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Carbenylative Amination with *N*-Tosylhydrazones

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ABSTRACT

A Pd-catalyzed reaction of vinyl iodides and *N*-tosylhydrazones that assembles η^3-allyl ligands through carbene insertion is demonstrated. Intramolecular trapping with nitrogen nucleophiles generates good yields of cinnamyl and pentadienyl amines like those found in alkaloid natural products. Carbenylative amination was the key reaction to complete the synthesis of the alkaloid caulophyllumine B. Migratory insertion was biased to provide allylamines with optical purity up to 64% ee, but in a lower yield.

Palladium-catalyzed carbenylative cross-coupling reactions are gaining increasing attention as analogues of carbonylative reactions with carbon monoxide. The initial applications of these reactions involved commercially available diazo compounds to generate products with new stereogenic centers;[1,2] but aryldiazomethanes are highly reactive requiring an alternative source of phenylcarbene precursors. Metalated *N*-tosylhydrazones decompose to give aryldiazo compounds in the Bamford–Stevens reaction[3] and can be used to generate metal-carbene intermediates in situ.[4] Barluenga and co-workers have demonstrated their utility in palladium-catalyzed cross-coupling reactions with aryl halides.[5] They can also be used in a net oxidative sequence with arylboronates.[6] Wang and co-workers have shown that they can be used in three-component cross-coupling reactions to generate a variety of propargylarenes.[7] When vinyl halides are used as substrates, carbenylative insertions generate η^3-allylpalladium intermediates that engage heteroatom nucleophiles. In this work we show that nitrogen nucleophiles are compatible with carbenylative insertions involving *N*-tosylhydrazones, providing direct access to alkaloid natural products.[8] Carbenylative insertions are complementary to the palladium-catalyzed hydroamination of aryl alkynes

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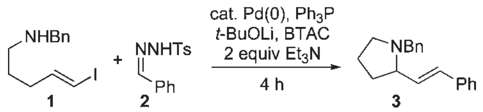
10.1021/ol301385g

because they can also be used to generate quaternary centers.[9]

Table 1. Optimization of Conditions for Carbenylative Amination with *N*-Tosylhydrazone **2**[a]

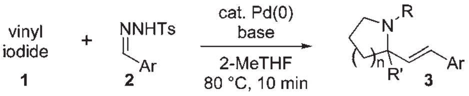


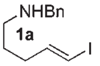
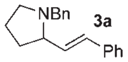
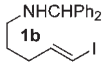
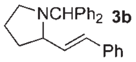
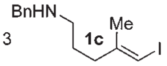
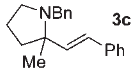
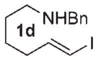
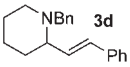
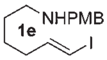
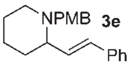
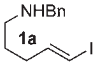
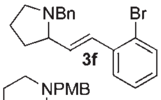
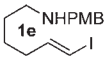
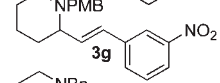
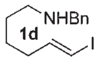
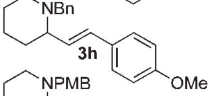
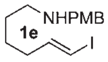
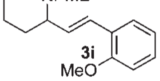
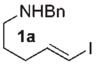
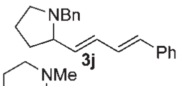
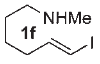
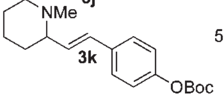
entry	equiv of **2**	equiv of *t*-BuOLi	equiv of BTAC	temp (°C)	solvent	yield of **3**
1	1.6	2.2	0.1	40	THF	63%
2[b]	1.6	2.2	0.1	40	THF	63%
3	1.6	2.2	1.0	40	THF	77%
4	1.6	5.2	1.6	40	THF	70%
5	1.6	1.6	1.0	40	THF	66%
6	1.6	2.2	1.0	23	THF	67%
7	1.6	2.2	1.0	60	THF	84%
8	1.6	2.2	1.0	80	2-MeTHF	85%
9	1.6	2.2	0.5	80	2-MeTHF	87%
10	1.6	2.2	0.1	80	2-MeTHF	85%
11	1.6	2.2	0	80	2-MeTHF	82%
12	1.6	2.7	1.0	80	2-MeTHF	83%
13	2.0	2.6	1.0	80	2-MeTHF	90%
14	2.8	3.4	1.0	80	2-MeTHF	95%
15	2.8	3.4	1.0	23	THF	68%

[a] Conditions: 2.5 mol % $Pd_2dba_3{\bullet}CHCl_3$, 15 mol % Ph_3P. [b] 20 equiv of H_2O.

We initiated our investigation using vinyl iodide **1**, with a pendant nitrogen nucleophile, which was mixed with *N*-tosylhydrazone **2** and lithium *tert*-butoxide. To enhance the solubility of the lithiated sulfonylhydrazone, 0.1 equiv of benzyl triethylammonium chloride (BTAC) was included in the reaction. Then, triethylamine was included because it had proven beneficial for carbenylative aminations during our previous studies.[2a] Using these conditions (Table 1, entry 1) the desired pyrrolidine, (*E*)-**3**, was obtained in 63% yield along with a small amount of the *Z* isomer (< 10%). Addition of 20 equiv of water (entry 2) enhanced the solubility of the lithiated hydrazone but did not change the yield. Notably, a similar yield was obtained when the *Z* isomer of vinyl iodide **1** was subjected to the reaction conditions.[2b] When the amount of BTAC was increased from 0.1 to 1.0 equiv the yield improved (entries 1 and 3). Increasing or decreasing the amount of alkoxide base relative to the hydrazone (entries 4 and 5) led to a slight reduction in yield. Temperature had a notable effect on the reaction yield (entries 6–8). As the temperature was increased, the yield of the desired product went up. Use of 2-methyltetrahydrofuran at 80 °C lead to an improved yield, but the yield was not improved at 90 °C, with dioxanes as the solvent. It should be noted that, at higher temperatures, the *Z* alkene isomer of the product was present in less than 1% yield. A beneficial effect of the phase-transfer catalyst was apparent at 80 °C; a similar trend was observed at lower temperatures (entries 8–11). Remarkably, the reactions were complete in less than 1 min at 80 °C, but as a matter of convenience, reactions were allowed to proceed for several hours. Lastly, observation of Buchwald–Hartwig type products in the aqueous fragments of the workup suggested that the *N*-tosylhydrazone was being depleted first and the remainder alkenyl iodide resulted in a dimer. Inclusion of additional *N*-tosylhydrazone and base afforded high yields (95%) of the desired (*E*)-styrenylpyrrolidine (entry 14). Additional *N*-tosylhydrazone and base did not improve the yield at lower temperature (entries 6 and 15).

Table 2. Scope of Carbenylative Amination with *N*-Tosylhydrazones[a]



entry	vinyl iodide	hydrazone	product	yield
1	 **1a**	**2a** Ar = Ph	 **3a**	95%
2	 **1b**	**2a** Ar = Ph	 **3b**	91%
3	 **1c**	**2a** Ar = Ph	 **3c**	90%
4	 **1d**	**2a** Ar = Ph	 **3d**	90%
5	 **1e**	**2a** Ar = Ph	 **3e**	73%
6	 **1a**	**2b** Ar = 2-BrPh	 **3f**	96% *E*/*Z* 5:1
7	 **1e**	**2c** Ar = 3-O_2NPh	 **3g**	75%
8	 **1d**	**2d** Ar = 4-MeOPh	 **3h**	60%
9	 **1e**	**2e** Ar = 2-MeOPh	 **3i**	78%
10	 **1a**	**2f** Ar = (*E*) CH=CHPh	 **3j**	85% *E*/*Z* 8:1
11	 **1f**	**2g** Ar = 4-BocOPh	 **3k**	50%

[a] Conditions: 2.5 mol % $Pd_2dba_3{\bullet}CHCl_3$, 15 mol % Ph_3P, 2.8 equiv of *N*-tosylhydrazone, 3.4 equiv of *t*-BuOLi, 1.0 equiv of $BnNEt_3Cl$, 2.0 equiv of Et_3N.

To better appreciate the structural requirements for the reaction, we applied the optimized reaction conditions to a series of related vinyl iodides (Table 2, entries 1–5). Reactions were complete within several minutes. Sterically

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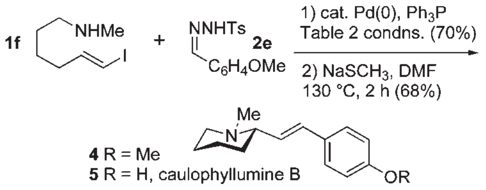
(9) (a) Lutete, L. M.; Kadota, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1622–1623. (b) Kadota, I.; Shibuya, A.; Lutete, L. M.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 4570–4571.

hindered amines, such as the benzhydryl derivative in **3b**, are tolerated on the nitrogen. Moreover, the reaction also tolerates a methyl group at the site of alkylation, generating a quaternary center in **3c**. Such products cannot be accessed through the intramolecular hydroamination of alkynes.[9] Six-membered rings (piperidines) such as **3d** are also formed in good yield. Lastly, **1e**, which contains an oxidatively labile amino protecting group, is also tolerated under the reaction conditions.

We next set out to test the scope of the reaction with respect to *N*-tosylhydrazone (Table 2, entries 6–10) using the same conditions employed in Table 2. Vinyl iodides **1a**, **1d**, **1e**, and **1f** were reacted with various *N*-tosylhydrazones to produce products in 50–96% yield. The ortho bromine substituent of hydrazone **2b** affords product in high yield in a 5:1 ratio of *E* and *Z* isomers. The bromine in **3f** provides a functional handle for lithiation or further palladium-catalyzed transformations. Both electron-rich methoxy substituents and electron-deficient nitro groups (entries 7–11) are tolerated. The low yield in the case of aryl carbonate **3k** is probably due in part to its nucleophilic sensitivity.[10] The reaction also works well with vinyl hydrazones such as **2f**, which was derived from cinnamaldehyde.

Given the functional group tolerance and broad substrate scope, the carbenylative amination is well suited for the synthesis of alkaloid natural products. Vinyl iodide **1f**, with an *N*-methyl group, and *N*-tosylhydrazone **2e** were successfully coupled via a carbenylative amination to provide methoxystyrene **4** in a 70% yield (Scheme 1). The methyl group was removed under nucleophilic conditions in 68% yield to provide the natural product caulophyllumine B.

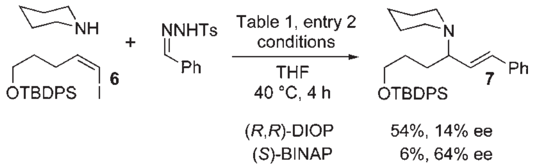
Scheme 1. Synthesis of (±)-Caulophyllumine B



Under our optimized conditions, the carbenylative amination reaction is less efficient when the amine is not tethered to the vinyl iodide (Scheme 2), mainly due to the fact that the *N*-tosylhydrazone generates a diazo compound too quickly for the catalytic cycle. When the reaction was performed at lower temperature (Table 1, entry 2 conditions, without Et_3N) the yield was slightly improved to 38%.

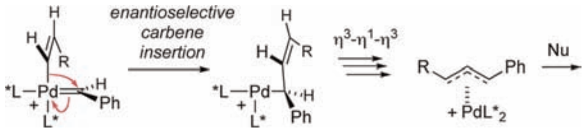
Mixed results were achieved when we tried to control asymmetry in the carbenylative amination using chiral phosphine ligands. When triphenylphosphine (Table 2, entry 1) was replaced with (*R*,*R*)-DIOP in the reaction of (*E*)-vinyl iodide **1a**, pyrrolidine **3a** was obtained in 86% yield but only 12% ee; the yield of **3a** was significantly lower with (*S*)-BINAP (19% yield and 17% ee). When chiral ligands were applied to the reaction of the (*Z*)-vinyl iodide **6**, the yields of allylic amine **7** were dramatically reduced: 54% with (*R*,*R*)-DIOP and 6% with (*S*)-BINAP. More importantly, with (*S*)-BINAP, the product was obtained in 64% ee, suggesting that the carbene insertion step, which sets the absolute stereochemistry (Scheme 3), has significant potential for ligand control, particularly when the vinyl iodide has a *cis*-substituent.

Scheme 2. Intermolecular Carbenylative Amination and Asymmetric Induction



It was noted that rapid reactions and high yields correlated inversely with enantiomeric excess. Reactions with BINAP were particularly slow, taking several hours. We believe that two types of catalytic species are competing in our asymmetric reactions: an agile achiral palladium species and a sluggish chiral palladium–phosphine complex. The achiral catalyst is clearly dominant over the chiral palladium–phosphine complex under the conditions that were optimized for triphenylphosphine. We expect those fortunes to be reversed with the right choice of ligand and conditions.

Scheme 3. Enantioselection Model: Carbene Insertion



In conclusion we have demonstrated that *N*-tosylhydrazones containing both aryl and vinyl substitutents can participate in a powerful palladium-catalyzed carbenylative amination reaction to generate pyrrolidine and piperidine ring systems that are common to alkaloid natural products. The reaction is tolerant of a wide range of functional groups on the amine nucleophile and the hydrazone substituent. The ligand (*S*)-BINAP provided promising levels of asymmetric induction but in low yield.

Acknowledgment. A.K. is supported by a graduate fellowship from the National Science Foundation.

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

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(10) Nakamura, K.; Nakajima, T.; Kayahara, H.; Nomura, E.; Taniguchi, H. *Tetrahedron Lett*. **2004**, *45*, 495–499.

The authors declare no competing financial interest.