Palladium(II)-Catalyzed Cyclization of Olefinic Tosylamides

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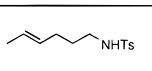
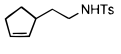
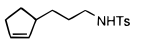
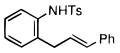
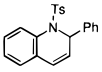
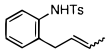
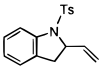
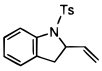
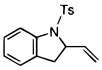
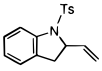
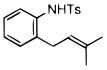
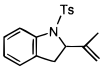
The palladium-catalyzed cyclization of simple olefinic amines,[1] tosylamides,[2] and carboxamides[3] has proven to be a particularly valuable route to a wide variety of nitrogen heterocycles. For example, the cyclization of *o*-vinylic[1d,h,2b,f] and *o*-allylic[1c−e,h] anilines or their tosyl derivatives by either stoichiometric amounts of palladium(II) salts or catalytic amounts of palladium(II) salts in the presence of benzoquinone as a reoxidant efficiently provides indoles. We recently reported the palladium-catalyzed conversion of alkenoic acids to unsaturated lactones[4] and enol silanes to enals and enones[5] using a remarkably simple, environmentally attractive catalyst system consisting of 5 mol % $Pd(OAc)_2$ under an atmosphere of O_2 in DMSO solvent with no additional reoxidants.[6,7] The recent report of one example of the cyclization of an olefinic tosylamide to an *N-allylic* tosylamide[8] using this same catalyst system, plus earlier reports of the cyclization of unsaturated tosylamides to *N-vinylic* tosylamides[1e,2a,i] by other palladium(II) catalyst systems, encourages us to report at this time our unusual results using the $Pd(OAc)_2/O_2$ catalyst on a variety of simple olefinic tosylamides.

Table 1. Palladium(II)-Catalyzed Cyclization of Olefinic Tosylamides

entry	tosylamide	procedure,[a] temp. (°C), time (h)	product[b]	% isolated yield (ratio)
1		A, 25, 72		93
2		A, 25, 72		86
3		A, 80, 96		82
				
4	H	A, 100, 48		38
5		B, 80, 72		48
6	Me	A, 40, 24		44
7		B, 40, 24		7
8		A, 25, 72		58
9		A, 80, 72		86
10		A, 100, 72		40
11		B, 100, 133		trace
12		A, 80, 18		62
13		A, 25, 72		88
	Z/*E* = 83:17			(95:5)
14		B, 25, 72		86
15	*Z*/*E* = 14:86	A, 25, 72		91
				(83:17)
16		B, 25, 72		88
17		B, 80, 72		62

[a] See the text and the supporting information for these procedures. [b] All products gave appropriate ^1H and ^{13}C NMR, IR, and mass spectral data.

We initially examined several simple olefinic tosylamides using our previously developed catalyst system (procedure A: 0.25 mmol of the tosylamide, 5 mol % $Pd(OAc)_2$, 2 equiv of NaOAc, and 5 mL of DMSO under 1 atm of O_2). The results of those cyclizations are reported in Table 1, entries 1−3. In general, acyclic and cyclic olefinic tosylamides can be cyclized to 5- and 6-membered ring products containing an *allylic* nitrogen moiety. This is in agreement with the very recent work of Andersson

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and co-workers,[8] but in sharp contrast to previous work on the cyclization of olefinic tosylamides using $PdCl_2$, where *N-vinylic* tosylamides were formed exclusively.[2a,i] Using our procedure, 6-membered ring closure appears to require higher temperatures than 5-membered ring formation. This is consistent with our previous work on the cyclization of alkenoic acids.[4] Hegedus previously found it very difficult to form 6-membered rings when cyclizing olefinic tosylamides using 10 mol % $PdCl_2$, 2 equiv of LiCl and Na_2CO_3, and 1 equiv of benzoquinone.[2a,i]

o-Vinylic tosylanilides can also be cyclized in modest yield by our catalyst system (Table 1, entries 4−8). Substantial amounts of starting material often remained unreacted. 2-Vinyl tosylanilide can be cyclized to the corresponding indole in 38% yield using procedure A (Table 1, entry 4). Better results (48% yield) could be obtained by simply omitting the NaOAc base completely (procedure B, Table 1, entry 5). While our catalyst offers obvious advantages over the previous use of stoichiometric amounts of Li_2PdCl_4 for this type of cyclization,[2b] 5 mol % of $PdCl_2$ plus benzoquinone may be more effective for substrates bearing a simple vinyl group.[2f] Therefore, no further attempts to improve these yields were made.

More substituted *o*-vinylic tosylanilides, such as those shown in entries 6−8 of Table 1, do not appear to have previously been subjected to palladium-promoted cyclization. Contrary to the cyclization of 2-vinyltosylanilide, the cyclization of 2-((*E*)-1-propenyl)tosylanilide gave a better yield of 2-methylindole using procedure A (compare entries 6 and 7 of Table 1). Unexpectedly, the palladium-catalyzed cyclization of 2-isopropenyltosylanilide produces the corresponding 3-methylene-2,3-dihydroindole in good yield, rather than the anticipated 3-methylindole (Table 1, entry 8). It should be noted that the commercial availability of 2-isopropenylaniline and thus easy access to *N*-tosyl 3-methylene-2,3-dihydroindole provides a useful general route to various 3-substituted indoles via ene chemistry.[9]

Our most surprising results have been obtained when cyclizing *o*-allylic tosylanilides (Table 1, entries 9−17). 2-Allylaniline has previously been cyclized to the 5-membered ring 2-methylindole using stoichiometric or catalytic amounts (plus benzoquinone) of $PdCl_2$.[1c,d] Using our catalyst and procedure A on the corresponding tosylamide, we obtain exclusively the corresponding 6-membered ring 1,2-dihydroquinoline derivative in excellent yield (Table 1, entry 9). This approach greatly simplifies the synthesis of this ring system.[10] Similarly, 2-methallylaniline has previously been cyclized to the 5-membered ring 2,2-dimethyl-2,3-dihydroindole using $PdCl_2$, followed by H_2,[1d] but we obtain the corresponding 6-membered ring 1,2-dihydroquinoline using our catalyst system and the corresponding tosyl derivative (Table 1, entry 10). Likewise, 2-cinnamyltosylanilide cyclizes to the corresponding 1,2-dihydroquinoline (Table 1, entry 12). 2-Crotylaniline can be stoichiometrically or catalytically cyclized by $PdCl_2$ to either 2-ethylindole or 2-methylquinoline using $PdCl_2$.[1d] While procedure A cyclizes the corresponding tosylanilide to a mixture of both the 2-vinyl-2,3-dihydroindole and 2-methyl-2,3-dihydroquinoline with the former predominating (Table 1, entries 13 and 15), procedure B gives exclusively the dihydroindole in high yield, no matter what the stereochemistry of the starting material (Table 1, entries 14 and 16). Scaling up the reaction described in entry 14 (Table 1) to 5 mmol afforded the pure dihydroindole in a 79% recrystallized yield. 2-Prenylaniline reacts with $PdCl_2$ in either stoichiometric or catalytic amounts to produce the corresponding 6-membered ring 2,2-dimethyl-1,2-dihydroquinoline,[1d] while our catalyst produces exclusively the corresponding 5-membered ring dihydroindole (Table 1, entry 17). Thus, by switching from the allylic anilines and $PdCl_2$ to the corresponding tosylamides and $Pd(OAc)_2$, one can dramatically change the nature of the products formed in these types of cyclizations.

While we have not attempted any mechanistic work on these reactions, it is clear that changing the nature of the group attached to nitrogen and the anion present in the palladium catalyst can change the nature of the cyclization remarkably. While aminopalladation mechanisms have commonly been suggested to account for the $PdCl_2$ cyclizations, it appears that our $Pd(OAc)_2$ catalyst can either alter the regiochemistry of ring closure during electrophilic aminopalladation or affect cyclization by an entirely different route involving initial π-allylpalladium formation and subsequent nucleophilic displacement of palladium by nitrogen. The latter pathway has recently been suggested for the cyclization of *N*,*N*-dimethyl-2-allylaniline to 1,1-dimethyl-1,2-dihydroquinolinium salts using $Pd(OAc)_2$[1k] and the cyclization of a polycyclic olefinic amine using catalytic $Pd(O_2CCF_3)_2$ and PPh_3, plus 1.1 equiv of benzoquinone.[1j] It appears that both mechanisms are involved in our cyclizations but that the palladium carboxylate reagents are more prone to direct cyclization by a π-allylpalladium intermediate.

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Supporting Information Available: General experimental procedure and characterization data for all products (4 pages).

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(10) For previous syntheses of *N*-tosyl-1,2-dihydroquinolines, see: (a) Engler, T. A.; Lynch, K. O., Jr.; Chai, W.; Meduna, S. P. *Tetrahedron Lett.* **1995**, *36*, 2713. (b) Tökes, A. L.; Antus, S. *Liebigs Ann. Chem.* **1994**, 911.