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Palladium-Catalyzed Intermolecular Hydroamination of Alkynes: A Dramatic Rate-Enhancement Effect of *o*-Aminophenol

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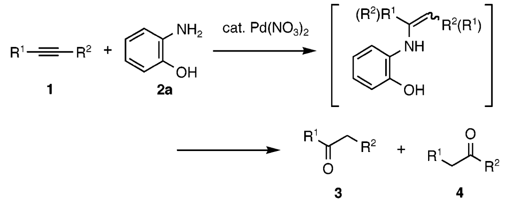
The addition of ammonia or primary and secondary amines to alkenes and alkynes, known as hydroamination,[1] is one of the most efficient approaches for the synthesis of higher substituted amines and their derivatives which are important bulk and fine chemicals or building blocks in organic chemistry. A variety of metals are known as efficient catalysts for the intermolecular hydroamination of alkynes, but almost all reactions are restricted to *terminal* alkynes,[2] and only a few efficient methods are applicable to *internal* alkynes.[3,4] Among the metals utilized for internal alkynes, titanium catalysts are the most effective and efficient,[4] although they are air- or light-sensitive and care should be taken in handling them. In the course of the palladium-catalyzed addition of phenols to diynes,[5] we have discovered that the intermolecular hydroamination of internal alkynes **1** with *o*-aminophenol **2a** proceeds very smoothly in the presence of $Pd(NO_3)_2$ catalyst (eq 1). The palladium catalyst is easy to handle, the hydroamination proceeds in very high-to-good yields, and the use of **2a** as an amine substrate dramatically enhances the reaction rate of the palladium-catalyzed hydroamination.[6]



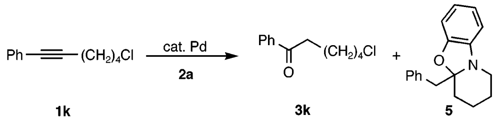
(1)

Table 1. Palladium-Catalyzed Hydroamination of Various Alkynes[a]

entry	R^1	R^2	**1**	reaction time, h	yield, %	**3**:**4**
1[c]	^{n}Pent	^{n}Pent	**1a**	12	76	–
2	^{n}Pent	^{n}Pent	**1a**	10	93	–
3	Ph	Ph	**1b**	7	81	–
4	Ph	Me	**1c**	5	65	2:1
5	Ph	^{n}Bu	**1d**	5	>99	1:1
6	^{n}Dec	H	**1e**	5	54	1:nd[d]
7	Ph	H	**1f**	5	40	1:nd[d]
8	Ph	$(CH_2)_4OMe$	**1g**	5	>99	1:1
9	Ph	$(CH_2)_4OBn$	**1h**	5	94	1:1
10	Ph	$(CH_2)_4OAc$	**1i**	5	95	1:1
11	Ph	$(CH_2)_4OTBS$	**1j**	20	58	2:1
12	Ph	$(CH_2)_4Cl$	**1k**	5	95	1:1[e]
13	$4\text{-}MeOC_6H_4$	^{n}Bu	**1l**	3	95	3:1
14	$4\text{-}MeC_6H_4$	^{n}Bu	**1m**	5	99	2:1
15	$4\text{-}FC_6H_4$	^{n}Bu	**1n**	5	99	2:1
16	$4\text{-}CF_3C_6H_4$	^{n}Bu	**1o**	20	62	1:2

[a] Reaction conditions: 0.5 mmol amine, 0.75 mmol alkyne, 15 mol % $Pd(NO_3)_2$, 1,4-dioxane, 120 °C. [b] Isolated yields. [c] The ratio of amine:alkyne was 1.0:1.2. [d] The corresponding aldehyde and its derivatives were not detected. [e] The ratio of **3k**:**5**.

The results are summarized in Table 1. The reaction of 6-dodecyne **1a** (1.2 equiv) with **2a** (1 equiv) in the presence of 15 mol % $Pd(NO_3)_2$ catalyst in 1,4-dioxane at 120 °C for 12 h, followed by hydrolysis of the reaction mixture and subsequent purification of the product gave 6-dodecanone **3a** in 76% yield (entry 1). We tested various kinds of palladium catalysts in the reaction of **1a** with **2a** under the conditions similar to those of entry 1. The use of $Pd_2(dba)_3 \cdot CHCl_3$, $PdCl_2$, $Pd(acac)_2$, $[(\eta^3\text{-}C_3H_5)PdCl]_2$, and Na_2PdCl_4 gave **3a** in the range of 62–68% yields, while that of $PdCl_2(dppf)$ and $PdCl_2(CH_3CN)_2$ afforded **3a** in 47–51% yields. Among the solvents examined, 1,4-dioxane gave the best result. ^{n}BuOH, DMF, DMSO, toluene, and octane were less effective. Accordingly, the use of strongly coordinating phosphine ligands or solvents is not desirable for the palladium-catalyzed hydroamination. The use of 1.5 equiv of alkyne **1a** gave **3a** in 93% yield (entry 2). The reaction of diphenylacetylene **1b** gave **3b** in 81% yield (entry 3). The hydroamination of the unsymmetrical alkynes **1c** and **1d** afforded a mixture of the regioisomeric products (entries 4 and 5). The hydroamination of the terminal alkynes **1e** and **1f** gave **3e** and **3f**, respectively, in lower yields (entries 6 and 7), due to competitive cyclotrimerization of the terminal alkynes under the palladium catalyst. Since the aldehydes **4e** and **4f** or their derivatives were not detected, the hydroamination of the terminal alkynes was very regioselective. Various protecting groups of alcohol were tolerated under the reaction conditions (entries 8–11). When the chloro-substituted alkyne **1k** was used, a 50:50 mixture of **3k** and **5** was obtained in 95% yield (entry 12, eq 2). The regioisomeric hydroamination product of **1k**, an enamine precursor of **4k**, would undergo the intramolecular replacement of the chlorine atom to produce a six-membered enamine and subsequently an imine derivative, and the intramolecular reaction of the resulting imine with phenolic OH would give **5**. The arylalkynes **1l** and **1m**, bearing an electron-donating group at the para position, gave the hydroamination products, with the predominant formation of **3** over **4**, in very high yields (entries 13 and 14). However, the reaction of **1o** having an electron-withdrawing group at the para position was sluggish, and the predominant formation of **4o** over **3o** was observed.



(2)

The hydroamination of **1a** with **2a** is representative. To a 1,4-dioxane suspension (0.05 mL) of 2-aminophenol **2a** (54.6 mg, 0.5 mmol) and $Pd(NO_3)_2$ (17.3 mg, 0.075 mmol) in the reaction vial was added 6-dodecyne **1a** (124.7 mg, 0.75 mmol) under an argon

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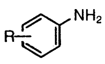
Table 2. Palladium-Catalyzed Hydroamination of **1a** with Arylamines **2**[a]



2

entry	R of **2**	reaction time, h	yield of **3**, %[b]
1	2-OH (**2a**)	10	96
2	3-OH (**2b**)	10	48
3	4-OH (**2c**)	20	30
4	2-CH_2OH (**2d**)	20	12
5	2-OMe (**2e**)	20	11
6	3-OMe (**2f**)	20	18
7	H (**2g**)	20	13

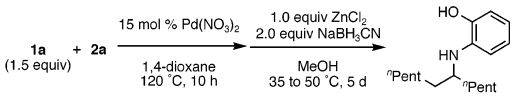
[a] Reaction conditions: 0.5 mmol amine, 0.75 mmol alkyne, 15 mol % $Pd(NO_3)_2$, 1,4-dioxane, 120 °C. [b] ^{1}H NMR yields, dibromomethane was used as an internal standard.

atmosphere. The suspension was heated at 120 °C for 10 h. The reaction mixture was cooled to room temperature and filtered through a short Al_2O_3 pad using diethyl ether as an eluent, and the resulting filtrate was concentrated. The residue was purified by column chromatography (silica gel, hexanes−ethyl acetate 50/1 to 10/1) to afford 6-dodecanone **3a** in 93% yield (86.0 mg).

The rate enhancement effect of *o*-aminophenol in the palladium-catalyzed hydroamination was investigated. The addition of aliphatic amines, such as ethanolamine and 2-aminomethylphenol, to **1a** in the presence of representative palladium catalysts including $Pd(NO_3)_2$ did not take place at all under various reaction conditions. The results of the hydroamination of **1a** with arylamines **2** in the presence of $Pd(NO_3)_2$ are summarized in Table 2.

Among the three-regioisomeric aminophenols **2a**−**c**, *o*-aminophenol **2a** was the most effective and efficient, and the hydroamination with *m*-aminophenol **2b** was faster than that with the para isomer **2c** (entries 1−3). These results suggest that the rate enhancement of **2a** is most probably due to the chelation effect of the ortho hydroxy group to the palladium atom. The hydroamination with *o*-hydroxymethylaniline **2d** was sluggish (entry 4); perhaps the chelation (and protonation ability to Pd) of this amino alcohol would be less effective. Interestingly, the addition of the methoxy-substituted amines **2e** and **2f** was also sluggish, despite *ortho* and *meta* substitution (entries 5 and 6). Accordingly, the presence of OH at the *ortho* position is essential to dramatically enhance the rate of hydroamination.[7] As expected, the hydroamination of aniline **2g** was sluggish, and the addition rates of **2d**−**g** were approximately of similar level.

For the purpose of obtaining an amine adduct, the reaction product of the hydroamination of **1a** with **2a** was reduced prior to hydrolyzing the reaction mixture (eq 3).[4h] Treatment with $NaBH_3CN$ and $ZnCl_2$ in MeOH gave *o*-*N*-(1-pentylheptyl)aminophenol **6** in 62% isolated yield.



(3)

6 (62 % yield)

Two major mechanisms have been proposed for the transition metal-catalyzed hydroamination of C−C multiple bonds: (1) activation of C−C multiple bonds through the coordination of MLn followed by the nucleophilic attack of amines to the electron-deficient alkenes and alkynes (C−C multiple bond activation) and (2) oxidative addition of N−H bond to MLn (with lower oxidation state) followed by the hydrometalation of alkenes and alkynes with the resulting M−H species (amine activation).[1b] Since the dramatic rate enhancement was observed in the case of **2a** and a phenolic OH was essential for this enhancement, a chelation effect of *o*-aminophenol is operative. Accordingly, it is most probable that an *o*-aminophenoxide palladium(II) complex and HX would be generated by the reaction of Pd(II) with 2-aminophenol, leading to an equiliblium with the *o*-hydroxyamido tautomer, and subsequent 1,2-insertion of an alkyne into the amido tautomer would give the product.[8] However, there is an alternative possibility that H−Pd-(2-aminophenoxide) species, generated by the reaction of 2-aminophenol with Pd(0), would react with an alkyne to produce a vinylpalladium intermediate, which would undergo tautomerization to give an amidopalladium species, and subsequent reductive elimination would afford the hydroamination product and Pd(0).[9] Now, we are in a position to carry out the hydroamination of alkynes very smoothly with high chemical yields in the presence of $Pd(NO_3)_2$ catalyst and *o*-aminophenol. Further extension of this palladium chemistry is continuing.

Supporting Information Available: Spectroscopic and analytical data of synthesized compounds and information on procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) It is conceivable that not only the chelation effect of OH but also the other factor, such as an acidity of phenol, is responsible for the rate enhancement.

(8) We appreciate very much one of the reviewers who suggested this mechanism.

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