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Intramolecular Hydroamination of Alkynes Catalyzed by $Pd(PPh_3)_4$/Triphenylphosphine under Neutral Conditions

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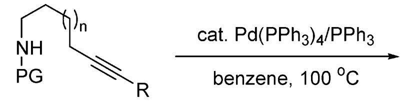
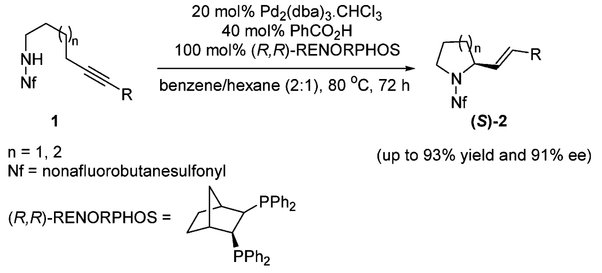


1　　**2**

n = 1, 2
PG = protecting group

The intramolecular hydroamination of alkynes tethered with amino group **1** in the presence of catalytic amounts of $Pd(PPh_3)_4$ and PPh_3 in benzene at 100 °C proceeded smoothly without the use of any additional acid source to afford five- and six-membered nitrogen heterocycles **2** in good to excellent yields. A compulsory addition of carboxylic acid as a cocatalyst was not needed, and the reaction could be carried out under essentially neutral conditions.

Nonfunctionalized carbon−carbon multiple bonds are generally unreactive toward nucleophiles because of their electron-rich π-orbitals. However, the use of transition metal catalysts enables the addition of nucleophiles to such unactivated C−C multiple bonds.[1] Nitrogen-containing heterocycles are main building blocks for many biologically important compounds. The hydroamination reaction of alkynes using transition metal catalysts is an attractive route to reach such compounds,[2] since the reaction proceeds in an atom-economical manner. Several catalytic systems have been explored to promote the hydroamination of carbon−carbon multiple bonds.[3] Recently, we reported that the palladium-mediated hydroamination of allenes,[4] enynes,[5] methylenecyclopropanes,[6] and cyclopropene[7] proceeded smoothly, giving the corresponding allylic amines in good to high yields. The presence of a carboxylic acid was needed as an unavoidable additive for the Pd-mediated inter- and intramolecular hydroamination of internal alkynes.[8] In these reactions, the presence of carboxylic acid as a cocatalyst modifies the palladium catalyst to a more active hydridopalladium species via in situ oxidative addition of Pd^0 into H-A. We also reported that an asymmetric version of the intramolecular hydroamination of alkynes proceeded smoothly by using a $Pd_2(dba)_3{\cdot}CHCl_3-PhCO_2H$ catalytic system in the presence of (*R,R*)-RENORPHOS as a chiral ligand to give various kinds of optically active five- and six-membered nitrogen heterocycles (eq 1).[8c]



(1)

1　　**(*S*)-2**

n = 1, 2
Nf = nonafluorobutanesulfonyl

(up to 93% yield and 91% ee)

The use of an stoichiometric amount of an expensive chiral ligand [(*R,R*)-RENORPHOS] for obtaining a better yield and high enatioselectivity was a drawback for this reaction, and thus we further struggled in this area to find much milder and more efficient reaction conditions. While we were searching for an alternative catalytic system, we found that the intramolecular hydroamination of alkynes proceeded without using an acid source. We report that in the presence of 15 mol % $Pd(PPh_3)_4$ and 10 mol % PPh_3 in benzene at 100 °C the intramolecular hydroamination reaction of alkynes tethered with amino group **1** proceeded well to give the corresponding nitrogen heterocycles **2** in good to excellent yields under essentially neutral conditions.

After several attempts, we found that the reaction of **1a** in the presence of 15 mol % $Pd(PPh_3)_4$ together with 10 mol % PPh_3 in benzene at 100 °C for 66 h produced the corresponding hydroamination product **2a** in 86%

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[2] Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127−2198.

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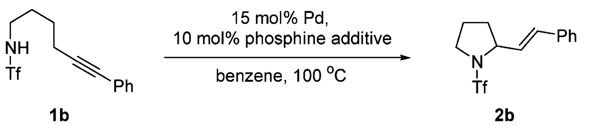
10.1021/jo050412w CCC: $30.25

TABLE 1. Optimization of Reaction Conditions for the Pd/Phosphine Additive Catalyzed Intramolecular Hydroamination of Alkynes[a]



(3)

entry	catalyst (15 mol %)	phosphine additive (10 mol %)	additional additive (10 mol %)	time (h)	**1b** yield (%)[b]	**2b** yield (%)[b]
1	$Pd(PPh_3)_4$	PPh_3		37	0	98 (87)
2		PPh_3		37	100	0
3	$Pd(PPh_3)_4$			37	84	trace
4	$Pd(PPh_3)_4$	$P(O)Ph_3$		41	18	41
5	$Pd(PPh_3)_4$	P(*o*-tolyl)$_3$		41	5	49
6	$Pd(PPh_3)_4$	dppp		41	13	63
7	$Pd(PPh_3)_4$	dppf		41	22	55
8	$Pd(PPh_3)_4$	PPh_3	CH_3CO_2H	16	trace	55
9	$Pd(PPh_3)_4$	PPh_3	$PhCO_2H$	9	0	28
10[c]	$Pd(PPh_3)_4$		$PhCO_2H$	overnight	0	94
11	$Pd_2dba_3.CHCl_3$	PPh_3		37	37	trace
12	$PdCl_2(PPh_3)_2$	PPh_3		37	88	0
13	$Pd(OAc)_2$	PPh_3		37	88	0
14	$[(\eta^3\text{-}C_3H_5)PdCl]_2$	PPh_3		37	80	0
15[d]	$Pd(PPh_3)_4$	PPh_3		37	0	77

[a] The reaction of **1b** (0.1 mmol) was carried out in the presence of 15 mol % palladium catalyst and 10 mol % phosphine additive in benzene (0.1 M) at 100 °C under argon unless otherwise noted. [b] Yield was calculated from ^{1}H NMR integration using CH_2Br_2 as an internal standard; isolated yield is in parentheses. [c] 15 mol % $PhCO_2H$ was used. [d] The reaction temperature was 120 °C.

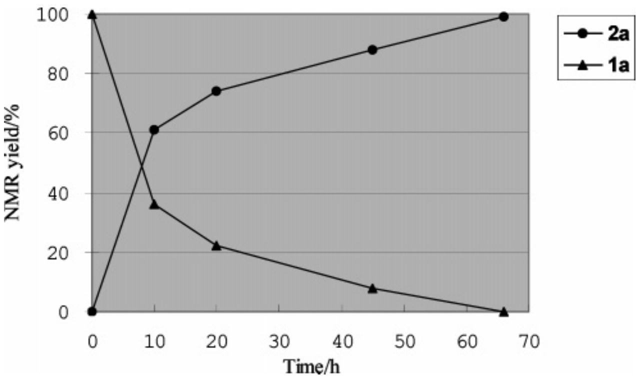
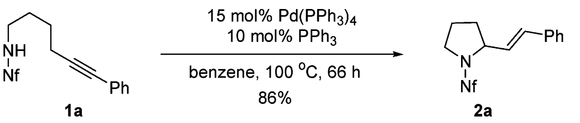


FIGURE 1. Time profile of the cyclization of **1a** (0.1 mmol) in the presence of 15 mol % $Pd(PPh_3)_4$ and 10 mol % PPh_3 in benzene (0.1 M) at 100 °C.

yield (99% NMR yield) (eq 2). As shown in Figure 1, the



(2)

time profile of the reaction of **1a** monitoring by NMR indicated that the complete conversion of the substrate occurred within 66 h. In contrast, the reaction of **1a** in the presence of 15 mol % $Pd(PPh_3)_4$ only *without the presence of additional PPh*$_3$ afforded only trace amounts of the product **2a** with the recovery of significant amounts of the starting material even after prolonged heating. The reaction of **1a** in the presence of 10 mol % PPh_3 only did not proceed at all, and the substrate was recovered. These results clearly indicate that combined use of $Pd(PPh_3)_4$ and PPh_3 is the key for cyclization of **1a**. Hartwig et al. apparently reported two examples of the Pd-catalyzed intermolecular hydroamination of cyclohexadiene without use of an acid additive.[9] In their report, $Pd(PPh_3)_4$ was generated in situ from $[(\eta^3\text{-}C_3H_5)PdCl]_2$ and PPh_3, and in general the use of a catalytic amount of trifluoroacetic acid was needed as a cocatalyst for the other examples. To the best of our knowledge, the $Pd(PPh_3)_4/PPh_3$ catalytic system for the catalytic hydroamination of alkynes has not been reported in the past.

We observed that the reaction of trifluoromethanesulfonyl (Tf)-substituted substrate **1b** was faster than that of **1a** having the nonafluorobutanesulfonyl (Nf) group. Hence, for further optimization of the reaction conditions, we chose **1b** as a model substrate (eq 3), and the results are summarized in Table 1. The substrate **1b** was cyclized in the presence of both 15 mol % $Pd(PPh_3)_4$ and 10 mol % PPh_3 to afford the pyrrolidine **2b** within 37 h with excellent yield (87%) (entry 1). In the absence of either $Pd(PPh_3)_4$ or PPh_3, essentially no reaction was observed, indicating the importance of the combination of both $Pd(PPh_3)_4$ and PPh_3 (entries 2 and 3). The use of other monodentate [$P(O)Ph_3$, P(*o*-tolyl)$_3$] and bidentate ligands [dppp = 1,3-bis(diphenylphosphino)-propane, dppf = 1,1′-bis(diphenylphosphino)-ferrocene] afforded the product in moderate yields (entries 4−7). The use of additional carboxylic acids was not essential for this transformation, resulting in poor chemical yields (entries 8 and 9). Although the intramolecular hydroamination using the $Pd(PPh_3)_4{-}PhCO_2H$ catalytic system without additional PPh_3 gave a high chemical yield in rather short reaction time (entry 10), we were motivated to carry out the present reaction under essentially neutral conditions. Other palladium catalysts such as $Pd_2dba_3{\cdot}CHCl_3$, $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$, $[(\eta^3\text{-}C_3H_5)PdCl]_2$, etc. were completely not effective (entries 11−14). Increasing reaction temperature up to 120 °C led to a moderate yield (entry 15).

The scope of the intramolecular hydroamination of alkynes is summarized in Table 2. Substrates **1c** and **1d**

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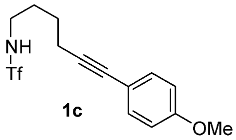
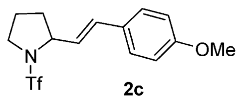
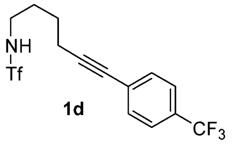
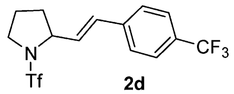
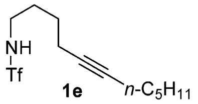
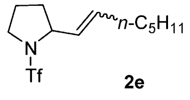
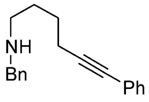
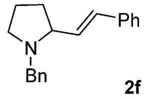
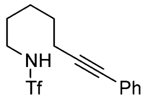
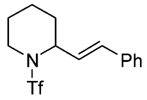
TABLE 2. Pd(PPh_3)$_4$/PPh_3-Catalyzed Intramolecular Hydroamination of Alkynes[a]

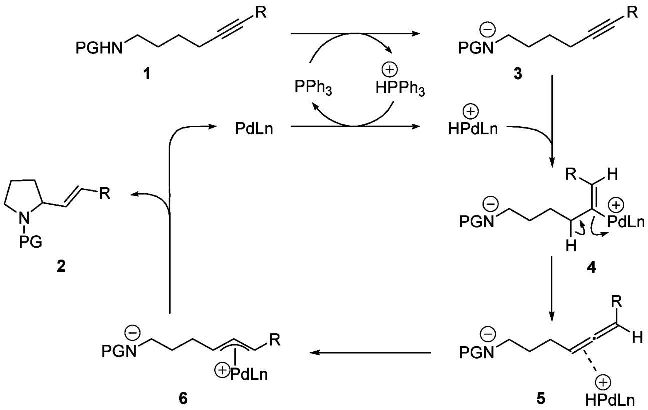
Entry	Substrate	Time/h	Product	Yield/%[b]
1[c]	 **1c**	38	 **2c**	75
2[c]	 **1d**	100	 **2d**	70
3	 **1e**	71	 **2e**	80[d]
4[c]	 **1f**	72	 **2f**	61
5	 **1g**	96	 **2g**	80

[a] The reaction of **1** (0.3 mmol) was carried out in the presence of 15 mol % Pd(PPh_3)$_4$ and 10 mol % PPh_3 in benzene (0.1 M) at 100 °C for the indicated reaction time under argon unless otherwise noted. [b] Isolated yield. [c] 30 mol % of Pd(Ph_3)$_4$ and 20 mol % of PPh_3 were used. [d] A mixture of *trans* and *cis* isomers (1.7:1) was obtained. The ratio was determined by ^{1}H NMR spectral analysis.

having methoxy and trifluoromethyl groups at the *para*-position of aromatic ring afforded the corresponding cyclized products **2c** and **2d**, respectively, in good yields, indicating that the substituents of aromatic ring did not exert a significant influence upon the cyclization (entries 1 and 2). In both cases, increased amounts of the catalyst were needed to obtain good chemical yields. The reaction of **1e**, having a pentyl group at the alkyne terminus, under the standard conditions proceeded smoothly to give a 1.7:1 mixture of *trans* and *cis* isomers of pyrrolidine **2e** in a good yield (entry 3). Not only Nf and Tf but also Bn could be used as a protecting group for the amine; **2f** was obtained from **1f** in 61% yield (entry 4). The cyclization of **1g** afforded the six-membered piperidine **2g** in a good yield (entry 5).

A proposed mechanism, which explains the role of triphenylphosphine as a cocatalyst in the present hydroamination reaction, is shown in Scheme 1, although it is highly speculative. Triphenylphosphine, acting as a Brϕnsted base, abstracts a proton from the nitrogen functionality at the early stage, producing **3** and a phosphonium ion [$HPPh_3$]$^+$. Hydropalladation of alkyne with the cationic palladium hydride species generated from Pd^0 and the phosphonium ion produces the vinylpalladium intermediate **4**.[10] The vinylpalladium intermediate **4** then undergoes β-elimination to give the allene **5** coordinated with the cationic palladium hydride. A subsequent hydropalldation of **5** furnishes the π-allylpalladium species **6**. Nucleophilic attack of the amine on the resulting π-allyl moiety gives the final product **2** along with regeneration of Pd^0. In our previous reports on the Pd/carboxylic acid catalyzed analogous reaction, we proposed the oxidative addition of Pd^0 to RCOO−H bond of acid as the very first step to generate catalytically active hydridopalladium complex.[8a−e] In contrast, formation of a phosphonium ion is the beginning step in the present transformation.

SCHEME 1. A Plausible Mechanism



In summary we have developed a simple and acid free hydroamination protocol for the synthesis of various nitrogen heterocycles. This reaction provides a very

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[10] In the palladium-catalyzed intramolecular hydrocarbonation of ϵ-alkynyl malononitriles, we proposed a rapid intramolecular cyclization of carbanion to the triple bond of alkyne coordinated with a cationic palladium hydride generated from Pd(OAc)$_2$ and a carbon pronucleophile; see: Tsukada, N.; Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2477−2480.

useful method for a catalytic synthesis of five- and six-membered nitrogen heterocycles. Now, it is clear that the catalytic intramolecular hydroamination of alkynes can be accomplished under essentially neutral conditions without using any acid source. We are further continuing our effort to develop a mild and an efficient asymmetric version of this hydroamination reaction and synthesizing various natural compounds by utilizing our methodology as the key step.[11]

Experimental Section

Representative Procedure for Intramolecular Hydroamination. To a mixture of $Pd(PPh_3)_4$ (17.3 mg, 0.015 mmol, 15 mol %), PPh_3 (2.6 mg, 0.01 mmol, 10 mol %), and *N*-trifyl-(6-phenyl-hex-5-ynyl)-amine **1b** (30.5 mg, 0.1 mmol) was added benzene (1.0 mL, 0.1 M) under argon atmosphere in a Wheaton microreactor. The mixture was stirred for 10 min at room temperature then heated at 100 °C. Progress of the reaction was monitored by TLC (hexane/ethyl acetate; 4/1). After complete consumption of the starting material, the reaction mixture was filtered through a short column of SiO_2 using diethyl ether as an eluent, and the resulting filtrate was concentrated. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate; 20/1−5/1) to afford *N*-triflyl-2-[(*E*)-2-phenylethenyl)pyrrolidine **2b** in 87% yield (26.5 mg).

Supporting Information Available: Starting material preparation; characterization data for all new compounds; and ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] Recently we reported the synthesis of indolizidine (−)-209D based on an intramolecular hydroamination strategy; see: Patil, N. T.; Pahadi, N. K.; Yamamoto, Y. *Tetrahedron Lett.* **2005**, *46*, 2101−2103.