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Regioselective Synthesis of 1,2-Dihydropyridines by Rhodium-Catalyzed Hydroboration of Pyridines

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Supporting Information

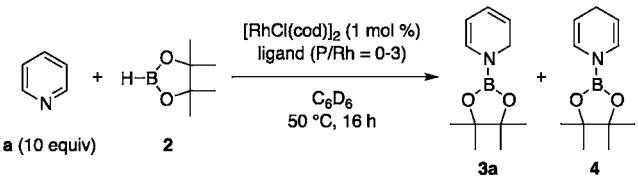
ABSTRACT: Pyridine undergoes addition of pinacolborane at 50 °C in the presence of a rhodium catalyst, giving *N*-boryl-1,2-dihydropyridine in a high yield. The selective 1,2-hydroboration also takes place in the reactions of substituted pyridines. In the reaction of 3-substituted pyridines, 3-substituted *N*-boryl-1,2-dihydropyridines are formed regioselectively.

Much interest has been focused on the dearomatizing transformations of pyridine derivatives, which lead to the synthesis of six-membered nitrogen-containing cyclic compounds directly.[1,2] These transformations are particularly attractive for obtaining partially unsaturated cyclic compounds such as 1,2-dihydropyridine derivatives, which are useful synthetic intermediates for the synthesis of nitrogen-containing organic molecules.[2,3] As exemplified by Fowler's $NaBH_4$ reduction of *N*-(alkoxycarbonyl)pyridinium chloride,[4] such dearomatizing transformations have been achieved mainly through formation of pyridinium salts,[2] in which nucleophilic attack to the pyridine ring is facilitated.[5] Transition-metal-catalyzed addition reactions to pyridines are also an attractive strategy for the reduction of pyridine rings without stoichiometric activation to form pyridinium salts, but such simple additions to pyridine derivatives are still unexplored. Although hydrogenation is the simplest reaction to reduce pyridine rings, the harsh reaction conditions and overreduction to form piperidine derivatives are often problematic.[6,7] Alternatively, catalytic hydrosilylations have been developed to obtain di- and tetrahydropyridines.[8,9] However, it should be noted that existing hydrosilylation systems have encountered low product selectivity,[8] overreaction,[9a,b] and a narrow substrate scope.[9c] Therefore, it is highly desirable to develop an efficient catalytic addition to pyridines that allows selective partial reduction to dihydropyridine derivatives.

Recently, we found that pyridine derivatives undergo addition of silylboronic esters in the presence of a palladium catalyst to give *N*-boryl-4-silyl-1,4-dihydropyridines.[10] This reaction is the first catalytic addition to pyridine derivatives to introduce non-hydrogen elements onto the carbon atoms of the pyridine ring. We assumed that one of the driving forces of the reaction is the formation of the boron−nitrogen bond, which is known to be a stable covalent bond. Then, we envisioned that use of boron-containing reagents would promote the addition to pyridine rings by virtue of the formation of a strong B−N bond. Herein, we describe the first transition-metal-catalyzed hydroboration of pyridines giving *N*-boryl-1,2-dihydropyridines in a regioselective manner.[11] It should be noted that magnesium-catalyzed hydroboration of pyridine derivatives has just been reported in the literature.[12] We believe that this reaction system is also driven by the formation of a B−N bond, although the magnesium-catalyzed reaction provides a route to 1,4-dihydropyridine derivatives.

The hydroboration of pyridine (**1a**, 10 equiv) was examined using pinacolborane (**2**)[13] in C_6D_6 (Table 1). No reaction took place at 50 °C in the absence of a rhodium catalyst (entry 1), whereas the addition of **2** to **1a** proceeded effectively in the presence of $[RhCl(cod)]_2$ (1.0 mol %) to give a mixture of *N*-borylated 1,2-dihydropyridine **3a** and 1,4-dihydropyridine **4** in a good combined yield (entry 2). It is interesting to note that the regioselectivity was dependent on the phosphorus ligands. Selective 1,4-hydroboration (**3a**:**4** = 1:99) was catalyzed by a Rh/PPh_3 catalyst generated in situ from $[RhCl(cod)]_2$ and PPh_3 (P/Rh = 1), although the yield was low owing to the

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



entry	ligand	P/Rh	conv. (%)[b,c]	yield (%)[d]	3a:4[c]
1[e]	–	–	0	0	–
2	none	–	90	62	23:77
3	PPh_3	1	80	23	1:99
4	$PCyPh_2$	1	72	27	26:74
5	PCy_2Ph	1	89	63	87:13
6	PCy_3	1	>99	91	91:9
7	PCy_3	2	95	83	98:2
8	PCy_3	3	44	27	93:7
9[f]	PCy_3	2	>99	93[g]	98:2

[a] **1a** (2.0 mmol), **2** (0.20 mmol), $[RhCl(cod)]_2$ (2.0 μmol), and ligand (0−0.012 mmol) were stirred in C_6D_6 (0.2 mL) at 50 °C for 16 h unless otherwise noted. [b] Conversion of **2**. [c] Determined by ^1H NMR. [d] Combined ^1H NMR yield of **3a** and **4** based on **2**. [e] In the absence of a rhodium catalyst. [f] 0.4 mmol scale reaction with 2 equiv of **1a** in toluene for 24 h. [g] Isolated yield.

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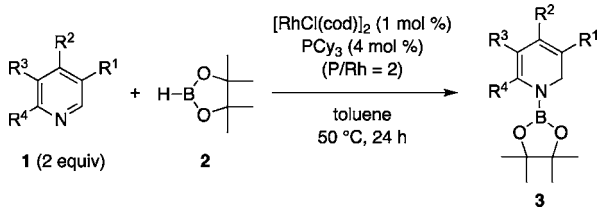
formation of unidentified byproducts (entry 3). In contrast, 1,2-hydroboration selectively took place in high yields, when the reaction was carried out using rhodium catalysts bearing PCy_2Ph (entry 5) and PCy_3 (entry 6). Finally, we found that a rhodium catalyst bearing PCy_3 (P/Rh = 2) was the most effective catalyst for 1,2-hydroboration of **1a**. The adduct was obtained in an 83% yield in a **3a:4** ratio of 98:2 (entry 7). On the other hand, use of 3 equiv of PCy_3 decreased the reaction rate (entry 8). By using a Rh/PCy_3 (P/Rh = 2) catalyst, hydroboration could be carried out under the reduced stoichiometry of **1a** (2 equiv), affording **3a** in 93% isolated yield with high isomeric purity (entry 9).[14]

Substituted pyridines **1b**−**1m** were subjected to hydroboration using the Rh/PCy_3 (P/Rh = 2) catalyst in toluene at 50 °C (Table 2).[14] The reaction of **2** with 4-picoline (**1b**), 4-ethylpyridine (**1c**), and 4-phenylpyridine (**1d**) proceeded effectively to give the corresponding 1,2-hydroboration products **3b**−**3d** in high yields (entries 1−3). Electron deficient 4-trifluoromethylpyridine (**1e**) was also applicable to the hydroboration, leading to the high-yield formation of the corresponding 1,2-dihydropyridine **3e** (entry 4). Remarkably, hydroboration of 3-substituted pyridines such as 3-picoline (**1f**), 3-methoxypyridine (**1g**), and 3-fluoropyridine (**1h**) gave 1,2-hydroboration products **3f**−**3h** with high regioselectivity, in which a hydrogen atom was selectively introduced to the more sterically congested 2-position (entries 5−7). In contrast, the reaction of methyl nicotinate (**1i**) gave a 33:67 mixture of **3i** and the regioisomer **3i′** ($R^3 = CO_2Me$, $R^1 = R^2 = R^4 = H$), although an ester group, which could not survive under the magnesium-catalyzed conditions,[12] was tolerable (entry 8). The hydroboration of 2-picoline (**1j**) also took place in a 1,2-addition fashion to afford **3j** in moderate yield in the presence of a large excess of **1j** (entry 9). The established catalytic conditions were applicable to hydroboration of 3,5-lutidine (**1k**) and 3,4-lutidine (**1l**), leading to the high-yield formation of the corresponding 1,2-dihydropyridines **3k** and **3l**, respectively (entries 10 and 11). The regioselectivity in the hydroboration of **1l** was again very high, and the regioisomeric product was not observed at all. Regioselective 1,2-hydroboration also took place in the reaction of methyl 6-methylnicotinate (**1m**), giving **3m** in high yield (entry 12). However, 2,6-lutidine did not react with **2** at all under the conditions.

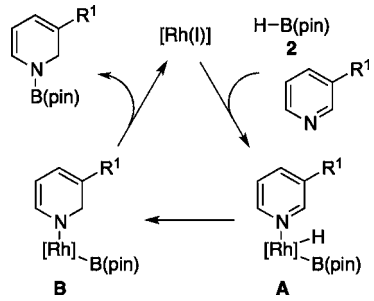
Table 2. Rhodium-Catalyzed 1,2-Hydroboration of Substituted Pyridines 1b−1m[a]



entry	R^1	R^2	R^3	R^4		yield (%)[b]
1	H	Me	H	H	**1b**	92 (**3b**)
2	H	Et	H	H	**1c**	82 (**3c**)
3[c]	H	Ph	H	H	**1d**	85[d] (**3d**)
4	H	CF_3	H	H	**1e**	92 (**3e**)
5	Me	H	H	H	**1f**	90 (**3f**)
6	OMe	H	H	H	**1g**	91 (**3g**)
7[c]	F	H	H	H	**1h**	72[d] (**3h**)
8[c]	CO_2Me	H	H	H	**1i**	78[e] (**3i**, **3i′**)
9[c,f]	H	H	H	Me	**1j**	58[d] (**3j**)
10	Me	H	Me	H	**1k**	96 (**3k**)
11	Me	Me	H	H	**1l**	88 (**3l**)
12[c,f]	CO_2Me	H	H	Me	**1m**	75 (**3m**)

[a] **1** (0.80 mmol), **2** (0.40 mmol), $[RhCl(cod)]_2$ (4.0 μmol), and PCy_3 (0.016 mmol) were stirred in toluene (0.2 mL) at 50 °C for 24 h. [b] Isolated yield based on **2**. [c] Carried out in C_6D_6. [d] ^1H NMR yield based on **2**. [e] Combined yield of a 33:67 mixture of **3i** and the regioisomer **3i′** ($R^3 = CO_2Me$, $R^1 = R^2 = R^4 = H$). [f] 10 equiv of **1** (4.0 mmol) were used.

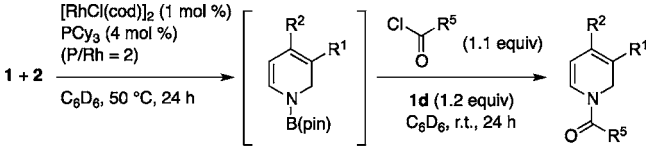
Scheme 1. Possible Reaction Mechanism



The oxidative addition of the B−H bond of **2** to Rh(I), as well as coordination of pyridine, gives complex **A**. Insertion of pyridine into the Rh−H bond takes place at the 1,2-positions of the pyridine ring with the Rh−N bond formation to give borylrhodium amide **B**. Finally, reductive elimination from **B** results in the formation of dihydropyridine and regeneration of Rh(I).

N-Boryl-1,2-dihydropyridines **3** are expected to be a new class of building blocks for the synthesis of six-membered nitrogen-containing cyclic compounds. We tested a conversion of **3** to the corresponding *N*-acyl derivatives, which are difficult to synthesize by Fowler's reduction (Scheme 2).[15] A C_6D_6 solution of dihydropyridines **3d** obtained by the hydroboration of **1d** was treated with acetyl and pivaloyl chlorides (1.1 equiv) in a one-pot manner. The reactions gave *N*-acetyl- and *N*-pivaloyl-1,2-dihydropyridines **5a** and **5b** in 73% and 71% overall yields, respectively. According to the one-pot procedure, 3-fluorinated **3h** could also be acylated to afford *N*-acetyl **6a** and *N*-pivaloyl **6b**. It should be noted that the acylation of the B−N bond could be successfully achieved in the presence of 4-phenylpyridine (**1d**, 1.2 equiv), whereas use of pyridine or triethylamine led to the formation of complex mixtures.

Scheme 2. Acylation of *N*-Boryl-1,2-dihydropyridines



5a (R^1 = H, R^2 = Ph, R^5 = Me) from **1d**, 73%
5b (R^1 = H, R^2 = Ph, R^5 = *t*-Bu) from **1d**, 71%
6a (R^1 = F, R^2 = H, R^5 = Me) from **1h**, 54%
6b (R^1 = F, R^2 = H, R^5 = *t*-Bu) from **1h**, 68%

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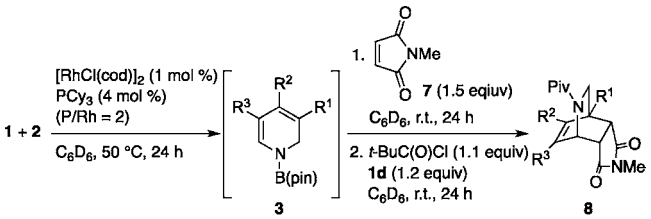
We separately examined a Diels–Alder reaction of **3** (Scheme 3). A C_6D_6 solution of **3** was reacted with *N*-methylmaleimide

Scheme 3. Diels–Alder Reaction of *N*-Boryl-1,2-dihydropyridines



8a ($R^1 = R^2 = R^3 = H$) from **1a**, 76%
8b ($R^2 = Ph$, $R^1 = R^3 = H$) from **1d**, 68%
8c ($R^1 = F$, $R^2 = R^3 = H$) from **1h**, 62%
8d ($R^1 = R^3 = Me$, $R^2 = H$) from **1k**, 81%

(**7**, 1.5 equiv). The Diels–Alder reaction took place at room temperature to give *N*-borylated 2-azabicyclo[2.2.2]octane (isoquinuclidine)[16] derivatives with high efficiency. These compounds were isolated in 62–81% total yields after acylation of the B–N bond with pivaloyl chlorides in the presence of **1d**. It is interesting to note that the corresponding *N*-acetyldihydropyridine **6a** did not react with **7** under the identical reaction conditions, suggesting that *N*-borylated dihydropyridine is much more reactive in the Diels–Alder reaction than the corresponding *N*-acyl derivatives.

In conclusion, we have established an efficient method for a dearomatizing conversion of unactivated pyridines to 1,2-dihydropyridines via rhodium-catalyzed hydroboration. Regioselective formation of *N*-boryl-1,2-dihydropyridines has been achieved using a rhodium catalyst bearing PCy_3 as a ligand. *N*-Boryl-1,2-dihydropyridines have been used in a Diels–Alder reaction to form an isoquinuclidine structure and found to be more reactive than the corresponding *N*-acetyl-1,2-dihydropyridines. Synthetic applications utilizing the *N*-borylated 1,2-dihydropyridines, as well as mechanistic details of the reaction, are now under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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(14) The *N*-borylated dihydropyridines **3** are air and moisture sensitive. Isolation of **3a–3c**, **3e–3g**, **3k**, and **3l**, which are derived from pyridines with low boiling points, was carried out as follows: After hydroboration, the reaction mixture was treated with activated charcoal. Filtration of the mixture under an atmosphere of nitrogen resulted in a rhodium-free colorless solution. The solution was concentrated in vacuo to remove volatiles including starting pyridines. Methyl nicotinate derived **3i** + **3i′** and **3m** could be purified by

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