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# PdI<sub>2</sub> as a Simple and Efficient Catalyst for the Hydroamination of Arylacetylenes with Anilines

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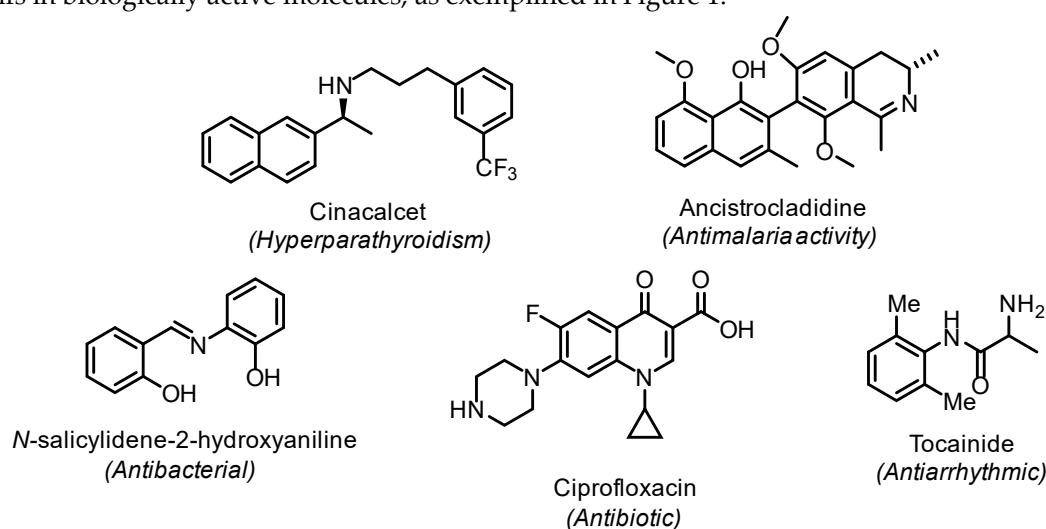
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**Abstract:** The hydroamination reaction is a convenient alternative strategy for the formation of C–N bonds. Herein, we report a new versatile and convenient protocol for the hydroamination of arylacetylenes with anilines using palladium iodide in the absence of any added ligand as catalyst. Mild conditions, excellent regio- and stereoselectivity, and high functional group tolerance are the main features of this methodology. A subsequent reduction step gives access to a wide variety of secondary aromatic amines.

**Keywords:** hydroamination; palladium; secondary amines; imines

## 1. Introduction

Amines, imines, and enamines are useful building blocks in organic synthesis and ubiquitous motifs in biologically active molecules, as exemplified in Figure 1.



**Figure 1.** Selected example of biologically active compounds containing amine, imine, or enamine functionalities.

One of the most attractive strategies for their preparation is the catalytic hydroamination of unsaturated compounds, such as alkenes or alkynes [1–8]. The hydroamination reaction, consisting of the addition of an N–H bond to a C–C multiple bond, features a 100% atom efficiency associated with the large availability of the starting materials (these are alkynes, alkenes, amines). Nevertheless, in order to promote the addition of the amino group on the multiple C–C bond, a high activation barrier, resulting from the repulsion between the high electron density of the nucleophile and the  $\pi$ -electrons of the multiple bond, needs to be overcome. In this context, metal catalysis can serve as a powerful tool to reduce the activation barrier either by coordinating the multiple bond and thus subtracting the electron density or by N–H metalation, resulting in a strongly nucleophilic metal amide moiety. Amide intermediates can be also generated by the oxidative addition of the N–H bond to the metal. Several metals have been found to catalyze hydroamination reactions. Early transition metals, such as Ti or Zr, as well as lanthanides, display high activity [9–14], although they are poorly stable, owing to their oxophilicity that renders them air and moisture sensitive. Late transition metals [15–19] feature a superior stability to moisture and air, together with broader functional group tolerance. Remarkably, cationic gold-based catalysts were highly active in the hydroamination of alkynes with amines [20–21]. The choice of the catalytic system is driven not only by the performance but also by its availability and cost. In this regard, palladium is clearly more attractive than rhodium, iridium, or gold.

Palladium-catalyzed hydroamination reactions have found several applications in the synthesis of biologically relevant heterocycles [22–25]. Alkynes [26], alkenes [27], dienes [28], and allenes [29] can serve as acceptor in combination with both aromatic and aliphatic amines. Despite the versatility of palladium-catalyzed hydroaminations, elaborate and expensive catalytic systems are often required. In particular, in the reaction between an alkyne and an aromatic amine, palladium has been employed in the presence of NHC [30] or NHCP [31] ligands. In both these cases, the catalytic precursor needs to be activated with a silver salt that acts as halogen scavenger. 3-Imino phosphine (3IP) ligands [32] also provide an efficient alternative but, similarly, a multistep synthesis for obtaining the catalytic active complex is required. Yamamoto and coworkers contributed significantly to the field by exploiting the possibility of using simple palladium salts such as palladium nitrate [33]. A dramatic rate enhancement effect was observed with 2-aminophenols, where the chelating OH group was crucial for the reaction outcome. Subsequently, the same research group was able to expand the reaction scope to variously substituted aryl amines resorting to an aqua palladium complex  $[\text{Pd}(\text{dppe})(\text{H}_2\text{O})_2](\text{TiO})_2$  [34]. The Yamamoto's group also reported the use of  $\text{Pd}(\text{PPh}_3)_4$  in combination with benzoic acid for the hydroamination of internal alkynes to allyl amines [35].

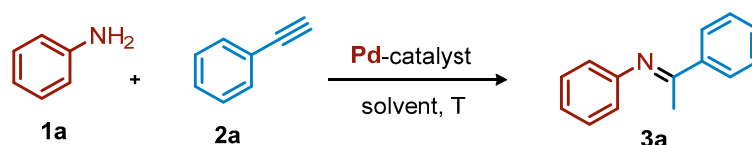
Owing to its flexibility and synthetic attractiveness, hydroamination reactions are still of high interest, and we recently reported the hydroamidation of propargylic ureas to give imidazolidin-2-ones and imidazol-2-ones [36]. In this work, we report the use of a cheap and commercially available palladium catalyst (i.e.,  $\text{PdI}_2$ ) for the hydroamination of arylacetylenes with anilines under mild reaction conditions and low catalyst loading.

## 2. Results and Discussion

The palladium-catalyzed intermolecular hydroamination reaction was initially investigated using aniline (**1a**, 1 equiv, 0.4 mmol) and phenylacetylene (**2a**, 1.2 equiv) as model substrates, in dioxane (0.2 M) as the solvent at 80 °C for 18 h, in the presence of catalytic amount of a palladium salt (2 mol%, Table 1). Palladium acetate did not provide any conversion, while palladium dichloride produced only traces of imine **3a** (Table 1, Entries 1–2). Gratifyingly, palladium iodide resulted in 73%  $^1\text{H}$ NMR yield of the hydroamination product, which was identified as (*E*)-*N*,1-diphenylethan-1-imine **3a** deriving from the Markovnikov addition to the triple bond followed by isomerization (Table 1, Entry 3). An excess of iodide anions (from added KI) caused a slight decrease in the catalytic activity of  $\text{PdI}_2$  (Table 1, Entry 4), and a similar outcome was found in the presence of  $\text{K}_2\text{PdI}_4$  (Table 1, Entry 5). This result is in agreement with Brunet's study, where  $\text{PtBr}_2$  was used in combination with bromide anions for the hydroamination of terminal alkynes [37]. The excess of iodide anions can in

this case be detrimental to the yield, since it can affect the equilibrium of species **I** and **II** in the catalytic cycle (see below). We then investigated the effect of concentration, temperature, catalyst loading, and solvent. At 0.4 M, compound **3a** was obtained with 81% yield (Table 1, entries 6), while a further increase of the concentration to 0.8 M led to a less satisfactory result (Table 1, entries 7). As expected, temperature also plays a fundamental role in this transformation. In fact, when the reaction was performed at 100 °C, we observed a slightly decrease in the yield of **3a** (Table 1, entry 8, 77%). Synthetically useful yields were still observed when reducing the catalyst loading to 1.0 mol% (Table 1, entry 9) and to 0.5 mol% (Table 1, entry 10) with yields of **3a** of 63% and 47%, respectively.

**Table 1.** Optimization study for the hydroamination of phenylacetylene with aniline<sup>a</sup>.



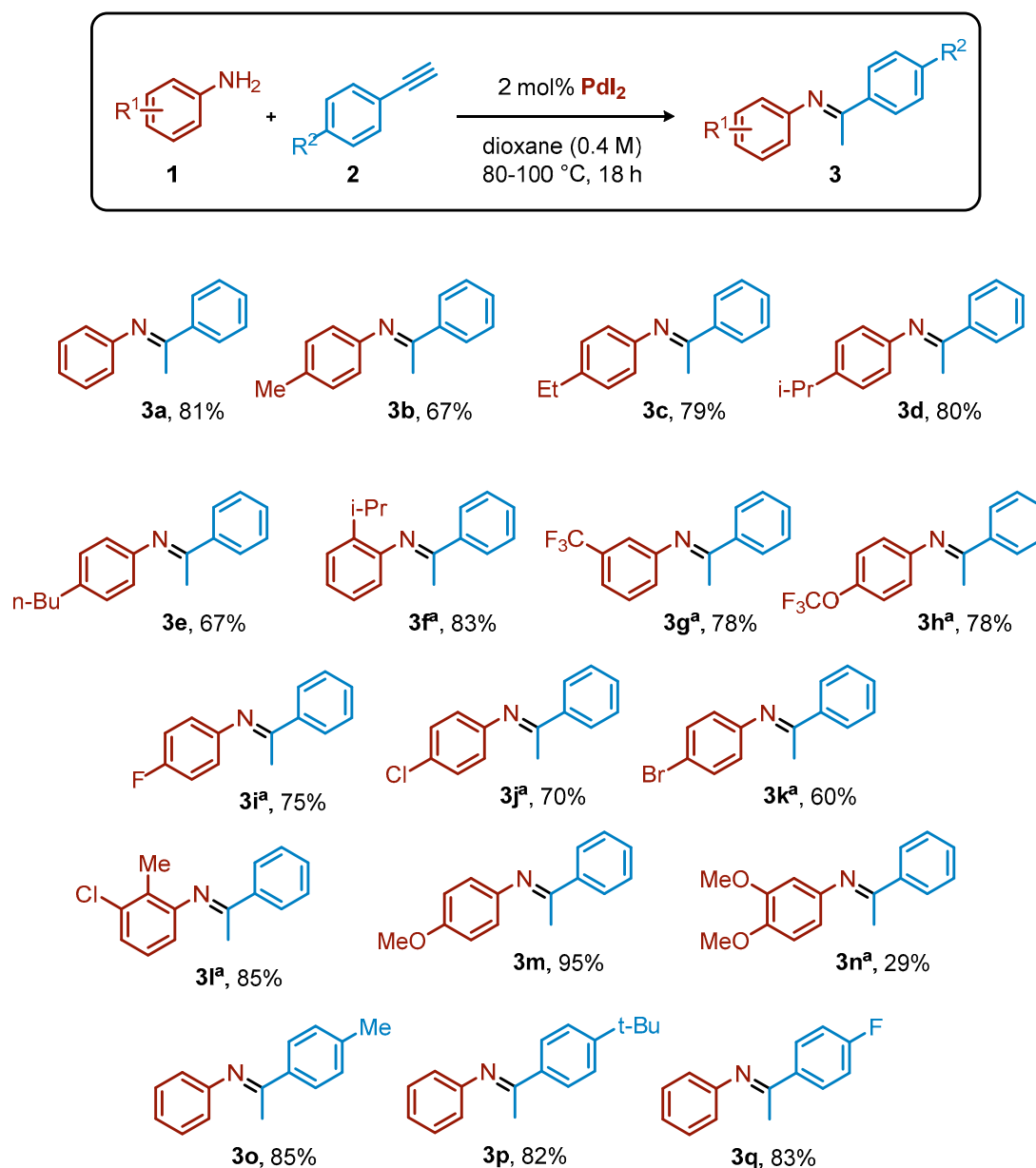
Entry	Pd source (%)	Conc. (M)	T (°C)	Solvent	Conv. (%) 1a	Yield <sup>b</sup> (%) 3a
1	Pd(OAc) <sub>2</sub> (2)	0.2	80	1,4-dioxane	<5	-
2	PdCl <sub>2</sub> (2)	0.2	80	1,4-dioxane	7	5
3	PdI <sub>2</sub> (2)	0.2	80	1,4-dioxane	91	73
4	PdI <sub>2</sub> (2) + KI (20%)	0.2	80	1,4-dioxane	82	64
5	K <sub>2</sub> PdI <sub>4</sub> (2)	0.2	80	1,4-dioxane	81	62
<b>6</b>	<b>PdI<sub>2</sub> (2)</b>	<b>0.4</b>	<b>80</b>	<b>1,4-dioxane</b>	<b>99</b>	<b>81</b>
7	PdI <sub>2</sub> (2)	0.8	80	1,4-dioxane	95	74
8	PdI <sub>2</sub> (2)	0.4	100	1,4-dioxane	99	77
9	PdI <sub>2</sub> (1)	0.4	80	1,4-dioxane	84	63
10	PdI <sub>2</sub> (0.5)	0.4	80	1,4-dioxane	69	47
11	PdI <sub>2</sub> (2)	0.4	80	DMF	<5	0
12	PdI <sub>2</sub> (2)	0.4	80	MeCN	38	27
13	PdI <sub>2</sub> (2)	0.4	80	toluene	47	36

<sup>a</sup> Reaction conditions: **1a** (1 equiv, 0.4 mmol), **2a** (1.2 equiv), Pd source, solvent, 18 h. <sup>b</sup> Yield calculated by <sup>1</sup>H NMR using dimethyl maleate as internal standard.

Lastly, different solvents were evaluated. Dimethylformamide (DMF) proved to be ineffective under these reaction conditions (entry 11), while acetonitrile and toluene allowed the formation of the desired imine **3a** even though in lower yields (entries 12 and 13).

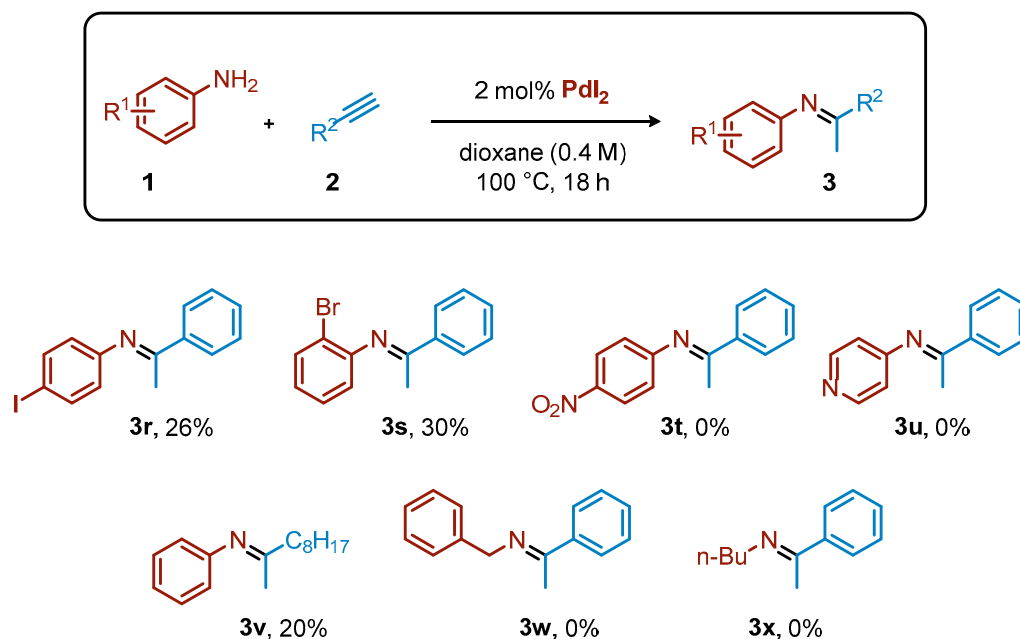
Once the best reaction conditions (Table 1, entry 6) were determined, we then investigated the scope for variously substituted anilines (**1**) and arylacetylenes (**2**) (Scheme 1). In general, the yields attained using PdI<sub>2</sub> as catalyst were comparable with the ones achieved with the previously employed more complex catalytic systems [30]. For example, different alkyl chains at the *para* position of the aniline provided good yields, irrespective of the length of the chain (yields of **3b**, 67%; **3c**, 79%; **3e**, 67%) or the steric hindrance (**3d**, 80%). Interestingly, an isopropyl group at the *ortho* position of the aniline also allowed an excellent product yield (**3f**, 83%). Fluoro-containing groups were well tolerated under these reaction conditions, regardless of their position or electronic properties. With a CF<sub>3</sub> group at the *meta* position, the expected imine **3g** was formed in 78% yield, and the same result was observed starting from the aniline ring bearing an OCF<sub>3</sub> substituent *para* to the NH<sub>2</sub> group (**3h**, 78%). *para*-Substituted anilines with fluoro, chloro, or bromo smoothly underwent the hydroamination, resulting in 75% (**3i**), 70% (**3j**), and 60% (**3k**) yields of the desired imines, respectively. Even a disubstituted aniline, such as 2-methyl-3-chloroaniline, behaved nicely, providing the corresponding product **3l** with 85% yield. The OMe substituent in *para* position on the aniline ring led to 95% yield of **3m**, while the presence of two OMe groups caused a significant decrease of the yield (**3n**, 29%).

The versatility of the process with respect to the nature of the arylacetylene partner was also considered. Both electron-withdrawing and electron-donating groups were highly compatible with the catalytic protocol, providing excellent yields of the corresponding imines (**3o–q**, 82–85%).



**Scheme 1.** Scope for the hydroamination of arylacetylene derivatives with anilines. Reaction conditions: **1** (1 equiv, 0.8 mmol), **2** (1.2 equiv, 1 mmol),  $\text{PdI}_2$  (2 mol%, 0.016 mmol), dioxane (2 mL), 80 °C, 18 h. Yield calculated by  $^1\text{H}$  NMR using dimethyl maleate as internal standard. <sup>a</sup> Reaction performed at 100 °C.

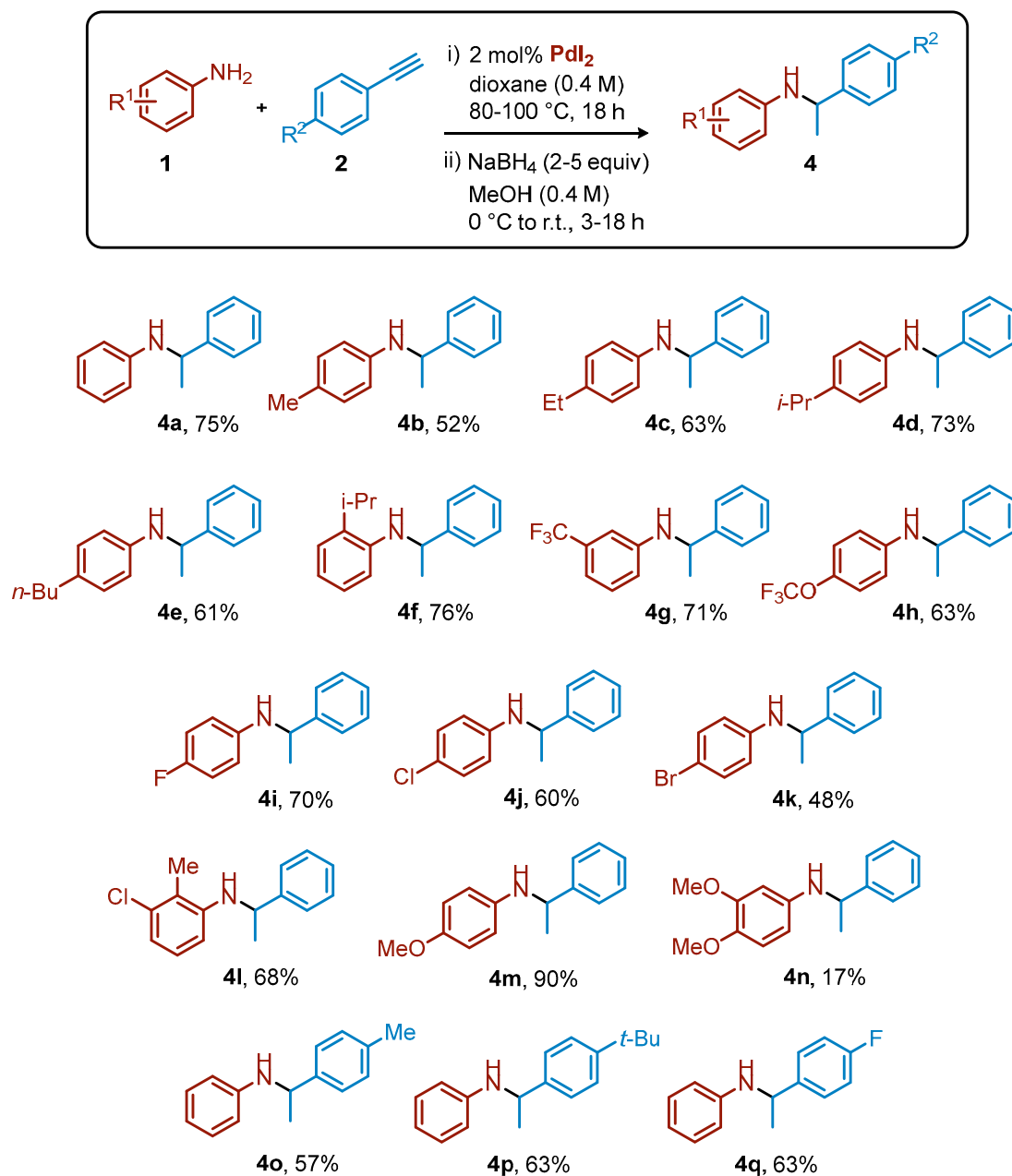
Other substrates were less tolerated (Scheme 2). For instance, 4-iodoaniline gave only 26% yield of the corresponding imine (**3r**). The iodide on the ring was highly reactive under palladium catalysis, leading to a complex mixture of byproducts. For the same reason, 2-bromoaniline in combination with phenyl acetylene gave only 30% of the expected **3s**. The presence of a strongly electron-withdrawing group, such as the nitro group on the aniline ring, completely inhibited the process. Alkylacetylenes were considerably less reactive than arylacetylenes, as exemplified by the formation of **3v** in 20% yield starting from 1-decyne. Primary alkylamines were not reactive under the optimized conditions, likely due to their pronounced coordinating nature.



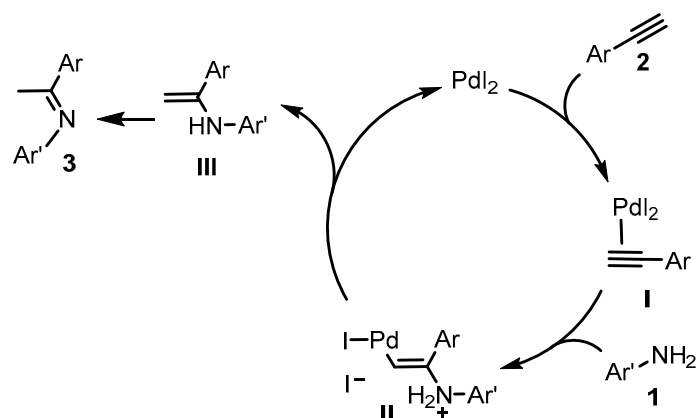
**Scheme 2.** Limitations for the PdI<sub>2</sub>-catalyzed hydroamination of acetylene derivatives. Yield calculated by <sup>1</sup>H NMR.

Not surprisingly, imine products **3** were unstable under acidic conditions and the isolated yields after column chromatography were very low. We then decided to reduce compounds **3** to the corresponding, more stable secondary amines **4**, using simple and inexpensive NaBH<sub>4</sub>. The overall isolated yields for the two-step synthesis of secondary amines **4** (*I step*: PdI<sub>2</sub>-catalyzed hydroamination and *II step*: reduction) starting from anilines and terminal arylacetylenes, reported in Scheme 3, ranged from 17% to 90%. In some cases, the two-step yield was about 20% lower than the corresponding NMR hydroamination yield (**4o-q**). This was mainly due to a non-optimized reduction procedure, which can be improved with the use of alternative reduction reagents, such as NaBH<sub>3</sub>CN.

From a mechanistic point of view, coordination of the triple bond of **2** to PdI<sub>2</sub> generates the π-complex **I** (Scheme 4). This type of coordination makes the triple bond susceptible to undergo nucleophilic attack of the nitrogen atom of amine **1** resulting in the vinylpalladium iodide intermediate **II**. Then, protonolysis of **II** regenerates PdI<sub>2</sub> and leads to enamine intermediate **III**, which readily tautomerizes to imine **3**. The presence of the iodide counteranion in the process is crucial and we believe that its role may be connected, on one hand, to its higher ability to act as the leaving group in the nucleophilic attack step and, on the other hand, to its higher electron-releasing power, which tends to favor the protonolysis step [38]. Moreover, iodide anions display a superior ability to stabilize palladium(II) species, compared to other counteranions, such as acetates [39]. Efforts at understanding the effect of iodide anions in this transformation are underway in our laboratories [40].



**Scheme 3.** Overall isolated yields for secondary amines **4** after two steps (hydroamination and reduction).



**Scheme 4.** Proposed mechanism for PdI<sub>2</sub>-catalyzed hydroamination of terminal alkynes **2** with anilines **1** leading to imines **3** through the formation of vinylamines **III** as intermediates.

### 3. Materials and Methods

#### 3.1. Materials

All chemicals were purchased from commercial sources and used as received. Dioxane and methanol were dried and stored over molecular sieves previously activated in an oven at 300 °C overnight. Catalytic reactions were carried out under nitrogen using the standard Schlenk technique. Reaction mixtures were analyzed using a GC Agilent Technologies 7820A GC System equipped with FID detector and column Agilent Technologies 19091J 413 (30mX0,32mm) and a gas chromatograph Agilent Technologies 6890N Network GC System equipped with quadrupole Agilent Technologies 5973 Network Mass Selective Detector and column Fused Silica Capillary Column (30mX0,25mm) for GC-MS analyses. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded at 300 K on a Bruker 400 MHz using the solvent as internal standard (7.26 ppm for <sup>1</sup>H NMR and 77.16 ppm for <sup>13</sup>C NMR for CDCl<sub>3</sub>). The terms m, s, d, t, q and quint represent multiplet, singlet, doublet, triplet, quadruplet, and quintuplet respectively, and the term br means a broad signal.

#### 3.2. General Procedures

##### 3.2.1. Hydroamination of Terminal Alkynes with Anilines

A flame-dried test tube of 10 mL was charged with palladium iodide (0.016 mmol, 2 mol%), aniline **1** (0.8 mmol, 1 equiv) and alkyne **2** (1 mmol, 1.2 equiv). The test tube was sealed with a rubber cup, filled with nitrogen, evacuated, and backfilled with nitrogen three times. Then, dry 1,4-dioxane (2 mL) was added. The tube was placed in an oil bath at 80 or 100 °C and stirred for 18 hours. The reaction crude was cooled to room temperature, filtered through celite, and dried under reduced pressure. The <sup>1</sup>H NMR analysis on the reaction crude using dimethyl maleate as the internal standard was immediately acquired to determine the yield of imine **3**.

##### 3.2.2. Reduction of Imine **3** to Secondary Amine **4**

The hydroamination crude was transferred in a two-neck round-bottom flask and dissolved in dry methanol (2 mL). The flask was placed in an ice bath and sodium borohydride (2–5 equiv) was added portion wise. The mixture was stirred at 0 °C until a complete conversion of **3**, detected by TLC analysis. The mixture was quenched with 2 mL of KOH (1M). The crude was diluted with 20 mL of EtOAc, washed with water and brine and dried over MgSO<sub>4</sub>. The pure amine **4** was obtained after flash column chromatography using a mixture of hexane and EtOAc as eluent.

#### 3.3. Product Characterization

*N*-(1-Phenylethyl)aniline (**4a**) was synthesized from aniline (73  $\mu$ L) and phenylacetylene (105  $\mu$ L) following the general hydroamination procedure. Two equiv of NaBH<sub>4</sub> were employed during the reduction step. The reaction crude was purified by flash column chromatography using hexane/ethyl acetate (98:2) as eluent to give **4a** (118 mg, 75%) as pale-yellow oil. The spectroscopic data of **4a** are consistent with literature values [41]. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.46 (d, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.18 (t, *J* = 7.9 Hz, 2H), 6.75 (t, *J* = 7.3 Hz, 1H), 6.62 (d, *J* = 7.8 Hz, 2H), 4.57 (q, *J* = 6.7 Hz, 1H), 4.38 (br s, 1H), 1.60 (d, *J* = 6.7 Hz, 3H).

4-Methyl-*N*-(1-phenylethyl)aniline (**4b**) was synthesized from *p*-toluidine (86 mg) and phenylacetylene (105  $\mu$ L) following the general hydroamination procedure. Four equiv of NaBH<sub>4</sub> were employed during the reduction step. The reaction crude was purified by flash column chromatography using hexane/ethyl acetate (98:2) as eluent to give **4b** (88 mg, 52%) as yellow oil. The spectroscopic data of **4b** are consistent with literature values [41]. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.55 (d, *J* = 7.7 Hz, 2H), 7.49 (t, *J* = 7.1 Hz, 2H), 7.43–7.37 (m, 1H), 7.10 (d, *J* = 7.7 Hz, 2H), 6.63 (d, *J* = 7.8 Hz, 2H), 4.64 (q, *J* = 6.8 Hz, 1H), 4.05 (br s, 1H), 2.39 (s, 3H), 1.68 (d, *J* = 6.9 Hz, 3H).

4-Ethyl-*N*-(1-phenylethyl)aniline (**4c**) was synthesized from 4-ethylaniline (99  $\mu$ L) and phenylacetylene (105  $\mu$ L) following the general hydroamination procedure. Two equiv of NaBH<sub>4</sub> were employed during the reduction step. The reaction crude was purified by flash column chromatography using hexane/ethyl acetate (98:2) as eluent to give **4c** (113 mg, 63%) as yellow oil. The spectroscopic data of **4c** are consistent with literature values [42]. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.50 (d, *J* = 7.6 Hz, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.06 (d, *J* = 8.5 Hz, 2H), 6.60 (d, *J* = 8.4 Hz, 2H), 4.58 (q, *J* = 6.7 Hz, 1H), 4.19 (br s, 1H), 2.63 (q, *J* = 7.6 Hz, 2H), 1.62 (d, *J* = 6.7 Hz, 3H), 1.28 (t, *J* = 7.6 Hz, 3H).

4-Isopropyl-*N*-(1-phenylethyl)aniline (**4d**) was synthesized from 4-isopropylaniline (108 mg) and phenylacetylene (105  $\mu$ L) following the general hydroamination procedure. Two equiv of NaBH<sub>4</sub> were employed during the reduction step. The reaction crude was purified by flash column chromatography using hexane/ethyl acetate (98:2) as eluent to give **4d** (140 mg, 73%) as orange viscous oil. The spectroscopic data of **4d** are consistent with literature values [43]. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.45 (d, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 7.04 (d, *J* = 8.2 Hz, 2H), 6.56 (d, *J* = 8.2 Hz, 2H), 4.52 (q, *J* = 6.7 Hz, 1H), 4.32 (br s, 1H), 2.83 (hept, *J* = 6.9 Hz, 1H), 1.57 (d, *J* = 6.7 Hz, 3H), 1.24 (d, *J* = 6.9, 6H).

4-Butyl-*N*-(1-phenylethyl)aniline (**4e**) was synthesized from 4-butyylaniline (119 mg) and phenylacetylene (105  $\mu$ L) following the general hydroamination procedure. Two equiv of NaBH<sub>4</sub> were employed during the reduction step. The reaction crude was purified by flash column chromatography using hexane/ethyl acetate (98:2) as eluent to give **4e** (124 mg, 61%) as dark orange oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.44 (d, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.54 (d, *J* = 8.4 Hz, 2H), 4.52 (q, *J* = 6.7 Hz, 1H), 4.29 (br s, 1H), 2.52 (t, *J* = 7.7 Hz, 1H), 1.64–1.51 (m, 5H), 1.42–1.34 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  145.3, 144.9, 132.1, 129.1 (2C), 128.7 (2C), 127.0, 126.1 (2C), 113.7 (2C), 54.1, 34.8, 34.0, 25.0, 22.4, 14.1.

2-Isopropyl-*N*-(1-phenylethyl)aniline (**4f**) was synthesized from 2-isopropylaniline (108 mg) and phenylacetylene (105  $\mu$ L) following the general hydroamination procedure. Two equiv of NaBH<sub>4</sub> were employed during the reduction step. The reaction crude was purified by flash column chromatography using hexane/ethyl acetate (98:2) as eluent to give **4f** (145 mg, 76%) as yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.40 (d, *J* = 7.7 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.28–7.21 (m, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 6.97 (t, *J* = 7.7 Hz, 1H), 6.73 (br s, 1H), 6.45 (br s, 1H), 4.55 (q, *J* = 6.7 Hz, 1H), 4.07 (br s, 1H), 3.02 (br s, 1H), 1.61 (br s, 3H), 1.35 (d, *J* = 6.7 Hz, 6H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  145.5, 143.9, 131.8, 128.8, 126.9, 126.7, 125.9, 124.9, 117.2, 111.8, 53.5, 27.5, 25.5, 22.5, 22.4.

*N*-(1-Phenylethyl)-3-(trifluoromethyl)aniline (**4g**) was synthesized from 3-trifluoromethylaniline (100  $\mu$ L) and phenylacetylene (105  $\mu$ L) following the general hydroamination procedure. Two equiv of NaBH<sub>4</sub> were employed during the reduction step. The reaction crude was purified by flash column chromatography using hexane/ethyl acetate (98:2) as eluent to give **4g** (151 mg, 71%) as dark yellow oil. The spectroscopic data of **4g** are consistent with literature values [44].



$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39–7.31 (m, 4H), 7.29–7.23 (m, 1H), 7.17 (t,  $J = 7.9$  Hz, 1H), 6.90 (d,  $J = 7.6$  Hz, 1H), 6.80 (s, 1H), 6.65 (d,  $J = 8.2$  Hz, 1H), 4.51 (q,  $J = 6.7$  Hz, 1H), 1.57 (d,  $J = 6.7$  Hz, 3H).

*N*-(1-Phenylethyl)-4-(trifluoromethoxy)aniline (**4h**) was synthesized from 4-trifluoromethoxyaniline (108  $\mu\text{L}$ ) and phenylacetylene (105  $\mu\text{L}$ ) following the general hydroamination procedure. Two equiv of  $\text{NaBH}_4$  were employed during the reduction step. The reaction crude was purified by flash column chromatography using hexane/ethyl acetate (98:2) as eluent to give **4h** (142 mg, 63%) as dark orange oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.44–7.34 (m, 4H), 7.32–7.24 (m, 1H), 6.98 (d,  $J = 8.7$  Hz, 2H), 6.55–6.42 (m, 2H), 4.47 (q,  $J = 6.7$  Hz, 1H), 4.14 (br s, 1H), 1.55 (d,  $J = 6.7$  Hz, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  146.1, 144.8, 140.3 (q,  $J = 1.7$  Hz), 128.8 (2C), 127.1, 125.8 (2C), 122.3 (2C), 120.7 (q,  $J = 255.1$  Hz), 113.5 (2C), 53.8, 25.1.

4-Fluoro-*N*-(1-phenylethyl)aniline (**4i**) was synthesized from 4-fluoroaniline (76  $\mu\text{L}$ ) and phenylacetylene (105  $\mu\text{L}$ ) following the general hydroamination procedure. Two equiv of  $\text{NaBH}_4$  were employed during the reduction step. The reaction crude was purified by flash column chromatography using hexane/ethyl acetate (95:5) as eluent to give **4i** (120 mg, 70%) as dark orange oil. The spectroscopic data of **4i** are consistent with literature values [41].  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.44–7.33 (m, 4H), 7.32–7.24 (m, 1H), 6.90–6.79 (m, 2H), 6.51–6.43 (m, 2H), 4.46 (q,  $J = 6.7$  Hz, 1H), 3.96 (br s, 1H), 1.55 (d,  $J = 6.7$  Hz, 3H).

4-Chloro-*N*-(1-phenylethyl)aniline (**4j**) was synthesized from 4-chloroaniline (102 mg) and phenylacetylene (105  $\mu\text{L}$ ) following the general hydroamination procedure. Five equiv of  $\text{NaBH}_4$  were employed during the reduction step. The reaction crude was purified by flash column chromatography using hexane/ethyl acetate (95:5) as eluent to give **4j** (111 mg, 60%) as orange solid. The spectroscopic data of **4j** are consistent with literature values [41].  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.46–7.38 (m, 4H), 7.37–7.29 (m, 1H), 7.17–7.09 (m, 2H), 6.55–6.47 (m, 2H), 4.52 (q,  $J = 6.7$  Hz, 1H), 4.12 (s, 1H), 1.58 (d,  $J = 6.7$  Hz, 3H).

4-Bromo-*N*-(1-phenylethyl)aniline (**4k**) was synthesized from 4-bromoaniline (138 mg) and phenylacetylene (105  $\mu\text{L}$ ) following the general hydroamination procedure. Two equiv of  $\text{NaBH}_4$  were employed during the reduction step. The reaction crude was purified by flash column chromatography using hexane/ethyl acetate (98:2) as eluent to give **4k** (106 mg, 48%) as red solid. The spectroscopic data of **4k** are consistent with literature values [42].  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38–7.31 (m,  $J = 7.3, 6.1$  Hz, 4H), 7.30–7.23 (m, 1H), 7.21–7.14 (m, 2H), 6.40 (d,  $J = 8.8$  Hz, 2H), 4.46 (q,  $J = 6.7$  Hz, 1H), 4.10 (br s, 1H), 1.53 (d,  $J = 6.7$  Hz, 3H).

3-Chloro-2-methyl-*N*-(1-phenylethyl)aniline (**4l**) was synthesized from 3-chloro-2-methylaniline (119  $\mu\text{L}$ ) and phenylacetylene (105  $\mu\text{L}$ ) following the general hydroamination procedure. Three equiv of  $\text{NaBH}_4$  were employed during the reduction step. The reaction crude was purified by flash column chromatography using hexane/ethyl acetate/ $\text{CH}_2\text{Cl}_2$  (89:2:9) as eluent to give **4l** (134 mg, 68%) as dark yellow oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41–7.34 (m, 4H), 7.32–7.25 (m, 1H), 6.89 (t,  $J = 8.0$  Hz, 1H), 6.77 (d,  $J = 8.0$  Hz, 1H), 6.33 (d,  $J = 8.1$  Hz, 1H), 4.57 (q,  $J = 6.7$  Hz, 1H), 4.04 (br s, 1H), 2.36 (s, 3H), 1.62 (d,  $J = 6.7$  Hz, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  146.3, 144.8, 134.5, 128.8 (2C), 127.2, 127.1, 125.8 (2C), 119.4, 118.0, 109.7, 53.7, 25.3, 13.8.

4-Methoxy-*N*-(1-phenylethyl)aniline (**4m**) was synthesized from 4-methoxyaniline (98 mg) and phenylacetylene (105  $\mu\text{L}$ ) following the general hydroamination procedure. Two equiv of  $\text{NaBH}_4$  were employed during the reduction step. The reaction crude was purified by flash column chromatography using hexane/ethyl acetate (98:2) as eluent to give **4m** (181 mg, 90%) as orange crystals. The spectroscopic data of **4m** are consistent with literature values [41].  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.44–7.33 (m, 4H), 7.30–7.25 (m, 1H), 6.77–6.71 (m, 2H), 6.55–6.50 (m, 2H), 4.46 (q,  $J = 6.6$  Hz, 1H), 4.00–3.60 (two signals: br s, 1H and s, 3H centred at 3.74 ppm), 1.54 (d,  $J = 6.7$  Hz, 3H).

3,4-Dimethoxy-*N*-(1-phenylethyl)aniline (**4n**) was synthesized from 3,4-dimethoxyaniline (123 mg) and phenylacetylene (105  $\mu\text{L}$ ) following the general hydroamination procedure. Five equiv of  $\text{NaBH}_4$  were employed during the reduction step. The reaction crude was purified by flash column chromatography using hexane/ethyl acetate/ $\text{CH}_2\text{Cl}_2$  (89:2:9) as eluent to give **4n** (35 mg, 17%) as dark red oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38 (d,  $J = 7.6$  Hz, 2H), 7.32 (t,  $J = 7.7$  Hz, 2H), 7.27–7.19 (m, 1H),

6.65 (d,  $J = 8.6$  Hz, 1H), 6.20 (s, 1H), 6.05 (d,  $J = 8.6$  Hz, 1H), 4.43 (q,  $J = 6.7$  Hz, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 1.53 (d,  $J = 6.7$  Hz, 3H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  149.7, 144.9, 141.7, 128.7, 127.0, 126.0, 112.8, 104.9, 99.8, 56.5, 55.6, 54.9, 24.8.

*N*-(1-(*p*-Tolyl)ethyl)aniline (**4o**) was synthesized from aniline (72  $\mu\text{L}$ ) and 4-ethynyltoluene (122  $\mu\text{L}$ ) following the general hydroamination procedure. Three equiv of  $\text{NaBH}_4$  were employed during the reduction step. The reaction crude was purified by flash column chromatography using hexane/ethyl acetate (98:2) as eluent to give **4o** (96 mg, 57%) as yellow oil. The spectroscopic data of **4o** are consistent with literature values [43].  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38 (d,  $J = 8.3$  Hz, 2H), 7.29–7.17 (m, 4H), 6.82–6.73 (m, 1H), 6.64 (d,  $J = 6.0$  Hz, 2H), 4.60–4.54 (m, 1H), 3.97 (br s, 1H), 2.44 (s, 3H), 1.60 (d,  $J = 6.7$  Hz, 3H).

*N*-(1-(4-(*tert*-Butyl)phenyl)ethyl)aniline (**4p**) was synthesized from aniline (72  $\mu\text{L}$ ) and 4-*tert*-butylphenylacetylene (179  $\mu\text{L}$ ) following the general hydroamination procedure. Three equiv of  $\text{NaBH}_4$  were employed during the reduction step. The reaction crude was purified by flash column chromatography using hexane/ethyl acetate (98:2) as eluent to give **4p** (128 mg, 63%) as orange solid. The spectroscopic data of **4p** are consistent with literature values [45].  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40–7.27 (m, 4H), 7.16–7.07 (m, 2H), 6.66 (t further split,  $J = 7.3$ , 1H), 6.55 (d,  $J = 8.5$  Hz, 2H), 4.50 (q,  $J = 6.7$  Hz, 1H), 4.03 (br s, 1H), 1.53 (d further split,  $J = 6.7$ , 3H), 1.35–1.30 (m, 9H).

*N*-(1-(4-Fluorophenyl)ethyl)aniline (**4q**) was synthesized from aniline (72  $\mu\text{L}$ ) and 4-fluorophenylacetylene (110  $\mu\text{L}$ ) following the general hydroamination procedure. Three equiv of  $\text{NaBH}_4$  were employed during the reduction step. The reaction crude was purified by flash column chromatography using hexane/ethyl acetate (98:2) as eluent to give **4q** (108 mg, 63%) as dark orange oil. The spectroscopic data of **4q** are consistent with literature values [41].  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.43–7.34 (m, 2H), 7.21–7.13 (m, 2H), 7.06 (t,  $J = 8.7$  Hz, 2H), 6.74 (t,  $J = 7.3$  Hz, 1H), 6.57 (d,  $J = 7.6$  Hz, 2H), 4.52 (q,  $J = 6.7$  Hz, 1H), 4.24 (br s, 1H), 1.55 (d,  $J = 6.8$  Hz, 3H).

#### 4. Conclusions

In conclusion, we developed a simple and versatile palladium-catalyzed protocol for the hydroamination of terminal arylacetylenes with anilines, in the absence of organic ligands or additives. This novel methodology features high functional group tolerance and offers a valuable alternative to reported methods for the synthesis of secondary aromatic amines. The presence of iodide anions was crucial to achieve good to excellent yields of the corresponding imine products. We envisage wide diffusion of this versatile methodology within the organic chemistry community.

**Supplementary Materials:** The following are available online at [www.mdpi.com/2073-4344/10/2/176/s1](http://www.mdpi.com/2073-4344/10/2/176/s1), Copies of NMR spectra.

**Author Contributions:** A.C. co-supervised the project and wrote the original draft of the paper; A.V. carried out most of the NMR analyses; D.G.F. carried out the catalytic experiments and the chromatographic separations; R.M., B.G., and E.M. were involved in writing and editing the manuscript; N.D. supervised the project and revised the paper.

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**Conflicts of Interest:** The authors declare no conflict of interest.

#### References

1. Huo, J.; He, G.; Chen, W.; Hu, X.; Deng, Q.; Chen, D. A minireview of hydroamination catalysis: Alkene and alkyne substrate selective, metal complex design. *BMC Chem.* **2019**, *13*, 89–101.
2. Patel, M.; Saunthwal, R.K.; Verma, A.K. Base-Mediated Hydroamination of Alkynes. *Acc. Chem. Res.* **2017**, *50*, 240–254.

3. Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L.J. Late Transition Metal-Catalyzed Hydroamination and Hydroamidation. *Chem. Rev.* **2015**, *115*, 2596–2697.
4. Hartwig, J.F. Carbon–heteroatom bond formation catalysed by organometallic complexes. *Nature* **2008**, *455*, 314–322.
5. Muller, T.E.; Hultsch, K.C.; Yus, M.; Foubelo, F.; Tada, M. Hydroamination: Direct addition of amines to alkenes and alkynes. *Chem. Rev.* **2008**, *108*, 3795–3892.
6. Severin, R.; Doye, S. The catalytic hydroamination of alkynes. *Chem. Soc. Rev.* **2007**, *36*, 1407–1420.
7. Pohlki, F.; Doye, S. The catalytic hydroamination of alkynes. *Chem. Soc. Rev.* **2003**, *32*, 104–114.
8. Müller, T.E.; Beller, M. Metal-initiated amination of alkenes and alkynes. *Chem. Rev.* **1998**, *98*, 675–704.
9. Chen, J.; Lu, Z. Asymmetric hydrofunctionalization of minimally functionalized alkenes via earth abundant transition metal catalysis. *Org. Chem. Front.* **2018**, *5*, 260–272.
10. Griffin, S.E.; Pacheco, J.; Schafer, L.L. Reversible C–N Bond Formation in the Zirconium-Catalyzed Intermolecular Hydroamination of 2-Vinylpyridine. *Organometallics* **2019**, *38*, 1011–1016.
11. Eedugurala, N.; Hovey, M.; Ho, H.-A.; Jana, B.; Lampland, N.L.; Ellern, A.; Sadow, A.D. Cyclopentadienyl-bis(oxazoline) Magnesium and Zirconium Complexes in Aminoalkene Hydroaminations. *Organometallics* **2015**, *34*, 5566–5575.
12. Reznichenko, A.L.; Hultsch, K.C. Early Transition Metal (Group 3–5, Lanthanides and Actinides) and Main Group Metal (Group 1, 2, and 13) Catalyzed Hydroamination. In *Hydrofunctionalization*; Ananikov, V.P., Tanaka, M., Eds.; Springer: Berlin/Heidelberg, Germany, 2011; Volume 43, pp. 51–114.
13. Reznichenko, A.L.; Nguyen, H.N.; Hultsch, K.C. Asymmetric intermolecular hydroamination of unactivated alkenes with simple amines. *Angew. Chem. Int. Ed.* **2010**, *49*, 8984–8987.
14. Hong, S.; Marks, T.J. Organolanthanide-Catalyzed Hydroamination. *Acc. Chem. Res.* **2004**, *37*, 673–686.
15. Yahata, K.; Kaneko, Y.; Akai, S. Cobalt-Catalyzed Intermolecular Markovnikov Hydroamination of Nonactivated Olefins: N<sub>2</sub>-Selective Alkylation of Benzotriazole. *Org. Lett.* **2020**, *22*, 598–603.
16. Yang, X.-H.; Lu, A.; Dong, V.M. Intermolecular Hydroamination of 1,3-Dienes To Generate Homoallylic Amines. *J. Am. Chem. Soc.* **2017**, *139*, 14049–14052.
17. Gurak, J.A.; Yang, K.S.; Liu, Z.; Engle, K.M. Directed, Regiocontrolled Hydroamination of Unactivated Alkenes via Protodepalladation. *J. Am. Chem. Soc.* **2016**, *138*, 5805–5808.
18. Sevov, C.S.; Zhou, J. (Steve); Hartwig, J.F. Iridium-Catalyzed, Intermolecular Hydroamination of Unactivated Alkenes with Indoles. *J. Am. Chem. Soc.* **2014**, *136*, 3200–3207.
19. Cooke, M.L.; Xu, K.; Breit, B. Enantioselective Rhodium-Catalyzed Synthesis of Branched Allylic Amines by Intermolecular Hydroamination of Terminal Allenes. *Angew. Chem. Int. Ed.* **2012**, *51*, 10876–10879.
20. Malhotra, D.; Mashuta, M.S.; Hammond, G.B.; Xu, B. A Highly Efficient and Broadly Applicable Cationic Gold Catalyst. *Angew. Chem. Int. Ed.* **2014**, *53*, 4456–4459.
21. Lavallo, V.; Wright, J.H.; Tham, F.S.; Quinlivan, S. Perhalogenated Carba-closo-dodecaborate Anions as Ligand Substituents: Applications in Gold Catalysis. *Angew. Chem. Int. Ed.* **2013**, *52*, 3172–3176.
22. Platon, M.; Amardeil, R.; Djakovitch, L.; Hierso, J.C. Progress in palladium-based catalytic systems for the sustainable synthesis of annulated heterocycles: A focus on indole backbones. *Chem. Soc. Rev.* **2012**, *41*, 3929–3968.
23. Banerjee, D.; Junge, K.; Beller, M. A General Catalytic Hydroamidation of 1, 3-Dienes: Atom-Efficient Synthesis of N-Allyl Heterocycles, Amides, and Sulfonamides. *Angew. Chem. Int. Ed.* **2014**, *53*, 1630–1635.
24. Lutete, L.M.; Kadota, I.; Yamamoto, Y. Palladium-catalyzed intramolecular asymmetric hydroamination of alkynes. *J. Am. Chem. Soc.* **2004**, *126*, 1622–1623.
25. Gabriele, B.; Salerno, G.; Fazio, A. General and regioselective synthesis of substituted pyrroles by Metal-Catalyzed or spontaneous cycloisomerization of (Z)-(2-En-4-ynyl) amines. *J. Org. Chem.* **2003**, *68*, 7853–7861.
26. Alonso, F.; Beletskaya, I.P.; Yus, M. Transition metal-catalyzed addition of heteroatom–hydrogen bonds to alkynes. *Chem. Rev.* **2004**, *104*, 3079–3160.
27. Michael, F.E.; Cochran, B.M. Room temperature palladium-catalyzed intramolecular hydroamination of unactivated alkenes. *J. Am. Chem. Soc.* **2006**, *128*, 4246–4247.
28. Löber, O.; Kawatsura, M.; Hartwig, J.F. Palladium-catalyzed hydroamination of 1, 3-dienes: A colorimetric assay and enantioselective additions. *J. Am. Chem. Soc.* **2001**, *123*, 4366–4367.
29. Besson, L.; Goré, J.; Cazes, B. Synthesis of allylic amines through the palladium-catalyzed hydroamination of allenenes. *Tetrahedron Lett.* **1995**, *36*, 3857–3860.

30. Chen, Q.; Lv, L.; Yu, M.; Shi, Y.; Li, Y.; Pang, G.; Cao, C. Simple, efficient and reusable Pd–NHC catalysts for hydroamination. *RSC Adv.* **2013**, *3*, 18359–18366.
31. Franco, D.; Marchenko, A.; Koidan, G.; Hurieva, A.N.; Kostyuk, A.; Biffis, A. Palladium (II) Complexes with *N*-Phosphanyl-*N*-heterocyclic Carbenes as Catalysts for Intermolecular Alkyne Hydroaminations. *ACS Omega* **2018**, *3*, 17888–17894.
32. Shaffer, A.R.; Schmidt, J.A. Palladium (II) 3-iminophosphine complexes as intermolecular hydroamination catalysts for the formation of imines and enamines. *Organometallics* **2008**, *27*, 1259–1266.
33. Shimada, T.; Yamamoto, Y. Palladium-catalyzed intermolecular hydroamination of alkynes: A dramatic rate-enhancement effect of *o*-aminophenol. *J. Am. Chem. Soc.* **2002**, *124*, 12670–12671.
34. Shimada, T.; Bajracharya, G.B.; Yamamoto, Y. Aquapalladium complex: A stable and convenient catalyst for the intermolecular hydroamination of alkynes. *Eur. J. Org. Chem.* **2005**, *2005*, 59–62.
35. Kadota, I.; Shibuya, A.; Lutete, L.M.; Yamamoto, Y. Palladium/benzoic acid catalyzed hydroamination of alkynes. *J. Org. Chem.* **1999**, *64*, 4570–4571.
36. Casnati, A.; Perrone, A.; Mazzeo, P.P.; Bacchi, A.; Mancuso, R.; Gabriele, B.; Maggi, R.; Maestri, G.; Motti, E.; Stirling, A.; et al. Synthesis of Imidazolidin-2-ones and Imidazol-2-ones via Base-Catalyzed Intramolecular Hydroamidation of Propargylic Ureas under Ambient Conditions. *J. Org. Chem.* **2019**, *84*, 3477–3490.
37. Brunet, J.J.; Chu, N.C.; Diallo, O.; Vincendeau, S. Platinum-catalyzed intermolecular hydroamination of terminal alkynes. *J. Mol. Catal. A Chem.* **2005**, *240*, 245–248.
38. Gabriele, B.; Salerno, G.; Costa, M. PdI<sub>2</sub>-Catalyzed Synthesis of Heterocycles. *Synlett* **2004**, *2004*, 2468–2483.
39. Maitlis, P.M.; Haynes, A.; James, B.R.; Catellani, M.; Chiusoli, G.P. Iodide effects in transition metal catalyzed reactions. *Dalton Trans.* **2004**, *21*, 3409–3419.
40. For a recent Pd-catalyzed transformation, involving a C–N bond formation, promoted by iodide anions, see: Casnati, A.; Fontana, M.; Coruzzi, G.; Aresta, B.M.; Corriero, N.; Maggi, R.; Maestri, G.; Motti, E.; Della Ca', N. Enhancing Reactivity and Selectivity of Aryl Bromides: A Complementary Approach to Dibenzo [b,f] azepine Derivatives. *ChemCatChem* **2018**, *10*, 4346–4352.
41. Liang, S.; Hammond, L.; Xu, B.; Hammond, G.B. Commercial Supported Gold Nanoparticles Catalyzed Alkyne Hydroamination and Indole Synthesis. *Adv. Synth. Catal.* **2016**, *358*, 3313–3318.
42. Wallach, D.R.; Stege, P.C.; Shah, J.P.; Chisholm, J.D. Brønsted acid catalyzed monoalkylation of anilines with trichloroacetimidates. *J. Org. Chem.* **2015**, *80*, 1993–2000.
43. Zhou, S.; Fleischer, S.; Jiao, H.; Junge, K.; Beller, M. Cooperative catalysis with iron and a chiral brønsted acid for asymmetric reductive amination of ketones. *Adv. Synth. Catal.* **2014**, *356*, 3451–3455.
44. Babu, N.S.; Reddy, K.M.; Prasad, P.S.; Suryanarayana, I.; Lingaiah, N. Intermolecular hydroamination of vinyl arenes using tungstophosphoric acid as a simple and efficient catalyst. *Tetrahedron Lett.* **2007**, *48*, 7642–7645.
45. Schroeter, F.; Lerch, S.; Kaliner, M.; Strassner, T. Cobalt-catalyzed hydroarylations and hydroaminations of alkenes in tunable aryl alkyl ionic liquids. *Org. Lett.* **2018**, *20*, 6215–6219.



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