ORGANIC LETTERS

2013
Vol. 15, No. 8
1966–1969

α-Palladation of Imines as Entry to Dehydrogenative Heck Reaction: Aerobic Oxidative Cyclization of *N*-Allylimines to Pyrroles

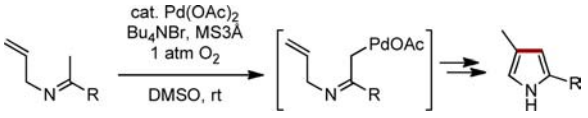
Zhiyuan Chen, Beili Lu, Zhenhua Ding, Ke Gao, and Naohiko Yoshikai*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

nyoshikai@ntu.edu.sg

Received March 11, 2013

ABSTRACT



We report here a palladium(II)-catalyzed oxidative cyclization reaction of *N*-allylimines derived from methyl ketones, typically acetophenones, affording pyrrole derivatives at room temperature under oxygen atmosphere. The reaction likely proceeds through α-palladation of the imine followed by olefin migratory insertion and β-hydride elimination, thus representing a new example of aerobic dehydrogenative Heck cyclization.

Catalytic oxidative linkage of two C−H bonds using molecular oxygen as a sole oxidant, producing water as the only byproduct, represents an ideal strategy for C−C bond formation.[1] With palladium catalysis, such transformations can be achieved through two major mechanistic pathways. One involves sequential palladation of two C−H bonds followed by reductive elimination (cross-dehydrogenative coupling),[2] and the other involves palladation of a C−H bond, alkene insertion into the resulting Pd−C bond, and β-hydride elimination (dehydrogenative Heck reaction).[3,4] Recently, our group reported an intramolecular example of the former type of transformation, that is, an oxidative cyclization reaction of *N*-arylimines to indoles with a catalytic system comprising $Pd(OAc)_2$, Bu_4NBr, and molecular oxygen in DMSO (Scheme 1a).[5,6] The reaction was proposed to involve palladation of the α-position of the imine through imine−enamine tautomerization,[7] intramolecular palladation of the aromatic ring, and reductive elimination. The same catalytic system also proved effective for dehydrogenative aromatization of cyclohexanone imines to arylamines, which presumably goes through α-palladation/β-hydride elimination sequences (Scheme 1b).[8−10] These previous studies guided us to find another type of dehydrogenative

(1) (a) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400. (b) Campbell, A. N.; Stahl, S. S. *Acc. Chem. Res.* **2012**, *45*, 851. (c) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (d) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780.

(2) For selected examples, see: (a) Brasche, G.; García-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2207. (b) Liégault, B.; Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008**, *73*, 5022. (c) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2009**, *74*, 4720. (d) Izawa, Y.; Stahl, S. S. *Adv. Synth. Catal.* **2010**, *352*, 3223. (e) Campbell, A. N.; Meyer, E. B.; Stahl, S. S. *Chem. Commun.* **2011**, *47*, 10257–10259.

(3) (a) Bras, J. L.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170. (b) Ferreira, E. M.; Zhang, H.; Stoltz, B. M. In *The Mizoroki−Heck Reaction*; Oestreich, M., Ed.; Wiley: Chichester, 2009; pp 345−382.

(4) For selected examples, see: (a) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578. (b) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072. (c) Engle, K. M.; Wang, D.-H.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 6169. (d) Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 14137.

(5) Wei, Y.; Deb, I.; Yoshikai, N. *J. Am. Chem. Soc.* **2012**, *134*, 9098.

(6) See also: (a) Shi, Z.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 9220. (b) Neumann, J. J.; Rakshit, S.; Dröge, T.; Würtz, S.; Glorius, F. *Chem.—Eur. J.* **2011**, *17*, 7298. (c) Würtz, S.; Rakshit, S.; Neumann, J. J.; Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 7230.

(7) (a) Liu, J.; Zhu, J.; Jiang, H.; Wang, W.; Li, J. *Chem.—Asian J.* **2009**, *4*, 1712. (b) Zhu, J.; Liu, J.; Ma, R.; Xie, H.; Li, J.; Jiang, H.; Wang, W. *Adv. Synth. Catal.* **2009**, *351*, 1229.

(8) Hajra, A.; Wei, Y.; Yoshikai, N. *Org. Lett.* **2012**, *14*, 5488.

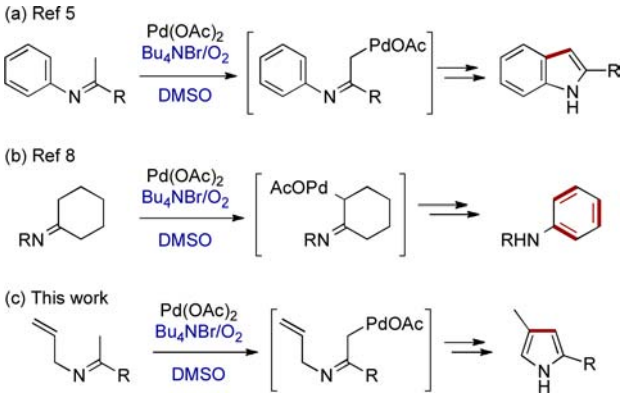
(9) Girard, S. A.; Hu, X.; Knauber, T.; Zhou, F.; Simon, M. O.; Deng, G. J.; Li, C.-J. *Org. Lett.* **2012**, *14*, 5606.

(10) For related Pd-catalyzed dehydrogenation reactions, see ref 7 and the following: (a) Izawa, Y.; Pun, D.; Stahl, S. S. *Science* **2011**, *333*, 209. (b) Diao, T.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 14566. (c) Diao, T.; Wadzinski, T. J.; Stahl, S. S. *Chem. Sci.* **2012**, *3*, 887. (d) Gao, W.; He, Z.; Qian, Y.; Zhao, J.; Huang, Y. *Chem. Sci.* **2012**, *3*, 883.

10.1021/ol400638q
Published on Web 04/02/2013

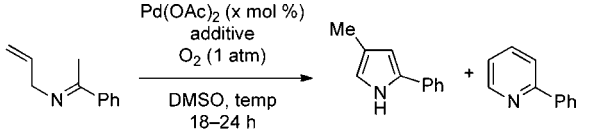
C−C bond formation reported herein, that is, an oxidative cyclization reaction of *N*-allylimines to pyrroles (Scheme 1c). The reaction would represent a new example of dehydrogenative Heck reaction, which is triggered by imine α-palladation and promoted with molecular oxygen as the sole oxidant.

Scheme 1. Aerobic Palladium Catalysis Involving Imine α-Palladation



The feasibility of the dehydrogenative Heck reaction was initially examined using imine **1a** derived from acetophenone and allylamine (Table 1). Our catalytic system for the indole synthesis, consisting of $Pd(OAc)_2$ (10 mol %), Bu_4NBr (2 equiv), 1 atm O_2, and DMSO, promoted the oxidative cyclization reaction to produce 2-phenyl-4-methylpyrrole **2a** in 31% yield along with a trace amount of 2-phenylpyridine **3a** (entry 1). The products **2a** and **3a** would have arisen from a common intermediate, i.e., α-palladated imine, through 5-*exo*- and 6-*endo* cyclizations, respectively (vide infra). Bu_4NBr turned out to be a critical additive because in its absence the reaction did not afford **2a** but produced **3a** in 10% yield (entry 2). Addition of 3 Å molecular sieves to the reaction using Bu_4NBr improved the yield of **2a** while completely shutting down the formation of **3a** (entry 3), while molecular sieves alone had only a small effect (entry 4). Bu_4NCl was similarly effective as Bu_4NBr (entry 5). Upon further optimization, the catalyst loading and the reaction temperature could be reduced to 5 mol % and room temperature (ca. 25 °C), respectively, with formation of the product **2a** in 76% isolated yield (entries 6 and 7). The use of DMSO as the solvent was also critical because little pyrrole formation was observed in DMF, 1,4-dioxane, and toluene (entries 8−10). The use of air instead of molecular oxygen significantly decreased the yield of **2a** (entry 11). Not unexpectedly, only a trace amount of **2a** was obtained under a nitrogen atmosphere (entry 12). In contrast to the results in entries 2 and 4, at room temperature, the reaction in the absence of Bu_4NBr afforded **2a** in a low yield but none of **3a** (entry 13). Other attempts to increase the yield of **3a** were unsuccessful. Note also that attempts on direct oxidative condensation of acetophenone and allylamine into **2a** failed, presumably because of facile oxidation of allylamine under oxidative palladium catalysis.

Table 1. Screening of Reaction Conditions[a]



				yield[b] (%)	
entry	*x*	additive	temp (°C)	**2a**	**3a**
1	10	Bu_4NBr (2 equiv)	60	31	3
2	10	None	80	0	10
3	10	Bu_4NBr (2 equiv), MS3 Å	60	62	0
4	10	MS3 Å	80	0	4
5	10	Bu_4NCl (2 equiv), MS3 Å	80	60	0
6	5	Bu_4NBr (2 equiv), MS3 Å	60	76	0
7	5	Bu_4NBr (2 equiv), MS3 Å	rt	76[c]	0
8[d]	5	Bu_4NBr (2 equiv), MS3 Å	rt	3	0
9[e]	5	Bu_4NBr (2 equiv), MS3 Å	rt	4	0
10[f]	5	Bu_4NBr (2 equiv), MS3 Å	rt	6	0
11[g]	5	Bu_4NBr (2 equiv), MS3 Å	rt	25	0
12[h]	5	Bu_4NBr (2 equiv), MS3 Å	rt	2	0
13	10	MS3 Å	rt	11	0

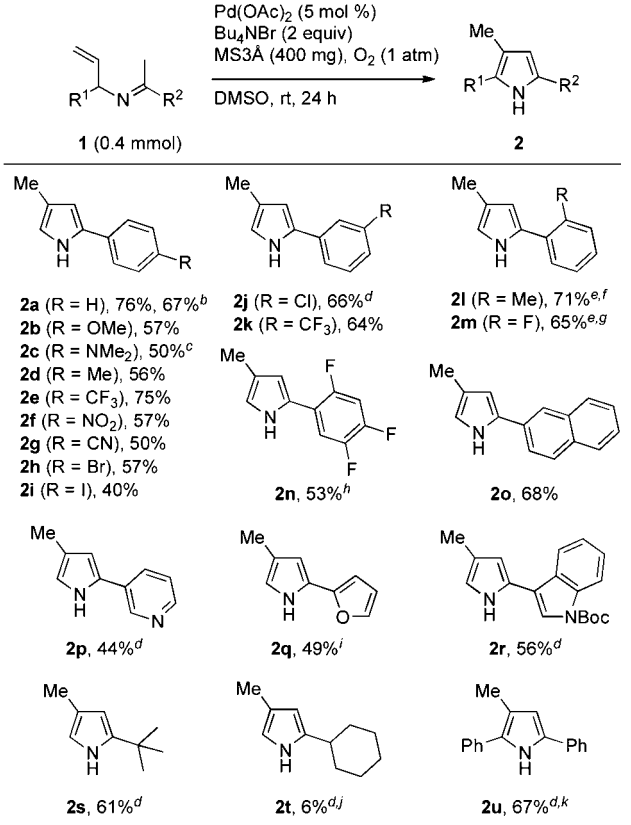
[a] The reaction was performed on a 0.4 mmol scale. *E*/*Z* ratio of **1a** was 12:1. The amount of MS3 Å was 100 mg per 0.1 mmol of **1a**. [b] Determined by GC using *n*-tridecane as an internal standard or by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard. [c] Isolated yield. [d] DMF was used instead of DMSO. [e] 1,4-Dioxane was used instead of DMSO. [f] Toluene was used instead of DMSO. [g] The reaction was performed under air. [h] The reaction was performed under N_2.

With the optimized catalytic system in hand, we explored the scope of the present cyclization reaction (Scheme 2). *N*-Allylimines derived from a series of aryl methyl ketones participated in the reaction to afford the corresponding 2-aryl-4-methylpyrroles **2a**−**o** in moderate to good yields.[11] The reaction tolerated a wide range of substituents including electron-donating methoxy and dimethylamino groups (see **2b** and **2c**), electron-withdrawing trifluoromethyl, nitro, and cyano groups (see **2e**−**g**,**k**), and halogen atoms (I, Br, Cl, F; see **2h**−**j**,**m**,**n**). The reaction of **1a** could be performed on a gram scale without significant decrease in the yield of **2a** (67%). The ortho-substituted acetophenone imines reacted sluggishly at room temperature and thus needed heating at 60 °C to achieve reasonable conversion (see **2l** and **2m**). This may be partly due to much poorer *E*/*Z* ratios of these imines (1:3.2 and 1.9:1 for **1l** and **1m**, respectively) compared to that of the others (> 10:1 for most cases); for the *Z*-isomer to participate in the cyclization reaction, isomerization of the C=N bond is necessary prior to or after α-palladation. Imines derived from heteroaryl methyl ketones cyclized to afford pyrroles having 3-pyridyl, 2-furyl, and 3-indolyl groups

(11) TLC analysis typically showed full consumption of the starting material and formation of the pyrrole product along with unindentified polar byproducts (i.e., baseline spots).

(**2p**−**r**) in moderate yields. Pinacolone-derived imine was also amenable to the present cyclization reaction, affording 2-(*tert*-butyl)-4-methylpyrrole **2s** in a respectable yield of 61%, whereas the reaction of cyclohexyl methyl ketone-derived imine produced the desired pyrrole **2t** in only 6% yield (estimated by GC and GCMS analysis). The allyl group on the imine substrate may have α-branching substituent, as imine derived from 1-phenylprop-2-en-1-amine and acetophenone afforded 2,5-diphenyl-3-methylpyrrole **2u** in 67% yield.

Scheme 2. Pyrrole Synthesis from *N*-Allylimines[a]



[a] Unless otherwise noted, the reaction was performed under the conditions shown in the equation, and the *E*/*Z* ratio of the starting material was >8:1. [b] The reaction was performed using 1.2 g of **1a** for 36 h. [c] The reaction time was 36 h. [d] MS4 Å was used instead of MS3 Å. [e] The reaction was performed at 60 °C for 30 h. [f] *E*/*Z* ratio of the imine was 1:3.2. [g] *E*/*Z* ratio of the imine was 1.9:1. [h] *E*/*Z* ratio of the imine was 4.5:1. [i] The reaction was performed with 10 mol % of $Pd(OAc)_2$ for 36 h. [j] Estimated by GC and GCMS analysis. [k] The reaction was performed at 60 °C for 24 h.

Limitations of the present oxidative cyclization reaction became clear through further exploration of imine substrates (Figure 1). Imines derived from 1,1,1-trifluoroacetone (**1v**) and cyclopropyl methyl ketone (**1w**) did not produce the expected pyrrole products. *N*-Cinnamylimines **1x** and **1y** and α-phenylacetophenone-derived imine **1z** also failed to undergo the cyclization reaction. In these cases, decomposition of the starting materials to unknown products was observed. Not unexpectedly, tetralone-derived imine **1aa** underwent dehydrogenation rather than oxidative cyclization,[8] affording *N*-allylnaphthalen-1-amine in 27% yield. The reaction did not tolerate the presence of acidic protons. For example, imine **1ab** bearing a primary amide group did not give the pyrrole product at all. Note also that imine **1ac** derived from acetophenone and homoallylamine did not afford any (six- or seven-membered) cyclization products.

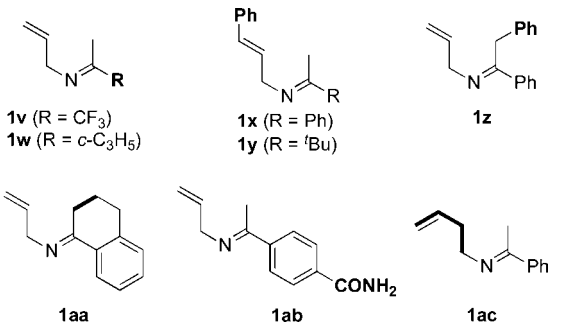
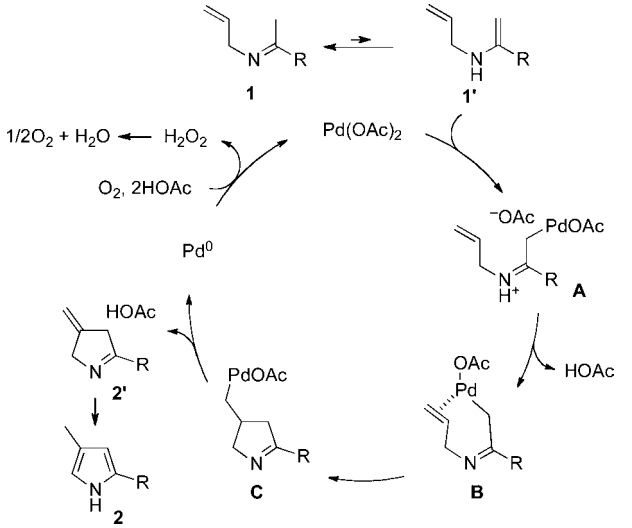


Figure 1. Substrates that failed to participate in the dehydrogenative Heck cyclization.

A proposed catalytic cycle for the present oxidative cyclization reaction is shown in Scheme 3. Tautomerization of imine **1** to enamine **1′** is followed by electrophilic palladation to give rise to, on elimination of HOAc, an α-palladated imine **B**. This intermediate then undergoes 5-*exo*-cyclization, the most common mode of cyclizations in intramolecular Heck reaction,[12,13] to give an alkylpalladium species **C**. Subsequent *β*-hydride elimination of the intermediate **C** affords 3-methylene-3,4-dihydro-2*H*-pyrrole **2′** and generates Pd(0). Isomerization and aromatization of **2′** furnishes the pyrrole product **2**, while Pd(0) is reoxidized to Pd(II) with the aid of molecular oxygen and acetic acid.[1a,b] As an alternative mechanistic possibility, a Wacker-type process involving nucleophilic

Scheme 3. Proposed Catalytic Cycle



addtion of enamine to the olefin moiety activated by Pd(II) may not be excluded. We speculate that the role of Bu_4NBr is to stabilize Pd nanoclusters and molecular Pd species through coordination of the bromide anion to Pd and electrostatic interaction between the thus-formed anionic species and the ammonium cation, as has been proposed for Heck reaction under related conditions.[14]

In summary, we have demonstrated that α-palladation of imine serves as an entry to dehydrogenative Heck cyclization, allowing facile conversion of acetophenone *N*-allylimines and related imines to pyrroles under mild aerobic conditions. While significant progress has been made in synthetic methods for pyrroles based on various transition metal-catalyzed C−H functionalization and condensation approaches,[15−18] the present dehydrogenative Heck reaction may serve as a complementary method in light of the accessible substitution patterns of such reactions. Further studies to address the limitations of the present reaction as well as to explore other types of transformations involving α-metalloimine and related species[19] are currently underway.

Acknowledgment. This work was supported by the National Research Foundation Singapore (NRF-RF2009-05 to N.Y.) and Nanyang Technological University. We thank Prof. Frank Glorius (University of Münster) for sharing with us the work of his group in this area prior to publication.

Supporting Information Available. Experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) (a) Machotta, A. B.; Oestreich, M. In *The Mizoroki−Heck Reaction*; Oestreich, M., Ed.; Wiley: Chichester, 2009; pp 179−213. (b) Muller, T.; Bräse, S. In *The Mizoroki−Heck Reaction*; Oestreich, M., Ed.; Wiley: Chichester, 2009; pp 215−258.

(13) For related intramolecular Heck reactions onto *N*-allyl group leading to pyrroles and indoles, see: (a) Yamagishi, M.; Nishigai, K.; Hata, T.; Urabe, H. *Org. Lett.* **2011**, *13*, 4873. (b) Jensen, T.; Pedersen, H.; Bang-Andersen, B.; Madsen, R.; Jørgensen, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 888.

(14) (a) Jefferey, T. *Tetrahedron* **1996**, *52*, 10113. (b) Phan, N. T. S.; Van Der Sluys, M.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 609.

(15) (a) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev.* **2013**, 10.1021/cr300333u. (b) Chiba, S. *Synlett* **2012**, 21.

(16) For C−H functionalization approaches, see: (a) Lian, Y.; Huber, T.; Hesp, K. D.; Bergman, R. G.; Ellman, R. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 629. (b) Wang, L.; Ackermann, L. *Org. Lett.* **2013**, *15*, 176. (c) Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9585. (d) Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 18326. (e) Dong, H.; Shen, M.; Redford, J. E.; Stokes, B. J.; Pumphrey, A. L.; Driver, T. G. *Org. Lett.* **2007**, *9*, 5191. (f) Yoshikai, N.; Wei, Y. *Asian J. Org. Chem.* **2013**, 10.1002/ajoc.201300016.

(17) For dehydrogenative condensation of alcohol and amine starting materials, see: (a) Michlik, S.; Kempe, R. *Nat. Chem.* **2013**, *5*, 140. (b) Zhang, M.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 597. (c) Srimani, D.; Ben-David, Y.; Milstein, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 4012. (d) Iida, K.; Miura, T.; Ando, J.; Saito, S. *Org. Lett.* **2013**, *15*, 1436.

(18) For selected other examples, see: (a) Humenny, W. J.; Kyriacou, P.; Sapeta, K.; Karadeolian, A.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 11088. (b) Trost, B. M.; Lumb, J.-P.; Azzarelli, J. M. *J. Am. Chem. Soc.* **2011**, *133*, 740. (c) Wang, H.-Y.; Mueller, D. S.; Sachwani, R. M.; Londino, H. N.; Anderson, L. L. *Org. Lett.* **2010**, *12*, 2290.

(19) Wei, Y.; Yoshikai, N. *J. Am. Chem. Soc.* **2013**, *135*, 3756.

The authors declare no competing financial interest.