-phenylacetic acid was able to increase the yield from 28% to 40% in THF solvent. Solvent screening showed that 1,4-dioxane was the best solvent for this cyclization reaction. Different ligands were then screened to obtain a better result (Scheme 2). The bidentate ligands 2,2'-bispyridine and 1,10-phenanthroline provided little activity, whereas the monodentate ligands pyridine and quinoline promoted the reaction, giving the desired cyclized product **2a** in 46% and 43% yields, respectively. With these promising preliminary results in hand, we decided to screen a series of substituted-pyridine ligands. Pyridine bearing a 2-methyl group led to an improvement in the catalytic activity; however, substituents such as Cl, CN, and OMe at the 2-position mostly inhibited the reaction. Interestingly, pyridine ligands bearing these substituents at the 3- or 4- positions successfully catalyzed the cyclization. This phenomenon may be caused by the coordinating effect of the Cl, CN, and OMe groups at the 2-position. Electron-donating substituents at the 3-position could enhance the yield more than substituents at the 2- and 4-positions. We next screened several pyridine ligands bearing two methyl groups at different positions, in order to obtain a higher yield of the desired product. However, it appears that an additional methyl group at a different position on the ring is detrimental to the product yield. Thus, the best ligand was found to be 3-methylpyridine (3-MePy).



Scheme 2. Ligand Screening.

Different carboxylic acids were tested to improve the yield (Table 1). The results suggest that their is a relationship between product yield and the acidity of the acids. For aliphatic carboxylic acids, product yield increased with increasing acidity (entries 1-4); however, too strong acid provided a lower yield (entry 5). The screening of different aromatic carboxylic acids also indicated that stronger acids can promote the reaction to give the desired cyclization product in better yield (entries 6-8). Finally, pentafluorobenzoic acid was found to be the best additive for this aza-Wacker/Heck tandem cyclization (entry 8).

Table 1. Screening of Acid Additive.



entry	acid additive	pKa	yield (%)
1	HCO_2H	3.74	61
2	CH_3CO_2H	4.74	55
3	$(CH_3)_3CCO_2H$	5.03	46
4	citric acid•H_2O	3.15	79
5	CF_3CO_2H	0.23	56
6	$PhCO_2H$	4.21	46
7	$PhCOCO_2H$	2.15	73
8	**$C_6F_5CO_2H$**	**1.60**	**86**

With the optimized reaction conditions in hand, the substrate scope was examined (Scheme 3). Substrates with one electron-donating substituent gave the desired products in better yields than those bearing electron-withdrawing substituents (**2b**~**2h**). For instance, product **2b** bearing a OMe group at the 5-position was obtained in 97% yield, whereas **2f** bearing a CF_3 group at the same position was furnished in just 58% yield. Substrates bearing two substituents were also employed in this reaction. However, product **2i** and **2j** were obtained in only moderate yields due to the instability of these substrates towards the oxidative conditions. The effect of different R^2 substituents on the olefin was also investigated (**2k**~**2q**). In general, the desired products were obtained in moderate to good yields. For example, high yields were observed for substrates bearing a $MeO(CH_2)_3$– or $Ph(CH_2)_2$–R^2 group (**2n** and **2o**). Substrate **1r** bearing a methyl group as R^3 gave the desired product in only 21% yield after hydrogenation of olefin group by Pd/C, with an unidentified complex mixture of byproducts formed. Similar situation was also observed for substrates bearing an aryl R^3 group (**2s**). In addition, when R^2 is H-atom, the substrate decomposed under our reaction conditions.

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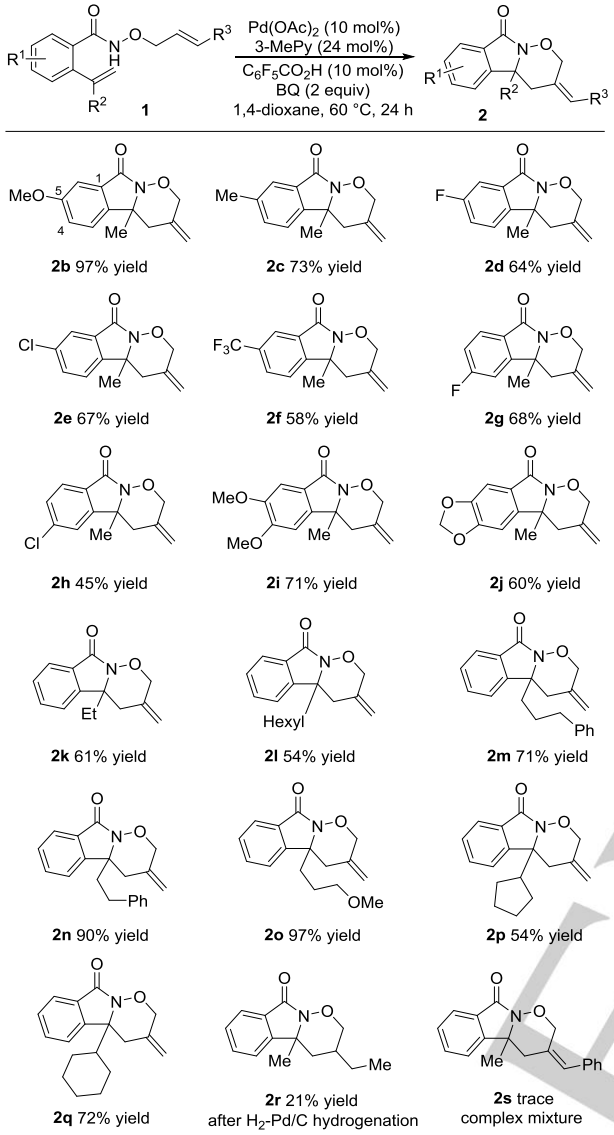
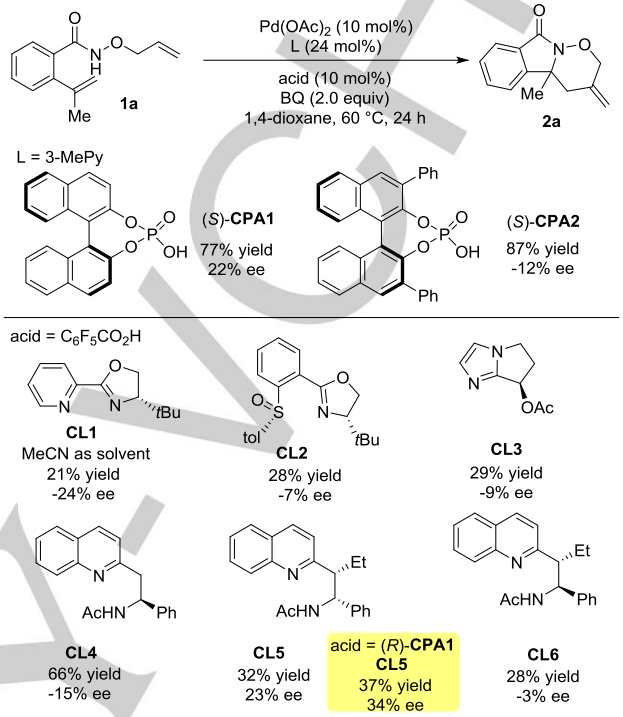


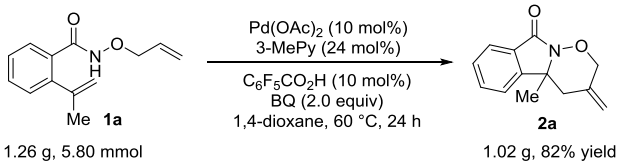
Scheme 3. Substrate Scope.

Attempts to establish an asymmetric version of our methodology were not successful (Scheme 4). The use of chiral Binol-derived phosphoric acid **CPA1** as the acid additive gave the desired product with 22% ee and 77% yield. However, *ortho*-Ph-substituted **CPA2**, could only promote the reaction to give the cyclized product in 12% ee, albeit in high yield. Four different types of chiral ligands were also tested. Pyridine-oxazoline ligand (**CL1**), which has shown excellent catalytic behavior for the Pd(II)-catalyzed difunctionalizations of olefins,[14] showed poor results in this reaction. Similarly low yields and enantioselectivity were observed when using the bidentate ortho-sulfinyl-substituted phenyl oxazoline ligand **CL2** and the monodentate ligand **CL3**.[15] Recently, the Yu group reported a novel class of quinoline-acetamide ligands that showed excellent catalytic ability for asymmetric C(sp^3)-H arylation,[16] which was enabled by the monodentate pyridine-type ligands used in previous reports.[17] Therefore, several such ligands were also screened in our reaction. **CL4** just bearing one chiral center showed moderate catalytic activity but poor enantio-inducing ability. An additional chiral stereogenic substituent significantly reduced the catalytic activity (**CL5** and **CL6**). The combination of **CL5** and (*R*)-**CPA1** provided product **2a** in slightly higher ee (34%).



Scheme 4. Attempts of asymmetric catalysis.

To test the practicality of our methodology, a gram-scale reaction using substrate **1a** was carried out (Scheme 5). The product **2a** was obtained in 82% yield, which is comparable to the yield shown in Table 2.



Scheme 5. Gram-Scale Reaction.

The cyclized product could be further manipulated (Scheme 6). The olefin bond of product **2a** was readily transformed to expoxide **3** by *m*CPBA or hydrogenated to give **4** via Pd/C catalysis. The cleavage of the allylic C-O bond was achieved via Pd/C-catalyzed hydrogenation in MeOH solvent with the concomitant reduction of the olefin, giving **5** in 60% yield. The N-O bond could also be cleaved using SmI_2 as a reductant, giving allylic alcohol product **6** in 61% yield.

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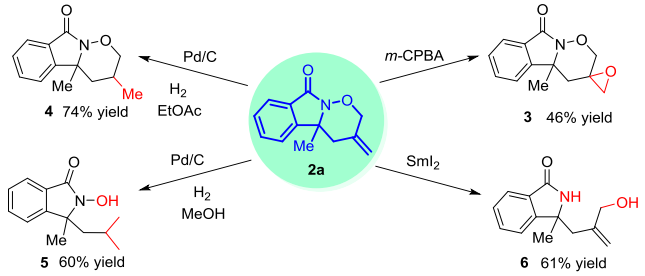
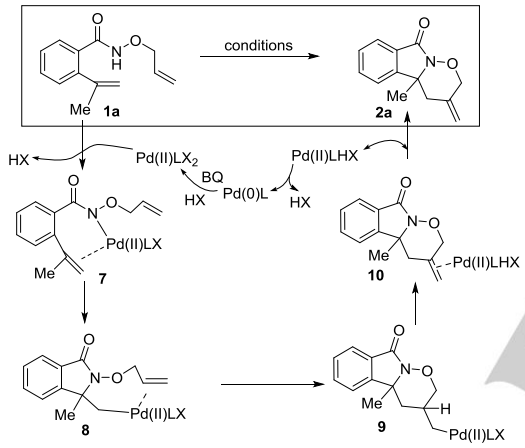


Scheme 6. Transformations of Product **2a**.

Finally, a catalytic cycle was proposed using **1a** as the model substrate (Scheme 7). Pd(II) catalyst coordinates with substrate to form complex **7**. Aminopalladation of **7** generates intermediate **8**. Then **8** undergoes migrative insertion to form intermediate **9**. *β*-Hydride elimination of **9** gives **2a** ligated Pd(II) complex **10**. This complex releases the desired product **2a** and Pd-H species. Pd-H species undergoes reductive elimination and oxidation by BQ to regenerate the Pd(II) catalyst.



Scheme 7. Proposed Catalytic Cycle.

In conclusion, we have developed a Pd(II)-catalyzed oxidative tandem cyclization for the construction of fused 5,6-bicyclic N,O-heterocycles. The combination of 3-methylpyridine ligand and pentafluorobenzoic acid additive effectively enabled this cyclization. A range of substrates were tolerated under the reaction conditions giving the desired heterocyclic products in moderate to good yields. The transformations of product **2a** were also carried out to show the applicability of our methodology. The asymmetric catalysis of this reaction appears challenging and the development of new chiral ligands to induce high enantioselectivity is currently under way in our group.

Acknowledgements

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Keywords: palladium • oxidative tandem cyclization • heterocycles • pyridine ligand • aza-Wacker cyclization

[1] a) J. R. Liddell, *Nat. Prod. Rep.* **2002**, *19*, 773; b) J. P. Michael, *Nat. Prod. Rep.* **2005**, *22*, 603; (c) J. P. Michael, *Nat. Prod. Rep.* **2007**, *24*, 191.

[2] a) D. O'Hagan, *Nat. Prod. Rep.* **2000**, *17*, 435; b) I. Coldham, R. Hufton, *Chem. Rev.* **2005**, *105*, 2765; c) J. C. Andrez, *Beilstein J. Org. Chem.* **2009**, *5*, 33; d) L. S. Fernandez, M. S. Buchanan, A. R. Carroll, Y. Feng, R. J. Quinn, V. M. Avery, *Org. Lett.* **2009**, *11*, 329.

[3] For reviews of cascade cyclization reactions, see: a) E. I. Negishi, C. Copéret, S. Ma, S. Y. Liou, F. Liu, *Chem. Rev.* **1996**, *96*, 365; b) M. Shibasaki, C. D. J. Boden, A. Kojima, *Tetrahedron* **1997**, *53*, 7371. c) G. Poli, G. Giambastiani, A. Heumann, *Tetrahedron* **2000**, *56*, 5959; d) G. Battistuzzi, S. Cacchi, G. Fabrizi, *Eur. J. Org. Chem.* **2002**, 2671; e) A. B. Dounay, L. E. Overman, *Chem. Rev.* **2003**, *103*, 2945. f) M. Shibasaki, E. M. Vogl, T. Ohshima, *Adv. Synth. Catal.* **2004**, *346*, 1533; g) J. T. Link, In *Organic Reactions*, *Vol. 60* (Ed: L. E. Overman), Wiley, New York, **2002**, p. 157; h) N. J. Race, I. R. Hazelden, A. Faulkner, J. F. Bower, *Chem. Sci.* **2017**, *8*, 5248.

[4] L. S. Hegedus, G. F. Allen, D. J. Olsen, *J. Am. Chem. Soc.* **1980**, *102*, 3583.

[5] M. A. Arai, K. Minori, A. Takayoshi, H. Sasai, *J. Am. Chem. Soc.* **2001**, *123*, 2907.

[6] a) K.-T. Yip, M. Yang, K.-L. Law, N.-Y. Zhu, D. Yang, *J. Am. Chem. Soc.* **2006**, *128*, 3130; b) W. He, K.-T. Yip, N.-Y. Zhang, D. Yang, *Org. Lett.* **2009**, *11*, 5626; c) K.-T. Yip, N.-Y. Zhu, D. Yang, *Org. Lett.* **2009**, *11*, 1911; d) K.-T. Yip, D. Yang, *Chem. - Asian J.* **2011**, *6*, 2166; e) Q.-S. Gu, D. Yang, *Angew. Chem. Int. Ed.* **2017**, *56*, 5886; *Angew. Chem.* **2017**, *129*, 5980; f) W. Du, Q. Gu, Y. Li, Z. Lin, D. Yang, *Org. Lett.* **2017**, *19*, 316.

[7] C. Ramalingan, K. Takenaka, H. Sasai, *Tetrahedron* **2011**, *67*, 2889.

[8] Y.-P. He, H. Wu, L. Xu, Y.-L. Su, L.-Z. Gong, *Org. Chem. Front.* **2014**, *1*, 473.

[9] For selected reviews, see: a) J. E. Bäckvall, *Acc. Chem. Res.* **1983**, *16*, 335; b) L. S. Hegedus, In *Comprehensive Organic Synthesis*, *Vol. 2* (Ed.: M. F. Semmelhack,), Pergamon, Elmsford, **1991**; pp 551-569; c) T. Hosokawa, S.-I. Murahashi, In *Handbook of Organopalladium Chemistry for Organic Synthesis*, *Vol. 2* (Eds.: E. Negishi, de A. Meijere), John Wiley and Sons, Inc.: New York, **2002**, pp 2169-2192; d) T. Hosokawa, In *Handbook of Organopalladium Chemistry for Organic Synthesis*, *Vol. 2* (Eds.: E. Negishi, de A. Meijere) John Wiley and Sons, Inc.: New York, **2002**, pp 2211-2225; e) J. M. Takacs, X. Jiang, *Curr. Org. Chem.* **2003**, *7*, 369; f) S. S. Stahl, *Angew. Chem. Int. Ed.* **2004**, *43*, 3400; g) G. Zeni, R. C. Larock, *Chem. Rev.* **2004**, *104*, 2285; h) M. S. Sigman, D. R. Jensen, *Acc. Chem. Res.* **2006**, *39*, 221; i) C. N. Cornell, M. S. Sigman, *Inorg. Chem.* **2007**, *46*, 1903; j) V. Kotov, C. C. Scarborough, S. S. Stahl, *Inorg. Chem.* **2007**, *46*, 1910; k) J. Muzart, *Tetrahedron* **2007**, *63*, 7505; l) E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318; m) A. Minatti, K. Muñiz, *Chem. Soc. Rev.* **2007**, *36*, 1142; n) J. A. Keith, P. M. Henry, *Angew. Chem. Int. Ed.* **2009**, *48*, 9038; o) J. E. Bäckvall, *Modern Oxidation Methods*, 2nd Edition, Wiley-VCH, Weinheim, Germany, **2010**; p) R. I. McDonald, G. Liu, S. S. Stahl, *Chem. Rev.* **2011**, *111*, 2981; q) N. A. Butt, W. Zhang, In *Topics in Heterocyclic Chemistry*, Vol. 32 (Ed.: J. P. Wolfe) Springer: Berlin, Heidelberg, **2013**, pp 77–108; q) B. M. Michel, L. D. Steffens, M. S. Sigman, In *Organic Reactions*, Vol. 84 (Ed.: S. E. Denmark) John Wiley and Sons, Inc.: New York, **2014**; pp 75-414; r) D. Wang, A. B. Weinstein, P. B. White, S. S. Stahl, *Chem. Rev*. **2018**, *118*, 2636.

[10] For oxy-Wacker-type reactions, see: a) F. Wang, Y. J. Zhang, H. Wei, J. Zhang, W. Zhang, *Tetrahedron Lett.* **2007**, *48*, 4083; b) Y. J. Zhang, F. Wang, W. Zhang, *J. Org. Chem.* **2007**, *72*, 9208; c) F. Wang, G. Yang, Y. J. Zhang, W. Zhang, *Tetrahedron* **2008**, *64*, 9413; d) Q. Liu, K. Wen, Z. Zhang, Z. Wu, Y. J. Zhang, W. Zhang, *Tetrahedron* **2012**, *68*, 5209.

For aza-Wacker-type reactions, see; e) F. Jiang, Z. Wu, W. Zhang, *Tetrahedron Lett.* **2010**, *51*, 5124; f) G. Yang, C. Shen, W. Zhang, *Angew. Chem. Int. Ed.* **2012**, *51*, 9141; *Angew. Chem.* **2012**, *124*, 9275; g) G. Yang, W. Zhang, *Org. Lett.* **2012**, *14*, 268

[11] Yang group has reported one example of substrate bearing electron-rich C=C bond as the second olefin-electrophile in ref. 6d.

[12] a) X. Kou, Y. Li, L. Wu, X. Zhang, G. Yang, W. Zhang, *Org. Lett.* **2015**, *17*, 5566; b) Y. Li, X. Kou, C. Ye, X. Zhang, G. Yang, W. Zhang, *Tetrahedron Lett.* **2017**, *58*, 285.

[13] Acid was a common additive for pyridine-ligand-promoted C-H activation reactions, see: a) G. Chen, T. Shigenari, P. Jain, Z. Zhang, Z. Jin, J. He, S. Li, C. Mapelli, M. M. Miller, M. A. Poss, P. M. Scola, K.-S. Yeung, J.-Q. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 3338; b) see ref. 17.

[14] G. Yang, W. Zhang, *Chem. Soc. Rev.* **2018**, *47*, 1783.

[15] Z. Zhang, F. Xie, J. Jia, W. Zhang, *J. Am. Chem. Soc*. **2010**, *132*, 15939.

[16] G. Chen, W. Gong, Z. Zhuang, M. S. Andra, Y.-Q, Chen, X. Hong, Y.-F. Yang, T. Liu, K. N. Houk, J.-Q. Yu, *Science* **2016**, *353*, 1023.

[17] J. He, S. Li, Y. Deng, H. Fu, B. N. Laforteza, J. E. Spangler, A. Homs, J.-Q. Yu, *Science* **2014**, *343*, 1216.

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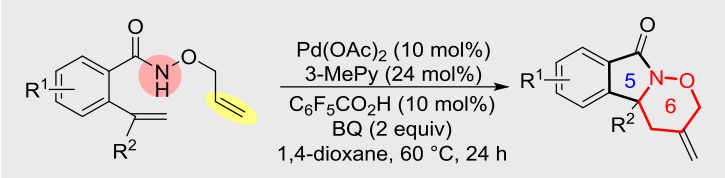

A Pd(II)-catalyzed tandem aza-Wacker/Heck cyclization was developed for the construction of a range of fused 5,6-bicyclic N,O-heterocycles. This reaction was enabled by the combination of 3-methylpyridine as a ligand and pentafluorobenzoic as an acidic additive

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