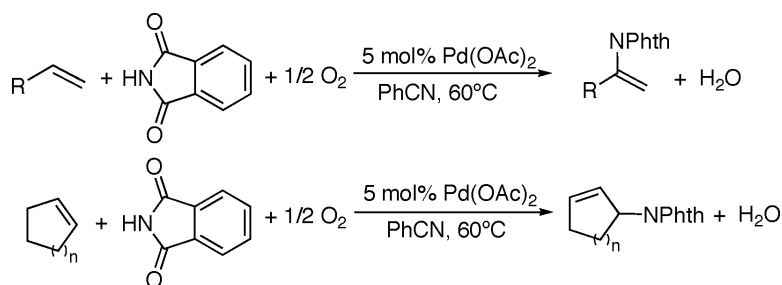# Aerobic Oxidative Amination of Unactivated Alkenes Catalyzed by Palladium

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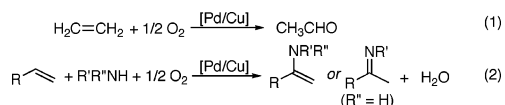
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Aerobic Oxidative Amination of Unactivated Alkenes Catalyzed by Palladium

Jodie L. Brice, Jenna E. Harang, Vitaliy I. Timokhin, Natia R. Anastasi, and Shannon S. Stahl*

Department of Chemistry, University of Wisconsin—Madison, 1101 University Avenue, Madison, Wisconsin 53706

Received November 6, 2004; E-mail: stahl@chem.wisc.edu

Metal-catalyzed addition of amines and related nucleophiles to alkenes represents a challenging but attractive strategy for the preparation of nitrogen-containing molecules.[1,2] Despite significant recent advances in this area, unactivated alkyl olefins, the most abundant and least expensive class of alkenes, are generally ineffective substrates.[2a,3] Since the discovery of the Wacker process (eq 1) in 1959,[4] significant efforts have focused on development of related methods for the oxidative amination of alkenes (eq 2).[5] Amines, however, often coordinate more strongly to palladium than alkenes and inhibit catalytic turnover. Recently, we and others demonstrated that nonbasic nitrogen nucleophiles, such as carboxamides, carbamates, and sulfonamides, undergo effective oxidative coupling with activated alkenes, including acrylic esters and styrene.[6,7] Here, we report the first general method for oxidative amination of unactivated alkyl olefins made possible by cocatalyst-free reaction conditions, in which the palladium catalyst undergoes direct dioxygen-coupled turnover.[8]

$$H_2C{=}CH_2 + 1/2\ O_2 \xrightarrow{\text{[Pd/Cu]}} CH_3CHO \qquad (1)$$

$$R\diagdown + R'R''NH + 1/2\ O_2 \xrightarrow{\text{[Pd/Cu]}} R\diagdown\overset{NR'R''}{} \text{ or } R\diagdown\overset{NR'}{} + H_2O \qquad (2)$$
(R'' = H)

The lack of precedent for oxidative amination of alkyl olefins prompted us to investigate the reactivity of norbornene, a strained cyclic alkene that undergoes metal-catalyzed hydroamination in certain cases.[9] Under conditions similar to those we employed previously for the oxidative amination of styrene, norbornene reacts with $TsNH_2$ to form a racemic mixture of the C_2-symmetric pyrrolidine, **1**, in good yield (Scheme 1). The product arises from

**Scheme 1.** Aerobic Oxidative Amination of Norbornene
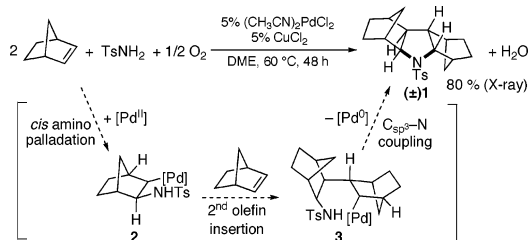
the oxidative coupling of two alkenes and the sulfonamide nucleophile. Its structure, established by X-ray crystallography, reveals that both equivalents of norbornene undergo *cis*-difunctionalization on the *exo* face of the alkene.[10] A mechanism consistent with these observations involves *cis*-aminopalladation of norbornene, alkene insertion into the Pd−C bond, and C−N reductive elimination. Documented examples of *cis*-aminopalladation are quite rare,[11,12] but two reasonable pathways include alkene insertion into a Pd−N bond (**4**)[11] or coordination of the sulfonyl oxygen to palladium followed by C−N bond formation via a six-membered transition state (**5**). Studies to probe these possibilities are ongoing. The multicomponent coupling sequence is probably facilitated by

the relative stability of intermediates **2** and **3** toward β-hydride elimination. The β-hydrogens in both structures either lie on the opposite face of the ring or occupy a bridgehead position.[13]
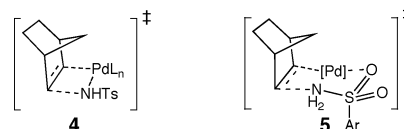
The oxidative amination of linear alkyl olefins exhibits some success under these reaction conditions. For example, 1-octene reacts with the secondary nucleophile phthalimide to generate amination products in ~60% yield, but a complex mixture of alkene isomers is formed. A solution to this problem arose from concurrent studies with styrene that revealed $Pd(OAc)_2$ is an effective oxidative amination catalyst even in the absence of a copper cocatalyst. For example, the oxidative amination of styrene with phthalimide generates the Markovnikov enimide product in good isolated yield (eq 3). With *p*-toluenesulfonamide as the nucleophile, the *N*-tosyl ketimine product is obtained (eq 4).
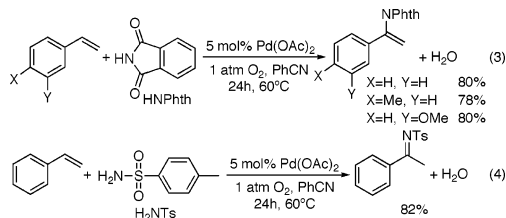
On the basis of these results, we screened a series of catalyst combinations for the reaction between 1-octene and phthalimide (Table 1). Amination products are formed in several cases with catalytic $PdCl_2$, $Pd(OAc)_2$, or $Pd(O_2CCF_3)_2$; however, the desired terminal enimide, **6**, is obtained in good yield only with $Pd(OAc)_2$ as the catalyst in the absence of a copper cocatalyst (entries 8, 10, and 12). Significant alkene isomerization occurs when $CuCl_2$ is added as a cocatalyst (entries 5, 13, and 17). Under these reaction conditions, rapid alkene isomerization occurs even in the absence of phthalimide.[14] Although the mechanism of alkene isomerization has not been established, acetate might serve as a base to deprotonate palladium hydrides that could isomerize alkenes. The ability of triethylamine to attenuate alkene isomerization with $PdCl_2$ as the catalyst is consistent with this hypothesis (entries 1 and 2). Pyridine and triphenylphosphine have little effect on the reaction at 5 mol % loading (entries 10 and 12), but larger quantities of pyridine inhibit the reaction (entry 11). ^{31}P NMR spectroscopy reveals that PPh_3 undergoes complete oxidation to the phosphine oxide during the reaction. The detrimental effect of cocatalysts and stoichiometric oxidants other than molecular oxygen ($CuCl_2$, entry 6; benzoquinone, entries 7 and 14) indicates that the use of molecular oxygen without cocatalysts may be essential to achieve the desired reactivity in palladium-catalyzed oxidation reactions.

Table 1. Catalyst Screening Data for the Aerobic Oxidative Amination of 1-Octene with Phthalimide[a]

entry	catalyst	additive	yield[b] (%)
1	Pd(CH₃CN)₂Cl₂		<1 (32)
2	PdCl₂	5% NEt₃	17 (37)
3		5% pyridine	<1 (40)
4		10% pyridine	3 (5)
5		5% CuCl₂	<1 (66)
6		3 equiv of CuCl₂	NR
7		2 equiv of benzoquinone	10 (28)
8	Pd(OAc)₂		81 (4)
9		5% NEt₃	17 (3)
10		5% pyridine	82 (3)
11		10% pyridine	<1 (0)
12		5% PPh₃	70 (5)
13		5% CuCl₂	<1 (79)
14		2 equiv of benzoquinone	10 (<1)
15	Pd(O₂CCF₃)₂		4 (1)
16		5% pyridine	3 (1)
17		5% CuCl₂	<1 (79)

[a] Reaction conditions: 3 mmol 1-octene, 0.5 mmol phthalimide, 0.025 mmol [Pd], additive, 0.75 M phthalimide in PhCN, 1 atm O₂, 60 °C, 24 h. [b] ¹H NMR yield of product containing terminal methylene with 1,3,5-trimethoxybenzene internal standard, based on initial phthalimide. Parentheses contain combined yield of all amination products with internal alkenes detected by gas chromatography.

Table 2. Cocatalyst-Free Aerobic Oxidative Amination of Aliphatic Olefins Catalyzed by Pd(OAc)₂[a]

Entry	Alkene	RR'NH	Product	Yield (%)[b]
1		PhthNH		90[d] (100:17)
2		PhthNH		87 (100:18)
3[c]		PhthNH		86
4		PhthNH		60 (75:28)
5		PhthNH		80[d] (100:6)
6		TsNH₂		64[d,e] (100:12)
7		TsNH₂		63
8[c]		TsN(H)Me		59
9[c]		PhthNH		92
10		PhthNH		56

[a] Reaction conditions: 12 mmol alkene, 2 mmol nucleophile, 0.1 mmol Pd(OAc)₂, 0.75 M HNRR' in PhCN, 1 atm O₂, 60 °C, 24 h. [b] Isolated yield based on nitrogen nucleophile after purification by flash column chromatography. Ratio in parentheses is (isomer shown:all other observed isomers). [c] With 24 mmol alkene, all other conditions the same. [d] Reaction performed under 3.5 atm O₂ in a sealed vessel. [e] After 48 h.

Cocatalyst-free conditions enable the aerobic oxidative amination of various other alkyl olefins, including both acyclic and cyclic substrates (Table 2). Good yields are obtained in the reaction between phthalimide and 1-hexene, 1-octene, and vinylcyclohexane (entries 1, 2, and 9), and an ester functionality is compatible with the reaction (entry 3). The reaction with vinylcyclohexene (entry 10) reveals that the terminal alkene can react selectively in the presence of an internal double bond. Sulfonamides also serve as effective nucleophiles (entries 7 and 8).

The oxidative amination of cyclic olefins, cyclooctene, and cyclopentene (entries 4−6) yields allylic amine products rather than the corresponding enamine or imine derivatives. These observations are readily explained if amination of the double bond occurs via *cis*-aminopalladation, as observed for norbornene (Scheme 1). If cyclic alkenes react in this manner, only the allylic C−H bond in the intermediate can achieve the orientation necessary for *syn-β*-hydride elimination.[13]

In conclusion, we have achieved a remarkably general method for aerobic oxidative amination of unactivated alkyl olefins, and the results highlight the value of cocatalyst-free oxidation conditions. Ongoing studies are focused on exploring the scope of this reactivity and probing the catalytic mechanism.

Supporting Information Available: Experimental descriptions (PDF) and X-ray crystallographic data (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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