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Palladium-Catalyzed Aerobic Oxidative Hydroamination of Vinylarenes Using Anilines: A Wacker-Type Amination Pathway

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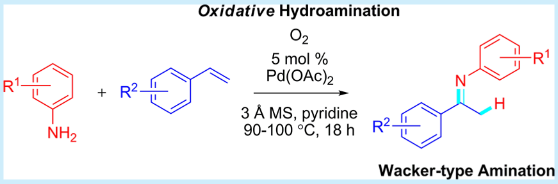
Supporting Information

ABSTRACT: A palladium-catalyzed intermolecular hydroamination of vinylarene derivatives using anilines has been developed for the first time under aerobic conditions, where the regioselective formation of *N*-arylketimines is accomplished. The current aerobic *oxidative* hydroamination pathway of anilines is distinct from that of palladium-catalyzed hydroamination reactions that proceed to give *sec*-arylethylamine and arylethylamine derivatives, identifying a longstanding missing reaction pathway, Wacker-type amination, to *N*-arylketimines using anilines. The ready availability of both starting materials, vinylarenes and anilines, offers an attractive and facile synthetic route to *N*-arylketimines in good to excellent yields.

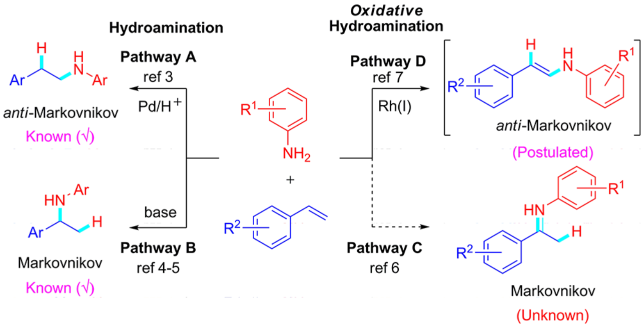


Amine derivatives continue to be a major source of innovation in the chemical sciences as they serve as basic scaffolds for the preparation of fine chemicals, pharmaceuticals, and natural products. One of the most direct synthetic methods to amine derivatives is the intermolecular addition of amines to unsaturated C−C multiple bonds, also known as hydroamination.[1] However, the development of hydroamination catalysts that defy the repulsive forces between π-electrons of C−C unsaturated bonds and lone-pair electrons of the amine nitrogen has met with significant challenges in the catalyst control over regioselectivity between Markovnikov and *anti*-Markovnikov products.[2] In general, the hydroamination of alkenes is more problematic than alkynes because of their lower reactivity and electron density. Thus, the intermolecular addition reactions between aniline and unactivated alkenes such as styrene are the hallmark of catalyst-controlled divergent hydroamination strategies (Scheme 1).

The pioneering work of Hartwig disclosed the palladium-catalyzed hydroamination of vinylarenes with anilines where the anti-Markovnikov products were exclusively obtained in the presence of an acid cocatalyst (Scheme 1, path A).[3] In contrast, the base-catalyzed Markovnikov hydroaminations of anilines to vinylarenes were observed by the groups of Hultzsch[4] and Doye,[5] demonstrating the possibility of complementary regiodivergent hydroamination of anilines (Scheme 1, path B). Nevertheless, the catalytic hydroamination of styrenes with anilines via *oxidative* addition remains an unsolved problem. Previously, the laboratory of Brunet in 1993 first reported the rhodium-catalyzed *oxidative* hydroamination of styrene using lithium anilide to give a 2:1 mixture of phenylketimine and *sec*-phenylethylamine.[6] Complementary to Brunet's work, the group of Beller in 2000 postulated the intermediacy of an *anti*-Markovnikov product from the rhodium-catalyzed *oxidative* hydroamination of styrenes using anilines (Scheme 1, path D),[7] where the formation of quinolines was observed in 13−48% yields. In 2003, the group of Stahl reported the palladium-catalyzed aerobic *oxidative* hydroamination of vinylarenes using amines with a relatively acidic N−H group in the presence of base. However, Stahl's *oxidative* hydroamination chemistry failed to work for aniline (Scheme 1, path C).[8] As a result, there exists a significant knowledge gap in the *oxidative* hydroamination of alkenes using less "nucleophilic" anilines, the only missing reaction pathway in the general realm of hydroamination of alkenes with anilines. Herein, we for the first time report a regioselective, simple, and general method for the synthesis of *N*-arylketimines from vinylarenes via a palladium-catalyzed aerobic *oxidative* hydroamination using anilines. The developed catalyst system represents a formal Wacker process,[9] an oxidation of the alkenes, where the hydrolysis of the ketimines leads to the Wacker oxidation products.

Our initial studies began by attempting the intermolecular reaction between styrene **1a** and aniline **2a** under different

Scheme 1. Divergent Hydroamination Pathways of Vinylarenes Using Anilines



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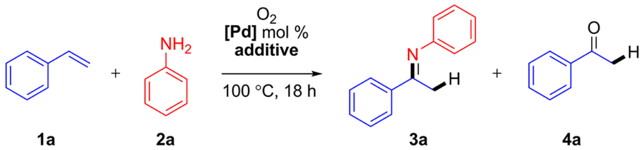
palladium salts, solvents, and reaction temperatures, where we observed the formation of phenylketimine **3a** and acetophenone **4a**, a hydrolyzed form of **3a**, as the only identifiable products in <5% yields at 100 °C.[10] With no apparent solvent effect in the *oxidative* hydroamination reaction, we opted for a neat reaction under aerobic conditions to re-evaluate the palladium salts (Table 1). Among palladium salts we screened (entries 1−7), the use of $Pd(OAc)_2$ led to the formation of **3a**/**4a** in a combined yield of 38% (entry 6). Speculating an inadvertent acid formation during the reaction that resulted in the formation of a hydrolyzed product **4a** from **3a**, we examined the role of base.[11] The addition of pyridine to the reaction mixture provided slightly improved yields of **3a**/**4a** to 47− 57% yields (entries 8−10); however, the formation of the hydrolyzed product **4a** could not be prevented with the use of pyridine. Next, we employed 3 Å molecular sieves to sequester water, a byproduct of dioxygen reduction.[12] Gratifyingly, the formation of **4a** was significantly reduced to less than 5% while the reaction yields were maintained at 51% (entry 11). Further optimization studies using the increased amount of styrene **1a** and the reduced amount of $Pd(OAc)_2$ led to yields of **3a**/**4a** to 60−78% (entries 12−14). Thus, the aerobic *oxidative* hydroamination of aniline **2a** using 20 equiv of styrene **1a** in the presence of 5 mol % of $Pd(OAc)_2$, 100 mol % of pyridine, and 20 mg/mmol of 3 Å MS at 90−100 °C was adopted as the optimal conditions (entries 13 and 15).[13] Further control experiments of the reaction confirmed the optimal amount of $Pd(OAc)_2$ (entry 16), the importance of 3 Å MS, not 4 Å MS, (entry 16),[14] the dual action between $Pd(OAc)_2$ and dioxygen,[15] and the absence of Wacker oxidation product, **4a**, in the absence of aniline **2a** (entry 17).

Table 1. Selected Optimization Conditions of Pd(II)-Catalyzed Aerobic *Oxidative* Hydroamination of Styrene Using Aniline[a]

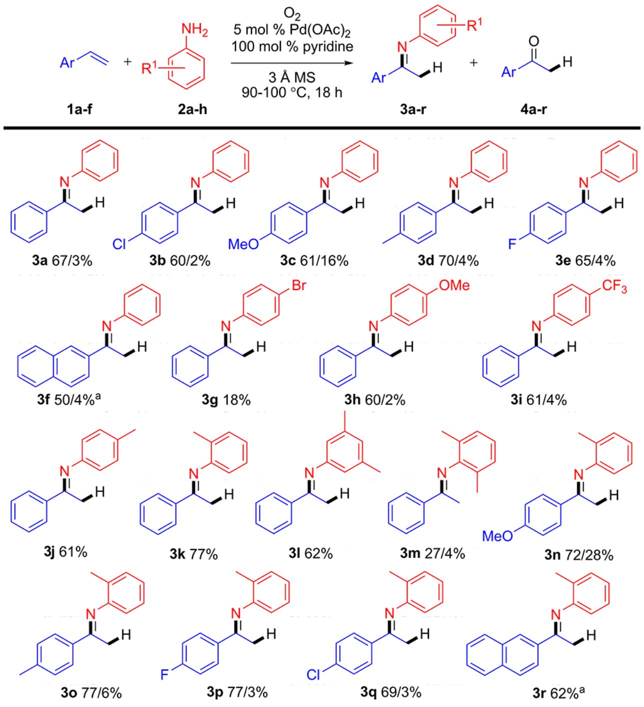


entry	Pd (mol %)	additive (mol %)	base	yield of 3a/4a[b] (%)
1	$PdCl_2$ (10)			0/0
2	$Pd(dppf)Cl_2$ (10)			0/0
3	$Pd(PPh_3)_2Cl_2$ (10)			2/0
4	$Pd_2(dba)_3$ (10)			13/2
5	$Pd(TFA)_2$ (10)			0/0
6	$Pd(OAc)_2$ (10)			32/6
7	$Pd(OAc)_2(PPh_3)_2$ (10)			13/7
8	$Pd(OAc)_2$ (10)		pyr (30)	40/7
9	$Pd(OAc)_2$ (10)		pyr (60)	28/22
10	$Pd(OAc)_2$ (10)		pyr (100)	30/27
11	$Pd(OAc)_2$ (10)	3 Å MS	pyr (100)	47/4
12[c]	$Pd(OAc)_2$ (5)	3 Å MS	pyr (100)	58/2
13[d]	$Pd(OAc)_2$ (5)	3 Å MS	pyr (100)	67/1
14[e]	$Pd(OAc)_2$ (5)	3 Å MS	pyr (100)	72/6
15[d,f]	$Pd(OAc)_2$ (5)	3 Å MS	pyr (100)	67/3
16[d]	$Pd(OAc)_2$ (3)	3 Å MS	pyr (100)	47/3
17[g]	$Pd(OAc)_2$ (5)	3 Å MS	pyr (100)	0/0

[a]Reaction conditions: **1a** (6.0 mmol), **2a** (0.6 mmol), Pd catalyst (mol %), base (mol %), powdered molecular sieves (20 mg/mmol), neat under O_2 balloon at 100 °C. [b]Yield was determined by ^1H NMR relative to internal standard, 1,3,5-trimethoxybenzene. [c]Reaction for 48 h. [d]Reaction using 20 equiv of **1a**. [e]Reaction using 40 equiv of **1a**. [f]Reaction at 90 °C. [g]Reaction without **2a**.

With the optimized reaction conditions in hand, the scope of the Pd-catalyzed aerobic *oxidative* hydroamination was investigated using various vinylarenes and anilines (Scheme 2). The examination of vinylarenes with different electronic properties indicated no significant influence of the electronic nature of vinylarenes, although the presence of an electron-donating methoxy group facilitated the hydrolysis of phenylketimines **3c** to acetophenone derivative **4c**. The use of 2-vinylnaphthalene **1f** under our optimized conditions only led to the formation of **3f** in 20% yield. However, the reduced amount of **1f** from 20 equiv to 5 equiv provided ketimine **3f** in an improved yield of 54%. Next, we examined various aniline derivatives with different electronic and steric properties. While the presence of aryl chloride did not affect the current Pd-catalyzed reaction (**3b**), aryl bromide was not tolerated in the *oxidative* hydroamination conditions, providing a complex mixture with only 18% yield of 4-bromophenylketimine **3g**. Anilines with different electronic properties also provided the desired phenylketimines (**3h**−**j**) in good yields. The steric effect of anilines was minimal (**3k**,**l**), but the use of 2,6-dimethylaniline gave the corresponding ketimine **3m** in about 30% yield. Among the tested aniline derivatives, the use of 2-methylaniline proved to be suitable for further substrate

Scheme 2. Scope of Pd(II)-Catalyzed Aerobic *Oxidative* Hydroamination*

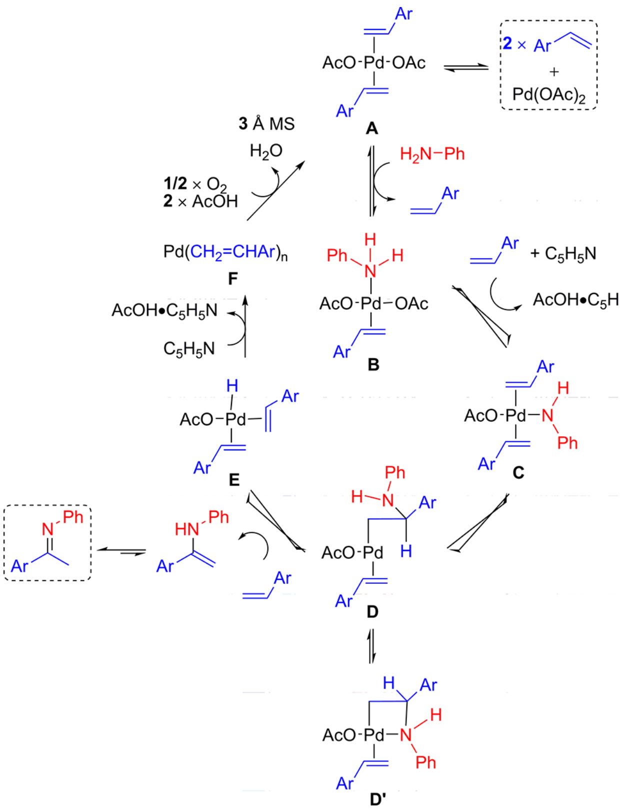


*Yields of 3/4 are shown. [a]Use of 5 equiv of 2-vinylnaphthalene.

screening. Indeed, 2-methylaniline smoothly underwent the intermolecular aerobic *oxidative* hydroamination with various vinylarenes to give the desired phenylketimine derivatives in excellent yields.

While the detailed reaction mechanism for the Wacker-type amination is yet to be studied,[16] it is reasonable to speculate the involvement of the Markovnikov addition of aniline to Pd(II)−styrene complexes followed by a sequential dioxygen-mediated regeneration of active Pd(II) catalysts (Scheme 3). As such, the Pd−styrene complex **A** undergoes a ligand exchange with aniline to give the complex **B**. A subsequent action of pyridine helps the removal of acetic acid to give the Pd−anilide complex **C**.[17] A migratory insertion, controlled by a sterically congested palladium complex, occurs to give Pd−alkyl complexes **D**/**D′** that undergo a hydride elimination to give the enamine and the palladium hydride **E**. The enamine product isomerizes to ketimine,[18] and the palladium hydride species **E** oxidatively regenerates the active catalyst **A**.[19] The proposed catalytic cycle is supported by our key experimental observations: (1) the high concentration of styrene positively influences the reaction conversion; thus, the high ratio between styrene and Pd catalyst is preferred;[20] (2) the control experiment without aniline did not provide the Wacker oxidation product, acetophenone **4a**, illustrating the involvement of aniline in the catalytic cycle; (3) the presence of pyridine improves the catalytic activity, thus pyridine may serve as both ligand and base;[21] and (4) the 3 Å MS primarily absorbs water to prevent the phenylketimine **3a** from hydrolyzing to acetophenone; thus, the 3 Å MS does not significantly influence the reaction rate.[22]

Scheme 3. Plausible Catalytic Cycle for the Pd-Catalyzed Aerobic *Oxidative* Hydroamination Using Anilines



To investigate our mechanistic proposal in Scheme 3, we have performed the kinetic studies, where we found the palladium catalyst with the first order reaction from the initial rate experiments (see the Supporting Information). However, the reaction after about 70% conversion appeared to be almost zero order with respect to Pd(OAc)$_2$. This scenario might be interpreted for the presence of alternative reaction pathways: (1) the possibility of hydroamination activity of the palladium hydride, **E**, to give *sec*-phenylethylamines[3] or (2) the reduction activity of **E** to reduce styrene to ethylbenzene derivatives.[7b] A close inspection of the reaction mixtures did not yield any *sec*-phenylethylamine product, and only on one occasion with the use of 4-fluorostyrene did we observe the formation of a reduced form, 1-ethyl-4-fluorobenzene, in <5%. Alternatively, the zero-order reaction rate at the later stage could be considered as the ineffective catalyst regeneration, Pd(II) from Pd(0) (Scheme 3, **F** to **A**). The formation of Pd(0) black was visible after the reaction, and the presence of ketimine products could competitively compete with aniline to coordinate to the metal center. Thus, the kinetic data as well as the experimental findings support the depletion of active Pd(II) catalyst for the observed kinetic profile. Furthermore, the kinetic isotope effect of 1.6 (k^H/k^D) using aniline-d_7 suggests the active involvement of aniline in the catalyst-turnover processes.[23] Previously, in the hydroamination of vinylarenes using anilines, Hartwig proposed the migratory insertion of vinylarene into a palladium hydride to give catalytic intermediates that reacted in the presence of excess aniline.[24] In his studies, the presence of both phenylketimine byproduct and palladium hydride intermediate was observed in an almost identical ratio to the palladium catalyst used. The reason why palladium hydride intermediate **E** did not initiate a typical hydroamination pathway of vinylarenes is not clear at this time. However, the high concentration of ligands such as styrene, pyridine, and phenylketimine should improve the short lifetime of the palladium hydride intermediate **E**, limiting the reaction with aniline to give *sec*-phenylethylamines.[25]

In summary, we have identified a novel aerobic *oxidative* hydroamination pathway of vinylarenes using anilines to mimic the Wacker-type amination process. The current *oxidative* hydroamination pathway is substantially different from the status quo of the hydroamination pathways of alkenes, where the formations of phenylethylamines and *sec*-phenylethylamines are achieved under metal and base catalysis. Defying the known hydroamination pathways of anilines is perhaps due to the higher concentration of vinylarenes that increased the Pd−styrene complexation in combination with a coordinatively non-innocent pyridine additive and 3 Å MS. Using structurally unaltered anilines, the palladium-catalyzed aerobic *oxidative* hydroamination of vinylarenes has been achieved for the first time. While more detailed mechanistic studies are needed, the current palladium catalyst system might be modulated for the complementary Wacker-type amination to *anti*-Markovnikov enamine products.[26] Additional studies to understand the mechanistic details and to extend the substrate scope to other amines are currently underway, and our results will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02532.

Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For general reviews, see: (a) Taube, R. In *Applied Homogeneous Catalysis*, 1st ed.; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, 1996; Vol. *1*, pp 507−526. (b) Müller, T. E.; Beller, M. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; Vol. *2*, pp 316−330. (c) Brunet, J. J.; Neibecker, D. In *Catalytic Heterofunctionalization from Hydroamination to Hydrozirconation*; Togni, A., Grützmacher, H., Eds.; Wiley-VCH: Weinheim, 2001; pp 91−141.

(2) For reviews, see: (a) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675−704. (b) Nobis, M.; Drießen-Hölscher, B. *Angew. Chem., Int. Ed.* **2001**, *40*, 3983−3985. (c) Seayad, J.; Tillack, A.; Hartung, C. G.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 795−813. (d) Roesky, P. W.; Müller, T. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 2708−2710. (e) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673−686. (f) Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367−391. (g) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795−3892. (h) Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L. J. *Chem. Rev.* **2015**, *115*, 2596−2697. (i) Margrey, K. A.; Nicewicz, D. *Acc. Chem. Res.* **2016**, *49*, 1997−2006. (j) Patel, M.; Saunthwal, R. K.; Verma, A. K. *Acc. Chem. Res.* **2017**, *50*, 240−254.

(3) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546−9547.

(4) Horrillo-Martínez, P.; Hultzsch, K. C.; Gil, A.; Branchadell, V. *Eur. J. Org. Chem.* **2007**, *2007*, 3311−3325.

(5) Jaspers, D.; Doye, S. *Synlett* **2011**, 1444−1448.

(6) Brunet, J.-J.; Neibecker, D.; Philippot, K. *Tetrahedron Lett.* **1993**, *34*, 3877−3880.

(7) (a) Beller, M.; Thiel, O. R.; Trauthwein, H.; Hartung, C. G. *Chem. - Eur. J.* **2000**, *6*, 2513−2522 For the Rh(I)-catalyzed anti-Markovnikov products using secondary amines, see:. (b) Beller, M.; Eichberger, M.; Trauthwein, H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2225−2227.

(8) (a) Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2003**, *125*, 12996−12997. (b) Timokhin, V. I.; Stahl, S. S. *J. Am. Chem. Soc.* **2005**, *127*, 17888−17893 For a review of the Pd-catalyzed oxidation reactions, see:. (c) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400−3420.

(9) For a review, see: Keith, J. A.; Henry, P. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 9038−9049.

(10) For the initial evaluations of key experimental parameters, see the Supporting Information.

(11) The use of other pyridine derivatives provided the formation of phenylketimine product **2a** in about 30% yields; however the employment of stronger bases such as Et_3N, K_2CO_3, and KOH significantly reduced the observed yields to about 5%. For example, the employment of lithium anilide resulted in 8% yield of phenylketimine **2a**.

(12) The optimal amount of 3 Å molecular sieves appears to be about 20 mg for 1 mmol of styrene where the phenylketimine product **2a** was obtained in 70% yield (8 mg/mmol; 52% and 32 mg/mmol; 68%).

(13) The optimized reaction conditions are run in neat without solvent; however, the presence of toluene or *o*-xylene in the same amount as styrene (i.e., 20 equiv) did not influence the reaction outcome (neat, 70%; in toluene, 68%; in *o*-xylene, 62%).

(14) Upon use of 4 Å MS, the phenylketimine product **2a** was obtained in 18% yield. While the precise reason for the low catalytic activity in the presence of 4 Å MS is not clear, the sequestration of palladium catalysts is possible through the absorption of palladium species to the surface of 4 Å MS. For the formation of 4 Å MS-supported Pd(II) catalysts, see: Dey, R.; Sreedhar, B.; Ranu, B. C. *Tetrahedron* **2010**, *66*, 2301−2305.

(15) The use of alternative oxidants such as oxone, *p*-benzoquinone, and $PhI(OAc)_2$ was not successful under argon atmosphere.

(16) An aqueous workup of the reaction provided the desired acetophenone products without loss of yields, thus providing the formal Wacker oxidation products.

(17) The possibility of H-bonding between Pd-bound aniline and acetate as a driving force to form the complex **C** from **B** was eliminated from our kinetic isotope effect experiments, where we found no isotope effect at the beginning of the reaction.

(18) Phenylketimine should be the thermodynamic product based on the ketimine−enamine tautomerization as found in the keto−enol tautomerization.

(19) Popp, B. V.; Stahl, S. S. *Chem. - Eur. J.* **2009**, *15*, 2915−2922.

(20) The ratio between vinylarene and $Pd(OAc)_2$ under our optimized conditions is 400:1, except for 2-vinylnaphthalene (100:1).

(21) The presence of pyridine additive helps the stability of palladium catalyst, making them less susceptible to decomposition to palladium(0) black. For the effect of pyridine in the intramolecular aerobic *oxidative* amination, see: Ye, X.; Liu, G.; Popp, B. V.; Stahl, S. S. *J. Org. Chem.* **2011**, *76*, 1031−1044.

(22) We did not observe the rate acceleration and the increase in the catalyst stability in the presence of 3 Å MS. The use of 3 Å MS without pyridine additive led to 27% yield of phenylketimine **2a**. For the beneficial effect of 3 Å MS in terms of catalyst stability and rate enhancement, see: Steinhoff, B. A.; King, A. E.; Stahl, S. S. *J. Org. Chem.* **2006**, *71*, 1861−1868.

(23) The KIE of 1.6 might be relevant to the different kinetic orders in substrates. For a discussion on either first or saturation dependence on [substrate] in the aerobic oxidative amination of styrene, see: Kotov, V.; Scarborough, C. C.; Stahl, S. S. *Inorg. Chem.* **2007**, *46*, 1910−1923.

(24) Nettekoven, U.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 1166−1167.

(25) The insertion of dioxygen into a palladium(II) hydride followed by reductive water removal cannot be ruled out. For the first crystallographic evidence for such a process, see: Denney, M. C.; Smythe, N. A.; Cetto, K. L.; Kemp, R. A.; Goldberg, K. I. *J. Am. Chem. Soc.* **2006**, *128*, 2508−2509.

(26) Because aliphatic alkenes are inert under our optimized conditions, the steric requirement of Pd−anilide complex **C** to Pd−alkyl complexes **D**/**D′** using bulky alkene ligands is currently assessed in order to induce the *anti*-Markovnikov reaction pathway.

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