

Palladium-Catalyzed Oxidative Amination of Alkenes: Improved Catalyst Reoxidation Enables the Use of Alkene as the Limiting Reagent

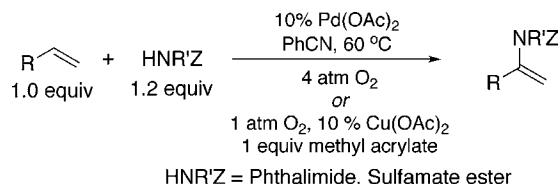
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Received August 5, 2007

ABSTRACT



Palladium-catalyzed methods for intermolecular aerobic oxidative amination of alkenes have been identified that are compatible with the use of alkene as the limiting reagent. These procedures, which enhance the utility of this reaction with alkenes that are not commercially available, are demonstrated with substrates bearing dialkyl ether, carboxyester, epoxide, and silyl ether groups.

Metal-catalyzed addition of nitrogen nucleophiles (e.g., amines, amides, carbamates) to alkenes represents a long-standing challenge in organic chemistry and an attractive target for the preparation of nitrogen-containing organic molecules.¹ Despite recent progress in this area, fundamental limitations remain. For example, innovative methods for the amination of vinyl arenes and dienes have been developed,² but in most cases, they are ineffective with alkyl olefins.³ Moreover, most of the amination reactions of this type

reported to date require the use of excess alkene (2–6 equiv relative to the nitrogen nucleophile).^{2–5} This feature limits the utility of these methods to commercially available or readily (and inexpensively) prepared alkenes. Recent efforts in our laboratory have been focused on Pd-catalyzed methods for intermolecular oxidative amination of alkenes, particularly

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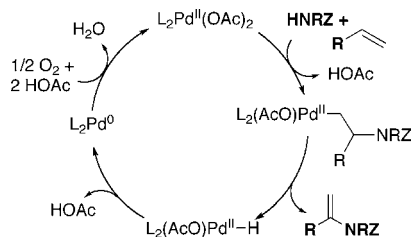
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(5) For examples of metal-catalyzed alkene-amination methods that employ alkene as the limiting reagent, see: (a) Södergren, M. J.; Alonso, D. A.; Bedekar, A. V.; Andersson, P. G. *Tetrahedron Lett.* **1997**, *38*, 6897–6900. (b) Guthikonda, K.; Du Bois, J. J. *Am. Chem. Soc.* **2002**, *124*, 13672–13673. (c) Siu, T.; Yudin, A. K. *J. Am. Chem. Soc.* **2002**, *124*, 530–531. (d) Di Chenna, P. H.; Robert-Peillard, F.; Dauban, P.; Dodd, R. H. *Org. Lett.* **2004**, *6*, 4503–4505. (e) Fruit, C.; Robert-Peillard, F.; Bernardinelli, G.; Müller, P.; Dodd, R. H.; Dauban, P. *Tetrahedron: Asymmetry* **2005**, *16*, 3484–3487. (f) Zhang, J.-L.; Che, C.-M. *Org. Lett.* **2002**, *4*, 1911–1914. (g) Li, J.; Chan, P. W. H.; Che, C.-M. *Org. Lett.* **2005**, *7*, 5801–5804. (h) Waser, J.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4099–4102. (i) Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2006**, *128*, 11693–11712. (j) Taylor, J. G.; Whittall, H. N.; Hii, K. K. *Org. Lett.* **2006**, *8*, 3561–3564.

Scheme 1. Palladium-Catalyzed Intermolecular Aerobic Oxidative Amination of Alkenes



those that employ O_2 as the stoichiometric oxidant (Scheme 1).^{1f,6} Initial results with vinyl arenes^{6a} were later extended to applications with unactivated alkyl olefins.^{6b} These results demonstrate a new class of oxidative C–N bond-forming reactions and represent a very efficient route to terminal enimides.⁷ Nevertheless, the utility of these reactions is diminished by the requirement for excess alkene. Here, we describe the development and application of aerobic oxidative amination methods compatible with the use of alkene as the limiting reagent. The results enhance the utility of these catalytic methods and provide a basis for the rational development of improved Pd catalysts.

Two observations from our prior studies illuminate the origin of the challenge in using alkenes as the limiting reagent: (1) the rate of Pd-catalyzed oxidative amination of alkenes depends upon the alkene concentration (ranging from first-order to saturation dependence)^{6c} and (2) a significant amount of catalyst decomposition occurs during the reactions in the form of Pd black. These observations indicate that lower alkene concentrations will reduce the catalytic turnover rate and increase complications associated with competing catalyst decomposition. The development of improved methods for catalyst oxidation should enhance catalyst stability and, potentially, lead to enhanced product yields at lower alkene concentrations.

Catalytic conditions were evaluated for the oxidative amination of tetradecene (**1**), a representative unactivated alkyl olefin, with phthalimide as the nitrogen nucleophile (Table 1). When the previously identified $Pd(OAc)_2$ /benzonitrile catalyst system was used with **1** as the limiting reagent and 1.2 equiv of phthalimide, the yield of the desired enamide product **2** was only 22% (entry 1). Substantial unreacted alkene was recovered (44%), together with alkene isomers of the product (**3**) and starting material (**4**). The internal alkenes **4** are unreactive toward oxidative amination under the reaction conditions.

The yield of the desired product **2** increased when the reaction was performed in the presence of $Cu(OAc)_2$ and

Table 1. Evaluation of Catalytic Conditions for Intermolecular Oxidative Amination of Alkenes^a

entry	Pd (mol %)	Cu (mol %)	additive	yield ^b (%) 2/3 (1/4)
1	$Pd(OAc)_2$ (5)	—	—	22/4 (44/13) ^c
2	$Pd(OAc)_2$ (5)	$Cu(OAc)_2$ (5)	—	42/8 (18/17) ^c
3	$Pd(OAc)_2$ (10)	—	—	36/8 (18/13) ^c
4	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$ (10)	—	51/11 (6/13) ^c
5	$(CH_3CN)_2PdCl_2$ (5)	$CuCl_2$ (5)	—	0/0 (0/95) ^c
6	$Pd(OAc)_2$ (5)	$Cu(OAc)_2$ (2 equiv)	—	36/6 ^d
7	$Pd(OAc)_2$ (5)	—	benzoquinone (1 equiv)	5/1 ^d
8	$Pd(OAc)_2$ (5)	$Cu(OAc)_2$ (5)	3 Å MS (10 mg)	13/3
9	$Pd(OAc)_2$ (5)	$Cu(OAc)_2$ (5)	NaOAc (1 equiv)	0/0 (96/0)
10	$Pd(OAc)_2$ (5)	$Cu(OAc)_2$ (5)	KH_2PO_4 (1 equiv)	52/11 (12/11)
11	$Pd(OAc)_2$ (5)	$Cu(OAc)_2$ (5)	$PhCO_2H$ (20 mol %)	49/10
12	$Pd(OAc)_2$ (5)	$Cu(OAc)_2$ (5)	cyclooctadiene (5 mol %)	49/10
13	$Pd(OAc)_2$ (5)	$Cu(OAc)_2$ (5)	methyl acrylate (1 equiv)	58/13 (6/13)^c
14 ^e	$Pd(OAc)_2$ (5)	$Cu(OAc)_2$ (5)	methyl acrylate (1 equiv)	45/9 (19/14) ^c
15 ^e	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$ (10)	4 atm O_2	50/12 (0/11) ^c
16 ^e	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$ (10)	methyl acrylate (1 equiv), 4 atm O_2	57/12 (0/11) ^c
17 ^e	$Pd(OAc)_2$ (10)	—	4 atm O_2	68/12 (5/11)^c

^a Reaction conditions: tetradecene (375 μ mol), phthalimide (450 μ mol), 1 atm of O_2 , 400 μ L of PhCN. ^b GC; int. std. = octadecane. ^c Yields determined by 1H NMR; int. std. = 1,3,5-trimethoxybenzene. ^d Reactions performed with 1 atm of ambient air. ^e Reaction conditions: tetradecene (1.0 mmol), phthalimide (1.2 mmol), 1.3 mL of benzonitrile.

increased catalyst loading (entries 2–4). Pd and Cu chloride complexes promoted nearly complete isomerization of the starting alkene, without forming **2** (entry 5). $Cu(OAc)_2$ was less effective when used as a stoichiometric oxidant rather than as a cocatalyst (entries 2 vs 6), and very little product was obtained with benzoquinone as a stoichiometric oxidant (entry 7).

Previous studies in our laboratory and others have demonstrated the ability of various additives to improve catalyst stability, including molecular sieves,⁸ anionic Brønsted bases,⁹ Brønsted acids,¹⁰ cyclooctadiene (COD), and methyl acrylate.^{6d,11} The beneficial effects of these additives have different origins. Molecular sieves provide a hetero-

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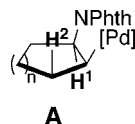
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geneous surface that inhibits bulk aggregation of Pd metal; anionic bases promote aerobic oxidation of the reduced catalyst; Brønsted acids are thought to stabilize Pd⁰ by reversible formation of more stable Pd^{II}–hydride species; and COD and methyl acrylate are good ligands for Pd⁰ that hinder catalyst aggregation. Representative results with these additives are shown in Table 1 (entries 8–13). Methyl acrylate proved to be the most effective additive. A 71% combined yield of oxidative amination products was obtained, primarily as the terminal enamide **2**, when 1 equiv of methyl acrylate was included in the reaction mixture (entry 13). Products arising from the oxidative amination of methyl acrylate were not detected. Other solvents were tested (dimethoxyethane, dimethylformamide, dichloroethane, acetonitrile, and toluene; data not shown), but none of these resulted in improved yields relative to benzonitrile.

Increasing the scale of the reaction to 1 mmol of alkene resulted in a lower product yield (entry 14 vs 13). Therefore, we reoptimized the reaction at this scale (entries 14–17). The results revealed that improved yields could be obtained at elevated O₂ pressure (4 atm), and the best outcome was observed when no cocatalyst or additive was included in the reaction mixture (entry 17).¹² Elevated O₂ pressure should improve catalyst stability by minimizing the steady-state concentration of Pd⁰ and thereby reduce its tendency to decompose via bimolecular aggregation.

The optimized, high-pressure oxidative amination conditions were evaluated with a number of terminal and cyclic alkenes (Table 2). The results provide some insight into the scope and limitations of the methods. The oxidative amination of simple linear alkenes produces enamides in good isolated yield (entries 1 and 2). Cyclic alkenes react to form allylic phthalimides. As we have discussed elsewhere,^{6b} allylic amination of cyclic alkenes probably arises from *cis*-aminopalladation to form an alkyl–Pd^{II} intermediate **A** that cannot undergo β-hydride elimination to form an enamide because the requisite hydrogen atom, H¹, is on the opposite face of the ring. Instead, β-hydride elimination proceeds away



from the C–N bond (H²) to produce the allylic product (entries 3–8). The homoallylic and other isomeric products arise from Pd–hydride-mediated migration of the double bond.^{6b,e,13} The oxidative amination of cyclopentene and cyclooctene was also achieved with the 2,2,2-trichloroethylsulfamate nucleophile (entries 4 and 7). For reasons that are not yet clear, cyclohexene is completely unreactive

(11) Intramolecular Pd-catalyzed oxidative amination reactions often benefit from the use of ligands for the Pd catalyst (e.g., pyridine and *N*-heterocyclic carbenes). Our previous studies, however, have shown that such ligands inhibit *intermolecular* oxidative amination reactions.^{6b}

(12) Caution should be taken when working with high pressures of O₂ in organic solvents, particularly on a large scale. We have demonstrated that identical results are obtained when the reactions are performed with a 4% O₂/N₂ mixture if the partial pressure of oxygen remains constant.

Table 2. Pd-Catalyzed Aerobic Oxidative Amination of Alkenes^a

R-CH=CH ₂ 1 equiv		+ HNRZ 1.2 equiv	10 mol % Pd(OAc) ₂ PhCN, 60 °C 4 atm O ₂	R-CH=CH-NRZ
entry	alkene	product	yield ^b (%)	
1			72 (4.9:1)	
2			67 (4.9:1)	
3			83 (9:1)	HNRZ = NPhth
4			54 (9:1)	HNRZ = H ₂ NSO ₃ CH ₂ CCl ₃
5			0	
6			44 (8.7:1:1.5)	HNRZ = NPhth
7			62 (1:3.2:1.3)	HNRZ = H ₂ NSO ₃ CH ₂ CCl ₃
8			24	
9			68	
10			63	
11			67 (5.6:1)	
12			63	
13			76 (9:1)	
14			17 (4.8:1)	
15			13 ^c	
16			70 (5.7:1)	
17			83 (5.3:1)	
18			77 (11.5:1)	
19			76	

^a Reaction conditions: Pd(OAc)₂ (0.01 mmol), alkene (1.0 mmol), nucleophile (1.2 mmol), benzonitrile (1.33 mL), 60 °C, 24 h. ^b Isolated yield. Isomer ratio determined by ¹H NMR spectroscopy. ^c Yield was determined by ¹H NMR relative to 1,3,5-trimethoxybenzene.

toward oxidative amination (entry 5). Styrene undergoes competitive formation of acetophenone, resulting in a low yield of the enamide product (entry 8).

The use of alkenes as a limiting reagent in these reactions is particularly important for more expensive or noncommer-

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cially available alkenes. We investigated the reactivity of various alkenes bearing oxygen-containing functional groups, including benzyl ethers, esters, epoxides, and silyl ethers (Table 2, entries 9–18). These substrates undergo oxidative amination with phthalimide to produce amino-oxygenated products that feature 1,2–1,3- and 1,4-relationships between the oxygen and nitrogen functional groups. Most of these reactions proceed in good yield; however, two limitations that were identified include substrates with a free alcohol or a trimethylsilyl ether, which react to form a complex product mixture and low yield of the desired enamide (entries 14 and 15). The latter limitation can be addressed by employing substrates with more stable silyl ethers (TES, TBS) (entries 16–19).

The reactions identified in this study represent the most effective catalytic methods to date for intermolecular aza-

Wacker reactions, and the ability to employ alkenes as the limiting reagents should significantly enhance their utility. Another important conclusion from this study is that even better aerobic oxidation reactions should be achievable (e.g., those compatible with ambient pressures of O₂) if more stable catalyst systems are identified.

Acknowledgment. We thank the NIH (R01 GM67173) for financial support of this work and Eli Lilly and Johnson-Matthey for generous donations of Pd salts.

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

OL701903R