

## Scope and Mechanism of Allylic C–H Amination of Terminal Alkenes by the Palladium/PhI(OPiv)<sub>2</sub> Catalyst System: Insights into the Effect of Naphthoquinone

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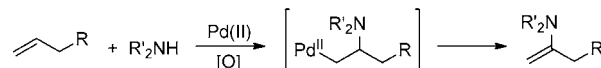
**Abstract:** Palladium-catalyzed oxidative amination of unactivated alkyl olefins has been developed to produce linear (*E*)-allylimides with high regioselectivity. This highly efficient transformation of alkenes has been achieved by enhancing the reoxidation of palladium with the strong oxidant PhI(OPiv)<sub>2</sub>. The present work also provides the first systematic analysis of the mechanism of the allylic C–H oxidative amination. It has been found that naphthoquinone (NQ) plays a vital role in promoting olefin coordination to the palladium catalyst: in the absence of NQ, the turnover-limiting step is olefin coordination to palladium catalyst; in the presence of NQ, the reaction involves a rapid equilibration to give a nitrogen-coordinated olefin-Pd(NQ) complex that undergoes turnover-limiting allylic C–H bond activation to generate a  $\pi$ -allyl-Pd intermediate. This work provides valuable insights for further studies on the functionalization of unactivated olefins.

### Introduction

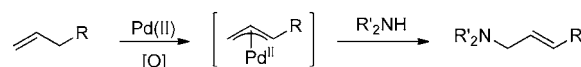
The ubiquity of nitrogen atoms in natural and synthetic products sparks interest in developing new methods for the preparation of nitrogen-containing molecules.<sup>1</sup> Among the strategies of C–N bond formation, the metal-catalyzed cross-coupling reaction represents one of the most powerful methods.<sup>2,3</sup> For instance, the palladium-catalyzed coupling of aryl halides with various amines, pioneered by both the Buchwald and Hartwig laboratories, have been extensively studied and broadly used to synthesize pharmaceutical compounds.<sup>4</sup> In contrast, oxidative-coupling reactions, particularly methods that enable direct amination of C–H bonds, have been the focus of recent interest.<sup>5–8</sup> For example, Rh-catalyzed C–H amination through highly reactive metallo-nitreneoids,<sup>5</sup> Pd- or Cu-mediated C–H oxidative amination assisted by directing groups,<sup>6</sup> and Pd-catalyzed allylic C–H oxidative amination<sup>7,8</sup> have been reported. Examples for the latter case are particularly scarce (Scheme 1b). More commonly, palladium-catalyzed amination of alkenes

### Scheme 1. Palladium-Catalyzed Oxidative Amination

a) oxidative amination of alkenes via aminopalladation



b) oxidative allyl amination of alkenes via C–H bond activation



proceeds through an aminopalladation pathway, rather than allylic C–H bond activation.<sup>3,9,10</sup> For instance, Stahl and co-workers have reported a few examples of palladium-catalyzed aerobic intermolecular oxidative amination of olefins to afford imine or enamine products (Scheme 1a).<sup>9</sup>

Because of the value of allylic amines in organic synthesis, methods to affect allylic amination of olefins have attracted

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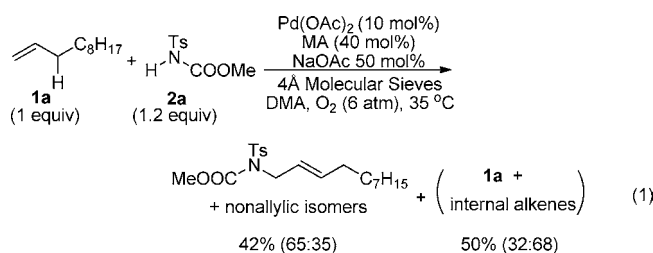
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substantial interest.<sup>11</sup> Very recently, several successful palladium-catalyzed intra- and intermolecular oxidative allylic C–H aminations of unactivated alkenes have been reported.<sup>8</sup> White and co-workers reported that the allylic C–H amination of terminal alkenes can be achieved using a Pd(II)-sulfoxide catalytic system: a catalytic amount of a Lewis acid [e.g., (salen)Cr<sup>III</sup>], or a Brønsted base was required to carry out the reaction, and a stoichiometric amount of benzoquinone (BQ) was used as the oxidant.<sup>8a,b</sup> Although the reactions produce oxidative amination products with high regioselectivity, the prolonged reaction time (72 h) and high catalyst loading (10 mol %) limit the utility of this transformation in organic synthesis. Meanwhile, palladium-catalyzed aerobic oxidative allylic amination of olefins was reported by our laboratory, and these reactions also afford linear allylamine derivatives with highly regioselectivity.<sup>8c</sup> However, for their broader applications in organic transformations, we need to

address the following limitations: (1) an excess of the alkene (3 equiv relative to the nitrogen nucleophile) and high catalyst loading (10–20 mol %) are required in order to have good yields; (2) dioxygen pressure (6 atm) is needed to achieve higher catalytic turnover; (3) a significant degree of double bond isomerization exists in the products (up to 40%). Herein, we describe a novel and highly efficient synthetic route to allylamine derivatives via highly selective palladium-catalyzed intermolecular oxidative allylic C–H amination. This new procedure, using PhI(OPiv)<sub>2</sub> as the oxidant along with a substoichiometric amount of naphthoquinone (NQ), provides major improvements: the olefin can be used as the limiting reagent, low catalyst loading (1–5 mol %) can be employed, and reaction times (5–8 h) are shortened. Furthermore, the detailed mechanistic studies reported here show that NQ plays a very important role in promoting olefin coordination to palladium catalyst resulting in turnover-limiting allylic C–H bond activation to give a  $\pi$ -allyl-Pd intermediate.

## Results and Discussion

One observation from our previous studies suggests that the limitation of using excess alkene substrates is due to the isomerization of terminal alkenes to internal alkenes, which are ineffective substrates for amination (eq 1).<sup>8c,12</sup> To achieve

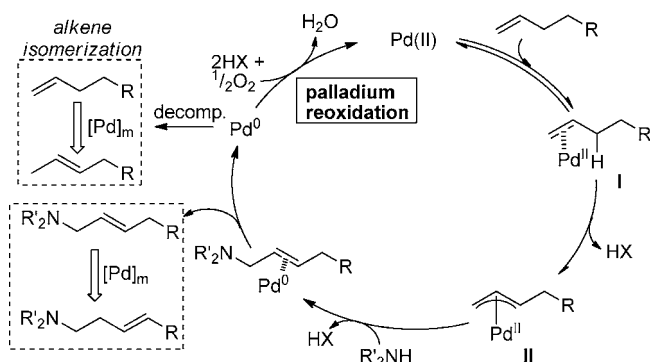
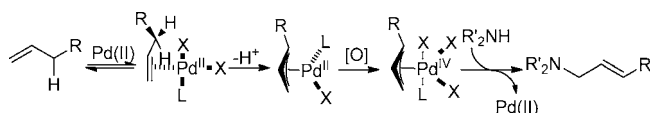


more efficient transformations of alkenes, alkene isomerization must be minimized. Mechanistically, the isomerization of terminal alkenes is possibly catalyzed by palladium black or Pd nanoparticles, generated from the catalyst decomposition due to the rate-limiting mass-transfer of oxygen gas into solution.<sup>13,14</sup> We hypothesized that, if soluble strong oxidants were used instead of oxygen, the reoxidation of Pd(0) might be more efficient (Scheme 2). In addition, the strong oxidants might oxidize the  $\pi$ -allyl-Pd(II) species directly to an allyl-Pd(IV) intermediate which could undergo reductive elimination to regenerate Pd(II) (Scheme 3).<sup>15</sup> Thus, the minimization or elimination of palladium catalyst decomposition might be expected, which could reduce or inhibit the alkene isomerization and result a more efficient allylic C–H oxidative amination.

Guided by this strategy, we initiated our studies by testing the reactions of 1-undecene **1a** with methyl *N*-tosylcarbamate **2a** catalyzed by Pd(OAc)<sub>2</sub> (5 mol %), in the presence of a

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- (12) There are a lot of palladium black observed in the reaction eq 1.
- (13) The catalyst decomposition is possibly resulted by rate-limiting mass-transfer of oxygen gas into solution, for detail see: Steinhoff, B. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 4348–4355, and references therein.
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**Scheme 2.** Possible Mechanism for the Oxidative Amination of Alkenes and Alkene Isomerization**Scheme 3.** Proposed Mechanistic Hypothesis for Allylic Oxidative Amination

stoichiometric amount of base<sup>16</sup> and various oxidants (Table 1). Although most of the oxidants examined (including *t*-butyl peroxide, hydrogen peroxide, *t*-butyl peracetate, K<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, and PhIO) produced significant quantities of linear (*E*)-allylic amination product **3a** with high regioselectivity (Table 1, entries 1–8), PhI(OPiv)<sub>2</sub> performed the best to afford **3a** in about 70% yield, including around 10% nonallylic isomers (entry 8). Furthermore, in the case of PhI(OPiv)<sub>2</sub>, we were delighted to discover that isomerization of **1a** was not detected. This observation prompted us to optimize the reaction conditions. We tested some electron-deficient alkenes, such as maleic anhydride (MA), BQ, and NQ as additives in this reaction: NQ (20 mol %) was found to give the best result (83% yield, entries 9–11). In addition, the amount of isomers of product **3a** were reduced to 7%. The isomers of product **3a** were further reduced by increasing the amount of Bu<sub>4</sub>NOAc; however, the reaction yield also decreased (entries 10 and 12–13). Control experiments indicated that both BQ and NQ<sup>17</sup> alone are not good oxidants for this transformation. In addition, no catalytic turnover was observed when NQ was used as the oxidant (entries 15–16).

With optimized reaction conditions, attention was turned to the scope of this Pd-catalyzed allylic C–H oxidative amination process. We first examined the reactivity of different nitrogen nucleophiles. Some *O*-alkyl *N*-sulfonylcarbamates, such as **2a–2d**, underwent effective oxidative amination with **1a** to afford corresponding products **3a–3d** with excellent yields and with only a small amount of nonallylic isomers (Table 2, entries

**Table 1.** Screen Result of Oxidative Allylic Amination with Various Oxidants<sup>a</sup>

entry	oxidant	additive	yield <sup>b</sup>
1	( <sup>t</sup> BuO) <sub>2</sub>		39% (57:43)
2	H <sub>2</sub> O <sub>2</sub> ·urea		20% (66:34)
3	<sup>t</sup> BuOOAc		43% (64:36)
4	K <sub>2</sub> S <sub>2</sub> O <sub>8</sub>		58% (65:35)
5	(PhCOO) <sub>2</sub>		70% (87:13)
6	PhIO		47% (84:16)
7	PhI(OAc) <sub>2</sub>		60% (90:10)
8	PhI(OPiv) <sub>2</sub>		68% (91:9)
9	PhI(OPiv) <sub>2</sub>	MA (20 mol %)	41% (90:10)
10	PhI(OPiv) <sub>2</sub>	NQ (20 mol %)	83% (93:7)
11	PhI(OPiv) <sub>2</sub>	BQ (20 mol %)	72% (91:9)
12 <sup>c</sup>	PhI(OPiv) <sub>2</sub>	NQ (20 mol %)	63% (95:5)
13 <sup>d</sup>	PhI(OPiv) <sub>2</sub>	NQ (20 mol %)	36% (99:1)
14 <sup>e</sup>	PhI(OPiv) <sub>2</sub>	NQ (20 mol %)	76% (90:10)
15 <sup>f</sup>	BQ		31% (71:29)
16 <sup>f</sup>	NQ		5% (nd)

<sup>a</sup> Reaction condition: **1a** (0.2 mmol), **2a** (0.4 mmol), oxidant (0.3 mmol), and Bu<sub>4</sub>NOAc (0.2 mmol) in NMP (0.25 mL) at 40 °C for 8 h.

<sup>b</sup> Isolated yield, the data in parentheses is the ratio of allylimide and nonallylic isomers, which determined by <sup>1</sup>H NMR. <sup>c</sup> Bu<sub>4</sub>NOAc (2 equiv).

<sup>d</sup> Bu<sub>4</sub>NOAc (3 equiv). <sup>e</sup> [Pd(OAc)(Allyl)]<sub>2</sub> (2.5 mol %). <sup>f</sup> Oxidant (2 equiv). MA = maleic anhydride, NQ = 1,4-naphthoquinone, BQ = benzoquinone.

1–4). Next, we examined a range of terminal alkenes bearing different functional groups, with various electronic and steric properties. In the case of alkene **1b** with a longer alkyl chain, the reaction afforded product **4** with results similar to **1a** (entry 5). When the alkene substrates **1c–1j**, bearing an imide, ester, ether, or carbonate group, were employed under similar reaction conditions, linear allylic amination products were formed with high selectivity and excellent yields (entries 6–15). Importantly, no isomers were detected in those reactions run in the presence of 20 mol % of base. The substrate **1k** bearing a bulky group, which was not a viable substrate with our previous catalytic system, afforded the corresponding products **13** in a moderate yield (entry 16). A number of allylarenes **1l–1p**, bearing electron-withdrawing and electron-donating groups, were demonstrated to be the most effective substrates under the standard reaction conditions (entries 17–24). In comparison, the substrates **1o** and **1p** with electron-withdrawing groups afforded a slightly lower yield than substrates **1m** and **1n** with electron-donating groups (entries 18, 21–23). It is very important that the reaction of **1m** underwent smooth oxidative amination in good yields with only 1–2 mol % catalyst loading (entries 19–20). For the enyne substrate **1q**, the reaction generated the conjugated enyne imide product **20** in 63% yield with a *Z:E* ratio of 30:70 (entry 25). Furthermore, this catalytic system is compatible with the substrates having Br and I: the reactions of **1h**, **1j**, and **1p** generated allylimides in good yields without halogen loss (entries 11, 15, and 23). Overall, compared to the aerobic oxidative conditions (olefin 3 equiv, Pd catalyst 10 mol %, see last column of Table 2),<sup>8c</sup> the newly discovered Pd(OAc)<sub>2</sub>/PhI(OPiv)<sub>2</sub> catalytic system provides a significant improvement in product yield and chemoselectivity (quite low-level of isomerization) and allows use of the olefin as the limiting reagent and is compatible with low catalyst loading (1–5 mol %).

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(16) In our previous studies,<sup>8c</sup> although the reaction afforded the allylic C–H amination product with very low yield (< 10%), the alkenes isomerization was inhibited when a stoichiometric amount of base (NaOAc) was used.

(17) 1,4-Naphthoquinone has been used as oxidant in palladium-catalyzed alcohol oxidation, see: Lloyd, W. G. *J. Org. Chem.* **1967**, *32*, 2816–2819.

**Table 2.** Pd-Mediated Oxidative Allylic C–H Amination<sup>a</sup>

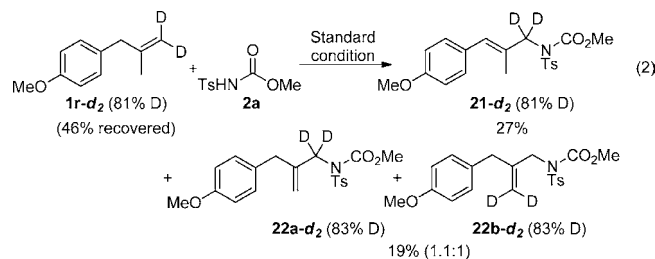
Entry	1	2	Products	Isolated Yield <sup>b</sup>		
				PhI(OPiv) <sub>2</sub>	O <sub>2</sub> (ref 8c) <sup>h</sup>	
1 <sup>c</sup>		<b>2a</b>		<b>3a</b> R' = Me Z = Ts	83% (91:9)	87% (70:30)
2 <sup>c</sup>		<b>2b</b>		<b>3b</b> R' = <sup>t</sup> Bu Z = Ts	88% (94:6)	69% (76:24)
3 <sup>c</sup>		<b>2c</b>		<b>3c</b> R' = Bn Z = Ts	77% (94:6)	63% (66:34)
4 <sup>c</sup>		<b>2d</b>		<b>3d</b> R' = <sup>t</sup> Bu Z = Ms	65% (88:12)	
5 <sup>c</sup>		<b>2a</b>		<b>4</b>	81% (90:10)	74% (57:43)
6		<b>2a</b>		<b>5</b> R = NPhth	79%	81% (91:9)
7		<b>2a</b>		<b>6</b> R = OCOOMe	82%	
8		<b>2a</b>		<b>7</b> R = OBz	95%	78% (92:8)
9		<b>2a</b>		<b>8</b>	81%	
10		<b>2a</b>		<b>9</b> Ar = Ph	80%	
11		<b>2a</b>		<b>10</b> Ar = <i>o</i> -BrBn	81%	
12		<b>2a</b>		<b>11a</b> R' = Me	94%	62%
13		<b>2b</b>		<b>11b</b> R' = <sup>t</sup> Bu	95%	65%
14		<b>2c</b>		<b>11c</b> R' = Bn	93%	
15		<b>2a</b>		<b>12</b>	86%	
16		<b>2a</b>		<b>13</b>	60%	12%
17		<b>2a</b>		<b>14</b> R = H	90%	70%
18		<b>2a</b>		<b>15</b> R = <i>p</i> -OMe	91%	71%
19 <sup>d</sup>		<b>2a</b>		<b>16</b> R = <i>o</i> -OMe	85%	
20 <sup>e</sup>		<b>2a</b>		<b>17</b> R = <i>p</i> -COOEt	76%	
21		<b>2a</b>		<b>18</b> R = <i>o</i> -Br	91%	75%
22		<b>2a</b>		<b>19</b>	84%	
23		<b>2d</b>		<b>20</b>	83%	
24		<b>2d</b>		<b>20</b>	82%	
25 <sup>f</sup>		<b>2a</b>		<b>20</b>	63% (30:70) <sup>g</sup>	

<sup>a</sup> The reaction was conducted on a 0.2 mmol scale in 0.25 mL of NMP; NQ = 1,4-naphthoquinone. <sup>b</sup> Isolated yield, the data in parentheses is the ratio of allylimide and the nonallylimide isomers which was determined by <sup>1</sup>HNMR. <sup>c</sup> Bu<sub>4</sub>NOAc (1 equiv). <sup>d</sup> Pd(OAc)<sub>2</sub> (2 mol %). <sup>e</sup> Pd(OAc)<sub>2</sub> (1 mol %). <sup>f</sup> Pd(OAc)<sub>2</sub> (10 mol %). <sup>g</sup> *Z*:*E* ratio of **20**. <sup>h</sup> The reaction condition of ref 8c: alkene **1** (3 equiv), imide **2** (1 equiv), and Pd catalyst (10 mol %).

**General Mechanistic Considerations.** Although the palladium-catalyzed allylic C–H oxidative functionalization of alkenes, such as acetoxylation, amination, and alkylation, have been studied, systematic mechanistic investigations are quite rare. We would like to understand the mechanism of the efficient palladium-catalyzed allylic C–H oxidative amination of alkenes described above to provide a rational basis for the further development of alkene functionalizations.

The products of these reactions are consistent with a mechanism involving a  $\pi$ -allylpalladium complex generated from allylic C–H activation. However, an alternative pathway involving *anti*-Markovnikov aminopalladation/ $\beta$ -hydride elimination cannot be excluded.<sup>18</sup> In order to differentiate between these two mechanistic scenarios, a deuterium labeled substrate **1r-d<sub>2</sub>** was treated under the standard reaction conditions. The aminopalladation/ $\beta$ -hydride elimination mechanism predicts formation of **22a-d<sub>2</sub>** but not **22b-d<sub>2</sub>**. The observed formation of nearly equal amounts of products **22a-d<sub>2</sub>** and **22b-d<sub>2</sub>**, however,

argued against the possibility of aminopalladation/ $\beta$ -hydride elimination pathway and in favor of a mechanism involving a  $\pi$ -allyl-Pd intermediate (eq 2).

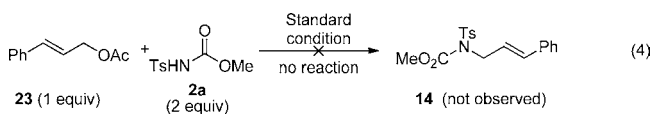
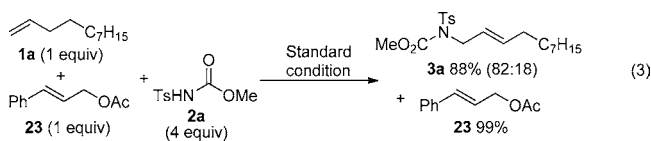


When a mixture of equal amounts of **1a** and cinnamyl acetate **23** was treated under the standard conditions, **3a** was formed in 88% yield, and substrate **23** was quantitatively recovered (eq 3). In a separate experiment, no reaction of **23** occurred (eq 4). Thus, the failure to observe the formation of cross amination

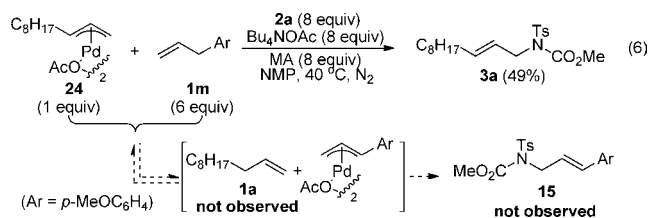
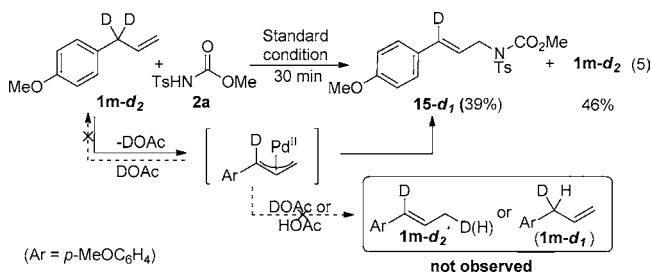
(18) For some examples on the palladium-catalyzed amination of alkenes with *N*-tosylcarbamate as nitrogen nucleophile, which were proposed to go through *trans*-aminopalladation pathway, see ref 9a and (a) Lei, A.; Lu, X. *Org. Lett.* **2000**, *2*, 2699–2702. (b) Lei, A.; Lu, X. *Org. Lett.* **2000**, *2*, 2357–2360. (c) Lei, A.; Liu, G.; Lu, X. *J. Org. Chem.* **2002**, *67*, 974–980, and the references therein.

(19) For the transformation via Pd(0/II) mechanism, White and coworker have reported that the reaction of allylic acetate with **2a** afforded the allylic amination product and isomer of allylic acetate, which involved an oxidative addition of Pd(0), see the Supporting Information of ref 8b.

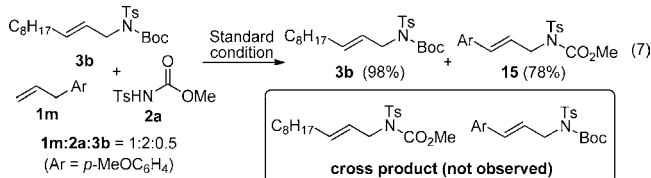
product **14** ruled out allylic acetate **23** as an intermediate.<sup>19</sup> These results are consistent with a mechanism involving allylic C–H bond activation to afford a  $\pi$ -allylpalladium intermediate which is then attacked by the nitrogen nucleophile (Scheme 2).



Several control experiments were performed: (1) the reaction of **1 m-d<sub>2</sub>** with **2a** afforded **15-d<sub>1</sub>** in 39% yield within 30 min, and 46% **1 m-d<sub>2</sub>** was recovered without any isomerization or loss of deuterium label from the starting material (eq 5); (2) the reaction of  $\pi$ -allylpalladium complex **24** with **2a**, in the presence of excess olefin **1m**, afforded amination product **3a** in 49% yield; no formation of olefin **1a** or cross amination product **15** was observed (eq 6). These results suggest that the allylic C–H bond activation is an irreversible step to generate a  $\pi$ -allyl-Pd intermediate.



Furthermore, no cross coupling amination products were observed in the reaction of **1m** and **2a** in the presence of **3b**. This establishes that the amination of the  $\pi$ -allyl-Pd complex is also an irreversible step (eq 7).



Finally, the stoichiometric reactions of  $\pi$ -allylPd complex **24** with nitrogen nucleophile **2a** were studied. As shown in Table 3, the reaction did not afford any amination products in the absence of NQ (entry 1). However, when benzoyl peroxide was added as the oxidant, the reaction afforded the amination product **3a** at 11% yield (entry 2). In the case of PhI(OAc)<sub>2</sub>, the reaction afforded amination products **25** in 40% yield,<sup>20</sup> even within a

**Table 3.** Amination of  $\pi$ -Allylpalladium Complex<sup>a</sup>

entry	[O]	time	product	yield <sup>b</sup>
1	none	9 h		
2	(PhCOO) <sub>2</sub>	9 h	<b>3a</b>	11% (only <i>E</i> )
3	PhI(OAc) <sub>2</sub>	9 h	<b>25</b>	40% (67:33)
4	PhI(OAc) <sub>2</sub>	40 min	<b>25</b>	34% (83:17)
5	NQ	9 h	<b>3a</b>	45% (only <i>E</i> )

<sup>a</sup> The reaction was conducted on a 0.05 mmol scale in 0.25 mL of NMP. <sup>b</sup> Isolated yield, the data in parentheses were the ratio of *E* and *Z*.

shorter reaction time (entries 3 and 4). In addition, the reaction afforded **3a** in 45% yield in the presence of NQ (entry 5).

These preliminary results demonstrate that this transformation proceeds by an irreversible allylic C–H activation to generate a  $\pi$ -allyl-Pd complex, followed by an irreversible nucleophilic attack to afford amination products.

**The Effect of Quinones.** In nearly every reaction studied thus far, the benzoquinone or its analogue was used as an oxidant to carry out the palladium reoxidation. Furthermore, benzoquinone has been demonstrated as a ligand to promote nucleophilic attack on the  $\pi$ -allyl-Pd complex.<sup>21,22</sup> However, the effect of benzoquinone on the allylic C–H bond activation has not been investigated.<sup>23</sup> As mentioned above, the palladium catalyzed allylic C–H amination reaction proceeds very well with quinones (20 mol %) in the presence of a stoichiometric amount of PhI(OPiv)<sub>2</sub>. In addition, the reaction can also be conducted in the absence of quinones. Thus, comparison of these two catalytic systems should provide an excellent opportunity to investigate the effect of quinones on the catalytic reaction.

First, a series of substituted quinones was investigated in the reactions of *p*-methoxy-allylbenzene **1m** with **2a**. Although all of these reactions afforded the oxidative amination product with good to excellent yields (Table 4), faster rates were observed in the presence of quinones bearing electron-withdrawing substituents. Furthermore, the independent studies found that the fastest initial rate was seen with NQ as the electron-withdrawing ligand, and the slowest rate was obtained in the absence of any quinone (Figure 1A). On the other hand, variation of the NQ concentration resulted in a systematic change in the reaction rate: a first-order dependence on [NQ] was seen at low concentration (below 0.08 M), and a zero-order dependence was seen at high concentration (above 0.15 M, Figure 1B). On the basis of these results, further kinetic studies focused on two catalytic systems: Pd(OAc)<sub>2</sub>/PhI(OPiv)<sub>2</sub> (without NQ) and Pd(OAc)<sub>2</sub>/NQ/PhI(OPiv)<sub>2</sub> (with NQ).

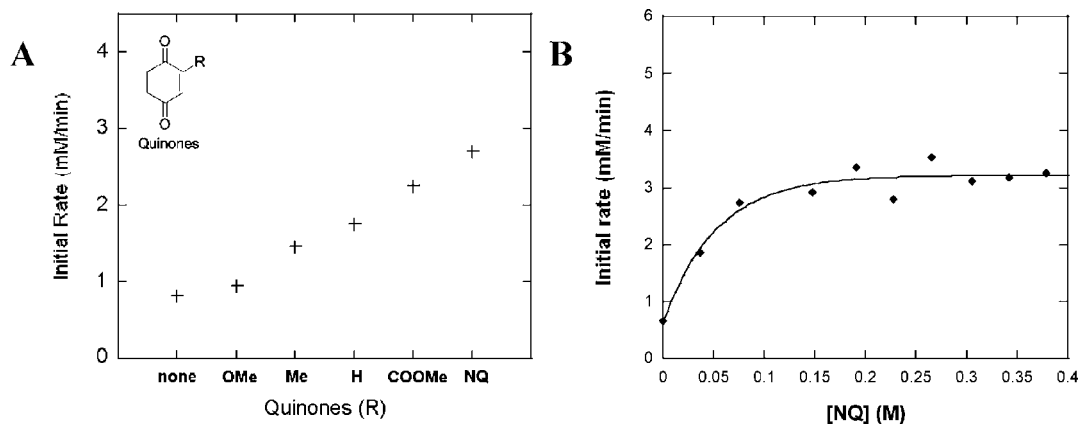
**Table 4.** Effect of Various Quinones<sup>a</sup>

additives (20 mol%)	Yield (%) <sup>b</sup>
none	70
Quinone	
R = OMe	75
Me	81
H	90
COOMe	84
NQ	95

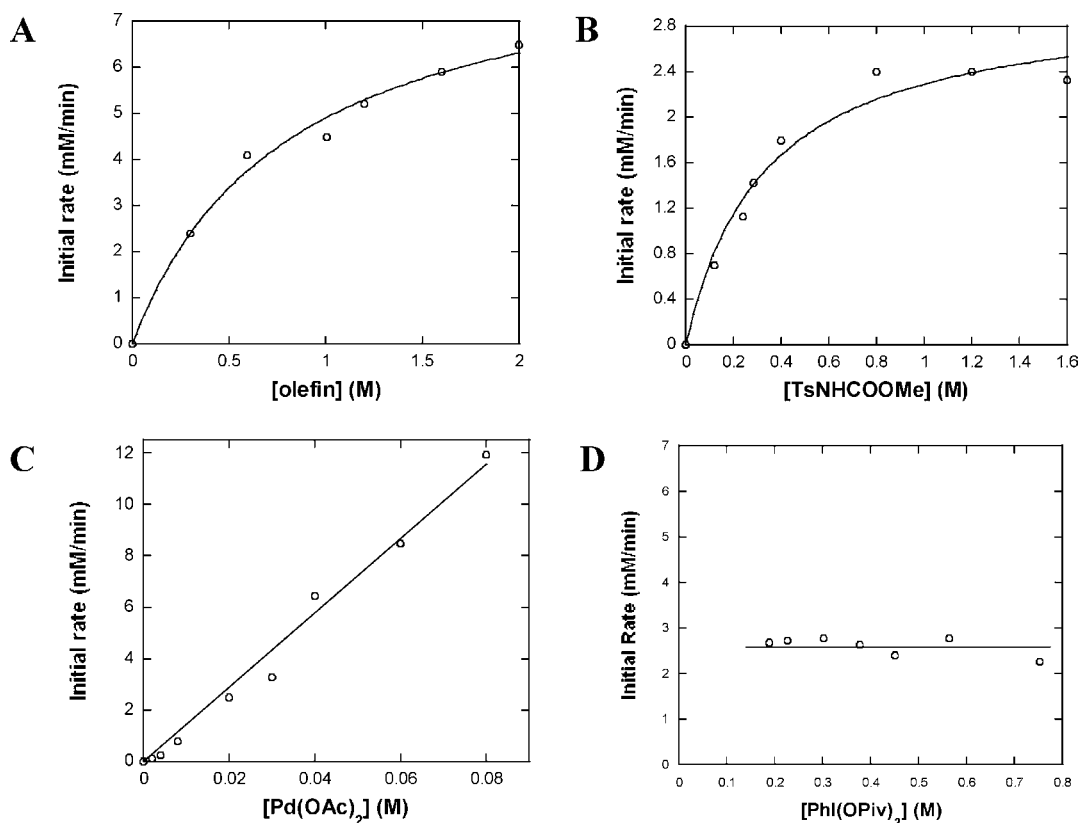
Quinones:

NQ:

<sup>a</sup> Reaction conditions: **1m** (0.2 mmol), **2a** (0.4 mmol), Pd(OAc)<sub>2</sub> (0.01 mmol), additive (0.04 mmol), Bu<sub>4</sub>NOAc (0.04 mmol), PhI(OPiv)<sub>2</sub> (0.3 mmol) in NMP (0.25 mL) at 40 °C. <sup>b</sup> Isolated yield.



**Figure 1.** Effect of the initial rate on the substituted quinones (A) and the dependence of initial rate on NQ concentration (B): (A) [olefin] = 0.377 M; [TsNHCOOMe] = 0.753 M; [PhI(OOC<sup>t</sup>Bu)<sub>2</sub>] = 0.565 M; [Bu<sub>4</sub>NOAc] = 0.075 M; [quinone] = 0.075 M; [Pd(OAc)<sub>2</sub>] = 0.019 M in NMP. (B) [olefin] = 0.377 M, [TsNHCOOMe] = 0.753 M, [PhI(OPiv)<sub>2</sub>] = 0.565 M; [Bu<sub>4</sub>NOAc] = 0.075 M; [Pd(OAc)<sub>2</sub>] = 0.019 M; [NQ] = 0–0.377 M in NMP.

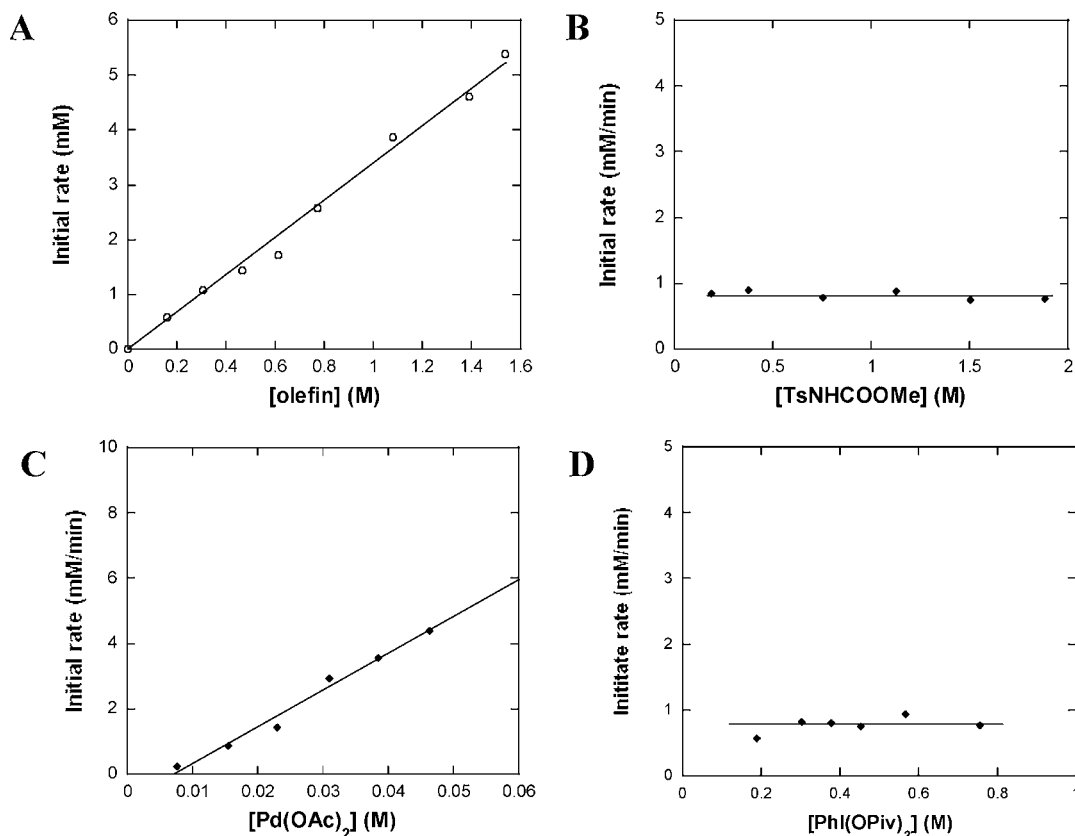


**Figure 2.** Dependence of the initial rate on olefin (A), nucleophile (B), catalyst (C), and oxidant (D) concentrations under the catalytic system with 1,4-naphthoquinone (NQ). Reaction condition: (A) [TsNHCOOMe] = 0.753 M, [PhI(OPiv)<sub>2</sub>] = 0.565 M, [Bu<sub>4</sub>NOAc] = 0.075 M, [NQ] = 0.075 M, [Pd(OAc)<sub>2</sub>] = 0.019 M, [olefin] = 0.283–1.883 M; (B) [olefin] = 0.377 M, [Pd(OAc)<sub>2</sub>] = 0.019 M, [PhI(OPiv)<sub>2</sub>] = 0.565 M, [NQ] = 0.075 M, [Bu<sub>4</sub>NOAc] = 0.075 M, [TsNHCOOMe] = 0.118–1.507 M; (C) [olefin] = 0.377 M, [TsNHCOOMe] = 0.753 M, [PhI(OPiv)<sub>2</sub>] = 0.565 M, [Bu<sub>4</sub>NOAc] = 0.075 M, [NQ] = 0.075 M, [Pd(OAc)<sub>2</sub>] = 0.002–0.075 M; (D) [olefin] = 0.377 M, [TsNHCOOMe] = 0.753 M, [Pd(OAc)<sub>2</sub>] = 0.018 M, [Bu<sub>4</sub>NOAc] = 0.075 M, [NQ] = 0.075 M, [PhI(OPiv)<sub>2</sub>] = 0.118–0.753 M.

**Kinetic Studies.** Kinetic studies revealed distinct differences between the two catalytic systems: one with NQ and one without NQ. The dependence of the initial rate on olefin, imides, palladium catalyst, and PhI(OPiv)<sub>2</sub> concentration was evaluated in each case by monitoring the formation of product by gas chromatography. In the catalytic system with NQ (standard reaction condition), the rate exhibited a saturation rate dependence on the olefin **1m** and on nucleophile **2a** concentration, and first-order dependence of catalyst concentration (Figure 2). In contrast, without NQ in the catalytic system, the rate exhibited first-order dependence on olefin concentration, zero-order

dependence on nitrogen nucleophile concentration, and first-order dependence on catalyst concentration (Figure 3). The rate exhibited zero-order dependence on the [PhI(OPiv)<sub>2</sub>] in both catalytic systems, indicating that palladium reoxidation is not the rate limiting step in either system.

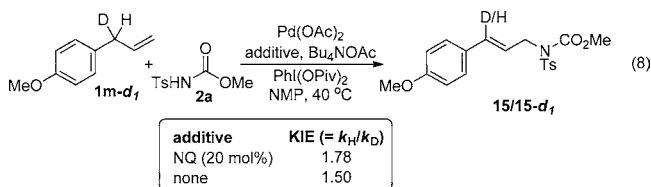
Deuterium kinetic isotope effects (KIEs) in the two catalytic systems were also evaluated under the standard conditions: intramolecular isotope effects were determined from the reaction of deuterium labeled olefin **1 m-d<sub>1</sub>** (eq 8); intermolecular deuterium kinetic isotope effects (KIEs) were determined by comparing the initial rates with substrates **1m** versus **1 m-d<sub>2</sub>**



**Figure 3.** Dependence of the initial rate on olefin (A), nucleophile (B), catalyst (C), and oxidant (D) concentrations in the absence of 1,4-naphthoquinone (NQ). Reaction condition: (A) [TsNHCOOMe] = 0.753 M, [PhI(OPiv)<sub>2</sub>] = 0.565 M, [Bu<sub>4</sub>NOAc] = 0.075 M, [Pd(OAc)<sub>2</sub>] = 0.019 M, [olefin] = 0.118–1.507 M; (B) [olefin] = 0.377 M, [Pd(OAc)<sub>2</sub>] = 0.019 M, [PhI(OPiv)<sub>2</sub>] = 0.565 M, [Bu<sub>4</sub>NOAc] = 0.075 M, [TsNHCOOMe] = 0.118–1.883 M; (C) [olefin] = 0.377 M, [TsNHCOOMe] = 0.753 M, [PhI(OPiv)<sub>2</sub>] = 0.565 M, [Bu<sub>4</sub>NOAc] = 0.075 M, [Pd(OAc)<sub>2</sub>] = 0.0077–0.046 M; (D) [olefin] = 0.377 M; [TsNHCOOMe] = 0.753 M; [Bu<sub>4</sub>NOAc] = 0.075 M; [Pd(OAc)<sub>2</sub>] = 0.019 M; [PhI(OPiv)<sub>2</sub>] = 0.188–0.753 M.

(Table 5). Similar intramolecular KIE values [ $k_H/k_D = 1.78$  (with NQ) and 1.50 (without NQ)] were obtained in the two catalytic systems. In contrast, while the NQ system showed an intermolecular KIE value ( $k_H/k_D = 1.83 \pm 0.1$ ) similar to the intramolecular isotope effect (entry 2),<sup>24</sup> almost no intermolecular kinetic isotope effect (KIE value:  $k_H/k_D = 0.93 \pm 0.1$ ) was observed in the catalytic system without NQ (entry 1).

Furthermore, kinetic isotope effects at different concentrations of nucleophile were studied in the presence of NQ. The observed kinetic isotope effects have no significant dependence on the concentration of nucleophile (Table 5, entries 2–5). In addition, when these reactions of **1 m-d<sub>2</sub>** were stopped by addition of excess pyridine at around 20% conversion, the starting material **1 m-d<sub>2</sub>** was recovered without any H/D scrambling (Table 5, entries 2–4), which indicated that the allylic C–H bond activation is an irreversible step.



**Proposed Mechanism and Analysis of Kinetic Data.** The palladium-catalyzed allylic C–H oxidative amination system containing many components and additives is very complex.

(20) The formation of **25** is raised from PhI and **3a** catalyzed by Pd catalyst, see the Supporting Information for details.

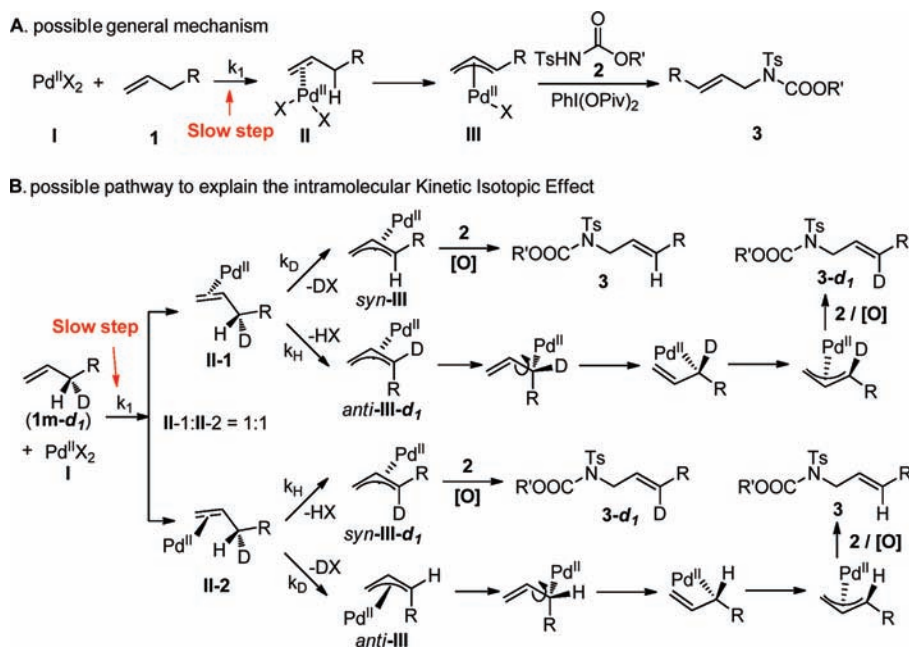
**Table 5.** Kinetic Isotope Effect at Different Concentrations of **2a** in the Presence of NQ<sup>a</sup>

Entry	[2a] (M)	KIE (= $k_H/k_D$ )	Notes
1	0.8	0.93 ( $\pm 0.1$ )	without NQ
2	0.8	1.83 ( $\pm 0.1$ )	Standard condition
3	0.4	1.64	with NQ (20 mol%)
4	1.2	1.88	
5	2.0	1.74	

<sup>a</sup> Reaction condition: olefin (0.2 mmol, 0.4 M), Pd(OAc)<sub>2</sub> (5 mol %), NQ (20 mol %), Bu<sub>4</sub>NOAc (20 mol %), PhI(OPiv)<sub>2</sub> (1.5 equiv), NMP.

Therefore, it is very difficult to access the precise mechanism of these catalytic systems. However, the kinetic data outlined above, together with isotopic labeling studies and kinetic isotope effects, provide valuable insight into the reaction mechanism.

(21) (a) Popp, B. V.; Stahl, S. S. *Top. Organomet. Chem.* **2007**, *22*, 149–189. (b) Bäckvall, J.-E.; Nordberg, R. E.; Wilhelm, D. *J. Am. Chem. Soc.* **1985**, *107*, 6892–6898. (c) Grennberg, H.; Simon, V.; Bäckvall, J.-E. *J. Chem. Soc., Chem. Commun.* **1994**, 265–266. (d) Bäckvall, J.-E.; Gogoll, A. *Tetrahedron Lett.* **1988**, *29*, 2243–2246. (e) Chen, M. S.; Prabakaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970.

**Scheme 4.** Possible Mechanism for the Pd-Catalyzed Allylic C–H Oxidative Amination Reaction in the Absence of NQ [NQ = 1,4-Naphthoquinone, X = OAc or OPiv]

**The Effect of NQ.** In the absence of NQ, the first-order dependence on both olefin and palladium catalyst suggests that the turnover-limiting step is likely the coordination of the olefin to palladium (Scheme 4A). This outcome is noteworthy because it contradicts the widespread assumption that the allylic C–H bond activation proceeds via fast  $\pi$ -complexation of the alkene to Pd, followed by subsequent slow hydrogen abstraction.<sup>25,26</sup> Increasing support for rate-limiting  $\pi$ -complexation of the alkene to Pd has been found in recent studies by Bercaw and co-workers.<sup>27</sup> The C–H activation step can also be ruled out as turnover-limiting based on the absence of an intermolecular kinetic isotope effect (KIE =  $0.93 \pm 0.1$ , Table 5, entry 1). The observed zero-order dependence on the nitrogen nucleophile rules out its involvement before the turnover limiting step. Thus,

nucleophilic attack on the  $\pi$ -allyl-Pd complex cannot be involved in the turnover limiting step. Moreover, the imide cannot be coordinated to Pd in the rate limiting step.

As mentioned above, a kinetic isotope effect was not observed in the intermolecular reaction. However, an intramolecular kinetic isotope effect was still observed (KIE = 1.50, eq 8). In order to explain this observation, the possible mechanism was drawn in Scheme 4B: although the turnover-limiting coordination of olefin to the palladium catalyst results in an equal amount of intermediate **II-1** and **II-2**, different rates of C–H versus C–D bond cleavage and the formation of *syn*- as well as *anti*-allyl-Pd complexes (*syn*- and *anti*-**III**) might result in the formation of different amounts of amination products **3-d<sub>1</sub>** and **3** (for details, see the Supporting Information).

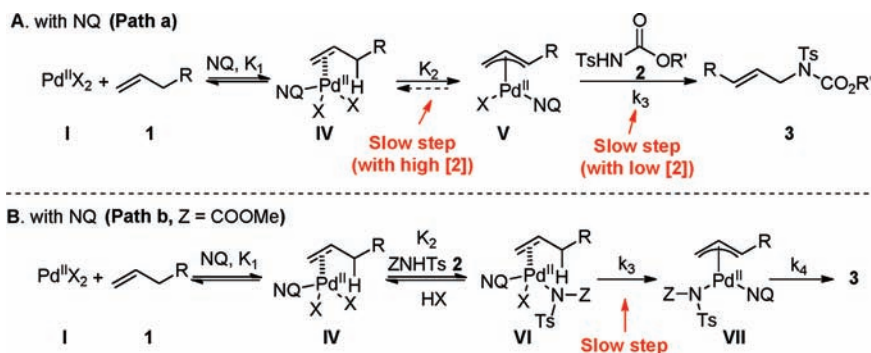
In the presence of NQ, the observed saturation dependences of olefin and nitrogen nucleophile rule out the coordination of olefin to palladium as the turnover-limiting step. The significant kinetic isotope effects observed in both intermolecular (KIE =  $1.83 \pm 0.1$ , Table 5, entry 2) and intramolecular reactions (eq 8, KIE = 1.78) indicate that the allylic C–H bond activation is involved in the turnover-limiting step under the standard conditions. The saturation rate dependence on the nitrogen nucleophile concentration in principle can be explained in two ways. First, there might be a kinetic competition between reversal of  $\pi$ -allyl-Pd complex formation and nucleophilic attack by the imide on the  $\pi$ -allyl-Pd complex: at high imide concentration, the rate would plateau and  $\pi$ -allyl-Pd complex formation would become rate limiting; but at low imide concentration, some reversal of the  $\pi$ -allyl-Pd complex back to alkene would compete with nucleophilic trapping by imide (Scheme 5A). Second, the reaction may involve rapid equilibration to give nitrogen coordinated Pd complex **VI** that undergoes turnover limiting allylic C–H activation (Scheme 5B).

These two possible mechanisms make different predictions about the loss of label from olefin **1 m-d<sub>2</sub>** and about variation of the kinetic isotope effect as a function of imide concentration. The kinetic competition mechanism (path a, Scheme 5A) predicts extensive H/D exchange and a diminished isotope effect

- (22) For the non-allylic substitution reaction systems, benzoquinone-promoted reductive elimination at Pd<sup>II</sup> is also well-precedented, see ref 31 and (a) Pérez-Rodríguez, M.; Braga, A. A. C.; Garcia-Melchor, M.; Pérez-Temprano, M. H.; Casares, J. A.; Ujaque, G.; de Lera, A. R.; Alvarez, R.; Maseras, F.; Espinet, P. *J. Am. Chem. Soc.* **2009**, *131*, 3650–3657. (b) Albéniz, A. C.; Espinet, P.; Martín-Ruiz, B. *Chem.–Eur. J.* **2001**, *7*, 2481–2489. (c) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 9651–9653.
- (23) Benzoquinone plays a important role in C<sub>sp</sub><sup>2</sup>-H activation, see: Chen, X.; Li, J.-J.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 78–79.
- (24) The similar kinetic isotope effect (KIE = 2.2) was obtained in the allylic alkylation with BQ as oxidant, see: (a) Lin, S.; Song, C.-X.; Cai, G.-X.; Wang, W.-H.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 12901–12903. Furthermore, the large KIE values (3.44–5.45) were observed in the allylic C–H activation of 1-methylenehexane with the stoichiometric amount of PdCl<sub>2</sub> in the various catalytic systems, for details see the following. (b) Chrisope, D. R.; Beak, P. *J. Am. Chem. Soc.* **1986**, *108*, 334–335. (c) Chrisope, D. R.; Beak, P.; Saunders, W. H. *J. Am. Chem. Soc.* **1988**, *110*, 230–238.
- (25) Maitlis, P. M.; Espinet, P.; Russel, M. J. H. In *Comprehensive Organometallic Chemistry*; Wilkinson, G.; Stone, F. G. A.; Abel, E. W., Eds.; Vol 6; Pergamon: Oxford, 1982.
- (26) The rate determining pre-equilibrium step is quite rare in the literature, see: (a) Trost, B. M.; Metzner, P. J. *J. Am. Chem. Soc.* **1980**, *102*, 3572–3577. (b) Trost, B. M.; Strege, P. E.; Weber, L.; Fullerton, T. J.; Dietsche, T. J. *J. Am. Chem. Soc.* **1978**, *100*, 3407–3415.
- (27) (a) Lin, B.-L.; Labinger, J. A.; Bercaw, J. E. *Can. J. Chem.* **2009**, *87*, 264–271. (b) Bercaw, J. E.; Hazari, N.; Labinger, J. A.; Oblad, P. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 9941–9943.



**Scheme 5.** Possible Mechanism To Explain the Saturation Rate Dependence on the Nitrogen Nucleophile Concentration in the Presence of NQ [NQ = 1,4-naphthoquinone, X = OAc or OPiv]



at low imide concentration, where the C–H activation step is partially reversible. In contrast, rate limiting C–H activation of a reversibly formed Pd complex VI predicts no H/D exchange and a isotope effect that does not change with imide concentration (path b, Scheme 5B). Experimentally, over a concentration range of imide, the intermolecular kinetic isotope effect was constant within experimental error (Table 5, entries 2–5). In addition, no H/D exchange was observed in the reactions of **1 m-d<sub>2</sub>**. These results are consistent with the mechanism involving rate limiting C–H activation of Pd complex VI (path b) and rule out the mechanism involving partially reversible C–H activation (path a).

A rate law was derived based on the proposed mechanism in Scheme 5B (eq 9).<sup>28</sup>

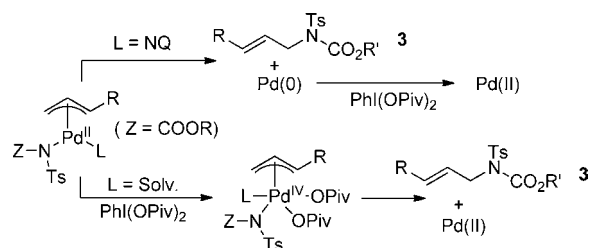
$$\text{rate} = \frac{K_1 K_2 k_3 [\mathbf{1}] [\mathbf{2}] [\text{NQ}] [\text{Pd}]_T}{[\text{HX}] + K_1 [\text{HX}] [\mathbf{1}] [\text{NQ}] + K_1 K_2 [\mathbf{1}] [\mathbf{2}] [\text{NQ}]} \quad (9)$$

The kinetic behaviors observed in the presence of NQ, such as the first order dependence on palladium catalyst, saturation dependences on olefin, NQ and nitrogen nucleophile are all readily accommodated with this rate law.

On the basis of the above analysis, the addition of NQ changes the reaction mechanism by enabling the fast and reversible coordination between olefin and palladium. The possible reason is that coordination of the  $\pi$ -acid ligand NQ increases the electron-deficiency of the palladium center,<sup>29</sup> which makes the olefin coordination step faster (Scheme 4A or 5B, step 1).<sup>30</sup> However, the precise nature of the interaction between NQ and palladium catalyst is not clear at this moment.<sup>31</sup>

**C–N Bond Formation and Catalyst Regeneration.** As shown in Scheme 6, there are two possible pathways for the C–N bond formation: (1) the  $\pi$ -allylPd(II) complex might react with nucleophilic reagent **2** to afford product and release Pd(0), which is then oxidized by PhI(OPiv)<sub>2</sub> to regenerate Pd(II) (Scheme 6, top); (2) the  $\pi$ -allylPd(II) intermediate, which is formed via oxidation of  $\pi$ -allylPd(II) by PhI(OPiv)<sub>2</sub>, might react with **2** to give amination product and Pd(II) (Scheme 6, bottom).

**Scheme 6.** Possible Mechanism for the C–N Bond Formation and Palladium Catalyst Regeneration



In the absence of NQ, the palladium-catalyzed oxidative amination reactions afford allylamine derivatives in good yield. However, no amination product was formed in the stoichiometric reaction of  $\pi$ -allyl-Pd complex **24** with imide **2a** (Table 3, entry 1). In contrast, this stoichiometric reaction afforded the amination product in the presence of oxidants (entries 2–4). These results indicate that the C–N bond formation in the absence of NQ probably involves a allyl-Pd(IV) intermediate, which comes from the oxidation of  $\pi$ -allyl-Pd(II) by oxidant (e.g., benzoyl peroxide and PhI(OPiv)<sub>2</sub>).<sup>15,32,33</sup> The high oxidation state Pd(IV) center would facilitate the reductive elimination to construct the C–N bond (Scheme 6, bottom).

(28) For deducing the rate expression, see the Supporting Information for details. In addition, it is hard to explain the relationship between the initiate rate and base concentration because this catalytic system is quite complex. But, if the base and PhI(OPiv)<sub>2</sub> was kept in the same concentration, the HX concentration should be a constant.

(29) For the review and selected examples on the related coordination between electron-deficient olefins and palladium, see: (a) Johnson, J. B.; Rovis, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 840–871. (b) Luo, X.; Zhang, H.; Duan, H.; Liu, Q.; Zhu, L.; Zhang, T.; Lei, A. *Org. Lett.* **2007**, *9*, 4571–4574. (c) Shi, W.; Luo, Y.; Luo, X.; Chao, L.; Zhang, H.; Wang, J.; Lei, A. *J. Am. Chem. Soc.* **2008**, *130*, 14713–14720. (d) Zhang, H.; Luo, X.; Wongkhan, K.; Duan, H.; Li, Q.; Zhu, L.; Wang, J.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B.; Lei, A. *Chem.—Eur. J.* **2009**, *15*, 3823–3829.

(30) The olefin-Pd(II) complexes are very reactive, which can be prepared from the reaction of olefin with highly nucleophilic palladium salt, such as PdCl<sub>2</sub>(PhCN)<sub>2</sub> or Na<sub>2</sub>PdCl<sub>4</sub>. However, there are no any records on the palladate of olefin with weak nucleophilic Pd(OAc)<sub>2</sub>. For details, see: Maitlis, P. M. In *The Organic Chemistry of Palladium*; Academic Press: New York and London, 1971; Vol 1.

(31) Because the observation of the Pd<sup>II</sup>(BQ) complex is extremely rare in the literature, and its isolation has remained unsuccessful, the relative study cannot currently be conducted by experiments. For the theoretical studies on allylPd(II)-BQ complexes by computational calculation, see: (a) Szabó, K. J. *Organometallic* **1998**, *17*, 1677–1686. (b) Karlsson, E. A.; Bäckvall, J.-E. *Chem.—Eur. J.* **2008**, *14*, 9175–9180.

(32) The allyl-Pd(IV) complexes have been reported from the reaction of stable Pd(II) cycle with allyl bromide, see: (a) Guo, R.; Portscher, J. L.; Day, V. W.; Malinakova, H. C. *Organometallic* **2007**, *26*, 3874–3883. (b) Canty, A. J.; Jin, H.; Roberts, A. S.; Skelton, B. W.; Trail, P. R.; White, A. H. *Organometallic* **1995**, *14*, 199–206. (c) Brown, D. G.; Byers, P. K.; Canty, A. J. *Organometallic* **1990**, *9*, 1231–1235. (d) Byers, P. K.; Canty, A. J. *J. Chem. Soc. Chem. Commun.* **1988**, 639–641.

(33) During our preparation of our manuscript, Szabó and coworkers recently reported a Pd-catalyzed allylic C–H acetoxylation of olefins with PhI(OAc)<sub>2</sub> as oxidant, in which they proposed a mechanism involving  $\eta^3$ -allyl-Pd(IV) intermediates, see: Pilarski, L. T.; Selander, N.; Böse, D.; Szabó, K. J. *Org. Lett.* **2009**, *11*, 5518–5521.

In the presence of NQ, the stoichiometric reaction of **2a** with **2a** in the presence of NQ produced allylic imide **3a** (Table 3, entry 5). Thus, an oxidation to Pd(IV) is not required for product formation (but might be involved). In the catalytic reaction in the presence of NQ, C–N bond formation occurs after the turnover-limiting allylic C–H bond activation. Thus, these two mechanisms are possible in this case, and it is difficult to differentiate at this moment.

### Summary

We have developed a highly efficient palladium-catalyzed oxidative amination of unactivated alkyl olefins to produce linear (*E*)-allylimide with high regioselectivity. The highly efficient transformation was achieved by facilitating the reoxidation of palladium catalyst with the strong oxidant PhI(OPiv)<sub>2</sub>. The present work also provides the first systematic analysis of the mechanism of the allylic C–H oxidative amination. It was found that the reaction proceeds by turnover-limiting olefin coordination to palladium catalyst in the absence of any quinone. However, a substoichiometric amount of NQ plays a vital role in promoting olefin coordination to the palladium catalyst, and

the reaction involves a rapid equilibration to give a nitrogen-coordinated olefin-Pd(NQ) complex that undergoes turnover-limiting allylic C–H bond activation to generate a  $\pi$ -allyl-Pd intermediate. This work provides valuable insights for further studies on the functionalization of unactivated olefins.

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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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