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Two-Faced Reactivity of Alkenes: *cis*- versus *trans*-Aminopalladation in Aerobic Pd-Catalyzed Intramolecular Aza-Wacker Reactions

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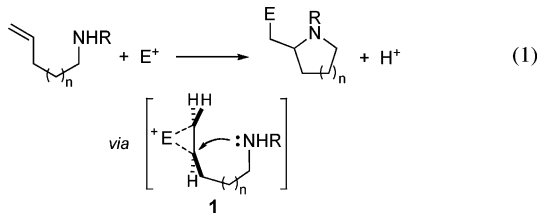
Abstract: A number of different Pd^{II} catalyst systems have been reported recently for the Wacker-type aerobic oxidative cyclization of alkenes bearing tethered nitrogen nucleophiles. This study examines the stereochemistry of the aminopalladation step with five different catalyst systems: $Pd(OAc)_2$/DMSO (**A**), PdX_2/pyridine [X = OAc (**B**), O_2CCF_3 (**C**)], $Pd(IMes)(O_2CCF_3)_2(OH_2)$ (**D**), and $Pd(O_2CCF_3)_2$/(−)-sparteine (**E**). Use of a stereospecifically deuterated cyclopentene substrate reveals that four of the five catalyst systems (**A**, **B**, **C**, and **E**) promote exclusive *cis*-aminopalladation of the alkene, whereas both *cis*- and *trans*-aminopalladation occur with the *N*-heterocyclic-carbene (NHC) catalyst system. If stoichiometric Brønsted base (NaOAc, Na_2CO_3) is added to the latter reaction conditions, however, only *cis*-aminopalladation is observed. The identity of the nitrogen nucleophile also affects the aminopalladation pathway, with results ranging from exclusively *cis*- to exclusively *trans*-aminopalladation. These results have important implications for ongoing efforts to develop enantioselective methods for Pd-catalyzed oxidative amination of alkenes.

Introduction

The prominence of nitrogen-containing heterocycles in natural products and biologically active molecules has prompted considerable efforts toward their synthesis. One powerful synthetic strategy consists of electrophile-promoted cyclization of alkenes bearing tethered amines or amides (eq 1).[1] Effective electrophiles



(1)

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range from strong Brønsted acids to main-group (e.g., selenium, halogens) and transition-metal reagents (mercury, gold and palladium),[1,2] and the reactions generally proceed via intramolecular nucleophilic attack on an electrophile-activated alkene intermediate, **1** (eq 1). The use of transition-metal electrophiles in alkene heterocyclization reactions is attractive because facile cleavage of the metal−carbon bond often enables the metal electrophile to be regenerated and used catalytically. Palladium-catalyzed "Wacker-type" heterocylizations represent prominent examples of this principle and find widespread use in the synthesis of oxygen and nitrogen heterocycles.[3] For example, various pyrrolidine derivatives can be accessed via Pd^{II}-catalyzed cyclization of δ,ϵ-unsaturated amine derivatives (Scheme 1). The aminopalladated intermediate **2** commonly undergoes β-hydride elimination to produce oxidative amination products such as **3**; however, a number of alternative products, such as **4**−**6** (Scheme 1), can be prepared by modifying the reaction conditions.[4,5]

Renewed interest in Pd-catalyzed oxidative heterocyclization reactions has been stimulated recently by the identification of new Pd catalysts and reaction conditions compatible with

(1) (a) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 411−454. (b) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321−3408. (c) Frederickson, M.; Grigg, R. *Org. Prep. Proced. Int.* **1997**, *29*, 33−62. (d) Frederickson, M.; Grigg, R. *Org. Prep. Proced. Int.* **1997**, *29*, 63−115. (e) Wirth, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 3740−3749.

(2) For selected recent examples, see: (a) Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 1471−1474. (b) Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 1070−1071. (c) Bender, C. F.; Widenhoefer, R. A. *Chem. Commun.* **2006**, 4143−4144. (d) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798−1799. (e) Takemiya, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 6042−6043. (f) Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179−4182. (g) Bender, C. F.; Widenhoefer, R. A. *Org. Lett.* **2006**, *8*, 5303−5305. (h) Han, X.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1747−1749.

(3) For leading references, see: (a) Hegedus, L. S. *J. Mol. Catal.* **1983**, *19*, 201−211. (b) Wolfe, J. P.; Thomas, J. S. *Curr. Org. Chem.* **2005**, *9*, 625−655. (c) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644−4680. (d) Tietze, L. F.; Sommer, K. M.; Zinngrebe, J.; Stecker. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 257−259.

(4) For example, see: (a) Tamaru, Y.; Hojo, M.; Higashimura, H.; Yoshida, Z.-I. *J. Am. Chem. Soc.* **1988**, *110*, 3994−4002. (b) Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690−7691. (c) Michael, F. E.; Cochran, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 4246−4247.

(5) In most cases, reactions of this type employ amine nucleophiles bearing electron-withdrawing groups (amides, sulfonamides, carbamates, etc.). In order to avoid modifying the nomenclature for each type of nucleophile, we use generic terms such as "aminopalladation" and "oxidative amination" to describe these reactions.

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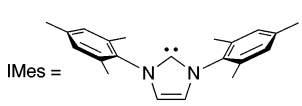
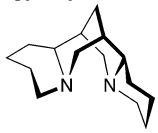
Table 1. Palladium(II) Catalyst Systems Employed in Direct-Dioxygen-Coupled Intramolecular Oxidative Amination Reactions

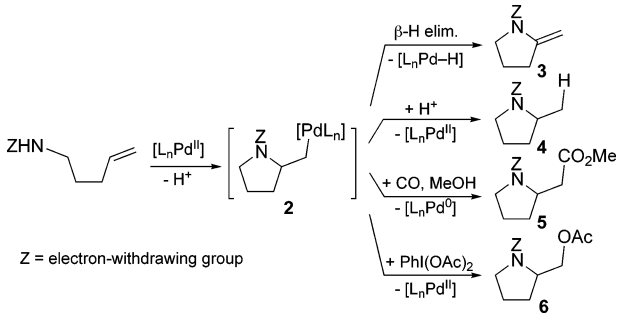
entry	catalysts	solvent	additive	abbreviation
1	$Pd(OAc)_2$	DMSO	NaOAc (2 equiv)	$Pd(OAc)_2$/DMSO (**A**)
2	$Pd(OAc)_2$/pyridine	toluene		$Pd(OAc)_2$/py (**B**)
3	$Pd(O_2CCF_3)_2$/pyridine	toluene	3 Å MS, Na_2CO_3 (2 equiv)	$Pd(O_2CCF_3)_2$/py (**C**)
4	$Pd(IMes)(O_2CCF_3)_2(OH_2)$[a]	toluene	benzoic acid (20 mol %)	$Pd(IMes)(O_2CCF_3)_2$/BzOH (**D**)
5	$Pd(O_2CCF_3)_2$/(−)-sparteine	toluene	3 Å MS, DIPEA[b] (2 equiv)	$Pd(O_2CCF_3)_2$/sp (**E**)

[a] IMes = *N*,*N*′-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (see below). [b]DIPEA = diisopropylethylamine.

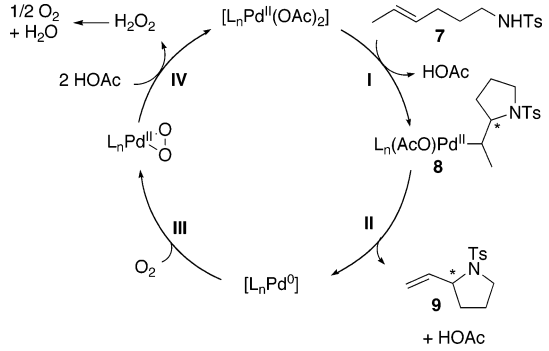




Scheme 1. Pyrrolidine Products Accessible via Intramolecular Aminopalladation of Alkenes



Scheme 2. Simplified Catalytic Cycle for Direct-Dioxygen-Coupled Pd-Catalyzed Intramolecular Oxidative Amination of Alkenes



efficient dioxgen-coupled turnover.[6] These reactions differ from earlier examples[7] because they often employ ligand-stabilized Pd catalysts and they undergo dioxygen-coupled turnover without requiring benzoquinone, Cu^{II}, or other redox-active cocatalysts. We have been particularly interested in oxidative amination reactions, and a simplified catalytic cycle for a representative reaction is shown in Scheme 2: aminopalladation of the alkene, followed by β-hydride elimination, generates the heterocyclic product **9** and a reduced Pd catalyst (steps I and II, Scheme 2). The reduced catalyst is then oxidized directly by molecular oxygen to regenerate the Pd^{II} catalyst (steps III and IV).

A variety of catalyst systems have been employed in intramolecular oxidative amination reactions of this type (Table 1). The groups of Larock and Hiemstra simultaneously discovered that $Pd(OAc)_2$ in dimethylsulfoxide (DMSO) catalyzes aerobic oxidative heterocyclization reactions in the absence of cocatalysts.[8] The presence of stoichiometric base (NaOAc) often enhances the yield of these reactions (Table 1, entry 1).[8b] Our group demonstrated that $Pd(OAc)_2$/pyridine (1:2) in toluene (entry 2) is one of the most efficient catalyst systems available for oxidative heterocyclization; turnover rates up to 70 h^{-1} were observed for intramolecular oxidative amination of alkenes.[9] Stoltz and co-workers later modified this catalyst system, using $Pd(O_2CCF_3)_2$/pyridine (1:4), 3 Å molecular sieves, and Na_2CO_3 (entry 3), to promote several different heterocyclization reactions, including oxidative aminations.[10] More recently, Pd catalysts bearing a single *N*-heterocyclic-carbene ligand (entry 4) have been utilized for intramolecular oxidative heterocyclizations.[11]

The simplicity of these catalyst systems, together with the prominent use of well-defined ancillary ligands, raises the prospect of enantioselective oxidative amination reactions. Aminopalladation of the alkene forms a new stereocenter adjacent to the nitrogen atom (step I, Scheme 2), and this stereocenter is retained in the product if β-hydride elimination proceeds away from this center, as in the formation of **9** (step II). Thus far, however, only one successful example of asymmetric Pd-catalyzed aerobic oxidative amination of alkenes has been identified: Yang and co-workers reported that the $Pd(O_2CCF_3)_2$/sp catalyst system (Table 1, entry 5) catalyzes tandem oxidative bicyclization reactions as shown in eq 2.[12] The conditions for these reactions resemble those reported previously by Stoltz et al. for related oxidative heterocylizations of phenol substrates (e.g., eq 3).[10,13c,14]

Despite this progress, the scope of asymmetric Wacker-type heterocyclizations remains quite narrow. Because of this limitation, we sought a better mechanistic understanding of Pd-

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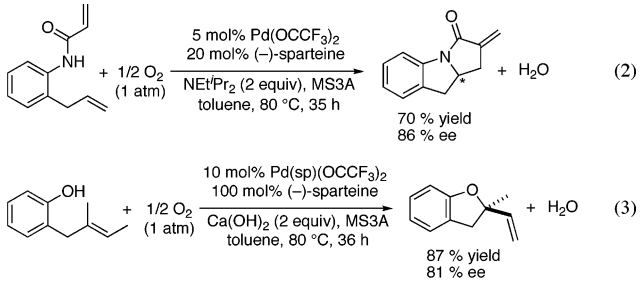
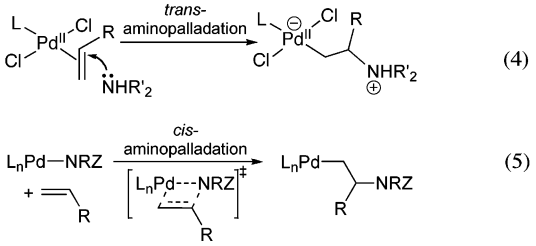


(2)

(3)

catalyzed aerobic oxidative amination reactions, particularly with respect to the stereochemistry-determining aminopalladation step (step I, Scheme 2). Early fundamental studies of aminopalladation reactions demonstrated that amine nucleophiles react with Pd-alkene complexes via external attack on the coordinated alkene (eq 4)[15] in a manner that reflects the general mechanistic model for electrophile-promoted nucleophilic additions to alkenes (eq 1). More recently, however, we[16] and others[17] have observed that certain Pd-catalyzed couplings of alkenes and nitrogen nucleophiles proceed via *cis*-aminopalladation, an outcome consistent with alkene insertion into a Pd−N bond (eq 5).[18] The stereochemistry of the aminopalladation step has



(4)

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profound implications for the rational development of asymmetric oxidative heterocylization reactions, and in the present study, we evaluate the full spectrum of reported Pd catalysts that promote intramolecular aerobic oxidative amination of alkenes (Table 1). Through the use of suitable substrate probes, we find that *cis*-aminopalladation is generally favored in these reactions; however, the pathway can be altered by the presence of additives (e.g., Brønsted acids) or by changing the identity of the nitrogen nucleophile. These results complement important recent insights into oxypalladation reactions[19] and provide a valuable framework for the pursuit of asymmetric oxidative aminocyclization reactions.

Scheme 3. Possible Outcomes for Pd-Catalyzed Oxidative Cyclization of **(*E*)-10**

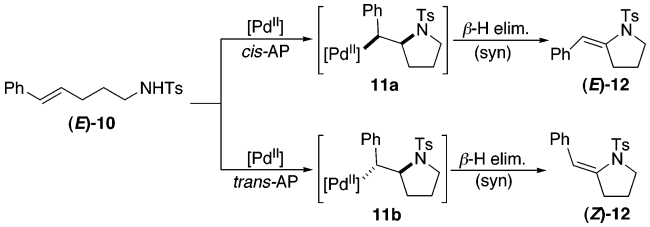
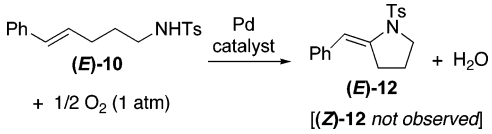


Table 2. Results for Palladium-Catalyzed Aerobic Oxidative Cyclization of **(*E*)-10**[a]



entry	Pd catalyst	yield **(*E*)-12** (%)[b]
1	$Pd(OAc)_2$/DMSO (**A**)	85 (10)
2	$Pd(OAc)_2$/py (**B**)	92
3	$Pd(O_2CCF_3)_2$/py (**C**)	70
4	$Pd(IMes)(O_2CCF_3)_2$/BzOH (**D**)	17 (68)
5	$Pd(O_2CCF_3)_2$/sp (**E**)	<4 (90)

[a] All reactions performed at 80 °C for 15 h, 0.1 mmol scale. [b]NMR yield (internal standard = 1,3,5-tri-*tert*-butylbenzene); recovered **(*E*)-10** in parentheses.

Results and Discussion

Stereochemical Outcome for the Oxidative Cyclization of a *trans*-Disubstituted Alkene. We initiated this study by investigating the oxidative cyclization of the phenyl-substituted alkene substrate **(*E*)-10** (Scheme 3). The possible products of this heterocyclization reaction provide mechanistic insights into the aminopalladation step: formation of **(*E*)-12** would arise from initial *cis*-aminopalladation (*cis*-AP) of the alkene followed by *syn*-β-hydride elimination from intermediate **11a**, whereas **(*Z*)-12** would arise from a sequence initiated by *trans*-aminopalladation (*trans*-AP) of **(*E*)-10** (Scheme 3).[20]

Substrate **(*E*)-10** was subjected to oxidative cyclization conditions for each of the five catalyst systems shown in Table 1, and the results are summarized in Table 2. The sole product observed from these reactions is **(*E*)-12**, indicating that the reactions proceed via *cis*-aminopalladation of the alkene (cf. Scheme 3). This product is formed in good yield with catalyst systems **A**−**C**, but only low yields are obtained with catalyst systems **D** and **E**, together with significant amounts of recovered starting material.

Investigation of the *cis* alkene **(*Z*)-10** under similar conditions led to lower yields and a more complicated product mixture

(14) For asymmetric oxidative cyclization reactions that employ benzoquinone as the oxidant, see: (a) Uozumi, Y.; Kato, K.; Hayashi, T. *J. Am. Chem. Soc*. **1997**, *119*, 5063−5064. (b) Uozumi, Y.; Kato, K.; Hayashi, T. *J. Org. Chem.* **1998**, *63*, 5071−5075. (c) Uozumi, Y.; Kyota, H.; Kato, K.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 1620−1625. (d) Arai, M. A.; Kuraishi, M.; Arai, T.; Sasai, H. *J. Am. Chem. Soc.* **2001**, *123*, 2907−2908. (e) Shinohara, T.; Arai, M. A.; Wakita, K.; Arai, T.; Sasai, H. *Tetrahedron Lett.* **2003**, *44*, 711−714.

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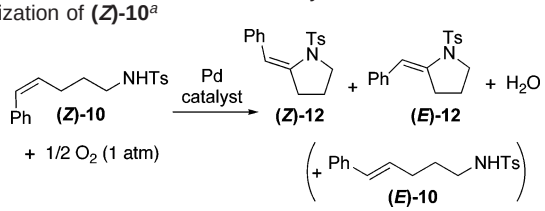
(18) No well-defined examples of alkene insertion into a Pd−N bond are currently known, but examples of alkene insertion into other transition-metal amido complexes have been reported: (a) Cowan, R. L.; Trogler, W. C. *Organometallics* **1987**, *6*, 2451−2453. (b) Casalnuovo, A. L.; Calabrese, J. C.; Milstein, D. *J. Am. Chem. Soc.* **1988**, *110*, 6738−6744. (c) Cowan, R. L.; Trogler, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4750 − 4761. (d) Gagné, M. R.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 275−294. (e) Zhao, P.; Krug, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 12066−12073.

(19) For related Wacker-type cyclizations involving *cis*-oxypalladation, see ref. 13c and Hayashi, T.; Yamasaki, K.; Mimura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3036−3037.

(20) *Anti*-β-hydride elimination reactions have been implicated in a number of Heck-type reactions, but the substrates possess unique structural properties and the examples are extremely rare relative to the ubiquitous cases of *syn*-β-hydride elimination. For a leading reference describing reactions that proceed via (formal) *anti*-elimination, see: Ikeda, M.; El Bialy, S. A. A.; Yakura, T. *Heterocycles* **1999**, *51*, 1957−1970.

Table 3. Results for Palladium-Catalyzed Aerobic Oxidative Cyclization of **(*Z*)-10**[a]



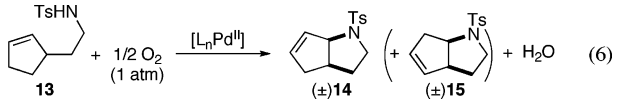
		yield (%)[b]			
entry	Pd catalysts	(*Z*)-10	(*E*)-10	(*Z*)-12	(*E*)-12
1	$Pd(OAc)_2$/DMSO (**A**)	31	21	25	16
2	$Pd(OAc)_2$/py (**B**)	<5	0	32	18
3	$Pd(O_2CCF_3)_2$/py (**C**)	12	0	34	22
4	$Pd(IMes)(O_2CCF_3)_2$/BzOH (**D**)	38	31	0	10
5	$Pd(O_2CCF_3)_2$/sp (**E**)	80	10	0	0

[a] All reactions performed at 80 °C for 15 h, 0.1 mmol scale. [b]NMR yield (internal standard = 1,3,5-tri-*tert*-butylbenzene).

(Table 3). With catalyst systems **A**−**C**, both product isomers, **(*E*)-12** and **(*Z*)-12**, were obtained. These results do not necessarily reflect the stereochemistry of the aminopalladation step, however, because isomerization of the *cis* alkene **(*Z*)-10** into the more stable *trans* isomer, **(*E*)-10**, was observed with three of the catalyst systems (**A**, **D**, and **E**). No isomeric starting material was detected in the reactions with catalyst systems **B** and **C**, but we cannot exclude the possibility that alkene isomerization occurs. For example, the lack of **(*E*)-10** might simply reflect its rapid consumption under the reaction conditions to produce **(*E*)-12**. The complexities associated with the reaction of **(*Z*)-10** prevent us from drawing mechanistic conclusions concerning the aminopalladation of this substrate.

The results obtained from the aerobic oxidative cyclization of **(*E*)-10** (Table 2) suggest that each of the five catalyst systems promotes *cis*-aminopalladation of the alkene. The presence of an aryl substituent on the alkene, however, might raise questions concerning the generality of this mechanistic pathway. Furthermore, because of the low product yields obtained with catalyst systems **D** and **E** and the complex product mixtures in the reaction of **(*Z*)-10**, we sought a less problematic substrate probe to evaluate the stereochemical course of these reactions.

Stereochemical Outcome for the Oxidative Cyclization of a Deuterium-Labeled Substrate. Introduction of a deuterium atom with appropriate regio- and stereochemistry into an oxidative cyclization substrate can provide a means to probe the pathway for aminopalladation of the alkene.[21] The cyclopentene derivative **13** (eq 6) undergoes efficient Pd-catalyzed oxidative cyclization under aerobic conditions to form the *cis*-fused [3.3.0] bicyclic product **14**.[8a,9,11b] Formation of byproduct



15 can arise from alkene isomerization of the initially formed product **14**. The stereospecifically labeled substrate *trans*-3-*d*-**13** can be used to gain insights into the stereochemical course of the oxidative cyclization reaction (Scheme 4). *Cis*-aminopalladation of the alkene will result in the Pd atom lying on the opposite face of the cyclopentane ring from the deuterium atom. Following β-hydride elimination (and, potentially, alkene isomerization), the products 3-*d*-**14** and 3-*d*-**15** will retain the deuterium label in its original position. In contrast, *trans*-aminopalladation of *trans*-3-*d*-**13** will result in either loss or migration of the deuterium atom in the products **14** and *trans*-2-*d*-**15**, respectively. The latter results arise from β-deuteride elimination from the *trans*-aminopalladation intermediate in which the Pd atom is adjacent to the deuterium atom on the same face of the five-membered ring.

Synthesis of the stereospecifically deuterium-labeled substrate *trans*-3-*d*-**13** was accomplished by the multistep sequence shown in Scheme 5.[22] Two key steps in this process are displacement of tosylate by deuteride ($LiBEt_3D$, step c) and the Ireland−Claisen rearrangement (step e), both of which proceed stereospecifically.[23]

Oxidative cyclization of *trans*-3-*d*-**13** with four of the five catalyst systems resulted in moderate to good yields of the bicylic products; a relatively low yield was obtained with the fifth Pd/(−)-sparteine catalyst system **E**, even though the catalyst loading was increased to 10 mol %[24] (Table 4). For catalyst systems **A**, **B**, **C**, and **E**, only the *cis*-aminopalladation products were obtained.[25] In contrast, the *N*-heterocyclic-carbene-based catalyst system **D** produced a nearly equal mixture of products arising from *cis*- and *trans*-aminopalladation. Enhanced levels of the alkene isomerization product **15** were observed with catalyst systems **C**, **D**, and **E**.

The results in Table 4 have been rationalized on the basis of the aminopalladation pathways shown in Scheme 4. An alternative possible mechanism for formation of the product **14** involves allylic C−D activation to form a π-allyl-Pd^{II} intermediate followed by C−N bond formation via nucleophilic attack of the sulfonamide on the allyl fragment (Scheme 6).[26] Several observations argue against this pathway. For example, predominant formation of 3-*d*-**14** would require allylic C−*H* activation

(21) For previous examples of the use of deuterium-labeled substrates to probe the stereochemistry of palladium-catalyzed reactions with alkenes, see refs 13c, 19, and (a) Grennberg, H.; Simmon, V.; Bäckvall, J.-E. *J. Chem. Soc., Chem. Commun.* **1994**, 265−266. (b) Lautens, M.; Ren, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9597−9605. (c) Kisanga, P.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 10017−10026. (d) Goj, L. A.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2001**, *123*, 11133−11147. (e) Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 2056−2057. (f) Franzén, J.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2003**, *125*, 6056−6057. (g) Hay, M. B.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 16468−16476.

(22) For synthesis details of deuterium-labeling substrates, see the Supporting Information.

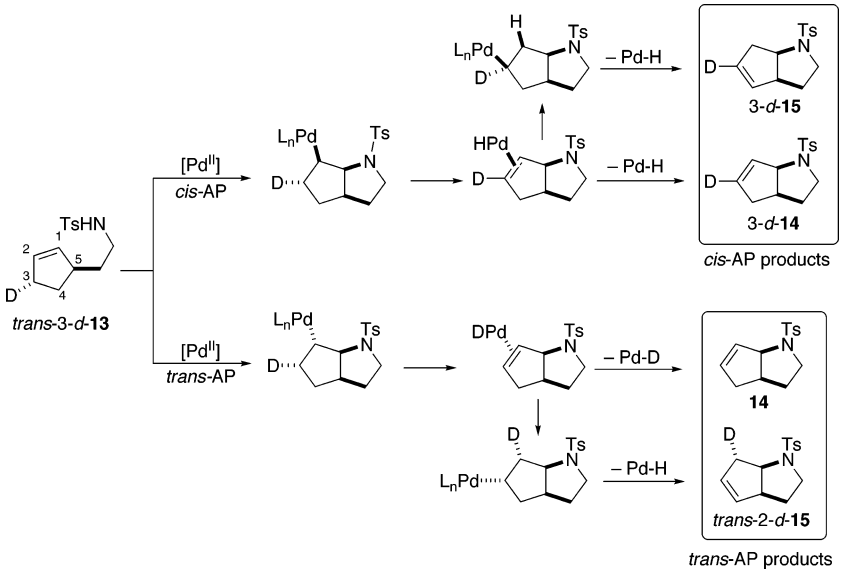
(23) For a detailed experimental description and compound-characterization data, see the Supporting Information.

(24) The low yield obtained with the Pd/(−)-sparteine catalyst might reflect the fact that chelating ligands tend to inhibit Pd-catalyzed oxidative heterocyclization. In addition, this result could arise from selective oxidation of a single enantiomer of *trans*-3-*d*-**13** (i.e., kinetic resolution of this substrate). Analysis of the product mixture by chiral SFC (Chiralcel OD-H), however, reveals that kinetic resolution of the substrate can only partly account for the low yield: the reaction of **13** catalyzed by the Pd/(−)-sparteine catalyst system produces **14** in 27% yield/44% ee and **15** in 17% yield/71% ee. We were unable to resolve the recovered starting material (56%) by chiral SFC.

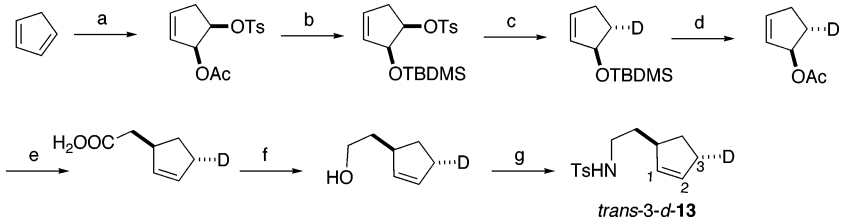
(25) A reviewer correctly noted that the stereochemical course of the reaction could be influenced by the presence of a deuterium kinetic isotope effect on the β-hydride elimination step. In order to address this possibility, we also prepared the diastereomeric substrate, *cis*-3-*d*-**13**. Oxidation cyclization of this substrate with the $Pd(OAc)_2$/DMSO and $Pd(OAc)_2$/py catalyst systems confirms that the reaction proceeds via *cis*-aminopalladation. For full details, see the Supporting Information.

(26) Formation of a π-allyl-Pd^{II} species via C−*H* activation from the 3-position of *trans*-3-*d*-**13** is expected to be unproductive because formation of the *cis*-fused bicyclic product would require *cis*-reductive elimination of the C−N bond. It has been shown that attack of "soft" nucleophiles such as sulfonamide on π-allyl-Pd species generally occurs via external (i.e., *trans*) attack on the π-allyl fragment: Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395−422.

Scheme 4. Possible Outcomes for Pd-Catalyzed Oxidative Cyclization of *trans*-3-*d*-**13**

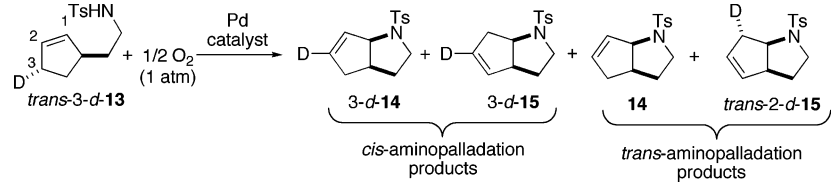


Scheme 5. Synthesis of the Deuterium-Labeled Substrate *trans*-3-*d*-**13**[a]



[a] Reaction conditions: (a) (i) $Pb(OAc)_4$, $HOAc/H_2O$, (ii) *p*-$MeC_6H_4SO_2Cl$, Et_3N, Me_3NHCl, CH_2Cl_2 (39%, two steps); (b) (i) K_2CO_3, MeOH, (ii) *t*-$BuMe_2SiCl$, imidazole (85%, two steps); (c) $LiBEt_3D$, THF (88%); (d) (i) TBAF, THF, (ii) Ac_2O, pyridine (70%, two steps); (e) LDA, *t*-$BuMe_2SiCl$, THF (73%); (f) $LiAlH_4$, Et_2O (91%); (g) (i) $MeSO_2Cl$, Et_3N, CH_2Cl_2, (ii) K_2CO_3, *p*-$MeC_6H_4SO_2NH_2$, DMF (81%, two steps).

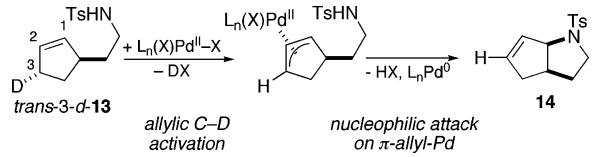
Table 4. Sterochemical Outcome for the Oxidative Cyclization of the Deuterium-Labeled Substrate *trans*-3-*d*-**13**[a]



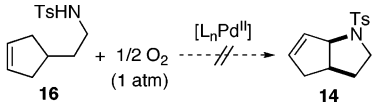
				product ratio[b]	
entry	Pd catalysts	time (h)	yield[b] (%)	*cis*-AP 3-*d*-**14**/3-*d*-**15**	*trans*-AP **14**/*trans*-2-*d*-**15**
1	$Pd(OAc)_2$/DMSO (**A**)	15	70	100:0	
2	$Pd(OAc)_2$/py (**B**)	15	84	98:2	
3	$Pd(O_2CCF_3)_2$/py (**C**)	15	85	88:12	
4	$Pd(IMes)(O_2CCF_3)_2$/BzOH (**D**)	72	60	43:8	37:12
5	$Pd(O_2CCF_3)_2$/sp (**E**)[c]	72	37[d]	59:41	

[a] All reactions performed at 80 °C; 5 mol % Pd; 0.1 mmol scale. [b]Determined by ^1H NMR spectroscopy (internal standard = 1,3,5-trimethoxybenzene). [c]10 mol % Pd. [d]45% starting material recovered.

Scheme 6. Possible π-Allyl-Pd Mechanism for the Oxidative Cyclization of *trans*-3-*d*-**13**



to occur followed by an unusual *cis*-reductive elimination of the C−N bond.[26] The isomeric product 3-*d*-**15** is not readily explained by a π-allyl mechanism. Finally, if the reaction proceeds via a π-allyl mechanism, the isomeric substrate **16** should convert readily to **14** under the oxidative cyclization conditions (eq 7). Attempts to use **16** as a substrate, however, resulted in nearly quantitative recovery of the starting material.



(7)

The oxidative cyclization of *trans*-3-*d*-**13** was also investigated with the $PdCl_2$/benzoquinone catalyst system originally reported by Hegedus and co-workers.[7c] Although multiple isomeric products were obtained, the major products, 3-*d*-**14**

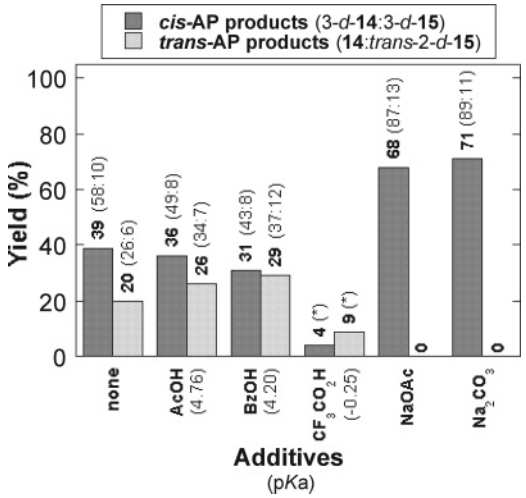
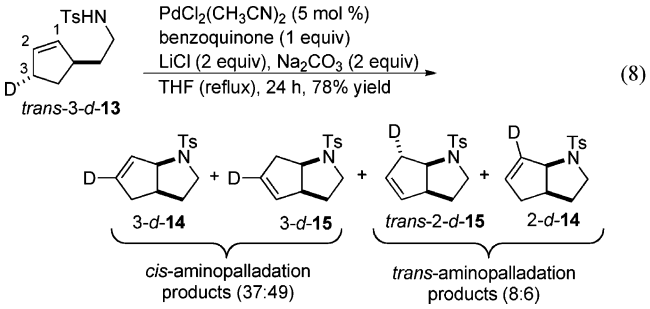


Figure 1. Effect of additives on the aminopalladation stereochemistry in the oxidative cyclization of *trans*-3-*d*-**13** catalyzed by 5 mol % (IMes)Pd(O$_2$CCF$_3$)$_2$(OH$_2$) (* - not determined). Reaction conditions: *trans*-3-*d*-**13** (0.05 mmol), Pd catalyst (2.5 μmol), additive (AcOH and BzOH, 20 mol %; CF_3CO_2H, 1 equiv; Na_2CO_3, 2 equiv), O_2 (1 atm), toluene (0.5 mL), 80 °C, 72 h.

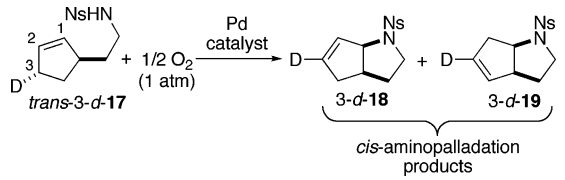
and 3-*d*-**15**, were those resulting from *cis*-aminopalladation of the alkene.[27] We also detected a small amount (10%) of isomerized starting material after the reaction was complete. The precise origin of minor product 2-*d*-**14** is not known; however, this species probably arose from isomerization of *trans*-2-*d*-**15**.



(8)

Stereochemical Modulation of the Aminopalladation Pathway: Additive Effects. The results in Table 4 reveal that aminopalladation of *trans*-3-*d*-**13** proceeds with high stereoselectivity with four of the five catalyst systems; only the catalyst bearing an *N*-heterocyclic carbene (NHC) ligand, (IMes)Pd(O$_2$CCF$_3$)$_2$(OH$_2$), yields products arising from both *cis*- and *trans*-aminopalladation. The origin of the latter divergent result was not immediately apparent; however, upon further analysis of the reaction conditions for the five different catalyst systems, we recognized that the NHC-coordinated catalyst is the only one that operates under acidic conditions (in the presence of BzOH). The other four catalyst systems possess exogenous Brønsted base (**A**, **C**, and **E**) or employ a basic anionic ligand coordinated to Pd (acetate; **B**).[28] In our original investigation

Table 5. Sterochemical Outcome for the Oxidative Cyclization of the Deuterium-Labeled Substrate *trans*-3-*d*-**17**[a]



entry	Pd catalysts	time (h)	yield (%)[b]	product ratio[b] 3-*d*-**18**/3-*d*-**19**
1	Pd(OAc)$_2$/DMSO (**A**)	24	74	100:0
2	Pd(OAc)$_2$/py (**B**)	24	91	100:0
3	Pd(O$_2$CCF$_3$)$_2$/py (**C**)	24	86	90:10
4	Pd(IMes)(O$_2$CCF$_3$)$_2$/BzOH (**D**)	32	78	82:18

[a] All reactions performed at 80 °C; 5 mol % Pd; 33 μmol scale. [b]NMR yield, the product ratio was determined by NMR.

NHC−Pd catalysts for intramolecular oxidative amination reactions, the highest product yields were observed with BzOH as an additive. Nevertheless, we decided to reinvestigate the oxidative cyclization of *trans*-3-*d*-**13** with the NHC−Pd catalyst under various conditions: in the presence of base (NaOAc, Na_2CO_3), with Brønsted acids of differing pK_a values, and in the absence of additives. As shown in Figure 1, products arising from both *cis*- and *trans*-aminopalladation are obtained both in the absence of additives and in the presence of exogenous acid. The relative ratio of *cis*/*trans* aminopalladation decreases with increasing acid strength, ranging from approximately 2:1 in the absence of additives to 1:2 in the presence of trifluoroacetic acid. The overall yield is similar (approximately 60%) in the absence of additives and in the presence of acetic and benzoic acids. A considerably lower yield (13%) is obtained when the reaction is performed with trifluoroacetic acid. In the presence of added base (NaOAc, Na_2CO_3), only products derived from a *cis*-aminopalladation pathway are observed, and the overall yield is slightly higher than that in the presence of acid.

Stereochemical Modulation of the Aminopalladation Pathway: Substrate Effects. The influence of acid and base additives on the stereochemistry of the aminopalladation step raised the possibility that variation of the substrate pK_a could also influence the stereochemical course of the reaction. We, therefore, investigated the oxidative cyclization of *trans*-3-*d*-**17**, which possesses a *p*-nitrobenzenesulfonyl group (Ns) on the nitrogen atom, and *trans*-3-*d*-**20**, which features a tosyl-substituted carboxamide nucleophile. Both of these substrates are more acidic than the parent tosylamide substrate *trans*-3-*d*-**13**. Representative pK_a values for these groups in DMSO are 15.1 ($TsNH_2$),[29] 13.9 ($NsNH_2$),[29] and approximately 9 (RCONHTs).[30]

The reaction of *trans*-3-*d*-**17** yields heterocyclic product(s) that arise exclusively from *cis*-aminopalladation of the alkene (Table 5), even with the *N*-heterocyclic-carbene-coordinated catalyst in the presence of BzOH (entry 4). In all cases, the yields were slightly higher than those observed with the tosylamide substrate *trans*-3-*d*-**13**.

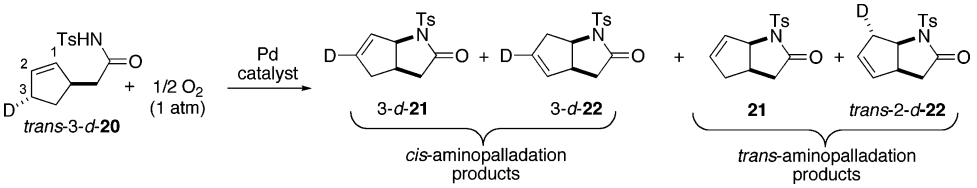
(27) In a recent study of Pd^{II}-catalyzed oxidative cyclization of *o*-allylphenols, Hayashi et al. observed primarily *trans*-oxypalladation of the alkene under the same conditions (see ref 19 for details).

(28) In our mechanistic studies of Pd(OAc)$_2$/py-catalyzed aerobic alcohol oxidation, we obtained NMR spectroscopic evidence that an acetate ligand serves as an internal base to promote formation of a Pd^{II}-alkoxide species: Steinhoff, B. A.; Guzei, I. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2004**, *126*, 11268−11278.

(29) Ludwig, M.; Pytela, O.; Vecera, M. *Collect. Czech. Chem. Commun.* **1984**, *49*, 2593−2601.

(30) The pK_a value of this substrate was not found; however, the pK_a of TsN(H)CO$_2$^{t}Bu is 8.5. See: Koppel, I.; Koppel, J.; Degerbeck, F.; Grehn, L.; Ragnarsson, U. *J. Org. Chem.* **1991**, *56*, 7172−7174.

Table 6. Sterochemical Outcome for the Oxidative Cyclization of the Deuterium-Labeled Substrate *trans*-3-*d*-**20**[a]



				product ratio[b]	
entry	Pd catalysts	time (h)	yield[b] (%)	*cis*-AP 3-*d*-**21**/3-*d*-**22**	*trans*-AP **21**/*trans*-2-*d*-**22**
1	$Pd(OAc)_2$/DMSO (**A**)	24	73		100:0
2	$Pd(OAc)_2$/py (**B**)	24	47	85:4	4:7
3	$Pd(O_2CCF_3)_2$/py (**C**)	24	83	78:6	14:2
4	$Pd(IMes)(O_2CCF_3)_2$/BzOH (**D**)	32	74	41:13	22:24
5	$Pd(IMes)(O_2CCF_3)_2/Na_2CO_3$ (**F**)	32	34	65:2	32:1

[a] All reactions performed at 80 °C; 5 mol % Pd; 33 μmol scale. [b]NMR yield, the product ratio was determined by NMR.

The results of the oxidative cyclization of *trans*-3-*d*-**20** are more complex. Use of the $Pd(OAc)_2$/DMSO catalyst system results in exclusive formation of the *trans*-aminopalladation product **21** (Table 6). With each of the other catalyst systems, including the NHC-coordinated catalyst with both acid and base additives, the oxidative cyclization of *trans*-3-*d*-**20** yields products arising from both *cis*- and *trans*-aminopalladation.

Analysis and Implications. In this study, we have probed the Wacker-type oxidative cyclization of sulfonamide-substituted aminoalkenes with several different Pd catalysts. The results reveal that these reactions generally favor *cis*- rather than *trans*-aminopalladation. This outcome is noteworthy because it contradicts widespread assumptions concerning the stereochemical course of such reactions. In recent studies, for example, the term "Wacker-type reaction" has been used as a mechanistic synonym for *trans*-heteropalladation of an alkene,[17b,d,31] or *trans*-heteropalladation of the alkene was simply assumed.[32] Such prevailing assumptions probably reflect the impact of elegant early studies by Stille, Bäckvall, Åckermark, Hegedus, and others who reported definitive examples of *trans*-heteropalladation of alkenes through isotopic labeling experiments and fundamental reactivity studies of Pd−alkene complexes.[33] These results were countered by Henry, however, who argued that data for the Wacker process itself were most consistent with *cis*-hydroxypalladation of ethylene.[34,35]

Recent studies by several laboratories, including our own, have provided increasing support for the viability of *cis*-heteropalladation of alkenes, including both oxy-[13c,19,21g,31] and aminopalladation.[16,17] The present study provides the first systematic analysis of intramolecular Wacker-type oxidative amination. Although *cis*-aminopalladation of the alkene is generally favored in these reactions, *trans*-aminopalladation is also possible and can predomimate, depending on the identity of the substrate, the catalyst, and/or the reaction conditions.[36] The energy barriers associated with *cis*- and *trans*-aminopalladation appear to be especially finely balanced with the NHC−Pd catalyst system (Figure 1). Products are observed from both *cis*- and *trans*-aminopalladation in the absence of additives and in the presence of acid (AcOH, BzOH, and TFA) (Figure 1); the selectivity shifts toward *trans*-aminopalladation with increasing acid strength. In contrast, use of stoichiometric base in the reaction (NaOAc or Na_2CO_3) leads to exclusive *cis*-aminopalladation of the alkene.

The precise origin of the preference for *cis*- or *trans*-aminopalladation is not known; however, the following mechanistic considerations provide the basis of ongoing investigations. *Trans*-aminopalladation presumably arises from a mechanism resembling classical electrophile-promoted addition of nucleophiles to alkenes (top pathway, Scheme 7; cf. eq 1): coordination of the alkene to the electrophilic Pd^{II} center, nucleophilic attack by the sufonamide nucleophile, and deprotonation of the zwitterionic intermediate **24**. *Cis*-aminopalladation probably arises from formation of a Pd^{II}-sulfonamidate intermediate followed by alkene insertion into the Pd−N bond (bottom pathway, Scheme 7).[18,37] Formation of the Pd-amidate species **25** liberates 1 equiv of HX and, therefore, should be

(31) (a) Wolfe, J. P.; Rossi, M. A. *J. Am. Chem. Soc.* **2004**, *126*, 1620−1621. (b) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 762−763.

(32) For example, see ref 4b and (a) Lei, A.; Lu, X.; Liu, G. *Tetrahedron Lett.* **2004**, *45*, 1785−1788. (b) Streuff, J.; Hövelmann, C. H.; Nieger, M.; Muñiz, K. *J. Am. Chem. Soc.* **2005**, *127*, 14586−14587.

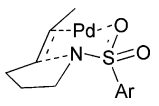
(33) For leading references, see ref 15 and (a) Stille, J. K.; James, D. E. *J. Organomet. Chem.* **1976**, *108*, 401−408. (b) James, D. E.; Hines, L. F.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 1806−1809. (c) Bäckvall, J. E.; Åkermark, B.; Ljunggren, S. O. *J. Chem. Soc., Chem. Commun.* **1977**, 264−265. (d) Stille, J. K.; Divakaruni. R. *J. Am. Chem. Soc.* **1978**, *100*, 1303−1304. (e) Bäckvall, J. E.; Åkermark, B.; Ljunggren, S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411−2416. (f) Stille, J. K.; Divakaruni, R. *J. Organomet. Chem.* **1979**, *169*, 239−248. (g) Kurosawa, H.; Majima, T.; Asada, N. *J. Am. Chem. Soc.* **1980**, *102*, 6996−7003. (h) Andell, O. S.; Bäckvall, J. E. *J. Organomet. Chem.* **1983**, *244*, 401−407. (i) Bäckvall, J. E.; Heumann, A. *J. Am. Chem. Soc.* **1986**, *108*, 7107−7108. (j) Åkermark, B.; Söderberg, B. C.; Hall, S. S. *Organometallics* **1987**, *6*, 2608−2610.

(34) For extensive analysis of the mechanistic pathway of the parent Wacker process, see: Henry, P. M. *Palladium Catalyzed Oxidation of Hydrocarbons*; D. Reidel Publishing Co.: Boston, 1980.

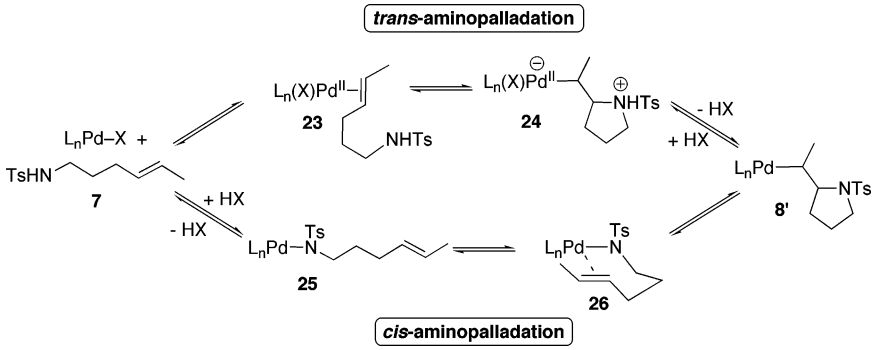
(35) (a) Henry, P. M. *J. Am. Chem. Soc.* **1966**, *88*, 1595−1597. (b) Gragor, N.; Henry, P. M.; *J. Am. Chem. Soc.* **1981**, *103*, 681−682. (c) Wan, W. K.; Zaw, K. Henry, P. M. *J. Mol. Catal.* **1982**, *16*, 81−87. (d) Wan, W. K.; Zaw, K.; Henry, P. M. *Organometallics* **1988**, *7*, 1677−1683. (e) Zaw, K.; Henry, P. M. *J. Org. Chem.* **1990**, *55*, 1842−1847. (f) Hamed, O.; Thompson, C.; Henry, P. M. *J. Org. Chem.* **1997**, *62*, 7082−7083. (g) Hamed, O.; Henry, P. M. *Organometallics* **1997**, *16*, 4903−4909.

(36) The apparent discrepancy between our observations (which favor *cis*-aminopalladation reactions) and the early studies of Pd-mediated alkene amination (which favor *trans*-aminopalladation reactions; ref 15) undoubtedly reflects differences between the substrates (sulfonamides vs alkylamines) and/or reaction conditions (catalytic vs precomplexation of the alkene at low temperature followed by addition of stoichiometric amine nucleophile).

(37) Another mechanism that could account for *cis*-aminopalladation of an alkene involves a six-membered electrocyclic transition state (see below). See ref 16a.



Scheme 7. Primary Steps Associated with Intramolecular *Trans*- and *Cis*-Aminopalladation of Alkenes



favored in the presence of a Brønsted base (and disfavored by the presence of acid). The *trans*-aminopalladation also requires the loss of HX (i.e., **24** → **8′**); however, this step occurs after the C−N bond has formed, and the zwitterionic intermediate **24** should be much more acidic than the free sulfonamide. Thus, strong exogenous base is probably not needed to form **8′**.

Several other observations can be rationalized by these mechanisms. Increasing the acidity of the sulfonamide nucleophile by using the Ns rather than the Ts derivative (**17** and **13**, respectively) leads to exclusive *cis*-aminopalladation by the NHC−Pd catalyst, even in the presence of benzoic acid (Table 5, entry 4). This result possibly arises from more facile formation of the Pd−N(Ns)R species analogous to **25** in Scheme 7.

The stereoselectivity for cyclization of the tosyl-substituted carboxamide substrate **20** is less readily understood. With this substrate, we observe mostly (but not exclusively) *cis*-aminopalladation of the alkene with catalyst systems operating in toluene (**B**, **C**, **D**, and **F**). The anion arising from deprotonation of the carbonyl/sulfonyl imide in **20** is more stable than a sulfonamidate anion and, thus, might undergo more facile ionization of the Pd−N bond, resulting in the formation of some *trans*-aminopalladation product. Exclusive *trans*-aminopalladation of the alkene is observed with the $Pd(OAc)_2$/DMSO catalyst system (**A**). In DMSO, acetate is a sufficiently strong base to deprotonate the imide of **20** in solution,[38] without requiring stabilization of the nitrogen anion by coordination to the metal center. Good solvation of the imide anion by the polar solvent DMSO could account for preferential alkene activation by Pd^{II}, which leads to *trans*-aminopalladation. Further work will be needed to test these hypotheses.

The results of this study have important implications for the development of enantioselective Pd-catalyzed oxidative cyclizaton reactions. The highest levels of enantioselectivity undoubtedly will be observed when only a single aminopalladation pathway is operating, and knowledge of the mechanism for the stereochemistry-determining aminopalladation step will play an important role in guiding rational catalyst design efforts.

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Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(38) The pK_a of acetic acid in DMSO is 12.3: Maran, F.; Celadon, D.; Severin, M. G.; Vianello, E. *J. Am. Chem. Soc.* **1991**, *113*, 9320−9329.