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Aerobic Intramolecular Oxidative Amination of Alkenes Catalyzed by NHC-Coordinated Palladium Complexes

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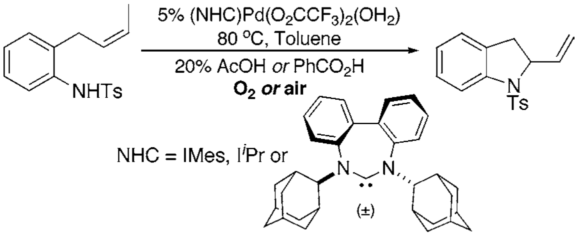
ABSTRACT



Palladium(II) complexes bearing a single *N*-heterocyclic carbene ligand serve as effective catalysts for the aerobic oxidative cyclization of alkenes with pendant sulfonamides. The use of carboxylic acid cocatalysts (AcOH and $PhCO_2H$) often leads to significant improvements in catalyst stability and product yield and enables catalytic turnover to be achieved with air, rather than pure oxygen gas, as the source of O_2.

Palladium-catalyzed, Wacker-type oxidative cyclization of alkenes represents an attractive strategy for the synthesis of heterocycles.[1] This reaction class, which has rich historical precedent,[2] has been the subject of considerable recent attention. Current efforts are especially focused on the development of asymmetric reactions,[3,4] new synthetic transformations (e.g., 1,2-difunctionalization of alkenes),[5,6] and methods that employ molecular oxygen as the terminal oxidant.[7,8] Here, we report the use of *N*-heterocyclic carbene (NHC)-coordinated Pd^{II} catalysts, (NHC)Pd-$(O_2CCF_3)_2(OH_2)$, for the intramolecular oxidative amination of alkenes. The reactions can proceed with air, rather than pure oxygen gas,

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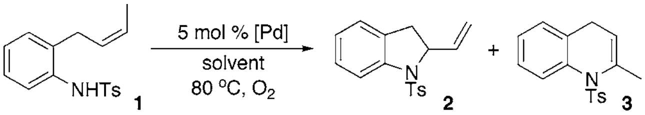
10.1021/ol060327q CCC: $33.50

Table 1. Catalyst Screening Data for the Aerobic Oxidative Amination of **1**[a]



entry	catalyst	solvent	additive	% yield of **2/3**[b]
1	$[IMesPdCl_2]_2$	toluene		0/0
2	$IMesPd(OAc)_2OH_2$	toluene		83/7
3	**$IMesPd(TFA)_2OH_2$**	**toluene**		**88/1**
4	$IPrPd(TFA)_2OH_2$	toluene		85/1
5	$IMesPd(TFA)_2OH_2$	toluene	3A MS	35/2
6	$IMesPd(TFA)_2OH_2$	toluene	1 equiv of NaOAc	88/7
7	$IMesPd(TFA)_2OH_2$	toluene	1 equiv of KH_2PO_4	81/1
8	$IMesPd(TFA)_2OH_2$	toluene	1 equiv of MgO	70/3
9	$IMesPd(TFA)_2OH_2$	toluene	1 equiv of $NaHCO_3$	75/2
10	$IMesPd(TFA)_2OH_2$	toluene	1 equiv of KOtBu	42/0
11	$IMesPd(TFA)_2OH_2$	toluene	20% pyridine	20/4
12	$IMesPd(TFA)_2OH_2$	toluene	10% CF_3CO_2H	34/0
13	**$IMesPd(TFA)_2OH_2$**	**toluene**	**10% AcOH**	**94/0**
14	**$IMesPd(TFA)_2OH_2$**	**toluene**	**20% $PhCO_2H$**	**91/4**
15	$Pd(OAc)_2$	toluene		54/5[c]
16	$Pd(OAc)_2$	toluene	20% $PhCO_2H$	45/0[c]
17	$Pd(OAc)_2$	toluene	20% pyridine	80/0
18	$IMesPd(TFA)_2OH_2$	CH_3CN		18/0
19	$IMesPd(TFA)_2OH_2$	DME		34/0
20	$IMesPd(TFA)_2OH_2$	DMF		46/0
21	$IMesPd(TFA)_2OH_2$	$CHCl_3$		2/0

[a] Reaction conditions: substrate (100 μmol), Pd (5 μmol), additive, 1 mL of solvent, 1 atm of O_2, 80 °C, 4 h. [b] ^1H NMR yield, internal standard = 1,3,5-trimethoxybenzene. No additional products are generally observed; the remainder is unreacted starting material. [c] An unidentified byproduct (15−20%, based on mass balance) is also obtained.

as the source of oxidant if carboxylic acid cocatalysts are employed in the reaction, and they also constitute the first catalytic application of Pd complexes bearing a new class of seven-membered NHC ligands that we recently described.[9]

Ongoing studies in our laboratory are focused on the development of dioxygen-coupled methods for both intra- and intermolecular oxidative amination of alkenes.[8e,10] Preliminary mechanistic insights into the oxidative amination of styrene prompted us to evaluate the NHC-coordinated Pd complex, $[(IPr)PdCl_2]_2$, in such reactions;[10a,11] however, this complex proved to be less effective than other Pd catalysts, such as $(Et_3N)_2PdCl_2$. Nevertheless, prospects for the use of NHC ligands in Pd-catalyzed oxidation reactions have been clearly demonstrated by Sigman and co-workers.[12] In particular, they reported a new class of NHC−Pd complexes, $(NHC)Pd(O_2CR)_2(OH_2)$, that are highly effective catalysts for aerobic alcohol oxidation.[12a,d] Recently, Muñiz showed that these complexes are also effective for the oxidative cyclization of several *o*-allylphenol substrates.[8f] These examples highlight prospects for the use of NHC ligands in catalytic oxidation reactions.[13]

We intiated our studies by evaluating IMes- and IPr-coordinated Pd complexes[11] as potential catalysts for the aerobic oxidative cyclization of the *cis*-crotyl tosylanilide substrate **1** (Table 1). To ensure maximum data reliability, we independently synthesized the Pd complexes used in this study rather than preparing them in situ from the corresponding PdX_2 source and imidazolium salt of the carbene. The $(IMes)Pd(O_2CCF_3)_2(OH_2)$ complex, which is the most effective catalyst, was also characterized by X-ray crystallography (Figure 1).[14]

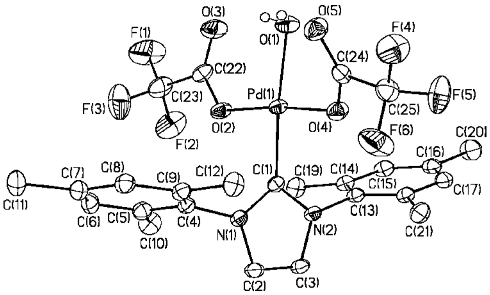


Figure 1. Molecular structure of $(IMes)Pd(O_2CCF_3)_2(OH_2)$. Hydrogen atoms are omitted for clarity. Thermal ellipsoids are shown at 30% probability.

Pd−chloride complexes, $[IMesPdCl_2]_2$ (Table 1, entry 1) and IMesPd(allyl)Cl (not shown), were ineffective as catalysts; however, complexes with acetate or trifluoroacetate (TFA) as the anionic ligand were quite successful (entries

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(7) For recent reviews describing direct dioxygen-coupled Pd-catalyzed oxidative cyclization reactions, see: (a) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400−3420. (b) Stoltz, B. M. *Chem. Lett.* **2004**, *33*, 362−367. (c) Sigman, M. S.; Schultz, M. J. *Org. Biomol. Chem.* **2004**, *2*, 2551−2554. (d) Stahl, S. S. *Science* **2005**, *309*, 1824−1826.

(8) See, for example: (a) van Benthem, R. A. T. M.; Hiemstra, H.; van Leeuwen, P. W. N. M.; Geus, J. W.; Speckamp, W. N. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 457−460. (b) Rönn, M.; Bäckvall, J.-E.; Andersson, P. G. *Tetrahedron Lett.* **1995**, *36*, 7749−7752. (c) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584−3585. (d) Larock, R. C.; Pace, P.; Yang, H.; Russell, C. E.; Cacchi, S.; Fabrizi, G. *Tetrahedron* **1998**, *54*, 9961−9980. (e) Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 164−166. (f) Muñiz, K. *Adv. Synth. Catal* **2004**, *346*, 1425−1428.

(9) (a) Scarborough, C. C.; Grady, M. J. W.; Guzei, I. A.; Gandhi, B. A.; Bunel, E. E.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 5269−5272. (b) Scarborough, C. C.; Popp, B. V.; Guzei, I. A.; Stahl, S. S. *J. Organomet. Chem.* **2005**, *690*, 6143−6155.

(10) (a) Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2003**, *125*, 12996−12997. (b) Brice, J. L.; Harang, J. E.; Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2005**, *127*, 2868−2869. (c) Timokhin, V. I.; Stahl, S. S. *J. Am. Chem. Soc.* **2005**, *127*, 17888−17893.

(11) Abbreviations: IPr = *N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidine; IMes = *N*,*N*′-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene; DMAP = 4-(*N*,*N*′-dimethylamino)pyridine.

(12) (a) Jensen, D. R.; Schultz, M. J.; Mueller, J. A.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3810−3813. (b) Jensen, D. R.; Sigman, M. S. *Org. Lett.* **2003**, *5*, 63−65. (c) Mueller, J. A.; Goller, C. P.; Sigman, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9724−9734. (d) Schultz, M. J.; Hamilton, S. S.; Jensen, D. R.; Sigman, M. S. *J. Org. Chem.* **2005**, *70*, 3343−3352. (e) Cornell, C. N.; Sigman, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 2796−2797.

(13) For a review of the use of NHCs in metal-catalyzed oxidation reactions, see: Rogers, M. M.; Stahl, S. S. *N-Heterocyclic Carbenes in Transition Metal Catalysis*; Glorius, F., Ed.; Springer: New York, 2006; in press.

(14) For related crystallographically characterized $(NHC)Pd(O_2CR)_2$ complexes, see refs 9b, 12a, and 12c, and the following: Viciu, M. S.; Stevens, E. D.; Petersen, J. L. *Organometallics* **2004**, *23*, 3752−3755.

2−4). Use of the more basic acetate ligand results in slightly higher quantities of the 6-endo cyclization product **3**, but both anionic ligands enable formation of the dihydroindole product **2** in >80% yield. The identity of the carbene ligand (IMes vs IPr) has little effect on the reaction (entries 3 and 4). Molecular sieves, which are commonly employed in Pd-catalyzed aerobic oxidation reactions (entry 5), have a detrimental effect on the reaction yield.[15] More polar solvents also were less effective (entries 18−21).

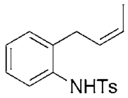
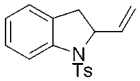
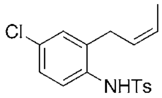
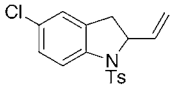
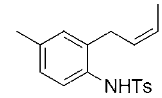
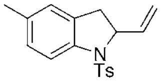
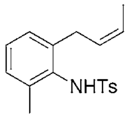
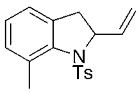
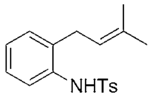
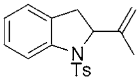
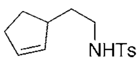
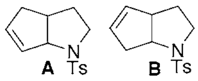
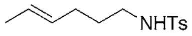
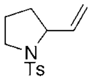
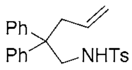
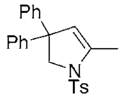
In the oxidative cyclization of *o*-allylphenols catalyzed by NHC−Pd complexes,[8f] it was noted that base (20 mol % DMAP[11] and 2 equiv Na_2CO_3) was required to avoid side reactions and maintain catalyst stability. In the current amination reactions, however, anionic bases and pyridine generally lead to inferior results (Table 1, entries 6−11). In contrast, the best results are obtained under *acidic* conditions, namely, in the presence of catalytic quantities of acetic or benzoic acid (entries 13 and 14).

For comparison, palladium acetate (alone or with cocatalytic benzoic acid) is a moderately effective catalyst for the reaction (Table 1, entries 15 and 16). Better results were obtained with $Pd(OAc)_2$/pyridine (entry 17), a catalyst system that we have described previously for such reactions.[8e] The oxidative cyclization of **1**, however, proceeds most effectively with the NHC-based catalysts.[16]

On the basis of these results, we employed 5 mol % of $(IMes)Pd(TFA)_2(OH_2)$ with cocatalytic acetic acid as the starting point to test the reactivity of other substrates. Cyclization of a series of olefinic tosylamides proceeds in good yield (Table 2). In scale-ups, we observed that yields were often a few percent higher with benzoic acid as the cocatalyst rather than acetic acid. Aromatic-ring substituents have little effect on the success of the reaction, although the *p*-chloro substrate (entry 3) reacts slightly faster than those bearing a methyl substituent in the ortho or para position (entries 3 and 4). We have initiated mechanistic studies to probe the origin of this effect.

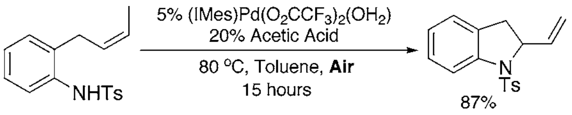
Changing the degree of substitution on the alkene from di- to trisubstituted has a detrimental influence. The trisubstituted alkene (entry 5) does not react effectively under standard conditions; however, a moderate yield of the desired product was obtained if the reaction was performed in the presence of base (1 equiv of sodium acetate). The origin of this acid/base effect is not presently understood. Alkyl tosylamide substrates (entries 6−8) are generally less reactive than the tosylanilides. The longer reaction times required for these substrates partly reflects the lower temperature employed to obtain optimal yields. At higher temperatures, competing substrate decomposition is observed. Geminal disubstitution significantly improves substrate reactivity (entry 8); the analogue lacking gem-diphenyl substitution yields only trace product under similar conditions.

Table 2. Intramolecular Oxidative Amination of Olefinic Substrates

entry	substrate	time	product[a]	% yield
1		4 h		86[b]
2		5 h		79[c]
3		8 h		72[c]
4		8 h		75[c]
5		6 d		56[d]
6		6 d		65[e] (85:15)
7		3 d		55[e]
8		24 h		70[e]

[a] Substrate (0.5 mmol), $IMesPd(O_2CCF_3)_2$ (0.025 mmol), 5 mL of toluene, 1 atm of O_2. [b] Acetic acid (0.10 mmol), 80 °C. [c] Benzoic acid (0.10 mmol), 80 °C. [d] Sodium acetate (0.50 mmol), 80 °C. [e] Benzoic acid (0.10 mmol), 60 °C.

An important goal in the development of aerobic oxidation reactions is to identify conditions compatible with the use of air as the source of O_2. Building on insights reported by Sigman et al. for the aerobic oxidation of alcohols,[12a,c] we find that the oxidative cyclization of **1** proceeds successfully when the reaction is performed under ambient air, but only if acetic acid (or another carboxylic acid) is present as a cocatalyst (eq 1).[17,18] When the cyclization of **1** under air is



(1)

attempted in the absence of carboxylic acid, formation of palladium black and low yields are observed. The reaction time under air is elongated relative to the pure-O_2 conditions (cf. Table 2, entry 1), but final yields are virtually identical. Despite the longer reaction time, this observation highlights

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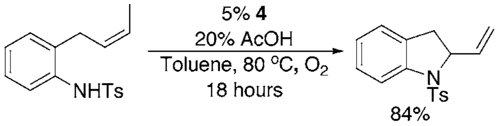
(15) For a discussion of molecular sieves in Pd-catalyzed aerobic oxidation reactions, see: Steinhoff, B. A.; King, A. E.; Stahl, S. S. *J. Org. Chem.* **2006**, *71*, 1861−1868.

(16) The stability of the NHC−Pd complex during catalytic turnover has been confirmed by monitoring the reaction in situ by ^1H NMR spectroscopy.

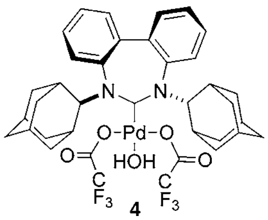
(17) The use of 5% $Pd(OAc)_2$/20% $PhCO_2H$ as a catalyst under an air atmosphere generates the product in 46% yield under identical conditions.

prospects for this important simplification of the conditions for aerobic oxidative cyclization reactions.

We recently reported a series of Pd complexes bearing a new class of carbene ligands based on a seven-membered heterocyclic ring,[9] and the $Pd(TFA)_2$ complex **4** has been characterized previously by X-ray crystallography.[9b] The aerobic oxidative cyclization of **1** (eq 2) catalyzed by **4** represents the first successful application of these seven-membered carbenes as ancillary ligands in a catalytic reaction. We are hopeful that ongoing efforts will lead to the development of enantiomerically resolved analogues of these ligands that will find use in asymmetric catalysis.



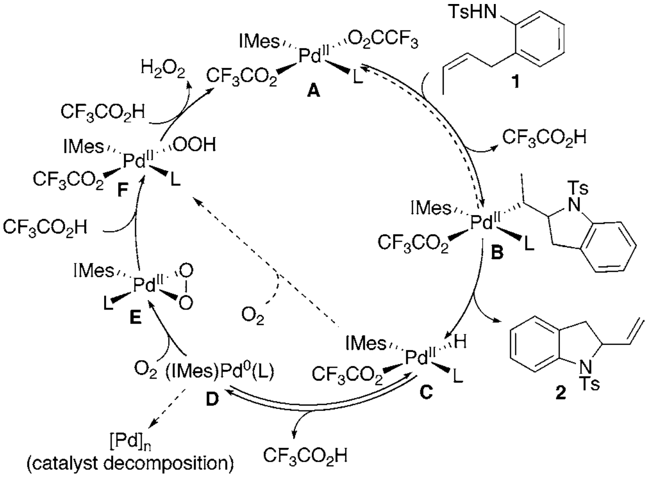
(2)



4

A proposed catalytic cycle for these reactions is shown in Scheme 1. Aminopalladation (**A** + **1** → **B)** generates the heterocyclic ring and an intermediate alkyl−Pd(II) intermediate. Our recent study of Pd-catalyzed oxidative amination of styrene suggests this step might be reversible.[10c] β-Hydride elimination from **B** generates the product **2** and Pd^{II}−H intermediate **C**. The precise role of the carboxylic acid cocatalyst is not known, but we speculate that it plays an important role in catalyst stabilization and reoxidation by O_2. In studies of aerobic alcohol oxidation catalyzed by NHC-coordinated Pd complexes, Sigman et al. observed that carboxylic acids enhance the catalyst lifetime.[12c] They propose that the acid reacts reversibly with Pd(0) to form Pd(II)-hydrides, which are less susceptible to decomposition (i.e., **C** ⇔ **D**, Scheme 1). In addition, they observe that low concentrations of acid increase the rate. Recently, we prepared a series of NHC-coordinated Pd^{II}−H complexes and investigated their reactivity with molecular oxygen.[19a] We find that carboxylic acids promote the oxygenation of Pd^{II}−H (i.e., the net reaction, **C** + O_2 → **F**, Scheme 1). The origin of this effect is not yet known, but it provides a possible explanation for the improved catalyst performance in the presence of carboxylic acids. The Pd^{II}−hydroperoxide product **F** can undergo subsequent protonolysis[19b] to release hydrogen peroxide (which disproportionates into water and O_2) and catalytically active Pd(II), **A**.

Scheme 1. Proposed Catalytic Cycle for Intramolecular Oxidative Amination of Alkenes Catalyzed by $(IMes)Pd^{II}(O_2CCF_3)_2$



In conclusion, we have demonstrated that NHC-coordinated Pd complexes are effective catalysts for the intramolecular oxidative amination of alkenes with molecular oxygen as the stoichiometric oxidant. The beneficial effect of carboxylic acid cocatalysts is noteworthy and is currently the subject of a mechanistic study.

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Supporting Information Available: Experimental procedures, characterization data, and crystallographic data for $(IMes)Pd(TFA)_2(OH_2)$ (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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[18] Additional examples of air-promoted Pd-catalyzed oxidation reactions are known. See, for example: (a) Larock, R. C.; Wei, L.; Hightower, T. R. *Synlett* **1998**, 522−524. (b) Bagdanoff, J. T.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 353−357. (c) Enquist, P.-A.; Lindh, J.; Nilsson, P.; Larhed, M. *Green Chem.* **2006**, *8*, 338−343. (d) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528−2529.

[19] (a) Konnick, M. M.; Gandhi, B. A.; Guzei, I. A.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2904−2907. (b) Konnick, M. M.; Guzei, I. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2004**, *126*, 10212−10213.