A Highly Effective Catalyst System for the Pd-Catalyzed Amination of Vinyl Bromides and Chlorides
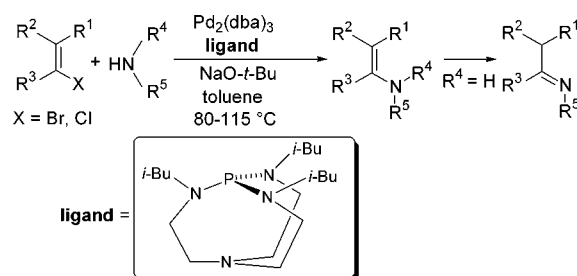
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ABSTRACT

A highly efficient synthesis of enamines and imines by Pd-catalyzed amination of vinyl bromides or chlorides with amines is described using the Pd$_2$(dba)$_3$/P(i-BuNCH$_2$CH$_2$)$_3$N catalyst system.

Palladium-catalyzed Buchwald–Hartwig amination is a powerful method for constructing aromatic C–N bonds in synthetically useful arylamines.[1] Consequently, considerable attention has been devoted to the development of ligand supported palladium catalyst systems for this process.[2,3] It is important to note that most of these studies were performed with a wide variety of aryl iodides, bromides, and chlorides as electrophilic coupling partners. By contrast, examples of amination of vinyl halides leading to enamines (or imines) are rare.[4]

Enamines are important synthetic intermediates,[5] especially in the alkylation and acylation of ketones as pioneered by Stork.[6] Although several methods[7] are known for synthesizing enamines (and imines), a palladium-catalyzed Buchwald–Hartwig amination could constitute a significant

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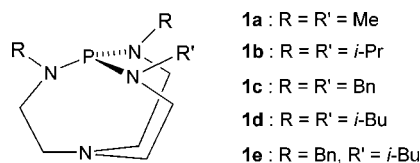
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advancement in the aforementioned methodology and it could also overcome several limitations associated with the present approaches. Surprisingly, it was only in 2002, almost a decade after the first palladium-catalyzed amination of aryl halides was reported,[8] that Voskoboynikov[9] reported for the first time the cross-coupling of vinyl bromides with azoles and phenothiazine using a Pd(dba)$_2$/P(t-Bu)$_3$ catalyst system. Soon after Voskoboynikov's report, Barluenga et al. demonstrated that vinyl bromides can be effectively coupled with a wide variety of amines using BINAP as a ligand in combination with either Pd(OAc)$_2$ or Pd$_2$(dba)$_3$.[10] These workers also demonstrated the suitability of vinyl chlorides as coupling partners in the aforementioned process when [2,2′-(biphenyl)P(t-Bu)$_2$(NMe$_2$)] was employed as the ligand.[11]

In recent years, we have reported on the palladium-catalyzed cross-coupling of aryl halides with amines,[3] arylboronic acids,[12] and organostannanes.[13] These processes are successfully accomplished with the use of palladium catalysts supported by ligand **1d** (Figure 1). In a continuation

1a : R = R' = Me
1b : R = R' = i-Pr
1c : R = R' = Bn
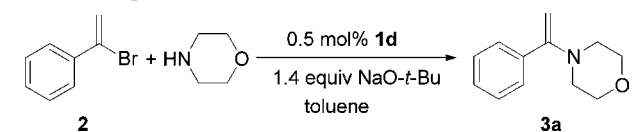**1d** : R = R' = i-Bu
1e : R = Bn, R' = i-Bu

Figure 1. Proazaphosphatranes used in this study.

of these studies, we document herein a highly active palladium catalyst utilizing ligand **1d** for the efficient synthesis of enamines. Our process is effective for the amination of both vinyl bromides and chlorides. The method also uses much lower palladium and ligand loadings (in the case of vinyl bromides), and it proceeds in shorter reaction times compared with those in previous reports.

For the optimization of reaction conditions, we examined the amination reaction of α-bromostyrene (**2**) with morpholine in toluene using **1d** as the ligand and NaO-t-Bu as the base (Table 1). Both Pd(OAc)$_2$ and Pd$_2$(dba)$_3$ were found to

(7) Using amine-substituted Wadsworth−Emmons reagents: (a) Martin, S. F.; Gompper, R. *J. Org. Chem.* **1974**, *39*, 2814. Using condensation reactions: (b) White, W. A.; Weingarten, H. *J. Org. Chem.* **1967**, *32*, 213. (c) Hickmott, P. W. *Tetrahedron* **1982**, *38*, 1975. Via methylenation of amides: (d) Petasis, N. A.; Lu, S. P. *Tetrahedron Lett.* **1995**, *36*, 2393. Via hydroamination of alkynes: (e) Barluenga, J.; Aznar, F. *Synthesis* **1975**, 704.

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Table 1. Optimization of Reaction Conditions

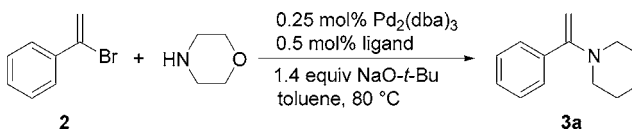| entry	catalyst (mol %)	time (h)	T (°C)	yield^a (%)
1	Pd(OAc)$_2$ (0.25)	7	80	83
2^b	Pd$_2$(dba)$_3$ (0.25)	8	80	2
3	Pd$_2$(dba)$_3$ (0.25)	3	80	95
4	Pd$_2$(dba)$_3$ (0.25)	8	rt	nr^c
5	none^d	12	80	nr^c

^{a} Isolated yields (average of two runs). ^{b} The reaction was performed in the absence of **1d**, and the yield was based on ^{1}H NMR spectroscopic integration. ^{c} nr = no reaction. ^{d} In the absence of palladium but with **1d** present.

be suitable palladium sources. The reaction conditions shown in entry 3 of Table 1 proved to be optimal. Thus, with 0.25 mol % of Pd$_2$(dba)$_3$ and 0.5 mol % of **1d** (L/Pd = 1), the desired enamine **3a** was obtained in 95% isolated yield in 3 h at 80 °C.

The NMR spectra (^{1}H and ^{13}C) of enamine **3a** were very clean after the workup. The crude reaction mixture was filtered through Celite followed by removal of solvent under reduced pressure. No silica gel column chromatography was performed on any of the enamines described in this paper owing to their acid-sensitive nature.[10a] Further control experiments showed the need for palladium, ligand, and a reaction temperature of 80 °C (Table 1, entries 2−5).

A screening study of proazaphosphatranes was also performed (Table 2). Except for proazaphosphatrane **1a** (R

Table 2. Survey of Proazaphosphatranes

entry	ligand	time (h)	yield^a (%)
1	**1a**	8	trace
2	**1b**	6	94
3	**1c**	3.5	93
4	**1d**	3	95
5	**1e**	4	93

^{a} Isolated yields (average of two runs).

= R′ = Me, entry 1), the other proazaphosphatranes possessing varying degrees of additional steric hindrance [i.e., isopropyl (**1b**, entry 2), benzyl (**1c**, entry 3), isobutyl (**1d**, entry 4), or a combination of benzyl and isobutyl groups (**1e**, entry 5)] on the PN$_3$ nitrogens provided active palladium catalysts. High activity displayed by ligands **1b**, **1c**, and **1e** is surprising as they were either ineffective or showed only moderate activity in the amination reactions performed on aryl bromides and chlorides.[3b,e]

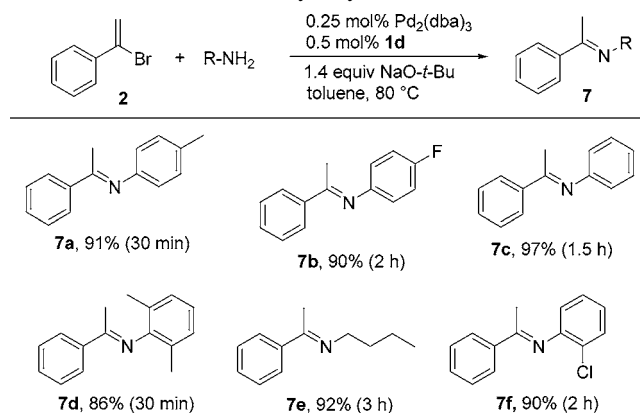| vinyl bromide	amine	time (h)	product	yield (%)[b]
4	morpholine	2.0	**5a**	98
4	piperidine	1.5	**5b**	97
4	(dioxolane-piperidine)	2.0	**5c**	99
4	HN(CH$_2$Ph)$_2$	3.0	**5d**	98
4	HN(Et)(CH$_2$Ph)	4.0	**5e**	88
4	HN(CH$_3$)(Ph)	3.0	**5f**	99
4	Bu$_2$NH	2.0	**5g**	96
4	Et$_2$NH	1.5	**5h**	98
4	HN(Et)(Ph)	2.0	**5i**	96
2	(dioxolane-piperidine)	1.0	**3b**	96
2	HN(CH$_3$)(Ph)	2.0	**3c**	93
2	piperidine	1.5	**3d**	98
(cyclohexenyl bromide)	morpholine	2.0	**6**	91

[a] Reaction conditions: Pd$_2$(dba)$_3$ (0.25 mol %), **1d** (0.5 mol %), NaO-*t*-Bu (1.4 equiv), toluene (4 mL), 80 °C. [b] Isolated yields (average of two runs).

Further studies to establish the scope of the reaction were performed with commercially available **1d** as the ligand. As is evident from Table 3, both α-bromostyrene and β-bromostyrene were efficiently coupled with cyclic secondary amines, acyclic secondary amines, and secondary aliphatic amines, affording the desired enamines in excellent yields. It is noteworthy that only very short reaction times (1−4 h) are needed for these reactions to proceed to completion. Another appealing aspect of our method is the catalyst loading (0.5 mol % of Pd and 0.5 mol % of ligand **1d**) which is at least 2-fold (and in some cases 6-fold) less than was used for the Pd/BINAP catalyst system reported by

Barluenga.[10a,b] For example, reactions shown for the formation of **3b,c** and **5a,c,d,f** in Table 3 and for **3a** in Table 1 when performed with the Pd/BINAP catalyst system required 3 mol % of Pd and 6 mol % of BINAP, compared with the 0.5 mol % of Pd and 0.5 mol % of **1d** that provided these enamines in comparable or higher yields.[10]

Next, we investigated the coupling of vinyl bromides with primary amines (Scheme 1). Enamines initially formed in

Scheme 1. Synthesis of Imines from **2** Using the Pd$_2$(dba)$_3$/**1d** Catalyst System[a]

7a, 91% (30 min)   **7b**, 90% (2 h)   **7c**, 97% (1.5 h)

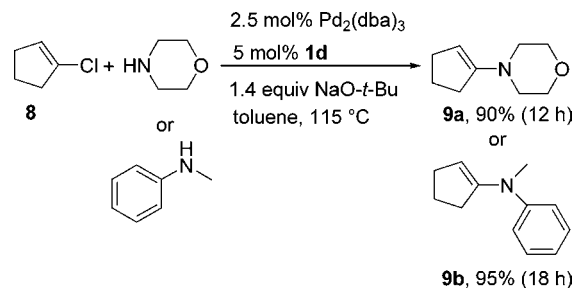**7d**, 86% (30 min)   **7e**, 92% (3 h)   **7f**, 90% (2 h)

[a] Isolated yields (average of two runs) and reaction times appear in parentheses.

these reactions tautomerized to give the more stable imine form. In nearly all cases, excellent yields of the desired imines were obtained. As expected, aromatic amines coupled faster (30 min to 2 h) than aliphatic amines (3 h). The reaction of a sterically hindered primary amine, such as 2,6-dimethylaniline, also proceeded efficiently.

Enamine formation via the palladium-catalyzed amination of a vinyl chloride was also briefly explored (Scheme 2).

Scheme 2. Synthesis of Enamines from the Vinyl Chloride **8** Using the Pd$_2$(dba)$_3$/**1d** Catalyst System[a]

9a, 90% (12 h)
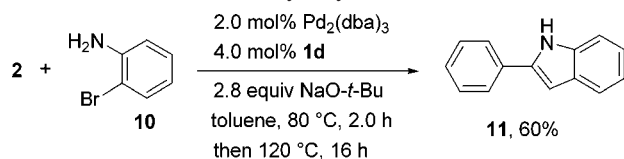or
9b, 95% (18 h)

[a] Isolated yields (average of two runs) and reaction times appear in parentheses.

For these studies, 1-chlorocyclopentene (**8**) was chosen as a prototypical substrate. Unfortunately, our standard conditions proved inapplicable to vinyl chlorides. Pleasingly, however,

8 reacted efficiently with morpholine and *N*-methylaniline at elevated temperature (115 °C) and higher catalyst loading (5 mol % Pd and 5 mol % **1d**). We are now focusing on widening the scope of vinyl bromides and chlorides that can employed in amination reactions to include deactivated and sterically hindered examples.

Finally, we successfully extended our method to the synthesis of the indole **11** by a cascade alkenyl amination followed by an intramolecular Heck reaction in one pot (Scheme 3). A yield comparable with that obtained using

Scheme 3. Reaction of Vinyl Bromide **2** with *o*-Bromoaniline **10** for the Synthesis of 1*H*-Indole **11** Using the Pd$_2$(dba)$_3$/**1d** Catalyst System[a]

[a] Isolated yield (average of two runs).

the Pd/DavePhos system (64%)[14] was achieved with lower palladium and ligand loadings. Further efforts are underway to determine the scope of such cascade reactions.

In summary, an efficient and general catalyst system based on commercially available Pd$_2$(dba)$_3$ and proazaphosphatrane **1d** has been developed for the reaction of vinyl bromides and chlorides with amines to afford enamines and imines in excellent yields.[15] The use of lower palladium and ligand loading, shorter reaction times, and a relatively mild temperature (80 °C for vinyl bromides) are salient features of this method.

Supporting Information Available: Experimental procedures, references for known products, complete characterization of previously unknown products, and copies of ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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