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Palladium-Catalyzed Alkene Carboamination Reactions of Electron-Poor Nitrogen Nucleophiles

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Dedicated to Prof. Dr. Stephen L. Buchwald on the occasion of his 60th birthday.

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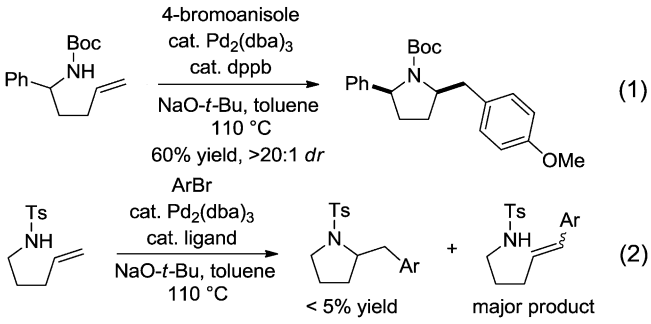
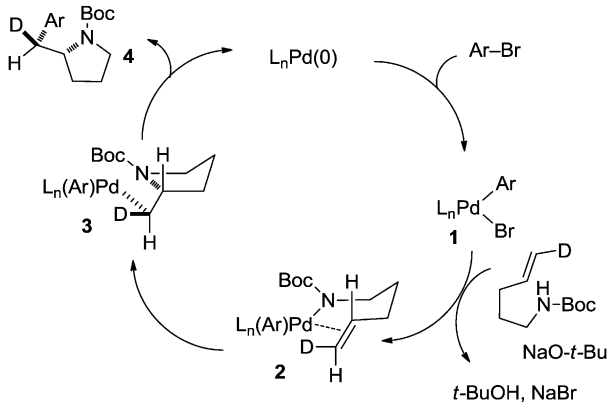
Abstract: Modified reaction conditions that facilitate Pd-catalyzed alkene carboamination reactions of electron-deficient nitrogen nucleophiles are reported. Pent-4-enylamine derivatives bearing *N*-tosyl or *N*-trifluoroacetyl groups are coupled with aryl triflates to afford substituted pyrrolidines in good yield. These reactions proceed *via* a mechanism involving *anti*-aminopalladation of the alkene, which differs from previously reported analogous reactions of *N*-aryl- and *N*-Boc-pentenylamines. The application of these conditions to a formal synthesis of (±)-aphanorphine is also described.

Keywords: alkenes; aryl halides; heterocycles; palladium

Over the past decade our group has developed and investigated a series of Pd-catalyzed alkene carboamination reactions for the synthesis of medicinally relevant nitrogen heterocycles.[1] These transformations effect the cross-coupling of an aryl or alkenyl halide with a nitrogen nucleophile that contains a pendant alkene, and result in the formation of a ring, a C–N bond, a C–C bond, and up to two stereocenters. For example, we have illustrated that this method can be used for the stereoselective construction of *N*-protected pyrrolidines from substituted pent-4-enylamine derivatives [Eq. (1)].[2] These reactions are broadly effective with substrates bearing *N*-aryl, *N*-acetyl, *N*-Boc, or *N*-Cbz groups. However, the efficacy of these reactions is linked to the nucleophilicity of the cyclizing nitrogen atom, and substrates that contain highly electron-withdrawing protetcting groups, such as *N*-tosyl or *N*-trifluoroacetyl, undergo Heck arylation of the alkene rather than carboamination to afford the desired heterocycle [Eq. (2)].[3,4,5,6]



Our prior studies have shown that the mechanism of these reactions involves oxidative addition of the aryl halide to Pd(0) to generate **1**, which undergoes substitution with the nitrogen nucleophile to afford **2** (Scheme 1). The key C–N bond-forming event occurs through *syn*-migratory insertion of the alkene into the Pd–N bond of **2** to yield **3**, which undergoes C–C bond-forming reductive elimination to generate the product **4**.[1] The *syn*-aminopalladation step is facilitated by relatively electron-rich nitrogen nucleophiles, and the rate of this step slows dramatically as the nu-



Scheme 1. *syn*-Aminopalladation mechanism.

cleophilicity of the nitrogen atom decreases.[7] Thus, for electron-poor nucleophiles such as tosyl-protected amines, Heck-type arylation of the alkene outcompetes the alkene carboamination process.

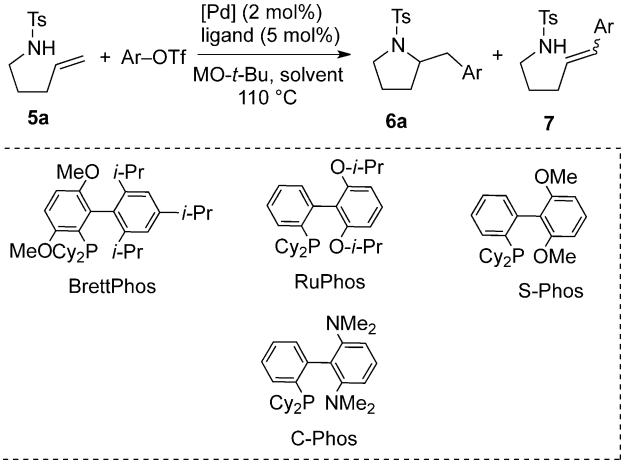
We recently reported a new variant of the Pd-catalyzed alkene carboamination reactions whereby *N*-allylsulfamides were transformed to cyclic sulfamides.[8] During the course of those studies we discovered that reaction conditions that favored the *syn*-aminopalladation mechanistic pathway illustrated above led to the formation of significant amounts of side products resulting from competing Heck arylation. However, this undesired side reaction was minimized through use of modified conditions in which the reactions were carried out in a relatively polar solvent ($PhCF_3$) with aryl triflates rather than aryl bromides as coupling partners. Given the success of these conditions with the relatively electron-poor sulfamide substrates, we reasoned that similar conditions may prove useful for Pd-catalyzed carboamination reactions of other electron-poor nitrogen nucleophiles, such as *N*-tosyl or *N*-trifluoroacetyl protected amines. This would broaden the array of nitrogen protecting groups tolerated in these reactions, and would significantly expand the scope of this methodology.

To test this hypothesis we examined the Pd-catalyzed coupling of **5a** with phenyl triflate or *p*-tolyl triflate (Table 1). A series of Buchwald-type biarylphosphine ligands was surveyed,[9] as these provided optimal results in our prior studies with sulfamides.[8] After some experimentation we found that use of a catalyst composed of $Pd(OAc)_2$/CPhos, LiO-*t*-Bu as base, and $PhCF_3$ as solvent provided the highest yield of desired product **6a** and only a small amount of Heck arylation side product **7**.

Following our preliminary optimization studies we proceeded to examine the coupling of phenyl triflate with several *N*-tosyl-pent-4-enylamine derivatives. As shown in Table 2, in most instances reactions proceed in good yield. However, in contrast to analogous transformations of *N*-Boc or *N*-acetyl protected pentenylamines, diastereoselectivities were low (*ca.* 1–2:1) in most cases. Substitution at the internal alkene carbon atom was tolerated to some extent, although the yield for product **6g** was modest. Efforts to employ substrates bearing internal alkenes were unsuccessful. In addition, attempts to form six-membered heterocycles using this method provided low yields (<35%) of the desired products.

The reactivity of several different aryl triflates was also examined (Table 3), and the presence of electron-donating groups and electron-withdrawing groups was tolerated. Moreover, the sterically hindered 1-naphthyl triflate was successfully coupled with *N*-tosyl-pent-4-enylamine in 72% yield to afford **6h**. The presence of functional groups such as aryl chlorides, nitriles, and non-enolizable ketones did not

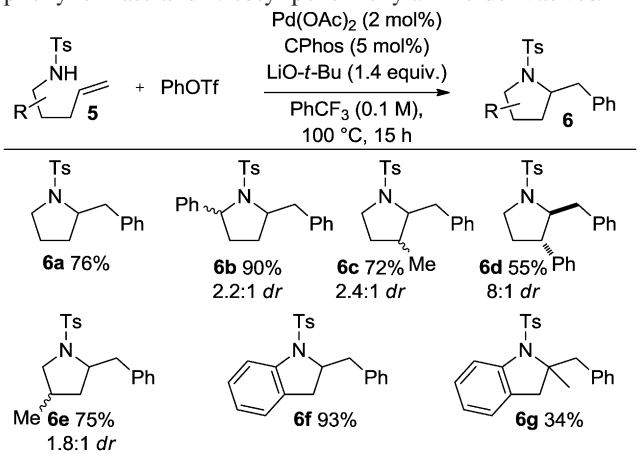
Table 1. Optimization studies.[a]



[Pd]	Ligand	M	**6a** [%][b]	**7** [%][b]
$Pd_2(dba)_3$	BrettPhos	Na	10[c]	trace
$Pd_2(dba)_3$	RuPhos	Na	38[c]	12
$Pd_2(dba)_3$	SPhos	Na	20[c]	33
$Pd(OAc)_2$	RuPhos	Li	66[c]	<10
$Pd(OAc)_2$	SPhos	Li	66[c]	<10
$Pd(OAc)_2$	CPhos	Li	70[e]	8
$Pd(OAc)_2$	CPhos[d]	Li	76[e]	8

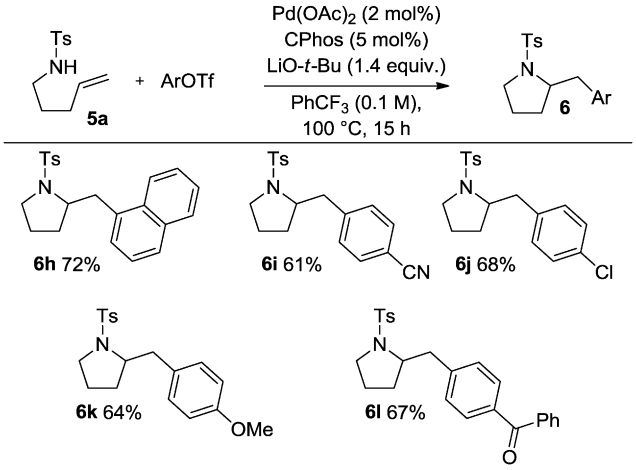
[a] *Conditions:* 1.0 equiv. **5a**, 1.2 equiv. ArOTf, 1.4 equiv. MO-*t*-Bu, 1 mol% $Pd_2(dba)_3$ or 2 mol% $Pd(OAc)_2$, toluene, 110 °C.
[b] Yield determined by ^{1}H NMR using 1,10-phenanthrene as an internal standard. In most instances the mass balance consisted of unreacted starting material **5a**.
[c] Ar = *p*-Tol.
[d] $PhCF_3$ was used as solvent with a reaction temperature of 100 °C.
[e] Ar = Ph.

Table 2. Pd-catalyzed carboamination reactions between phenyl triflate and *N*-tosyl-pent-4-enylamine derivatives.[a]



[a] *Conditions:* 1.0 equiv. **5**, 1.2 equiv. ArOTf, 1.4 equiv. LiO-*t*-Bu, 2 mol% $Pd(OAc)_2$, $PhCF_3$, 100 °C. Yields are isolated yields (average of two experiments).

Table 3. Pd-catalyzed carboamination reactions between aryl triflates and *N*-tosyl-pent-4-enylamine.[a]

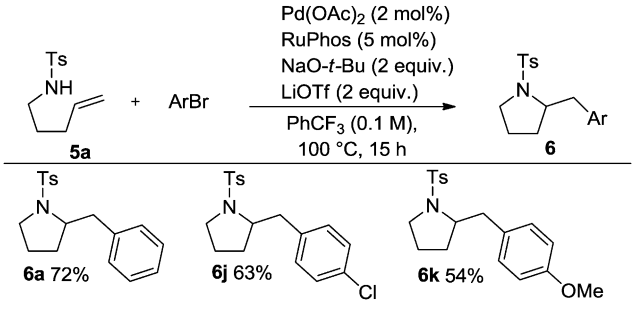


[a] *Conditions:* 1.0 equiv. **5a**, 1.2 equiv. ArOTf, 1.4 equiv. LiO-*t*-Bu, 2 mol% $Pd(OAc)_2$, $PhCF_3$, 100 °C. Yields are isolated yields (average of two experiments).

have a deleterious effect on reactivity or chemical yield.

Finally, the Pd-catalyzed carboamination of **5a** with several different aryl bromide electrophiles was achieved by using RuPhos as ligand, NaO-*t*-Bu as base, and 2 equiv. of LiOTf as an additive for these reactions (Table 4). Under these conditions, yields with

Table 4. Pd-catalyzed carboamination reactions between aryl bromides and *N*-tosyl-pent-4-enylamine.[a]

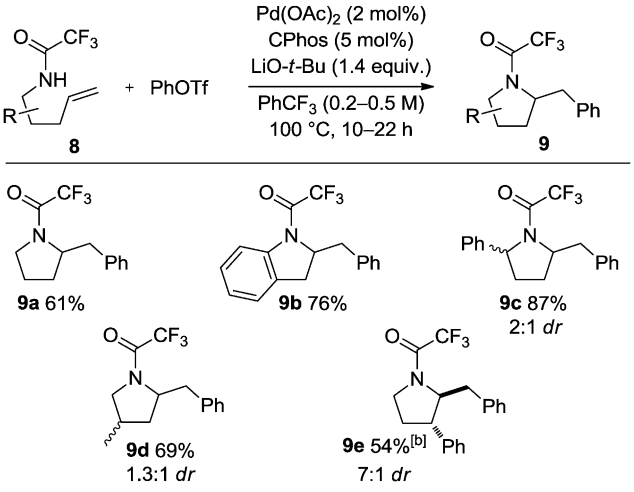


[a] *Conditions:* 1.0 equiv. **5a**, 2.0 equiv. ArBr, 2.0 equiv. NaO-*t*-Bu, 2.0 equiv. LiOTf, 2 mol% $Pd(OAc)_2$, $PhCF_3$, 100 °C. Yields are isolated yields (average of two experiments).

aryl bromides were similar to those obtained with aryl triflate electrophiles. The role of the LiOTf additive could be to facilitate *in situ* formation of palladium triflate complexes, or the lithium cation may lead to pseudocationic complexes by binding to the halide ligand on Pd.[10] Alternatively LiOTf may also increase the polarity (ionic strength) of the reaction medium.[11]

We also explored the reactivity of pent-4-enylamine substrates bearing *N*-trifluoroacetyl groups. As shown in Table 5, these transformations were also effective with a range of different amine substrates, although yields were generally lower than for the analogous tosyl-protected derivatives. Diastereoselectivities were also modest, with the exception of **9e**, which contains a relatively bulky phenyl substituent.

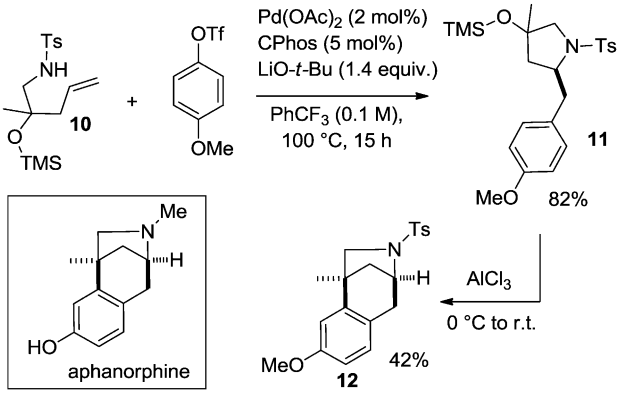
Table 5. Pd-catalyzed carboamination reactions between phenyl triflate and *N*-trifluoroacetyl-pent-4-enylamine.[a]



[a] *Conditions:* 1.0 equiv. **8**, 1.2 equiv. PhOTf, 1.4 equiv. LiO-*t*-Bu, 2 mol% $Pd(OAc)_2$, $PhCF_3$, 100 °C. Yields are isolated yields (average of two experiments).

[b] The reaction was conducted using 2 equiv. PhOTf, 4 mol% $Pd(OAc)_2$ and 10 mol% CPhos.

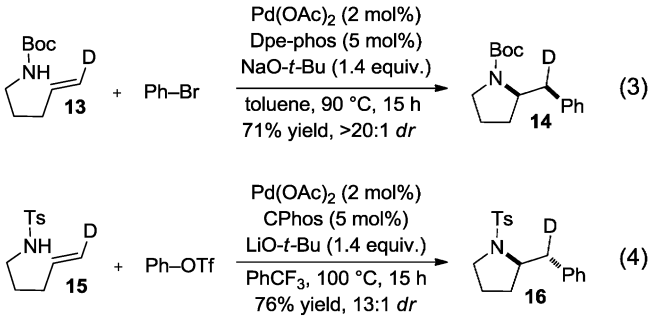
To illustrate the potential utility of this transformation, we carried out a short formal synthesis of (±)-aphanorphine (Scheme 2). We had previously prepared an intermediate closely related to **11** *via* Pd-catalyzed carboamination of a Boc-protected pentenylamine derivative analogous to **10** followed by cleavage of the Boc-group and reprotection with TsCl.[12]



Scheme 2. Formal synthesis of aphanorphine.

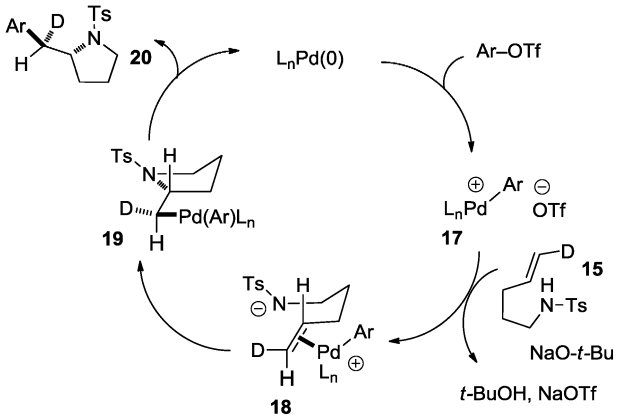
We were unable to directly access **11** *via* Pd-catalyzed carboamination due to the poor reactivity of substrate **10**. However, use of our newly developed conditions led to the conversion of **10** to **11** in 82% yield. Subsequent intramolecular Friedel–Crafts alkylation of **11** afforded **12**, which is an *N*- and *O*-protected analog of aphanorphine.[13]

The contrast in stereocontrol observed in reactions of *N*-tosyl *vs.* *N*-Boc protected pentenylamines prompted us to explore the stereochemistry of the alkene addition process, as we felt this could indicate that the two types of substrates react *via* different mechanisms.[14] We have previously shown that carboamination reactions of Boc-protected substrates proceed with *syn*-addition of the nitrogen atom and the aryl group to the alkene.[2d] For example, the coupling of deuterated substrate **13** with bromobenzene using a $Pd(OAc)_2$/Dpe-phos catalyst afforded **14** in 71% yield and >20:1 *dr* [Eq. (3)]. In contrast, we found that the coupling of tosyl-protected substrate **15** with phenyl triflate using our optimized conditions described above provided **16** in 76% yield and 13:1 *dr* [Eq. (4)]. This product results from *anti*-addition of the nitrogen atom and the aryl group to the double bond in **15**.[15]

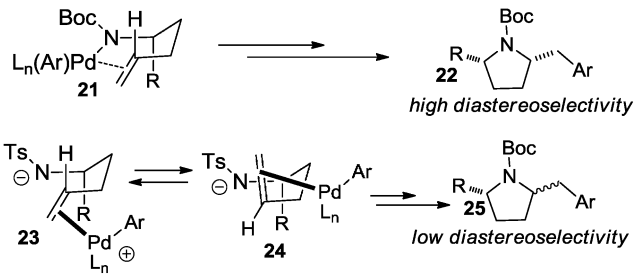


These results suggest that the mechanism of Pd-catalyzed alkene carboamination reactions of *N*-tosylpent-4-enylamines with aryl triflates is indeed different from that of the analogous Boc-protected substrates with aryl bromides. As shown below (Scheme 3), the mechanism with tosyl-protected derivatives is initiated by oxidative addition of the aryl triflate to Pd(0). However, upon formation intermediate **17** binds to the alkene to afford **18**, which then undergoes *anti*-aminopalladation[16] to generate **19**. Reductive elimination then leads to C–C bond formation to yield the product **20** with regeneration of the Pd(0) catalyst.

The modest diastereoselectivity observed in reactions of *N*-tosylamine derivatives (e.g., in the formation of **6b** or **9c**) is likely due to the possibility of the aminopalladation step occurring from either conformer **23** or **24**, which are likely close in energy (Scheme 4).[17] In contrast, reactions that proceed *via*



Scheme 3. *anti*-Aminopalladation mechanism.



Scheme 4. Pathway for diastereomer formation.

syn-aminopalladation appear to occur *via* a highly organized transition state (**21**) in which the alkene π-bond is eclipsed with the Pd–N bond.

The results presented above, along with those described in our recent studies on Pd-catalyzed alkene carboamination reactions of *N*-allyl sulfamides[8] and *N*-tosyl-*N*-propargyl guanidines,[18] illustrate that transformations of relatively non-nucleophilic substrates that fail under *syn*-aminopalladation conditions can (in cases examined thus far) be achieved using conditions that promote *anti*-aminopalladation. Our prior mechanistic studies have shown that the rate of *syn*-aminopalladation is directly related to the nucleophilicity of the N-atom; electron-withdrawing N-substituents dramatically slow this process.[7] In addition, Stahl has illustrated that alkene aminopalladation reactions are reversible when the N-atom bears an electron-withdrawing group.[19] Thus, the *syn*-aminopalladation/reductive elimination sequence is unfavorable for electron-poor nucleophiles, and competing Heck arylation predominates. In contrast, it appears that when *anti*-aminopalladation conditions are employed the rates of *anti*-aminopalladation from **18** and subsequent reductive elimination from **19** are faster than the carbopalladation that would lead to Heck-arylation side products.

In conclusion, we have developed new reaction conditions for Pd-catalyzed alkene carboaminations that allow for use of electron-withdrawing *N*-tosyl

and *N*-trifluoroacetyl protecting groups. Although diastereoselectivities are typically modest, chemical yields are generally good, and this represents a useful expansion in the scope of alkene carboamination methodology. Future work will be directed towards the development of enantioselective variants of these transformations.

Experimental Section

General Procedure for Pd-Catalyzed Carboamination Reactions

An oven-dried test tube equipped with a magnetic stirbar and a rubber septum was cooled under a stream of nitrogen and charged with $Pd(OAc)_2$ (2 mol%), CPhos or RuPhos (5 mol%), and LiO-*t*-Bu (1.4 equiv.). The tube was purged with nitrogen and then a solution of the aryl triflate (1.2 equiv.) in CF_3Ph (1 mL) was added and the resulting mixture was stirred at room temperature for 1 min. A solution of the *N*-protected amine substrate (1 equiv.) in CF_3Ph (1.5 mL) was added, and the mixture was heated to 100 °C for 15 h. The mixture was then cooled to room temperature, saturated aqueous NH_4Cl (2 mL) was added, the organic layer was removed, and the aqueous layer was extracted with dichloromethane (4×2 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The crude product was then purified *via* flash chromatography.

Acknowledgements

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