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Palladium-Catalyzed Regioselective Silaboration of Pyridines Leading to the Synthesis of Silylated Dihydropyridines

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Supporting Information

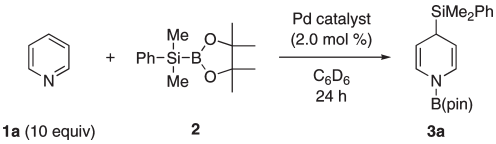
ABSTRACT: The addition of silylboronic esters to pyridine takes place in toluene at 50 °C in the presence of a palladium catalyst to give *N*-boryl-4-silyl-1,4-dihydropyridines in high yield. The regioselective 1,4-silaboration also proceeds in the reaction of 2-picoline and 3-substituted pyridines, whereas 4-substituted pyridines undergo 1,2-silaboration to give *N*-boryl-2-silyl-1,2-dihydropyridines regioselectively.

Catalytic reactions for the functionalization and transformation of pyridine and its derivatives have gained much attention in synthetic organic chemistry.[1] A particular difficulty lies in the addition reactions of pyridine, which give functionalized dihydropyridine derivatives. Although such conversions can be achieved by some stoichiometric reactions using alkali metals[2] or strong nucleophiles such as organolithiums,[3] applications of these reactions are limited because of the harsh reaction conditions and the instability of the products. Conversion of pyridine to more reactive pyridinium salts has been used as an alternative way to transform pyridine into dihydropyridines.[4] The transition-metal-catalyzed addition reaction of *unactivated* pyridine has been recognized as a rather difficult reaction and is much less explored.[5] Hydrogenation[6] and hydrosilylation,[7−9] both of which allow the introduction of hydride onto the pyridine ring, are the only successful catalytic processes reported to date. It would be highly attractive to establish a new catalytic addition reaction by which a non-hydrogen functional group can be introduced onto the carbon atoms of pyridine.

During our ongoing study of catalytic silaboration of unsaturated hydrocarbons,[10] we fortuitously found that a pyridine ring can undergo addition of silylboronic esters in the presence of a catalyst. Here we describe a palladium-catalyzed addition of silylboronic esters to pyridines. The reaction achieves the dearomatizing conversion of pyridines to dihydropyridines under mild conditions, with the introduction of a silyl group on a carbon atom of the pyridine ring.

Pyridine (**1a**, 10 equiv) was reacted with $Me_2PhSi-B(pin)$ (**2**) in C_6D_6 in the presence of $(\eta^3\text{-}C_3H_5)PdCl(L)$ (L = tertiary phosphine)[11] (2.0 mol %) as a catalyst precursor (Table 1). No reaction took place when the reaction was carried out at 50 °C in the absence of palladium or even in the presence of a palladium catalyst bearing PPh_3 (entries 1 and 2). In sharp contrast, the reaction proceeded with a palladium catalyst bearing cyclohexyl-substituted phosphines (entries 3−5). The reaction gave dihydropyridine derivative **3a** through regioselective introduction of the boryl group onto the nitrogen atom and the silyl group onto the C4 carbon atom.[12] Although PCy_2Ph and PCy_3 were both effective for the silaboration (entries 4 and 5), we decided that PCy_3 was the ligand of choice because the reaction proceeded more cleanly (entry 5). Full conversion of **2** was achieved at a prolonged reaction time (96 h) at 50 °C in toluene, and **3a** was isolated in 94% yield (entry 5). No reaction took place at 25 °C (entry 6), and a reduced yield was observed at 80 °C (entry 7). The complex consisting of palladium and PCy_3 in a 1:1 ratio was crucial for high catalyst activity. A phosphine-free palladium complex did not work as a catalyst (entry 8), and additional PCy_3 completely shut down the catalytic activity (entry 9). A catalyst generated in situ from $Pd(dba)_2$ and PCy_3 (P:Pd = 1:1) showed comparable efficiency to $(\eta^3\text{-}C_3H_5)PdCl(PCy_3)$ (entry 10), indicating that the reaction proceeds via a mechanism involving Pd(0).

Table 1. Screening of Reaction Conditions in the Silaboration of 1a[a]



1a (10 equiv) **2** **3a**

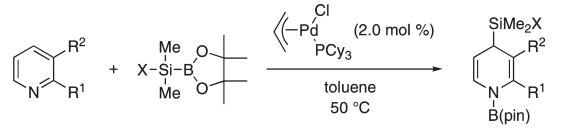
entry	catalyst precursor	temp (°C)	conv. of **2** (%)[b]	yield of **3a** (%)[b]
1[c]	none	50	0	0
2	$(\eta^3\text{-}C_3H_5)PdCl(PPh_3)$	50	0	0
3	$(\eta^3\text{-}C_3H_5)PdCl(PCyPh_2)$	50	45	36
4	$(\eta^3\text{-}C_3H_5)PdCl(PCy_2Ph)$	50	93	77
5	$(\eta^3\text{-}C_3H_5)PdCl(PCy_3)$	50	83 (>99[d])	79 (94[e])
6	$(\eta^3\text{-}C_3H_5)PdCl(PCy_3)$	25	0	0
7	$(\eta^3\text{-}C_3H_5)PdCl(PCy_3)$	80	>99	44
8	$[(\eta^3\text{-}C_3H_5)PdCl]_2$[f]	50	0	0
9	$(\eta^3\text{-}C_3H_5)PdCl(PCy_3)$ + PCy_3[g]	50	0	0
10	$Pd(dba)_2$ + PCy_3[g]	50	91	85

[a] Conditions: **1a** (1.0 mmol), **2** (0.10 mmol), Pd catalyst (2.0 μmol) were stirred in C_6D_6 (0.2 mL) at 50 °C for 24 h. [b] ^1H NMR yield based on **2**. [c] Carried out in the absence of Pd. [d] Conversion after 96 h. [e] Isolated yield for a 0.4 mmol scale reaction in toluene for 96 h. [f] 1.0 mol % dimer was used. [g] 2.0 mol %.

Received: March 5, 2011
Published: April 21, 2011

dx.doi.org/10.1021/ja2020229 | *J. Am. Chem. Soc.* 2011, 133, 7324–7327

Table 2. 1,4-Silaboration of Pyridines 1a−f[a]



1a-1f (2-10 equiv) **2** (X = Ph) **4** (X = Cl) **3** (X = Ph) **5** (X = Cl)

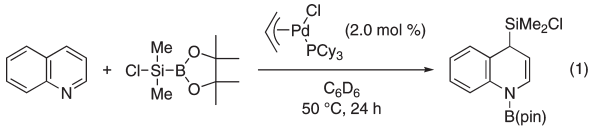
entry	R^1	R^2	1	Si−B	time (h)	yield (%)[b]
1[c]	H	Me	**1b**	**2**	96	92 (**3b**)
2[c]	H	OMe	**1c**	**2**	96	95 (**3c**)
3[c,d]	H	Ph	**1d**	**2**	96	79[e] (**3d**), 59[f] (**8d**)
4[c,d]	H	CO_2Me	**1e**	**2**	96	72[e] (**3e**), 62[f] (**8e**)
5[c]	Me	H	**1f**	**2**	96	no reaction
6[g]	H	H	**1a**	**4**	24	90 (**5a**)
7[g]	H	Me	**1b**	**4**	24	89 (**5b**)
8[g]	Me	H	**1f**	**4**	24	90 (**5c**)

[a] Conditions: **1** (0.80 or 4.0 mmol), **2** or **4** (0.40 mmol), and (η^3-C_3H_5)PdCl(PCy_3) (8.0 μmol) were stirred in toluene (0.2 mL) at 50 °C. [b] Isolated yield based on **2** or **4**. [c] **1** (4.0 mmol) was used. [d] Carried out in C_6D_6. [e] ^{1}H NMR yield based on **2**. [f] Isolated yield based on **2** after conversion to 4-silylpyridine **8** (see eq 3). [g] **1** (0.80 mmol) was used.

Various pyridines **1a**−**f** were subjected to the silaboration using the Pd/PCy_3 catalyst system (Table 2). The reactions of **2** with 3-picoline (**1b**) and 3-methoxypyridine (**1c**) proceeded smoothly to give the corresponding 1,4-adducts **3b** and **3c** in high yields (entries 1 and 2). The silaboration with **2** was also applicable to 3-phenylpyridine (**1d**) and methyl nicotinate (**1e**), resulting in efficient formation of **3d** and **3e**, respectively (entries 3 and 4). Because these 1,4-dihydropyridine derivatives were difficult to separate from the remaining **1**, isolation was carried out after conversion to 4-silylpyridines **8** via reaction with benzaldehyde (see below). In contrast to the successful silaboration of 3-substituted pyridines, 2-picoline (**1f**) did not react with **2** at all under the same reaction conditions (entry 5). A silylboronic ester **4**[13] bearing chlorine on the silicon atom was found to be more reactive than **2** (entries 6−8). The additions of **4** to **1a** and **1b** were complete within 24 h and gave the corresponding 1,4-adducts **5a** and **5b** in high yields (entries 6 and 7). It should be noted that **4** reacted even with 2-picoline (**1f**) to afford **5c** in high yield (entry 8).

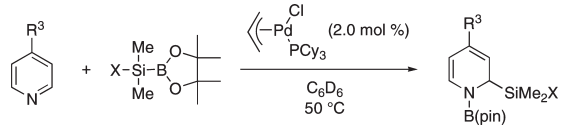
Silaboration of 4-substituted pyridines was then examined (Table 3). We found that the 1,2-additions of **2** to 4-picoline (**1g**) and 4-phenylpyridine (**1h**) proceeded to give the corresponding *N*-boryl-2-silyl-1,2-dihydropyridines **6a** and **6b** regioselectively in high yields (entries 1 and 2). The silaboration of **1h** took place more efficiently when the reaction was carried out using **4** (entry 3). 4-(Dimethylphenylsilyl)pyridine (**8a**), which was prepared via silaboration of **1a** followed by treatment with benzaldehyde (see eq 2), also underwent silaboration with **4**, giving disilylated **7b** (entry 4).

Quinoline (**1i**) also reacted with **4** under the Pd/PCy_3-catalyzed conditions, giving the 1,4-adduct **5d** as the major product (81%) (eq 1).



1i (2 equiv) **4** **5d** (81%, NMR)

Table 3. 1,2-Silaboration of Pyridines 1g, 1h, and 8a[a]

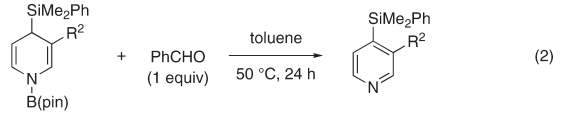


1g, **1h**, **8a** (2-10 equiv) **2** (X = Ph) **4** (X = Cl) **6** (X = Ph) **7** (X = Cl)

entry	R^3	1 or 8	Si−B	time (h)	yield (%)[b]
1[c]	Me	**1g**	**2**	96	79 (**6a**), 72[d] (**9a**)
2[c]	Ph	**1h**	**2**	96	81 (**6b**), 69[d] (**9b**)
3[e]	Ph	**1h**	**4**	24	93 (**7a**)
4[e]	$SiMe_2Ph$	**8a**	**4**	24	91 (**7b**)

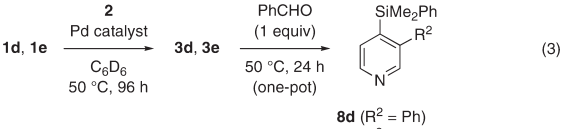
[a] Conditions: pyridine (0.80 or 4.0 mmol), silylboronic ester (0.40 mmol), and (η^3-C_3H_5)PdCl(PCy_3) (8.0 μmol) were stirred in C_6D_6 (0.2 mL) at 50 °C. [b] ^{1}H NMR yield based on **2** or **4**. [c] **1** (4.0 mmol) was used. [d] Isolated yield based on **2** after conversion to 2-silylpyridine **9** (see eq 4). [e] **1** (0.80 mmol) was used.

The dihydropyridines obtained by the silaboration are expected to show unique reactivities.[4,14] The reactions of Me_2PhSi-substituted **3** and **6** with benzaldehyde (1 equiv) resulted in aromatization of the dihydropyridine cores to give silylated pyridines **8** and **9**, respectively, in high yields (eqs 2−4).[15] As mentioned above, some dihydropyridine derivatives (**3d**, **3e**, **6a**, and **6b**) that were difficult to isolate were directly converted into the pyridine derivatives for isolation (eqs 3 and 4).

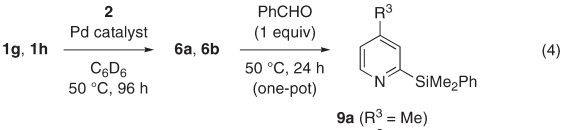


3a (R^2 = H)
3b (R^2 = Me)
3c (R^2 = OMe)

8a (R^2 = H, 92%)
8b (R^2 = Me, 89%)
8c (R^2 = OMe, 86%)



8d (R^2 = Ph)
8e (R^2 = CO_2Me)
Yields are shown in Table 2.



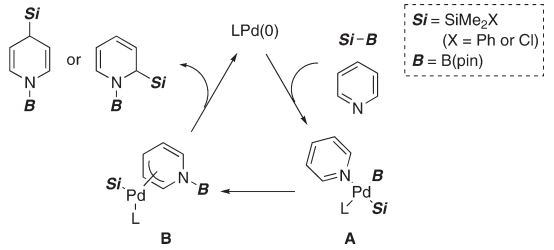
9a (R^3 = Me)
9b (R^3 = Ph)
Yields are shown in Table 3.

A possible catalytic cycle for the silaboration of pyridine is proposed in Scheme 1. Oxidative addition of the silylboronic ester to Pd(0) and coordination of pyridine gives complex **A**.[16] Regioselective insertion of pyridine into the Pd−B bond with introduction of the boryl group onto the nitrogen atom forms π-allylpalladium complex **B**.[17] Finally, reductive elimination from **B** results in the formation of the dihydropyridine and regeneration of Pd(0). Formation of the stable B−N bond may facilitate the formation of **B** in the catalytic cycle.[18]

In conclusion, we have established a new class of catalytic addition reactions that achieves dearomatizing conversion of pyridines to functionalized dihydropyridines. Regioselective

dx.doi.org/10.1021/ja2020229 |*J. Am. Chem. Soc.* 2011, 133, 7324–7327

Scheme 1. Possible Reaction Mechanism



introduction of the boryl and silyl groups is achieved efficiently by a palladium catalyst bearing PCy_3 as a ligand. Mechanistic details of the reaction and synthetic applications of the silylated *N*-boryldihydropyridines are now under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information. Experimental details and characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

K.O. acknowledges JSPS for fellowship support.

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