Inorg. Chem. **2007**, *46*, 1910–1923

Forum

Palladium-Catalyzed Aerobic Oxidative Amination of Alkenes: Development of Intra- and Intermolecular Aza-Wacker Reactions

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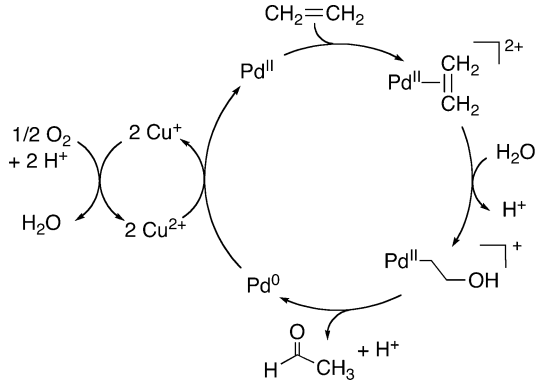
Received October 18, 2006

Palladium-catalyzed methods for the aerobic oxidative coupling of alkenes and oxygen nucleophiles (e.g., water and carboxylic acids) have been known for nearly 50 years. The present account summarizes our development of analogous aerobic oxidative amination reactions, including the first intermolecular aza-Wacker reactions compatible with the use of unactivated alkenes. The reactions are initiated by intra- or intermolecular aminopalladation of the alkene. The resulting alkylpalladium(II) intermediate generally undergoes β-hydride elimination to produce enamides or allylic amide products, but in certain cases, the Pd–C bond can be trapped to achieve 1,2-difunctionalization of the alkene, including carboamination and aminoacetoxylation. Mechanistic studies have provided a variety of fundamental insights into the reactions, including the effect of ancillary ligands on palladium catalysts, the origin of the Brønsted-base-induced switch in regioselectivity in the oxidative amination of styrene, and evidence that both *cis*- and *trans*-aminopalladations of alkenes are possible. Overall, these reactions highlight the potential utility of an "organometallic oxidase" strategy for the selective aerobic oxidation of organic molecules.

Introduction

The field of palladium catalysis began in the late 1950s with the discovery that palladium(II) chloride salts catalyze the aerobic oxidative coupling of ethylene and water to produce acetaldehyde in the presence of a copper cocatalyst (Scheme 1).[1] Since this discovery, palladium-catalyzed reactions have developed into some of the most versatile methods for the synthesis of organic molecules. Although the field began with an oxidation reaction, most of the widely used examples of palladium catalysis consist of nonoxidative methods, especially cross-coupling reactions between nucleophilic and electrophilic reaction partners.[2] Oxidation reactions tend to be more challenging because they require the use of an external oxidant and because the conditions are incompatible with air-sensitive phosphine ligands, which have been critical to the success of nonoxidative coupling reactions. As a result of these challenges, palladium-catalyzed oxidation reactions have received less attention than their nonoxidative counterparts. When we began our work in 2000, no "aza-Wacker" reactions involving intermolecular oxidative coupling of unactivated alkenes[3] and nitrogen nucleo-

Scheme 1. Catalytic Mechanism for the Wacker Process



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(1) Jira, R. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: New York, 2002; Vol. 1, pp 386−405.

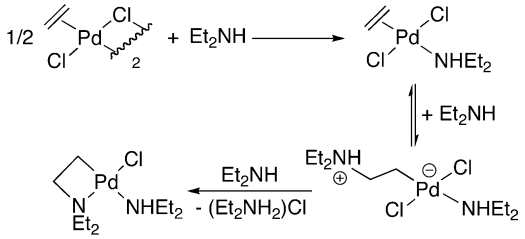
(2) The *mechanism* of cross-coupling reactions involves redox chemistry, for example, oxidative addition of aryl halides to palladium(0) and reductive elimination of C−C bonds from palladium(II). The overall transformations, however, are formally nonoxidative, similar to S_N2 displacement reactions.

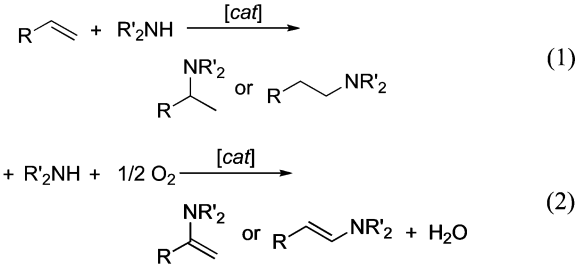
10.1021/ic061997v CCC: $37.00
Published on Web 03/12/2007

philes were known. The potential synthetic utility of such oxidative amination reactions, together with our broader interest in aerobic oxidation reactions, prompted us to explore this class of transformations.

Intermolecular coupling of amines and alkenes represents a highly efficient strategy for the synthesis of nitrogen-containing molecules, and metal-catalyzed methods for alkene hydroamination (eq 1) have been the focus of extensive attention.[4,5] Simple alkyl olefins represent the most abundant and least expensive class of alkenes, but these substrates tend to be unreactive toward metal-catalyzed hydroamination.[6,7] Various catalysts have been investigated to minimize the kinetic barriers in hydroamination reactions; however, such efforts do not address the intrinsic thermodynamic limitation. Very little driving force, if any, is present in hydroamination reactions. For example, Markovnikov addition of ammonia to propylene is predicted to be slightly endergonic at 25 °C (eq 1; R = CH_3, R′ = H; $\Delta G°_{calc}$ = +1.4 kcal/mol), and the reaction becomes more unfavorable at higher temperatures.[8] The reversibility of vinylarene hydroamination has been detected experimentally.[9] This thermodynamic limitation can be overcome, however, by performing an oxidative amination reaction, whereby reduction of an oxidant provides a strong driving force for the reaction (e.g., eq 2). For example, the aerobic oxidative amination of propene is favored by >35 kcal/mol (eq 2; R = CH_3, R′ = H).[10] Although the requirement for a stoichiometric oxidant adds complexity to the reaction, oxidative amination products have enhanced appeal because they possess greater functionality than hydroamination products and, therefore, have greater potential utility and/or flexibility in synthetic chemistry. The ability to use molecular oxygen or a related, low-cost, environmentally benign oxidant would make such reactions particularly attractive.

Scheme 2. Stoichiometric Reaction of Diethylamine with an Ethylene/Palladium(II) Complex





(1)

(2)

At first glance, aza-Wacker reactions appear to be a straightforward extension of the parent Wacker process, involving replacement of water with a nitrogen nucleophile in the C−heteroatom bond-forming step (cf. Scheme 1). It was recognized quite early, however, that most amines are better ligands for palladium(II) than alkenes.[11] Therefore, palladium(II)-mediated intermolecular reactions between alkenes and amines were generally limited to stoichiometric examples in which an alkene−Pd^{II} complex was formed at low temperature (e.g.,−40 °C) followed by the addition of the amine nucleophile (Scheme 2).[12]

Catalysis was first achieved in *intramolecular* oxidative amination reactions, which benefit from a significantly lower entropic penalty than intermolecular reactions. Initial work demonstrated the ability of anilines to undergo oxidative cyclization (eq 3),[13] but later work highlighted the benefit of nonbasic nitrogen nucleophiles such as sulfonamides[14] (e.g., eq 4) and ureas,[15] which are less susceptible to catalyst

(3) The term "unactivated alkene" is subject to a variety of interpretations. In the present context, we use this term to mean simple alkyl olefins, which traditionally have been among the least reactive alkenes in catalytic *intermolecular* amination reactions. Vinyl ethers, vinylarenes, dienes, and other alkenes containing electron-withdrawing or -donating groups or possessing the ability to chelate a metal center exhibit varying levels of "activation". In addition, substrates that undergo *intramolecular* reaction should not be described as "unactivated" alkenes because of their intrinsic entropic "activation" relative to substrates that undergo intermolecular reaction.

(4) Ricci, A., Ed. *Modern Amination Methods*; Wiley-VCH: New York, 2000.

(5) For recent reviews and highlights, see: (a) Roundhill, D. M. *Catal. Today* **1997**, *37*, 155−165. (b) Müller, T. E.; and Beller, M. *Chem. Rev.* **1998**, *98*, 675−703. (c) Nobis, M.; Driessen-Hölscher, B. *Angew. Chem., Int. Ed.* **2001**, *40*, 3983−3985. (d) Brunet, J.-J.; Neibecker, D. In *Catalytic Heterofunctionalization*; Togni, A., Grützmacher, H., Eds.; Wiley-VCH: New York, 2001; pp 91−141. (e) Beller, M.; Breindl, C.; Eichberger, M.; Hartung, C. G.; Seayad, J.; Thiel, O. R.; Tillack, A.; Trauthwein, H. *Synlett* **2002**, 1579−1594. (f) Roesky, P. W.; Müller, T. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 2708−2710. (g) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673−686.

(6) Coulson, D. R. *Tetrahedron Lett.* **1971**, *12*, 429−430.

(7) Most of the successful examples have been achieved only recently: (a) Ryu, J.-S.; Li, G. Y.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 12584−12605. (b) Brunet, J.-J.; Cadena, M.; Chu, N. C.; Diallo, O.; Jacob, K.; Mothes, E. *Organometallics* **2004**, *23*, 1264−1268. (c) Wang, X.; Widenhoefer, R. A. *Organometallics* **2004**, *23*, 1649−1651. (d) Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 1471−1474. (e) Sakai, N.; Ridder, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 8134−8135. (f) Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179−4182. (g) Li, Z.; Zhang, J.; Brouwer, C.; Yang, C.-G.; Reich, N. W.; He, C. *Org. Lett.* **2006**, *8*, 4175−4178. (h) Zhang, J.; Yang, C.-G.; Reich, N. W.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798−1799. (i) Brouwer, C.; He, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1744−1747. (j) Brunet, J.-J.; Chu, N. C.; Diallo, O. *Organometallics* **2005**, *24*, 3104−3110. (k) Karshtedt, D.; Bell, A. T.; Tilley, T. D. *J. Am. Chem. Soc.* **2005**, *127*, 12640−12646.

(8) Gas-phase free energies of eqs 1 and 2 were obtained from density functional theory calculations (B3LYP/6-311++G**). Benchmarking studies comparing experimental and calculated energies suggest that the calculated values are within approximately 3 kcal/mol of the experimental data. See: Curtiss, L. A.; Raghavachari, K.; Redfern, P. C.; Pople, J. A. *J. Chem. Phys.* **1997**, *106*, 1063−1079.

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(10) Formation of the Markovnikov enamine product in eq 2 is favored by 36.8 kcal/mol; formation of the imine tautomer is even more favorable, ΔG = −40.7 kcal/mol.

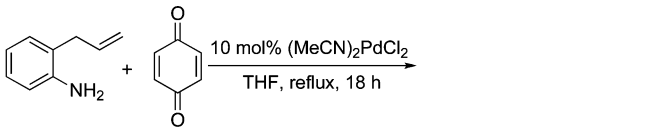
(11) Hegedus, L. S. *Tetrahedron* **1984**, *40*, 2415−2434.

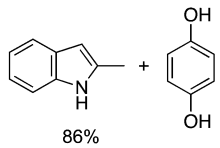
(12) (a) Åkermark, B.; Bäckvall, J. E.; Hegedus, L. S.; Zetterberg, K.; Siirala-Hansén, K.; Sjöberg, K. *J. Organomet. Chem.* **1974**, *72*, 127−138. (b) Hegedus, L. S.; Åkermark, B.; Zetterberg, K.; Olsson, L. F. *J. Am. Chem. Soc.* **1984**, *106*, 7122−7126.

(13) (a) Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800−5807. (b) Hegedus, L. S.; McKearin, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 2444−2451.

(14) Hegedus, L. S.; Holden, M. S. *J. Org. Chem.* **1986**, *51*, 1171−1174.

poisoning because they are poor ligands for palladium(II). Similar nucleophiles were employed in the intermolecular amidation of acrylates and related alkenes activated toward nucleophilic attack by the presence of an electron-withdrawing group (eq 5).[16]





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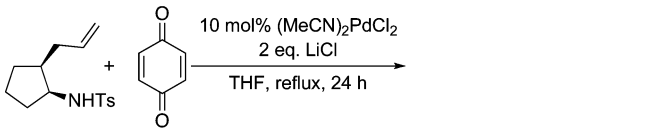

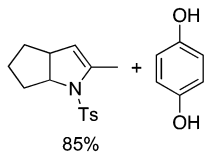

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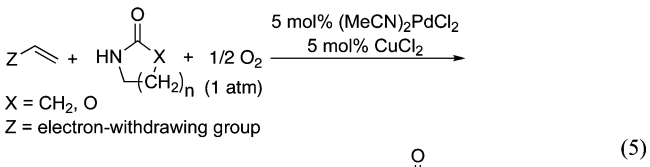
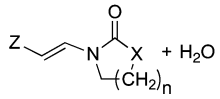
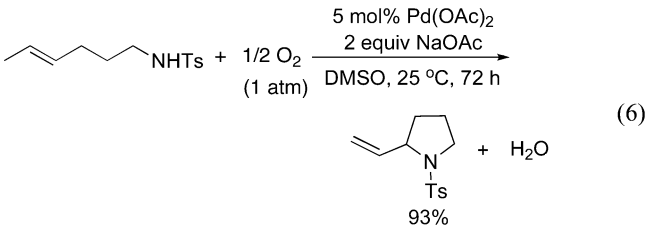




(5)

Our own interest in alkene oxidative amination arose from our broader interest in "organometallic oxidase" reactions, such as the Wacker process (Scheme 1), that mediate substrate oxidation by a sequence of organometallic steps followed by regeneration of the oxidized catalyst with molecular oxygen.[17] Unlike other aerobic oxidation reactions that feature O-atom transfer from dioxygen to the organic substrate, oxidase reactions can be applied to a broad array of oxidative transformations, including aminations. We were particularly intrigued by results from the groups of Larock and Hiemstra, who demonstrated that palladium acetate in dimethyl sulfoxide (DMSO) catalyzes aerobic oxidative heterocyclization reactions without a need for benzoquinone or other redox-active cocatalysts (eq 6).[18] Subequent reports by Uemura[19] and Sheldon[20] highlighted related cocatalyst-free palladium catalysts for aerobic alcohol oxidation. Within this context, we sought to develop improved catalysts for the oxidative amination of alkenes that would lead to more efficient and selective methods for the synthesis of nitrogen heterocycles and, ultimately, enable aerobic intermolecular oxidative amination of unactivated alkenes.

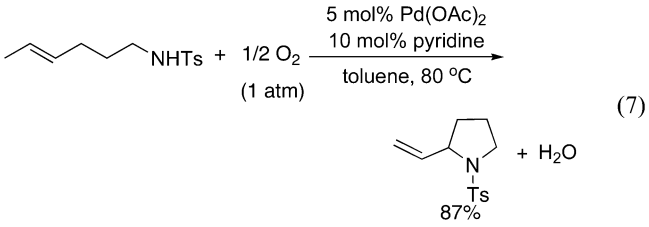


(6)

Intramolecular Oxidative Amination of Alkenes

Pyrrolidines and related heterocycles are commonly found in biologically active compounds, and considerable effort has been directed toward the development of new methods for their synthesis.[21] Palladium-catalyzed reactions provide useful strategies for the preparation of such structures.[22] Intramolecular oxidative amination reactions also provided a logical starting point for the exploration of new catalyst systems. Specifically, we sought methods that could achieve greater catalytic efficiency than previous examples, including those with improved turnover rates and catalyst lifetimes and those compatible with the use of dioxygen rather than benzoquinone as the oxidant (cf., eqs 3, 4, and 6). Whereas the previous palladium(II)-catalyzed oxidative heterocyclization reactions generally utilized catalysts consisting of PdX_2 complexes dissolved in polar, coordinating solvents, we were interested in identifying well-defined catalyst systems with organic ligands coordinated to the Pd^{II} center because such systems ultimately might enable the development of enantioselective transformations.

Our initial efforts to develop intramolecular oxidative amination reactions focused on the $Pd(OAc)_2$/pyridine catalyst system, which had been reported by Uemura as an effective catalyst system for aerobic alcohol oxidation.[19] Under 1 atm of molecular oxygen, $Pd(OAc)_2$/pyridine (5:10 mol %) promotes the conversion of (*E*)-4-hexenyltosylamide to the pyrrolidine product in just 2 h (eq 7; cf. eq 6).[23]



(7)

The *p*-toluenesulfonyl group proved to be the best nitrogen substituent; however, substrates bearing the *p*-nitrophenyl-

(15) Tamaru, Y.; Hojo, M.; Higashimura, H.; Yoshida, Z.-i. *J. Am. Chem. Soc.* **1988**, *110*, 3994−4002.

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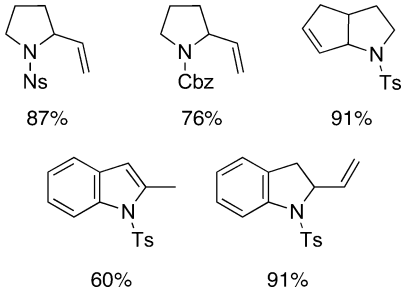
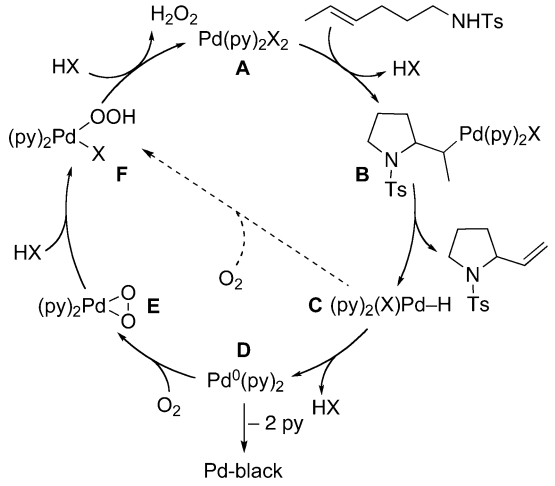
Chart 1. Products Obtained via $Pd(OAc)_2$/Pyridine-Catalyzed Aerobic Oxidative Cyclization



sulfonyl or Cbz [$PhCH_2OC(O)-$] groups also undergo effective cyclization (Chart 1).[24] The reaction proceeds well for both aromatic and aliphatic tosylamides and is tolerant to wide variations in solvent polarity, ranging from *N*,*N*-dimethylformamide and DMSO to toluene and heptane. Nonpolar solvents appear to be optimal, however, and they permit the reaction to be performed at significantly reduced catalyst loading. With 0.2 mol % $Pd(OAc)_2$ and 0.4 mol % pyridine in *p*-xylene, the hexenyltosylamide substrate reacts with a turnover rate of 70 h^{-1} during the first 2 h of the reaction, and turnover numbers of up to 250−300 are attained. These values are significantly higher than catalytic activities reported previously for similar oxidative amination reactions with other catalyst systems, and they are comparable to those observed with the highly active lanthanide catalysts in intramolecular (nonoxidative) hydroamination reactions.[25]

Detailed mechanistic studies of these oxidative amination reactions have not been performed; however, the catalytic cycle in Scheme 3 provides a framework for future investigation. Several valuable insights can be gained from our investigation of $Pd(OAc)_2$/pyridine-catalyzed aerobic alcohol oxidation.[26] For example, the latter studies reveal that pyridine is critical for efficient dioxygen-coupled oxidation

Scheme 3. Mechanism of Intramolecular Oxidative Amination



of the reduced catalyst.[27] In the absence of pyridine, a significant quantity of palladium black forms and lower catalytic turnovers are observed presumably because the palladium(0) form of the catalyst undergoes rapid decomposition into palladium black. Elevated concentrations of pyridine are not beneficial, however, because pyridine coordination to palladium(II) inhibits critical substrate oxidation steps (e.g., coordination of the substrate and β-hydride elimination). A palladium/pyridine ratio of 1:1 results in the highest initial catalytic turnover rates; however, at this low pyridine concentration, a low catalyst lifetime is observed. Similar qualitative results have been observed in the oxidative amination reactions, and such observations provide a partial explanation for the difficulty of developing asymmetric oxidative amination reactions. A large fraction of the effective chiral ligands in asymmetric catalysis are bidentate; however, bidentate ligands generally lead to much lower catalytic activity in the present reactions. Virtually no catalytic turnover is observed, for example, with bipyridine as the ligand.

Since our initial report of the use of the $Pd(OAc)_2$/pyridine system in intramolecular oxidative amination reactions, two extensions have been reported by other groups. Stoltz and co-workers employed similar catalytic conditions in the oxidative cyclization of several other alkene substrates bearing tethered oxygen and nitrogen nucleophiles (e.g., eq 8).[28] They also demonstrated that asymmetric oxycyclization of *o*-allylphenols can be achieved with [(−)-sparteine]$Pd(O_2CCF_3)_2$ as the catalyst. As might be expected from the mechanistic discussion above, the activity of the (−)-sparteine/palladium(II) catalyst system is significantly reduced relative to that of the $Pd(OAc)_2$/pyridine and $Pd(O_2CCF_3)_2$/pyridine systems, but good enantioselectivity (87% ee) was

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(21) (a) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435−446. (b) Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213−7256.
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(23) Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 164−166.
(24) In general, carbamates are more readily deprotected amine derivatives than sulfonamides, although both have been used widely in organic synthesis. For a general discussion of nitrogen protecting groups, see: Green, T. W., Wuts, P. G. M., Eds. *Protective Groups in Organic Synthesis*; Wiley-VCH: New York, 1999.
(25) (a) Gagné, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1989**, *111*, 4108−4109. (b) Gagné, M. R.; Nolan, S. P.; Marks, T. J. *Organometallics* **1990**, *9*, 1716−1718. (c) Gagné, M. R.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 275−294. (d) Gagné, M. R.; Brard, L.; Conticello, V. P.; Giardello, M. A.; Stern, C. L.; Marks, T. J. *Organometallics* **1992**, *11*, 2003−2005. (e) Giardello, M. A.; Conticello, V. P.; Brard, L.; Gagné, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1994**, *116*, 10241−10254. (f) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 1757−1771. (g) Tian, S.; Arredondo, V. M.; Stern, C. L.; Marks, T. J. *Organometallics* **1999**, *18*, 2568−2570. (h) Ryu, J.-S.; Marks, T. J.; McDonald, F. E. *Org. Lett.* **2001**, *3*, 3091−3094. (i) Molander, G. A.; Dowdy, E. D. *J. Org. Chem.* **1998**, *63*, 8983−8988. (j) Molander, G. A.; Dowdy, E. D. *J. Org. Chem.* **1999**, *64*, 6515−6517. (k) Kim, Y. K.; Livinghouse, T.; Bercaw, J. E. *Tetrahedron Lett.* **2001**, *42*, 2933−2935.
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(27) For direct observation of the reaction of dioxygen with a Pd^0 center bearing aromatic imine ligands, see the following: Stahl, S. S.; Thorman, J. L.; Nelson, R. C.; Kozee, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7188−7189.
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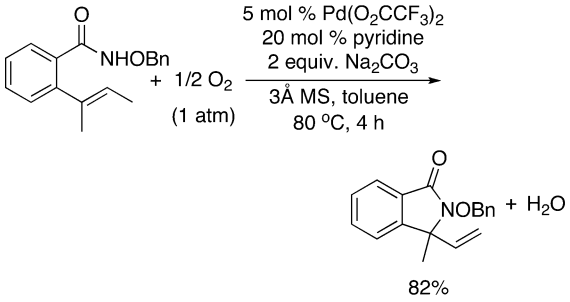
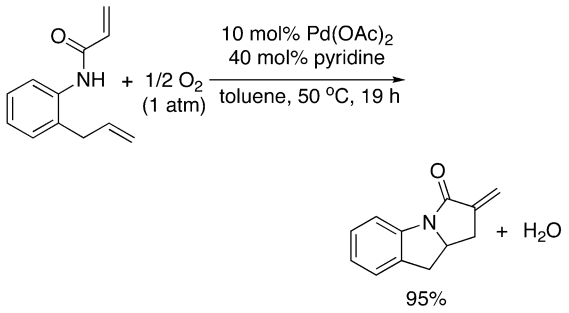
achieved for one of the two *o*-allylphenol substrates tested. Recently, Yang and co-workers reported an intramolecular oxidative carboamination reaction using a $Pd(OAc)_2$/pyridine catalyst system (e.g., eq 9).[29] This reaction, which is initiated by aminopalladation of the alkene of the allyl group, can be achieved with enantioselectivities of up to 91% ee with a (−)-sparteine/palladium(II) catalyst system. The reactions are noteworthy because they represent the best examples, to date, of enantioselective aerobic oxidative cyclization; however, key future challenges include the identification of chiral catalyst systems that can achieve higher activity and for which both enantiomers are readily available.



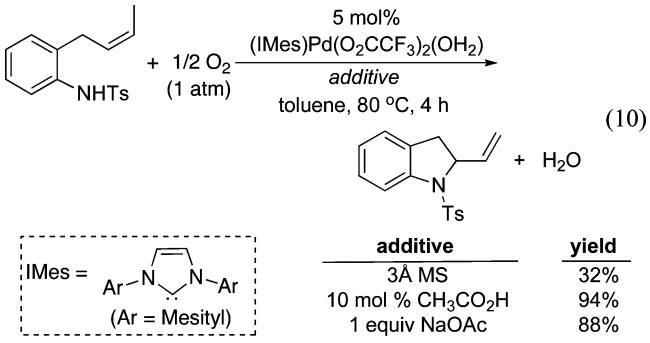
(8)



(9)

Our studies of $Pd(OAc)_2$/pyridine-catalyzed intramolecular oxidative amination of alkenes accomplished several important goals, namely, identification of a catalyst system with significantly improved activity and that undergoes efficient dioxygen-coupled turnover. Key challenges were also revealed. Pyridine is a kinetically labile ligand, and this trait contributes to catalyst instability at low pyridine concentration. Furthermore, chelating nitrogen ligands, which would seem to be amenable for use in asymmetric catalysis, significantly reduce catalytic activity. On the basis of these observations, we were attracted to a different class of palladium catalysts that possess a single monodentate N-heterocyclic carbene (NHC) ligand, $(NHC)Pd(O_2CR)_2(OH_2)$. These catalysts were originally developed by Sigman and co-workers for aerobic alcohol oxidation reactions.[30] The NHC ligand is a neutral donor ligand that is expected to remain coordinated to the Pd center throughout the catalytic cycle, and, therefore, excess donor ligand should not be necessary as in the palladium/pyridine catalyst system. In addition, the coordinated water molecule is labile and should enable facile substrate access to the palladium coordination sphere. NHCs are susceptible to oxidation to the corresponding cyclic ureas in the presence of dioxygen, but they have proven to be remarkably robust as ligands in palladium-catalyzed aerobic oxidation reactions.[31]

These previous studies prompted our investigation of NHC-coordinated palladium catalysts for use in intramolecular oxidative amination of alkenes. Screening of various NHC/palladium(II) complexes led to the identification of $(NHC)Pd(O_2CCF_3)_2(OH_2)$ as the optimal catalyst.[32] The reactions benefit from acid or base additives (eq 10). In addition to improving the reaction yields, cocatalytic quantities of carboxylic acid also enable the reaction to be performed with ambient air, rather than pure dioxygen, as the source of the oxidant. The precise origin of the additive effects is not fully understood. We have speculated that carboxylic acid cocatalysts improve catalyst stability, perhaps by reacting with palladium(0) to form a palladium(II)/hydrogen species that is less susceptible to aggregation into inactive palladium metal. Mechanistic studies supporting this hypothesis have been reported by Sigman and co-workers in aerobic alcohol oxidation reactions.[30d] In recent fundamental studies, we have observed that carboxylic acids promote the conversion of an NHC-coordinated palladium(II)-hydride species to a palladium(II)-hydroperoxide product in the presence of molecular oxygen (Scheme 3, dashed arrow).[33] Basic additives might have a beneficial influence on other steps in the catalytic cycle that involve the loss of acid (e.g., Scheme 3, **A** → **B**). Detailed insights into these effects await mechanistic studies.



(10)

A variety of substrates undergo oxidative cyclization with this catalyst system (Chart 2) and similar palladium catalysts have been employed by Muñiz in the oxidative cyclization of *o*-allylphenols.[34] The NHC/palladium(II) catalyst appears to be somewhat less effective than the $Pd(OAc)_2$/pyridine

(29) Yip, K.-T.; Yang, M.; Law, K.-L.; Zhu, N.-Y.; Yang, D. *J. Am. Chem. Soc.* **2006**, *128*, 3130−3131.

(30) (a) Sigman, M. S.; Jensen, D. R. *Acc. Chem. Res.* **2006**, *39*, 221−229 and references cited therein. (b) Jensen, D. R.; Schultz, M. J.; Mueller, J. A.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3810−3813. (c) Jensen, D. R.; Sigman, M. S. *Org. Lett.* **2003**, *5*, 63−65. (d) Mueller, J. A.; Goller, C. P.; Sigman, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9724−9734. (e) Schultz, M. J.; Hamilton, S. S.; Jensen, D. R.; Sigman, M. S. *J. Org. Chem.* **2005**, *70*, 3343−3352. (f) Cornell, C. N.; Sigman, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 2796−2797.

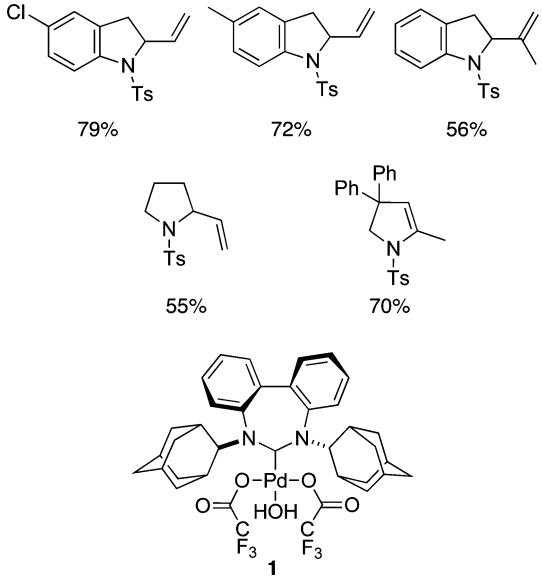
(31) Rogers, M. M.; Stahl, S. S. *N-Heterocyclic Carbenes in Transition Metal Catalysis*; Glorius, F., Ed.; Springer: New York, 2007; pp 21−46.

(32) Rogers, M. M.; Wendlandt, J. E.; Guzei, I. A.; Stahl, S. S. *Org. Lett.* **2006**, *8*, 2257−2260.

(33) Konnick, M. M.; Gandhi, B. A.; Guzei, I. A.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2904−2907.

(34) Muñiz, K. *Adv. Synth. Catal.* **2004**, *346*, 1425−1428.

Chart 2. Products Obtained via (IMes)Pd(O_2CCF_3)$_2$(OH_2)-Catalyzed Aerobic Oxidative Cyclization



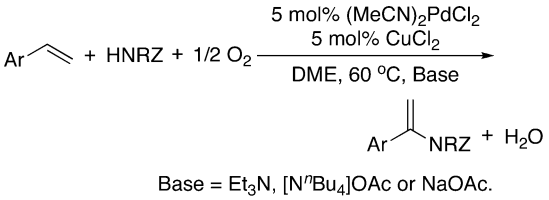
system with aliphatic tosylamide substrates. Nevertheless, this catalyst system is attractive for further study because it offers a well-defined palladium coordination environment with a single, robust neutral donor ligand. The growing availability of chiral NHC ligands[35] improves prospects that such catalysts might be effective in asymmetric oxidative cyclization reactions. Toward this end, we have also been exploring the development of axially chiral seven-membered NHCs.[36] Palladium complexes bearing these ligands (e.g., **1**) furnish oxidative cyclization products in yields similar to those with the IMes catalyst, although longer reaction times are currently required.

Intermolecular Oxidative Amination of Alkenes

In parallel with our studies of intramolecular oxidative amination reactions, we initiated efforts to develop analogous intermolecular reactions. The only precedent for intermolecular aza-Wacker reactions consisted of the formal oxidative conjugate addition of cyclic amides and carbamates to electron-deficient alkenes (eq 5).[16] Styrene, which is mildly activated toward nucleophilic attack at the terminal C atom, also exhibited some reactivity under the catalytic conditions, resulting in a 44% yield of the anti-Markovnikov oxidative amination product with oxazolidinone as the nucleophile. This study, despite its limitations, provided a critical starting point for our investigations. Styrene is intrinsically more reactive than simple alkyl olefins; however, it is considerably less "activated" than the intramolecular substrates described in the previous section and electron-deficient alkenes such as acrylates.

Our initial experiments focused on identifying improved reaction conditions for the oxidative amination of styrene with oxazolidinone. In the course of these screening studies, we discovered that either the Markovnikov or anti-Markovnikov oxidative amination may be acheived, depending on the conditions of the reaction (Scheme 4).[37] The use of $(MeCN)_2PdCl_2$ as the catalyst led to exclusive formation of the anti-Markovnikov product in 77% yield. If $(Et_3N)_2PdCl_2$ is used as the catalyst or $(MeCN)_2PdCl_2$ in combination with an anionic bases (e.g., acetate, carbonate), the Markovnikov enecarbamate product is formed in very high yield. This unusual switch in regioselectivity has important synthetic implications and raises a number of fundamental questions concerning the origin of this outcome.

The ability to achieve catalyst-controlled regioselectivity in coupling reactions with alkenes represents an important goal in synthetic chemistry. Unfortunately, the reaction yielding anti-Markovnikov amination products is presently limited in scope. Oxazolidinone is, by far, the most effective nucleophile, and even slight variations in the styrene substrate (e.g., the presence of electron-donating and -withdrawing substituents in the para position) result in lower yields. In contrast, the reactions yielding Markovnikov products are more versatile. A number of nonbasic nitrogen nucleophiles and vinylarenes proceed to the enamide products, often in quite good yields (eq 11 and Chart 3).[37] The primary sulfonamide nucleophile reacts to form an imine product, presumably via tautomerization of an initially formed enamide.



(11)

Analysis of the results in Scheme 4 suggested that the switch in regiochemistry correlates with the presence (or absence) of a Brønsted base. Namely, the addition of triethylamine or acetate to the original reaction conditions induces a switch in selectivity from the anti-Markovnikov product to the Markovnikov product. Subsequent mechanistic studies confirmed this hypothesis and provided fundamental insights into the origin of this effect.[38] Several key observations from our studies are summarized in Table 1. The reactions performed in the presence of a Brønsted base (i.e., those that generate the Markovnikov product) proceed 5−7-fold faster than the reaction performed in the absence of base (Table 1, entry 1). The former reactions exhibit no kinetic isotope effect, whereas the formation of the anti-Markovnikov product exhibits a substantial kinetic isotope effect (KIE) upon deuteration of the oxazolidinone substrate (KIE = 3.0; Table 1, entry 2). Finally, the reaction rates exhibit different

(35) For leading reviews, see: (a) Perry, M. C.; Burgess, K. *Tetrahedron: Asymmetry* **2003**, *14*, 951−961. (b) César, V.; Bellemin-Laponnaz, S.; Gade, L. H. *Chem. Soc. Rev.* **2004**, *33*, 619−636 and references cited therein.

(36) (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.

(37) Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2003**, *125*, 12996−12997.

(38) Timokhin, V. I.; Stahl, S. S. *J. Am. Chem. Soc.* **2005**, *127*, 17888−17893.

Scheme 4. Catalyst-Composition-Dependent Regioselectivity Switch in Styrene Amination

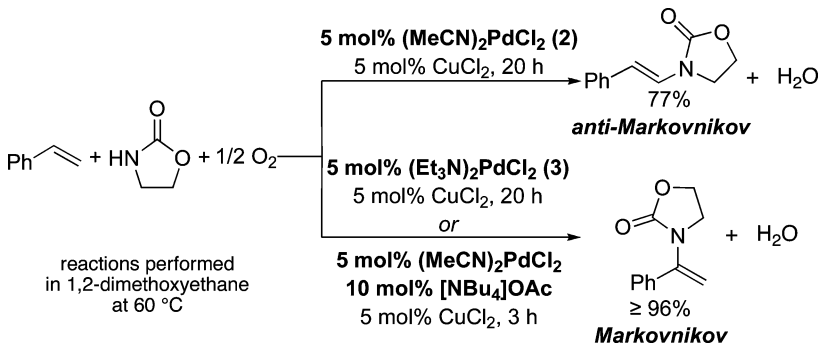


Chart 3. Selected Products from Aerobic Oxidative Amination of Vinylarenes Using $(MeCN)_2PdCl_2$ as a Catalyst in the Presence of a Base

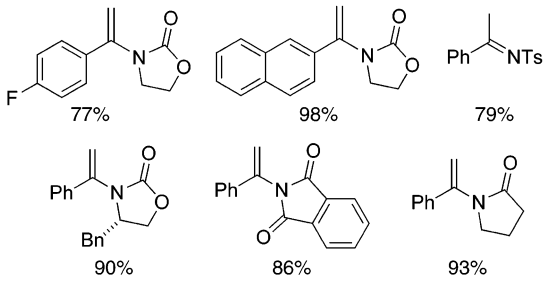


Table 1. Summary of Mechanistic Data for the Regioselective Aerobic Oxidative Amination of Styrene with Oxazolidinone Catalyzed by Palladium(II)

entry	experimental study	anti-Markovnikov	Markovnikov
1	relative reaction rate	1.0	5.0 (NEt_3), 7.4 (OAc^-)
2	KIE (k_{HNRZ}/k_{DNRZ})[a] (HNRZ = oxazolidinone)	3.0(1)	1.1(1)
3	kinetic order in [substrate]:		
	[styrene]	saturation	first order
	[oxazolidinone]	first order	saturation

[a] The KIE was based on a comparison of reaction rates performed with oxazolidinone and *N*-deuterated oxazolidinone as the nucleophile.

dependences on the styrene and oxazolidinone substrate concentrations. The rate of anti-Markovnikov product formation exhibits a saturation dependence on [styrene] and a linear, first-order dependence on [oxazolidinone]. In contrast, the rate of Markovnikov product formation in the presence of triethylamine as the Brønsted base exhibits a linear, first-order dependence on [styrene] and a saturation dependence on [oxazolidinone] (Table 1, entry 3). A mechanism consistent with these observations is shown in Scheme 5.

Key features of the proposed mechanism include the following. Styrene enters the coordination sphere of palladium(II) via substitution of a neutral donor ligand, such as MeCN or Et_3N. Addition of oxazolidinone to styrene may proceed with Markovnikov or anti-Markovnikov regioselectivity, and we propose that the formation of the Markovnikov aminopalladation intermediate **I** is kinetically favored. In the presence of triethylamine or another exogenous Brønsted base, such as acetate, this zwitterionic intermediate undergoes rapid, irreversible deprotonation to form $\mathbf{I_1}$, and subsequent β-hydride elimination yields the Markovnikov oxidative amination product. In the absence of an exogenous base, deprotonation of **I** will proceed more slowly. Under these conditions, reversible aminopalladation of styrene enables the formation of the thermodynamically preferred anti-Markovnikov intermediate, **I′**, which may be stabilized by the formation of a π-benzylic structure (i.e., **I″**). Retention of this stabilizing effect in the subsequent transition state results in preferential formation of $\mathbf{I_1}'$ over $\mathbf{I_1}$ and, ultimately, yields the anti-Markovnikov product. Rapid trapping of the kinetically favored Markovnikov aminopalladation adduct **I** by the exogenous base accounts for the elevated overall rates observed in the formation of the Markovnikov products. In contrast, formation of the anti-Markovnikov product proceeds with rate-limiting deprotonation of the aminopalladation adduct **I′** (or **I″**), and rate-limiting formation of $\mathbf{I_1}'$ accounts for the KIE when the oxazolidinone nucleophile is deuterated.

The proposed mechanism also accounts for the different kinetic order in substrate observed for the two different reaction paths (Table 1, entry 3). Formation of the Markovnikov product is proposed to proceed via rate-limiting C−N bond formation (k_2'), and the corresponding rate law for this process (eq 12) predicts a first-order dependence of the rate on [styrene] and a saturation dependence on [oxazolidinone]. In contrast, formation of the anti-Markovnikov product is predicted to exhibit a saturation dependence on [styrene] and a first-order dependence on [oxazolidinone] (eq 13).[39]

$$\text{rate (Markovnikov)} = \frac{k_1 k_2'[\mathrm{L}_n\mathrm{Pd{-}L'}][\mathrm{St}][\mathrm{HNRZ}]}{k_{-1}[\mathrm{L'}] + k_2'[\mathrm{HNRZ}]} \quad (12a)$$

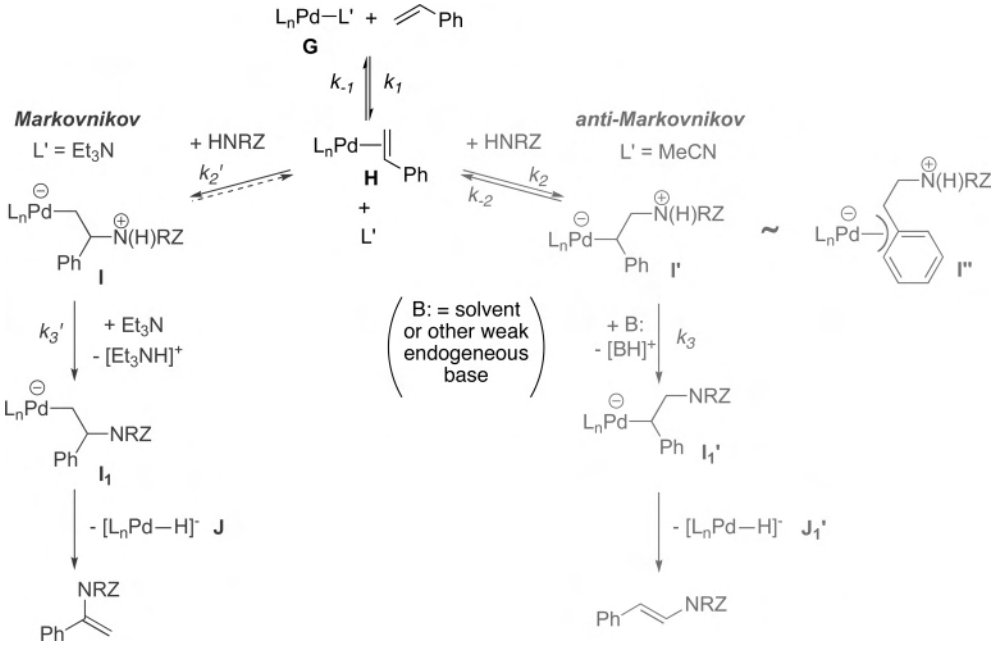
$$\sim \frac{c_1[\mathrm{St}][\mathrm{HNRZ}]}{c_2 + c_3[\mathrm{HNRZ}]} \quad (12b)$$

$$\text{rate (anti-Markovnikov)} = \frac{K_1 k_2 k_3[\mathrm{Pd}]_t[\mathrm{St}][\mathrm{HNRZ}]}{(K_1[\mathrm{St}] + [\mathrm{L}_n\mathrm{Pd}])(k_{-2} + k_3)} \quad (13a)$$

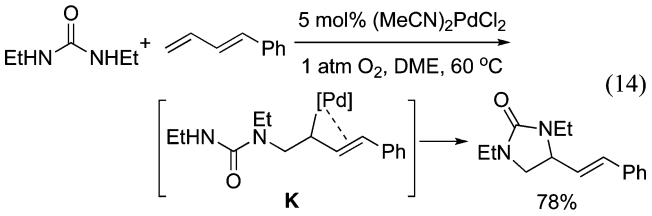
$$\sim \frac{c_1[\mathrm{St}][\mathrm{HNRZ}]}{c_2[\mathrm{St}] + c_3} \quad (13b)$$

This mechanism finds support from several additional lines of evidence. The stoichiometric reaction of dimethylamine to a well-defined palladium(II)/styrene complex has been shown to kinetically favor the formation of the Markovnikov aminopalladation product. Over time, however, this product isomerizes to the thermodynamically more stable anti-

Scheme 5. Proposed Mechanism for the Formation of Markovnikov and Anti-Markovnikov Products in the Palladium-Catalyzed Oxidative Addition of Oxazolidinone to Styrene



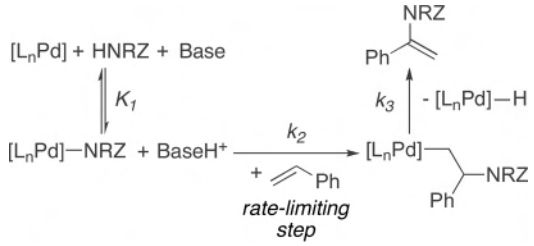
Markovnikov regioisomer.[40] These observations support the aminopalladation regioselectivity preferences proposed for Scheme 5. The recent 1,2-diamination of conjugated dienes with ureas (eq 14)[41] employs reaction conditions virtually identical with those in Scheme 4. Qualitative evidence suggests that this reaction proceeds through an η^3-allyl intermediate analogous to **I″**. Observation of *cis*-diamination for cyclic diene substrates is consistent with a stepwise mechanism consisting of *trans*-aminopalladation followed by backside attack on the π-allyl/palladium(II) intermediate **K** (eq 14).



(14)

The study of diene diamination provides support for *trans*-aminopalladation of alkenes. Our investigation of styrene oxidative amination did not distinguish between *trans*- and *cis*-aminopalladation. It is possible that the presence of a Brønsted base promotes the formation of the palladium(II)/amido complex that undergoes irreversible insertion of styrene with Markovnikov regioselectivity (Scheme 6). The rate law derived for such a mechanism is, in fact, consistent with the kinetic order for [styrene] and [oxazolidinone] observed in the formation of the Markovnikov product (eq 15).[42] Efforts to detect the formation of a palladium(II)/amido intermediate under the reaction conditions have been inconclusive thus far, but further studies are ongoing. More recent studies of intermolecular palladium-catalyzed oxidative amination reactions have provided stereochemical evidence for cis-aminopalladation (see below).

Scheme 6. Possible *Cis*-Aminopalladation Mechanism for the Formation of the Markovnikov Product in the Palladium-Catalyzed Oxidative Addition of Oxazolidinone to Styrene



$$\text{rate (Markovnikov)} = \frac{K_1 k_2 [\text{Pd}]_t [\text{St}][\text{HNRZ}][\text{base}]}{[\text{baseH}^+] + K_1[\text{HNRZ}][\text{base}]} \quad (15a)$$

$$\sim \frac{c_1[\text{St}][\text{HNRZ}]}{c_2 + c_3[\text{HNRZ}]} \quad (15b)$$

(39) Note that the palladium species "**G**" is not identical under the two reaction conditions. Triethylamine, which leads to the formation of the Markovnikov product, is also a good ligand for palladium, and the alkene complex **H** forms as a *steady-state* intermediate. In the absence of triethylamine, however, the kinetics are consistent with *pre-equilibrium* formation of the alkene complex **H**. This mechanistic distinction underlies the different [palladium] terms in the rate laws: $[L_nPd-L']$ for the Et_3N-containing reaction (eq 12a) and $[Pd]_t$ in the absence of Et_3N (eq 13a). For more detailed discussion of the kinetics and rate laws for these reactions, see ref 38 and associated Supporting Information.

(40) (a) Hahn, C.; Vitagliano, A.; Giordano, F.; Taube, R. *Organometallics* **1998**, *17*, 2060−2066. (b) Hahn, C.; Morvillo, P.; Vitagliano, A. *Eur. J. Inorg. Chem.* **2001**, 419−429. (c) Hahn, C.; Morvillo, P.; Herdtweck, E.; Vitagliano, A. *Organometallics* **2002**, *21*, 1807−1818.

(41) Bar, G. L. J.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 7308−7309.

(42) The alkene insertion step probably proceeds via the initial coordination of the alkene. A first-order dependence on [styrene] will be observed with or without precoordination of the alkene, provided the alkene adduct in the former case does not build up and contribute to the resting state of the catalyst.

Scheme 7. Oxidative Amination vs Vinyl Transfer in the Reaction of Vinyl Ethers

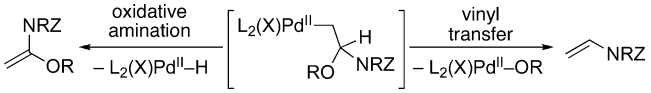
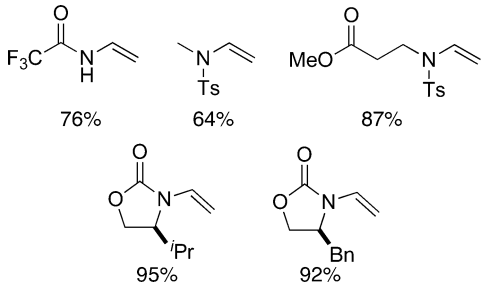
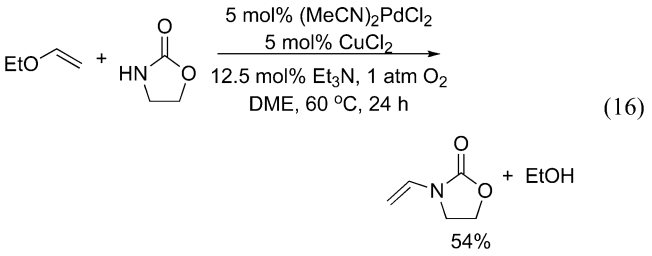


Chart 4. Selected Products of Vinyl Transfer from Butyl Vinyl Ether to Nonbasic Nitrogen Nucleophiles

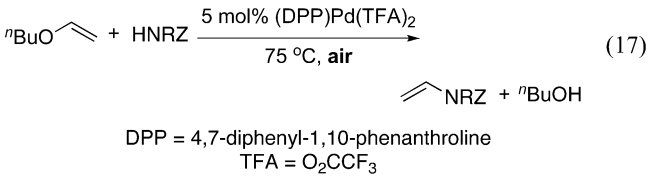


In the course of investigating other alkenes compatible with intermolecular oxidative amination, we tested the reactivity of vinyl ethers. The reaction of oxazolidinone with ethyl vinyl ether, however, resulted in oxygen-to-nitrogen vinyl transfer rather than oxidative amination (eq 16).[43] This product presumably arises via β-alkoxide elimination rather than β-hydride elimination, from the aminopalladation intermediate (Scheme 7).



(16)

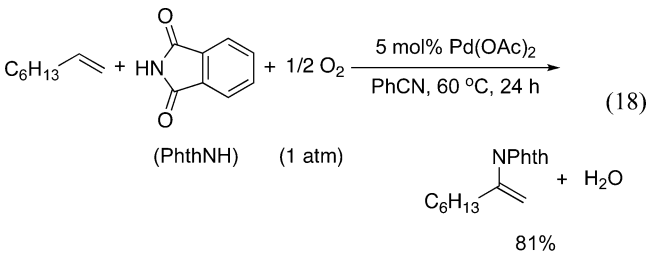
Various palladium(II) complexes were tested as catalysts for this reaction. (DPP)Pd(O_2CCF3)$_2$ (DPP = 4,7-diphenyl-1,10-phenanthroline) proved to be the most effective (eq 17), and vinyl transfer was successful with a variety of nonbasic nitrogen nucleophiles (Chart 4).[44] This reaction is formally a nonoxidative cross-coupling reaction, but improved results are obtained when the reaction is performed under an air or oxygen atmosphere (cf. eq 17). This evidence suggests that the catalyst remains in the 2+ oxidation state through the catalytic cycle, and the catalyst stability is improved in the presence of dioxygen because adventitious catalyst reduction can be reversed under the reaction conditions.



(17)

Simple alkyl olefins remain among the most challenging substrates for metal-catalyzed amination reactions.[7] Norbornene, which possesses significant ring strain, tends to be a relatively reactive alkyl olefin.[45] We therefore tested the reaction of norbonene with *p*-toluenesulfonamide under oxidative amination conditions similar to those used with styrene. The C_2-symmetric pyrrolidine (**4**) is formed in good yield (Scheme 8). The product stereochemistry can be explained by a reaction sequence consisting of *cis*-aminopalladation[46] of norbornene and insertion of a second 1 equiv of norbornene into the Pd−C bond, followed by C−N reductive elimination. This pathway is probably facilitated by the fact that β-H atoms in both of the intermediate structures lie on the opposite face of the ring with respect to the Pd atom or occupy a bridgehead position. Therefore, these intermediates are not susceptible to β-hydride elimination.

Following this encouraging result, we investigated reaction conditions for oxidative amination of 1-octene (eq 18). Phthalimide proved to be an effective nucleophile, and products were formed with several palladium(II) sources, including $PdCl_2$, $Pd(OAc)_2$, or $Pd(O_2CCF_3)_2$. In many cases, however, extensive alkene isomerization was observed, particularly in reactions containing $CuCl_2$ as a cocatalyst. Only with the use of $Pd(OAc)_2$ as the catalyst and in the *absence* of a copper cocatalyst was the desired terminal enimide obtained in good yield (eq 18).[47] The beneficial effect of $CuCl_2$ in the earlier studies of intermolecular oxidative amination (e.g., Schemes 4 and 8 and eq 11) probably reflects the ability of copper(II) to facilitate reoxidation of the palladium catalyst without promoting alkene isomerization; the substrates used in the earlier examples (vinylarenes and norbornene) are not susceptible to isomerization. Various additives were tested in the reactions (e.g., benzoquinone, pyridine, and NEt_3), but they either had little effect on the reaction or inhibited product formation.



(18)

Analogous cocatalyst-free conditions were employed in the aerobic oxidative amination of various acyclic and cyclic olefins (for selected examples, see Chart 5). Both phthalimide and sulfonamides are effective nucleophiles. The reaction

(43) Brice, J. L.; Meerdink, J. E.; Stahl, S. S. *Org. Lett.* **2004**, *6*, 1845−1848.

(44) A similar catalytic condition had been identified in related reactions involving vinyl transfer to alcohols: (a) Handerson, S.; Schlaf, M. *Org. Lett.* **2002**, *4*, 407−409. (b) Bosch, M.; Schlaf, M. *J. Org. Chem.* **2003**, *68*, 5225−5227.

(45) (a) Dorta, R.; Egli, P.; Zürcher, F.; Togni, A. *J. Am. Chem. Soc.* **1997**, *119*, 10857−10858. (b) Ackermann, L.; Kaspar, L. T.; Gschrei, C. J. *Org. Lett.* **2004**, *6*, 2515−2518. (c) Anderson, L. L.; Arnold, J.; Bergman, R. G. *J. Am. Chem. Soc.* **2005**, *127*, 14542−14543.

(46) (a) Ney, J. E.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3605−3608 and references cited therein. Examples of *trans*-aminopalladation are well documented. For leading references, see: (b) Åkermark, B.; Zetterberg, K. *J. Am. Chem. Soc.* **1984**, *106*, 5560−5561. (c) Bäckvall, J.-E. *Acc. Chem. Res.* **1983**, *16*, 335−342 and ref 12b.

(47) Brice, J. L.; Harang, J. E.; Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2005**, *127*, 2868−2869.

Scheme 8. Palladium-Catalyzed Aerobic Oxidative Amination of Norbornene

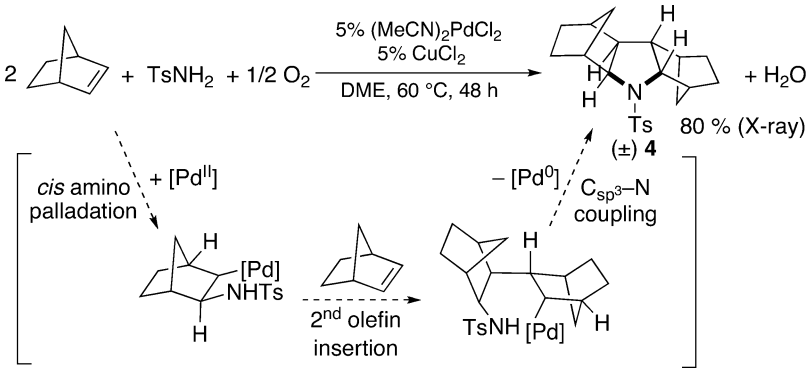
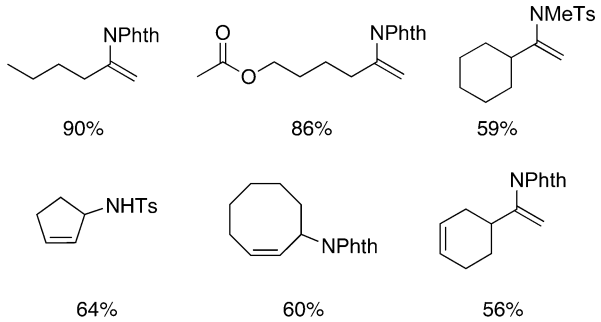
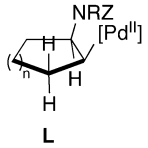


Chart 5. Selected Products Obtained in the $Pd(OAc)_2$-Catalyzed Aerobic Oxidative Amination of Unactivated Alkenes





L

with vinylcyclohexene suggests that terminal alkenes can react selectively in the presence of an internal double bond. The oxidative amination of cyclic olefins (cyclooctene and cyclopentene) yields allylic amine products rather than the corresponding enamine or imine derivatives. These observations can be explained by a mechanism involving *cis*-aminopalladation of the alkene, as observed for norbornene (Scheme 8). 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 (**L**).[48]

We conclude this section with a brief commentary on the differences observed between intra- and intermolecular oxidative amination reactions. The intramolecular reactions described in the previous section benefit from the use of ligands for the palladium catalysts (e.g., pyridine and NHCs). The detailed mechanism of these reactions has not yet been studied, but we postulate that the ligands promote catalyst reoxidation by dioxygen and stabilize the catalyst by hindering aggregation of palladium(0) into metallic palladium. The same ligands are detrimental to intermolecular oxidative amination reactions; the best results are obtained under "ligand-free" conditions. We speculate that these observations reflect ligand inhibition of the more challenging intermolecular palladium(II)-mediated substrate oxidation step(s). In the absence of ligands to promote catalyst oxidation, the use of a copper cocatalyst can be beneficial provided that the copper species does not cause the formation of unwanted side products. Mechanistic studies to probe these hypotheses and gain insights into the precise role of ligands and copper cocatalysts on the reactions are ongoing.

1,2-Oxidative Difunctionalization of Alkenes

Palladium-catalyzed oxidative amination reactions are initiated by aminopalladation of the alkene resulting in the formation of an alkyl/palladium(II) intermediate. The typical fate of this species is β-hydride elimination to furnish enamide (or allylamide) products (Charts 3 and 5); however, the reaction of norbornene (Scheme 8) reveals that under appropriate conditions the alkyl/palladium(II) intermediate can be diverted toward alternative products. Selective methods for the oxidative difunctionalization of alkenes have significant potential synthetic utility; however, methods to trap the incipient Pd−C bond must be efficient because this intermediate exhibits only transient lifetime. We have developed two different strategies to achieve this goal, one featuring intramolecular alkene insertion into the Pd−C bond and the other oxidative cleavage of the Pd−C bond to form a new C−O bond.

We envisioned that alkene insertion into the Pd−C bond could compete kinetically with β-hydride elimination if an alkene was tethered to the nitrogen nucleophile that participates in the intermolecular aminopalladation step. Such reactivity had been described previously by Oshima et al. with *stoichiometric* quantities of palladium(II) in the oxidative coupling of *N*-allyltosylamides and vinyl ethers (eq 19).[49−52] The pyrrolidine product likely forms via aminopalladation of the vinyl ether followed by insertion of the tethered olefin into the transient Pd−C bond (Scheme 9). A

(48) Ikeda, M.; El Bialy, S. A. A.; Yakura, T. *Heterocycles* **1999**, *51*, 1957−1970.

(49) (a) Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1987**, *28*, 809−812. (b) Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2050−2054.

(50) Analogous reactions were reported for allyl alcohols. See ref 49 and subsequent work by the groups of Morken and Hosokawa (refs 51 and 52, respectively).

(51) (a) Evans, M. A.; Morken, J. P. *Org. Lett.* **2005**, *7*, 3367−3370. (b) Evans, M. A.; Morken, J. P. *Org. Lett.* **2005**, *7*, 3371−3373. (c) Trudeau, S.; Morken, J. P. *Org. Lett.* **2005**, *7*, 5465−5468.

(52) Minami, K.; Kawamura, Y.; Koga, K.; Hosokawa, T. *Org. Lett.* **2005**, *7*, 5689−5692.

Scheme 9. Mechanism of Palladium-Mediated Oxidative Coupling of *N*-Allyltosylamides with Vinyl Ethers

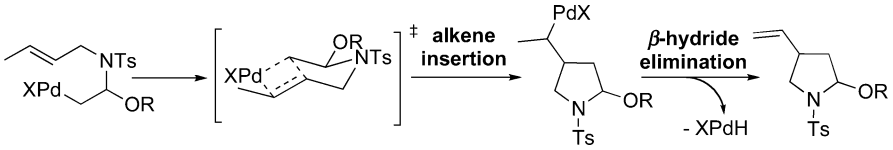
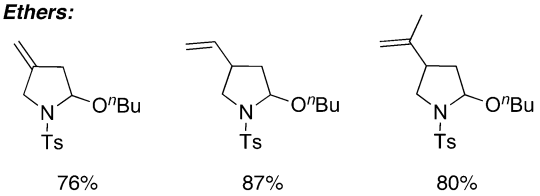
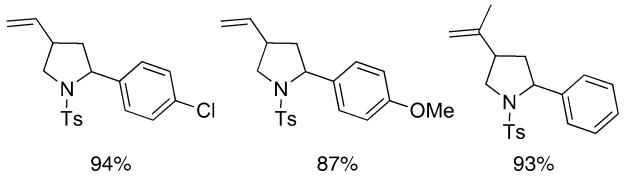


Chart 6. Selected Examples of Oxidative Coupling of *N*-Allyltosylamides with Styrene and *n*-Butyl Vinyl Ether

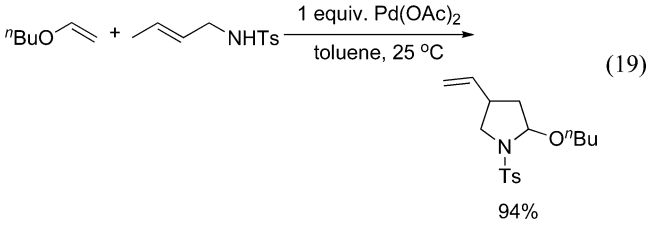
Vinyl Ethers:



Vinyl Arenes:

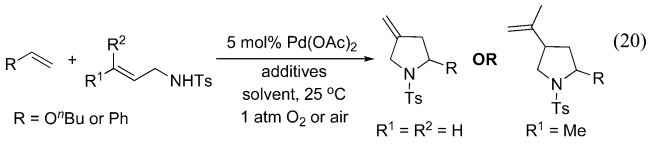


similar strategy is evident in the recent work of Yang et al. described above (eq 9).[29] Drawing from this precedent, we sought to develop a dioxygen-coupled variant of this transformation and to explore whether other alkenes were compatible with the reaction.[53]



(19)

Several alkene substrates were investigated as reaction partners in the oxidative coupling with *N*-allyltosylamides, and both vinyl ethers and vinylarenes proved to be effective (eq 20 and Chart 6). In our initial studies, PdX_2 sources (X = Cl, OAc, O_2CCF_3) were tested as catalysts in the absence of additives or cocatalysts; however, low conversion and significant palladium black formation was observed. The use of ligands such as pyridine or NHCs failed to improve the results. Subsequently, we screened a variety of other additives, and the empirically optimized conditions differed for the two alkene substrates (eq 20). In both cases, the reaction benefited from the presence of a cocatalytic copper(II) source. Catechol proved to be an additional effective cocatalyst in the reactions with butyl vinyl ether, a result that has precedent in oxidative coupling reactions of allyl alcohols reported by Hosokawa and co-workers.[52] Catechol did not benefit reactions with styrene. Instead, methyl acrylate proved to be a useful additive. We speculate that this electron-deficient alkene stabilizes palladium(0) intermediates in the catalytic reaction, thereby slowing catalyst decomposition. The precise role of catechol in the butyl vinyl ether reactions and the origin of the different solvent preference for the two alkene substrates have not been established.



(20)

Alkene	Additives	Solvent
butyl vinyl ether	5% $Cu(OAc)_2$, 10% catechol, 3Å MS	MeCN
styrene	5% $Cu(O_2CCF_3)_2$, 50% methyl acrylate	toluene

The carboamination reactions outlined above highlight prospects for palladium-catalyzed 1,2-difunctionalization reactions of alkenes, in this case via alkene insertion into the Pd−C bond formed in the aminopalladation step.[54] The final step in the oxidative amination of norbornene (Scheme 8) indicated that alkyl/palladium(II) intermediates also can be trapped to form C−heteroatom bonds. Similarly, early studies of stoichiometric aminopalladation of alkenes revealed that strong oxidants such as $Pb(OAc)_4$ and Br_2 induce C−heteroatom bond formation via oxidative cleavage of Pd−C bonds.[46c] More recently, $PhI(OAc)_2$ has been highlighted as an effective reagent for the oxidative cleavage of Pd−C bonds under catalytic conditions.[55,56] These observations prompted us to investigate $PhI(OAc)_2$ as a stoichiometric oxidant for palladium-catalyzed intermolecular aminoacetoxylation of alkenes.[57] This transformation represents a mechanistically and stereochemically distinct pathway for 1,2-difunctionalization of alkenes relative to the highly useful osmium(VIII)-catalyzed transformations.[58]

Our initial screening studies focused on the aminoacetoxylation of 1-octene in the presence of palladium(II), a nitrogen nucleophile and $PhI(OAc)_2$. $(MeCN)_2PdCl_2$ was the most effective palladium(II) source. The use of other palladium-

(53) Scarborough, C. C.; Stahl, S. S. *Org. Lett.* **2006**, *8*, 3251−3254.

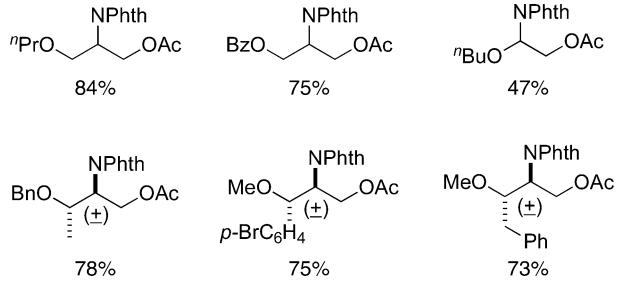
(54) Selected alternative strategies to achieve metal-catalyzed carboamination reactions of alkenes: (a) Ney, J. E.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 8644−8651. (b) Fritz, J. A.; Nakhla, J. S.; Wolfe, J. P. *Org. Lett.* **2006**, *8*, 2531−2534. (c) Nakhla, J. S.; Kampf, J. W.; Wolfe, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 2893−2901. (d) Harayama, H.; Abe, A.; Sakado, T.; Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *J. Org. Chem.* **1997**, *62*, 2113−2122. (e) Sherman, E. S.; Chemler, S. R.; Tan, T. B.; Gerlits, O. *Org. Lett.* **2004**, *6*, 1573−1575 and refs 14 and 42a.

(55) For use of $PhI(OAc)_2$ in the palladium-catalyzed oxidative functionalization of aryl C−H bonds, see: (a) Yoneyama, T.; Crabtree, R. H. *J. Mol. Catal. A: Chem.* **1996**, *108*, 35−40. (b) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300−2301. (c) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542−9543. (d) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790−12791.

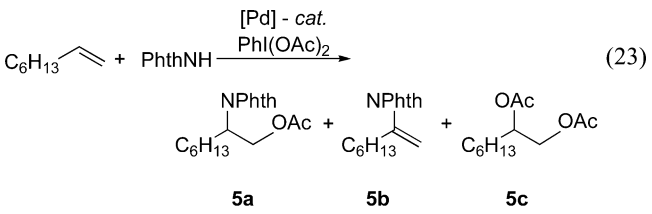
(56) For use of $PhI(OAc)_2$ in the palladium-catalyzed intramolecular aminoacetoxylation and diamination of alkenes, see: (a) Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690−7691. (b) Streuff, J.; Hövelmann, C. H.; Nieger, M.; Muñiz, K. *J. Am. Chem. Soc.* **2005**, *127*, 14586−14587.

(57) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179−7181.

Chart 7. Selected Examples from Aminoacetoxylation of Allyl and Vinyl Ethers Catalyzed by $(MeCN)_2PdCl_2$

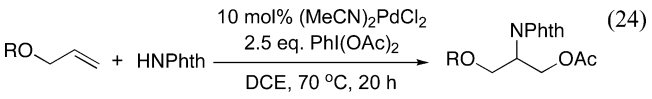


(II) sources, Brønsted bases, and both strong and weak donor ligands led to lower yields or inhibition of the reaction. Various nitrogen nucleophiles were tested, including succinimide, phthalimide, pyrrolidinone, oxazolidinone, and tosylamide, but only phthalimide led to aminoacetoxylation in useful yields (>50%). The latter observation currently represents a limitation of the reaction; however, phthalimide is a useful ammonia surrogate because the phthaloyl protecting group is relatively easily removed. Three different products are observed in the reaction with phthalimide: aminoacetoxylation product **5a**, enimide **5b**, and a vicinal diacetoxylation product **5c** (eq 23). A key feature of this reaction is the exquisite regioselectivity; no products arising from phthalimide addition to the terminal C atom are observed. This result is noteworthy because osmium-catalyzed aminohydroxylation often forms regioisomeric mixtures, often favoring the opposite regioisomer.[59]



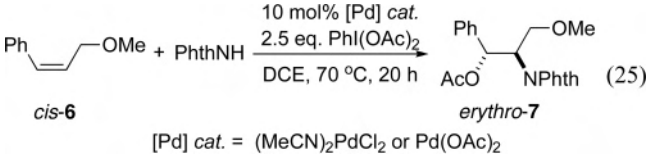
(23)

The evaluation of other alkene substrates revealed that allyl ethers and esters are particularly effective (eq 24 and Chart 7). Substrates that possess an additional substituent in the allylic position generate only a single diastereomeric product (Chart 7). Internal alkenes are generally ineffective substrates. For example, crotyl benzyl ether yields a complex mixture of products, none of which appears to be the desired aminoacetoxylation product.



(24)

Insights into the mechanism of this reaction were obtained from the aminoacetoxylation of *cis*-**6** (eq 25), which yields a single aminoacetoxylation product: *erythro*-**7**. The *trans* isomer of **6** does not undergo aminoacetoxylation under these conditions, thereby establishing that *cis*-**6** does not isomerize into the more stable *trans*-alkene prior to the formation of *erythro*-**7**.



(25)

The formation of *erythro*-**7** from *cis*-**6** could arise from two distinct reaction pathways (Scheme 10): (1) *trans*-aminopalladation followed by oxidative cleavage of the Pd−C bond with retention of stereochemistry or (2) *cis*-aminopalladation followed by oxidative cleavage of the Pd−C bond with inversion of stereochemistry. Literature precedents suggest that either sequence is possible.[60,61] To distinguish between these possibilities, one additional experimental result was necessary, namely, the product of palladium-catalyzed aerobic oxidative amination of *cis*-**6**. The enimide product formed in this reaction, (*Z*)-**8**, reveals that the aminopalladation step proceeds with *cis* stereoselectivity (Scheme 10). By extension, oxidative cleavage of the Pd−C bond must proceed with inversion of stereochemistry, that is, via S_N2 attack of acetate on a Pd^{IV}−C bond. The latter step resembles the C−O reductive elimination pathway that has been demonstrated for alkyl/platinum(IV) species.[62]

A *cis*-aminopalladation step arising from chelate-assisted alkene insertion into a Pd−N bond provides a rationale for the high diastereoselectivity observed in aminoacetoxylation of allylic ether substrates (cf. Chart 7 and Figure 1). The extremely high levels of regio- and diastereosectivity in the intermolecular aminoacetoxylation of alkenes may enable this reaction to become a useful method for the synthesis of amino alcohols and unnatural amino acid products.

Summary and Outlook

The studies outlined above highlight the ability of palladium(II) to catalyze the oxidative amination of alkenes and illustrate the broad potential utility of "organometallic oxidase" reactions. Reactions initiated by aminopalladation of an alkene can diverge in a variety of different, synthetically

(58) For selected reviews, see: (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547. (b) Nilov, D.; Reiser, O. *Adv. Synth. Catal.* **2002**, *344*, 1169−1173. (c) Bodkin, J. A.; McLeod, M. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2733−2746. (d) Muñiz, K. *Chem. Soc. Rev.* **2004**, *33*, 166−174. (e) The, recently discovered palladium-catalyzed, dialkoxylation of 2-vinylphenols proceeds by yet another mechanism involving quinone methide intermediates: Schultz, M. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 1460−1461.

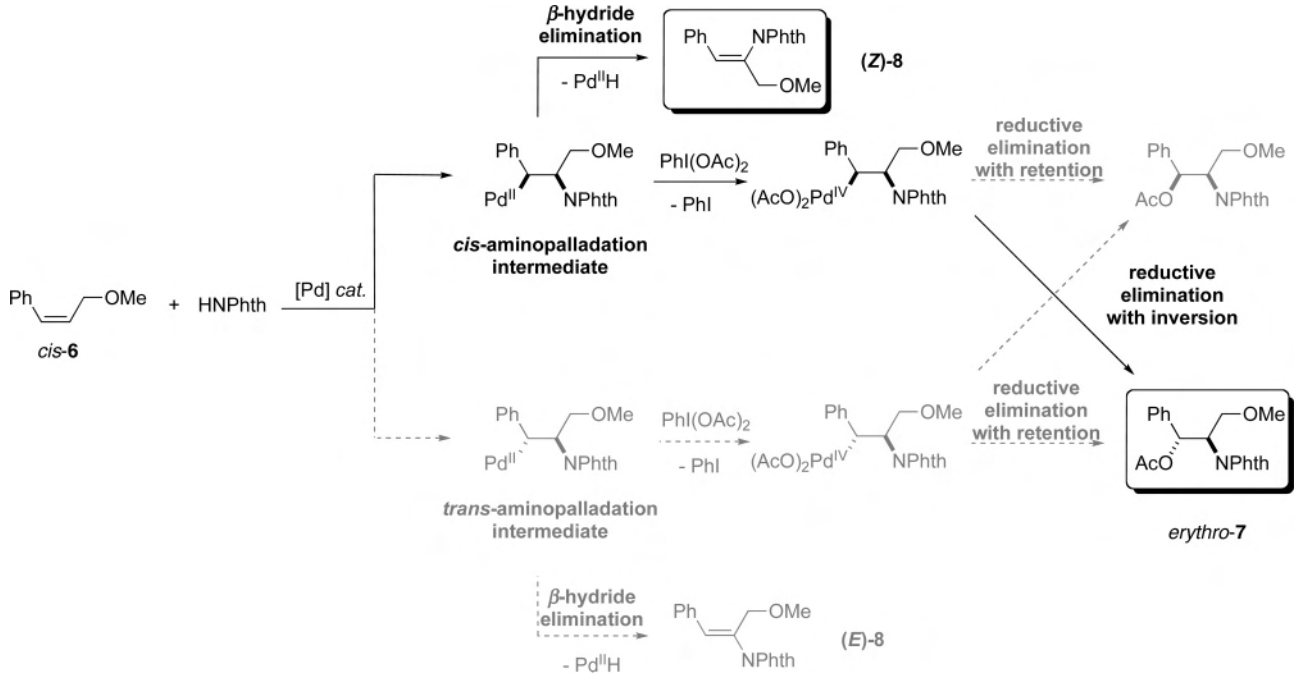
(59) For an exception in which osmium-catalyzed aminohydroxylation of styrenes was used to prepare α-arylglycines, see: Reddy, K. L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 1207−1217.

(60) Both *cis*- and *trans*-heteropalladations of alkenes are possible. See refs 28b and 54c, the following examples, and references cited therein: (a) Lei, A.; Lu, X.; Liu, G. *Tetrahedron Lett.* **2004**, *45*, 1785−1788. (b) Hamed, O.; Henry, P. M.; Thompson, C. *J. Org. Chem.* **1999**, *64*, 7745−7750. (c) Hayashi, T.; Yamasaki, K.; Mimura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3036−3037.

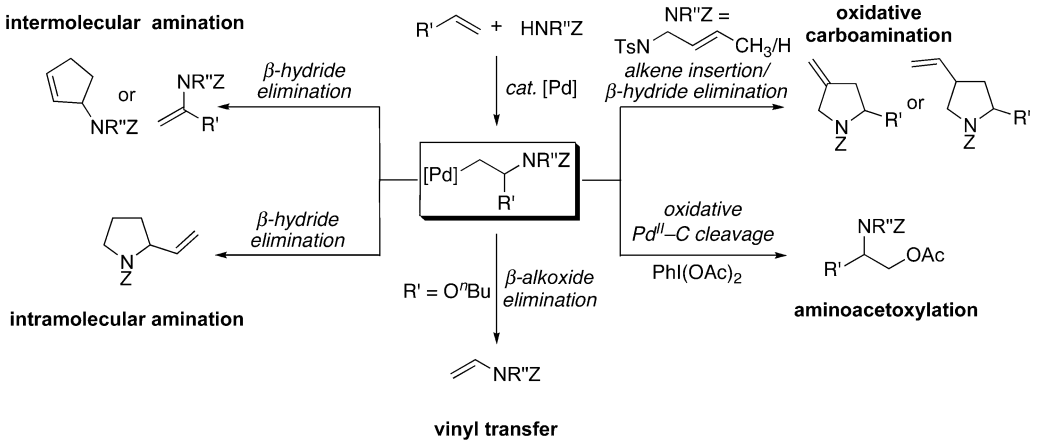
(61) The oxidative cleavage of Pd^{II}−C bonds has been observed to proceed with retention or inversion. See ref 46c, the following selected examples, and references cited therein: (a) Coulson, D. R. *J. Am. Chem. Soc.* **1969**, *91*, 200−202. (b) Wong, P. K.; Stille, J. K. *J. Organomet. Chem.* **1974**, *70*, 121−132. (c) Bäckvall, J.-E. *Tetrahedron Lett.* **1977**, *18*, 467−468. (d) Zhu, G.; Ma, S.; Lu, X.; Huang, Q. *J. Chem. Soc., Chem. Commun.* **1995**, 271−273.

(62) (a) Williams, B. S.; Goldberg, K. I. *J. Am. Chem. Soc.* **2001**, *123*, 2576−2587. (b) Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *Angew. Chem., Int. Ed.* **1998**, *37*, 2180−2192 and references cited therein.

Scheme 10. Mechanistic Explanation of the Stereochemical Outcome in Aminoacetoxylation of *cis*-**6**



Scheme 11. Reaction Pathways Observed Following Aminopalladation of Alkenes



useful directions (Scheme 11). In addition to terminal β-hydride elimination steps that form enamides and allylic amides, we have identified reactions that terminate by β-alkoxide elimination and by trapping of the Pd−C bond via alkene insertion and oxidative cleavage with $PhI(OAc)_2$.

The use of nonbasic nitrogen nucleophiles, including sulfonamides, phthalimide, and carbamates, appears to be critical to the success of the reactions. These nucleophiles are poor ligands for palladium(II) and, therefore, avoid poisoning of the catalyst in the manner observed for alkyl- and arylamines. The intramolecular oxidative amination reactions benefit from the use of monodentate ligands, which stabilize the catalyst by hindering palladium(0) aggregation and promote aerobic oxidation of the reduced catalyst. The effect of these ligands is not entirely beneficial, however. When pyridine is present in elevated concentrations, for example, it inhibits catalytic steps associated with palladium(II)-mediated substrate oxidation. Deleterious ligand effects appear to be even more problematic for intermolecular oxidative amination reactions. Most of the successful intermolecular reactions identified thus far employ "ligand-free" conditions. Under such conditions, copper cocatalysts or other additives often are necessary to prevent rapid catalyst decomposition. Another challenge in the development of intermolecular oxidative amination reactions is the general requirement for the use of excess alkene substrate (2−6 equiv) to obtain good yields relative to the nitrogen nucleo-

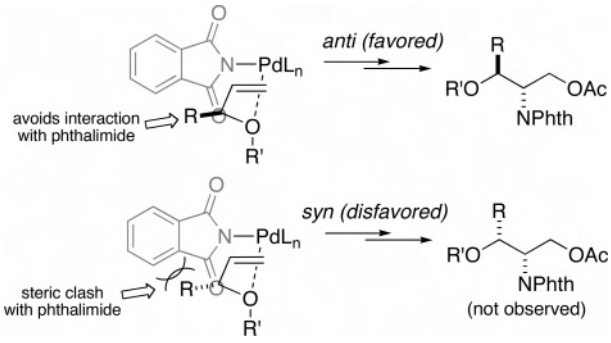


Figure 1. Model for the origin of high diastereoselectivity observed in the aminoacetoxylation of allylic ethers possessing a substituent in the allylic position.

phile as the limiting reagent. We are optimistic that this challenge can be overcome because, recently, we have succeeded in preparing a variety of phthalimide-derived enimides in good yield with a 1:1 ratio of alkene to phthalimide.[63]

The development of asymmetric catalytic applications of this chemistry remains an important goal in this area. A critical challenge will be the identification of ligands that not only provide a suitable chiral coordination environment at the metal center but also are compatible with efficient catalytic turnover. These studies will have to account for the stereochemistry of the aminopalladation step. Results from our laboratory[57] and others[60] suggest that both *trans*- and *cis*-aminopalladation are possible and, in some cases, both processes occur in parallel.[64] Fundamental insights into these steps will undoubtedly play an important role in future advances.

Acknowledgment. S.S.S. thanks each of his co-workers, whose hard work and intellectual contributions played a critical role in the development of this chemistry. He also is grateful to the NIH (RO1 GM67173) for their generous support of this research.

IC061997V

(63) Rogers, M. M.; Stahl, S. S., unpublished results.

(64) Liu, G.; Stahl, S. S., unpublished results.