Aquapalladium Complex: A Stable and Convenient Catalyst for the Intermolecular Hydroamination of Alkynes

Tomohiro Shimada,[a] Gan B. Bajracharya,[a] and Yoshinori Yamamoto*[a]

Keywords: Aquapalladium catalyst / Hydroamination / Alkynes / Arylamines / Imines

The intermolecular hydroamination of alkynes proceeds very smoothly in the presence of a catalytic amount of the aquapalladium complex [Pd(dppe)(H_2O)$_2$](TfO)$_2$. This reaction most probably proceeds through the formation of an equilibrium between the hydroxopalladium and the amidopalladium complexes, and subsequent aminopalladation of alkynes.

Introduction

Recently, the transition-metal-catalyzed intermolecular hydroamination of alkynes has been widely investigated.[1] This reaction is regarded as an atom-economical route by which to transform C−C unsaturated bonds into functional compounds. Moreover, this reaction provides a wide range of useful compounds that are utilized as fine chemicals and intermediates for pharmaceutical and industrial products. As a result of the great research efforts in this area, it is now feasible to carry out the intermolecular hydroamination of unactivated alkynes in the presence of different kinds of metal catalysts.[2−4] However, a major drawback of some catalysts lies in their air and/or light sensitivity, which demands they be handled with great care,[2e,2f,3] and in addition they can only be used for the hydroamination of terminal alkynes.[2a−2d] Recently, we reported that the intermolecular hydroamination of alkynes proceeds smoothly with *o*-aminophenols in the presence of a palladium catalyst that is easily handled without special care.[5] We assumed that the palladium phenoxide complex **A** would be formed from the reaction of *o*-aminophenol with PdX_2, which would be converted into the amidopalladium complex **B** by proton transfer, and then the amino-palladation of alkynes would take place (Scheme 1a).[5a] Accordingly, the key to the palladium-catalyzed hydroamination step must be the facile formation of the amido complex **B** by neighboring-group assistance of the *o*-phenolic OH group. This catalytic system could be applied to various alkynes, but the amine was limited to *o*-aminophenol and in some instances monosubstituted analogues of the aromatic ring produced the corresponding products with poor yields.

Stoichiometric conversion of a hydroxopalladium complex into its amido complex by treatment with amines was reported by López[6a] and Hartwig[6b−6d] and their co-workers; the thermodynamically more stable Pd−NH complexes **D** were yielded from the corresponding Pd−OH complexes (Scheme 1, b). Furthermore, Sodeoka and co-workers recently reported that Michael addition of activated methynes to α,β-unsaturated ketones was catalyzed by a aquapalladium complex.[7] It occurred to us that palladium-catalyzed hydroamination might proceed with aquapalladium and/or hydroxopalladium complexes if activation of an amine N−H bond occurs catalytically as shown in Scheme 1 (b).[8] Herein, we report that the intermolecular hydroamination of nonactivated internal alkynes with both nonactivated and activated arylamines takes place at 80 °C in the presence of the aquapalladium catalyst, [Pd(dppe)(H_2O)$_2$]$^{2+}$.[9]

Results and Discussion

First, we examined the reaction of 6-dodecyne (**1a**, 0.60 mmol) with aniline (**2a**) (0.50 mmol) in the presence of several different palladium catalysts [Equation (1)]. The imine product **3a**, obtained by hydroamination, was converted into the ketone **4a** upon treatment with silica gel.[3a] The use of Pd(NO_3)$_2$, which was an effective catalyst in the hydroamination reactions with *o*-aminophenol,[5a] gave **4a** in 37% yield. The other catalysts, such as [$PdCl_2$(dppe)], [$PdCl_2$(CH_3CN)$_2$] and [Pd_2(dba)$_3$]·$CHCl_3$, afforded no **4a** at all. However, the use of [Pd(dppe)(H_2O)$_2$](TfO)$_2$ gave **4a** in 64% yield; the yield of **4a** was increased to 74% by the use of 1.5 equiv. of **1a** in 1,4-dioxane (see Table 1, Entry 1). Interestingly, the use of [Pd(PPh_3)$_4$] (10 mol %) as catalyst gave a mixture of 6-phenylamino-7-dodecene and 5-phenylamino-6-dodecene in a combined yield of 42%, which

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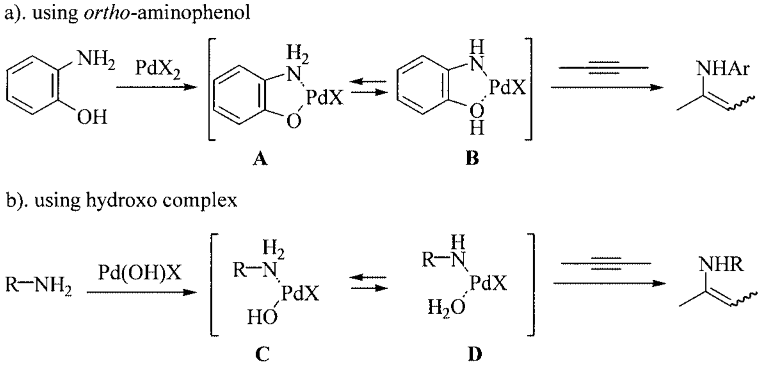
[a] Department of Chemistry, Graduate School of Science, Tohoku University,
Sendai 980-8578, Japan
Fax: (internat.) +81-22-217-6784
E-mail: yoshi@yamamoto1.chem.tohoku.ac.jp

Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

DOI: 10.1002/ejoc.200400568



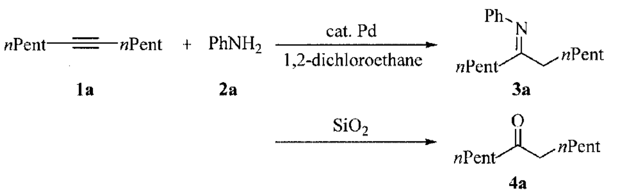
Scheme 1. Palladium-catalyzed hydroamination of alkynes

Table 1. Palladium-catalyzed intermolecular hydroamination of alkynes **1** with aniline **2a**

Entry[a]	R^1	R^2	**1**	Reaction time [h]	Yield [%][b]	**4:5**
1	*n*Pent	*n*Pent	**1a**	24	74	–
2	Ph	Ph	**1b**	18	96	–
3	Ph	*n*Bu	**1c**	24	99	2:1
4[c]	4-MeO-C_6H_4	*n*Bu	**1d**	24	82	3:1
5	3-MeO-C_6H_4	*n*Bu	**1e**	10	63	1:1
6	4-Br-C_6H_4	*n*Bu	**1f**	24	> 99	1:2
7	4-CF_3-C_6H_4	*n*Bu	**1g**	24	41	1:2
8	Ph	$(CH_2)_3OAc$	**1h**	20	> 99	4:1

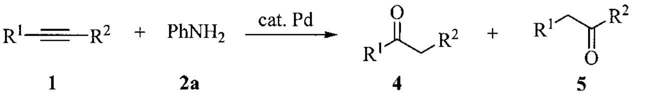
[a] Reaction conditions: i) aniline (0.50 mmol), alkyne (0.75 mmol), $[Pd(dppe)(H_2O)_2](TfO)_2$ (10 mol %), 1,4-dioxane (10 M), 80 °C; ii) SiO_2, CH_2Cl_2, room temp., 2 h. [b] Isolated yields. [c] Three equivalents of alkyne were used.

would have been obtained by a hydropalladation–dehydropalladation sequence.[10] This strongly suggests that this hydroamination reaction [Equation (1)] does not proceed through the hydropalladation mechanism.[11]



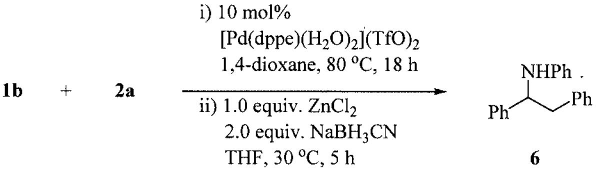
(1)

Next, we examined the scope of this reaction [Equation (2)], and the results obtained after hydrolytic work up are given in Table 1. Among the solvents examined, 1,4-dioxane gave the best result (Entry 1).[12] The reaction of the simple alkynes **1a–c** with aliphatic and aromatic substituents proceeded quite smoothly (Entries 1–3). The use of three equivalents of **1d**, which has an electron-donating group at the *para*-position, gave a 3:1 mixture of **4d** and **5d** in 82% yield (Entry 4). The arylalkynes **1e** and **1f** reacted similarly, giving a mixture of **4e** (**4f**) and **5e** (**5f**) in good to high yields (Entries 5 and 6), but **1g**, which has a CF_3 group at the *para*-position, gave a low yield (Entry 7). The acetoxy-substituted alkyne **1h** also reacted with aniline under the reaction conditions and the products were obtained in a quantitative yield (Entry 8).



(2)

We attempted to isolate the hydroamination product in the amine form prior to converting it into the ketone form. The aquapalladium complex catalyzed reaction of **1b** with **2a**, followed by reduction with $NaBH_3CN$, produced the corresponding amine **6** in 48% yield [Equation (3)].



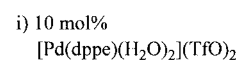
(3)

As can be seen in Equation (4) and Table 2, various substituted anilines **2** react with diphenylacetylene (**1b**) at 80 °C in 1,4-dioxane with 10 mol % $[Pd(dppe)(H_2O)_2](TfO)_2$ as catalyst.[13] The substituents on the aromatic ring of aniline had no significant effect on this reaction. The aniline derivatives that have an electron-donating group at the *para*-position reacted smoothly with **1b** under the standard conditions to give ketone **4b**. Although these reactions required a relatively long reaction time, very high product yields were achieved (Entries 1−3). The aniline derivatives that have an electron-withdrawing group at the *para*-position also provided the desired product in quantitative yield (Entries 4 and 5); however, the reaction with *p*-nitroaniline (**2g**) gave a lower yield (Entry 6). The product **4b** was obtained from 3-(trifluoromethyl)aniline (**2h**) and 3,5-dimethylaniline (**2i**) in > 99 and 68% yields, respectively (Entries 7 and 8). With the sterically hindered 2,6-dimethylaniline (**2j**) and pentafluoroaniline (**2k**), the hydrolysis product **4b** was isolated together with the corresponding (2,6-dimethylphenyl)(1,2-diphenylethylidene)amine (**3b**) and (1,2-diphenylethylidene)(pentafluorophenyl)amine (**3c**) with quantitative conversion after hydrolytic work up (Entries 9 and 10). This reaction also took place with 1-naphthylamine (Entry 11). A secondary amine that could not be used as an amine substrate in the hydroamination reaction with an early transition metal catalyst[2f,3] can be employed in this reaction; the reaction of *N*-methylaniline **2m** with diphenylacetylene (**1b**) and phenyl(butyl)acetylene (**1c**) proceeded smoothly and the corresponding products were obtained in high yields (Entries 12 and 13). In one set of experiments, the enamine product derived from **1b** and **2m** was reduced with H_2/Pd-C to give **7** in 45% yield [Equation (5)].

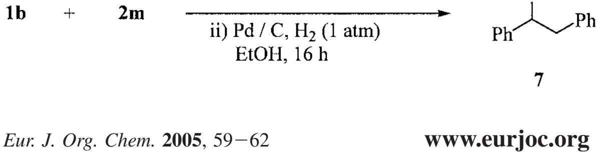
Table 2. Palladium-catalyzed intermolecular hydroamination of diphenylacetylene (**1b**) with arylamines **2**

Entry[a]	ArNH$_2$	**2**	Reaction time [h]	Yield [%][b]
1	4-HO-$C_6H_4NH_2$	**2b**	50	96
2	4-MeS-$C_6H_4NH_2$	**2c**	47	> 99
3	4-Me-$C_6H_4NH_2$	**2d**	46	91
4	4-F-$C_6H_4NH_2$	**2e**	24	> 99
5	4-CF_3-$C_6H_4NH_2$	**2f**	19	> 99
6	4-NO_2-$C_6H_4NH_2$	**2g**	55	40
7	3-CF_3-$C_6H_4NH_2$	**2h**	46	> 99
8	3,5-Me_2-$C_6H_3NH_2$	**2i**	22	68
9	2,6-Me_2-$C_6H_3NH_2$	**2j**	22	15[c]
10	$C_6F_5NH_2$	**2k**	18	45[d]
11	1-naphthylamine	**2l**	47	94
12	*N*-methylaniline	**2m**	3	84
13[e]	*N*-methylaniline	**2m**	7	83[f]

[a] Reaction conditions: i) aniline (0.50 mmol), alkyne (0.75 mmol), $[Pd(dppe)(H_2O)_2](TfO)_2$ (10 mol %), 1,4-dioxane (10 M), 80 °C; ii) SiO_2, CH_2Cl_2, room temp., 2 h. [b] Isolated yields. [c] Imine **3b** (85%) was isolated. [d] Imine **3c** (55%) was isolated. [e] Instead of diphenylacetylene **1b**, phenyl(butyl)acetylene **1c** was used. [f] The isomeric ratio of the corresponding products was 2:1.



(4)



(5)

A plausible mechanism for the hydroamination reaction is shown in Scheme 2. First, the hydroxopalladium complex **E** is produced in situ from the aquapalladium complex. The aminopalladium complex **F** is then generated from intermediate **E** by coordination of the amine. An equilibrium between **F** and the amidopalladium complex **G** forms, followed by the coordination of alkynes and subsequent insertion gives the vinylpalladium intermediate **H**.[14] Protonolysis of **H** yields the enamine **3′** and reproduces the palladium catalyst. Finally, enamine **3′** is converted into imine **3** under the reaction conditions.

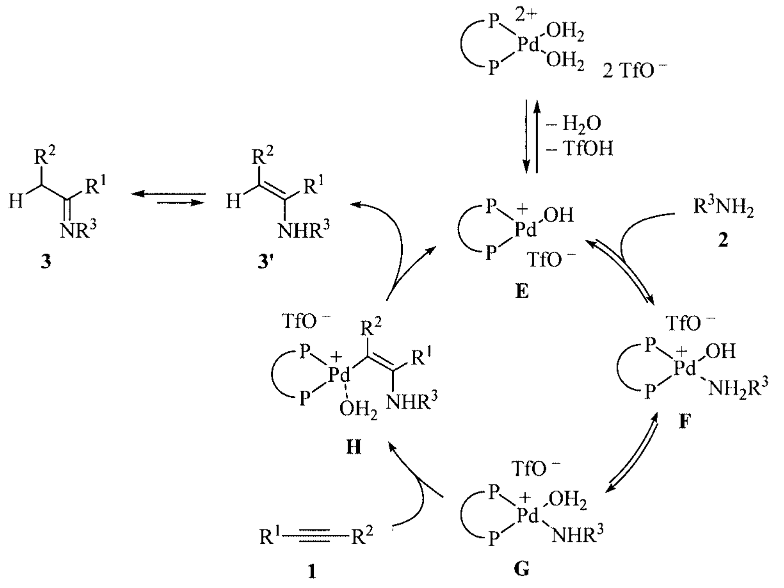
Conclusion

In this communication, we have demonstrated that a stable and convenient aquapalladium complex can be used as a catalyst for the intermolecular hydroamination of internal alkynes with arylamines. Compared with the previously known lanthanide and early transition metal catalysts, special care is not needed in the handling of the aqua complex. Further applications of the aqua complex are being investigated.

Experimental Section

General Remarks: ^{1}H and ^{13}C NMR spectra were recorded with JEOL JNM LA-300 (300 MHz) and JEOL JMTC-400/54/SS (400 MHz) spectrometers. ^{1}H NMR spectroscopic data are reported as follows: Chemical shift in ppm (δ) relative to the chemical shift of $CDCl_3$ at δ = 7.24 ppm, integration, multiplicities (s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet and br = broadened), and coupling constants (Hz). ^{13}C NMR spectroscopic data are reported in ppm (δ) relative to the central line of the triplet of $CDCl_3$ at δ = 77 ppm. IR spectra were recorded with a SHIMADZU FTIR-8200A spectrometer; absorption bands are reported in cm^{-1}. High-resolution mass spectra were obtained with JEOL JMS-DX303, JEOL JMS-AX500 and BRUKER APEXIII spectrometers. Column chromatography was carried out by employing silica gel 60 N (spherical, neutral, 40−100 μm, KANTO Chemical Co.). Analytical thin-layer chromatography (TLC) was performed on 0.2 mm Kieselgel 60 F_{254} (Merck) precoated plates. All manipulations were conducted under an argon atmosphere using standard Schlenk techniques.

Typical Procedure for the Aquapalladium-Catalyzed Hydroamination Reaction. The Synthesis of 6-Dodecanone (4a): 6-Dodecyne **1a** (124.7 mg, 0.75 mmol) was added to the reaction vial containing a 1,4-dioxane solution (0.05 mL) of aniline (**2a**, 46.6 mg, 0.5 mmol) and $[Pd(dppe)(H_2O)_2](TfO)_2$ (42.0 mg, 0.050 mmol) under argon. The solution was heated at 80 °C for 24 hours and then cooled to room temperature. After dilution with dichloromethane, SiO_2 was added successively and the suspension was stirred for 2 hours. The product was filtered through a short SiO_2 pad using diethyl ether as eluent, and the resulting filtrate was concentrated. The residue was purified by column chromatography [silica gel, hexane/ethyl acetate, 50:1 (200 mL) → 10:1 (until complete elution)] to afford 6-dodecanone (**4a**) in 74% yield (68.0 mg). ^{1}H NMR (300.40 MHz, $CDCl_3$): δ = 0.80−0.92 (m, 6 H), 1.15−1.37 (m, 10 H), 1.47−1.61 (m, 4 H), 2.36 (2t, J = 7.4, 7.4 Hz, 4 H) ppm. ^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 13.90, 14.01, 22.44, 22.48, 23.55, 23.83, 28.92, 31.42, 31.59, 42.76, 42.81, 211.77 (CO) ppm. IR (neat): $\tilde{\nu}$ =



Scheme 2. Plausible mechanism for the hydroamination reaction

2957, 2930, 2858, 1717 (CO), 1466, 1412, 1377 cm^{-1}. HRMS (EI): calcd for $C_{12}H_{24}O$ [M^+]: 184.1827; found: 184.1821.

Supporting Information: Spectroscopic and analytical data of synthesized compounds and information on procedures (for Supporting Information see also the footnote on the first page of this article).

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[9] We tried other aqua and hydroxo catalysts, however, slightly lower yields were obtained under similar conditions: $[Pd(dppp)(H_2O)_2](TfO)_2$ (33%), $[Pd(dppf)(H_2O)_2](TfO)_2$ (24%), $[Pd(\mu\text{-}OH)(dppe)]_2(TfO)_2$ (41%). We also examined the reaction of $[Pd(dppe)(CH_3CN)_2](TfO)_2$, which would act as a Lewis acid, and confirmed that the yield was low (50%).

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Received August 10, 2004