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Ruthenium-Catalyzed Regioselective 1,4-Hydroboration of Pyridines

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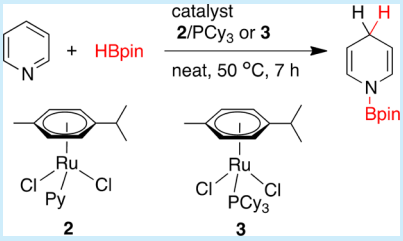
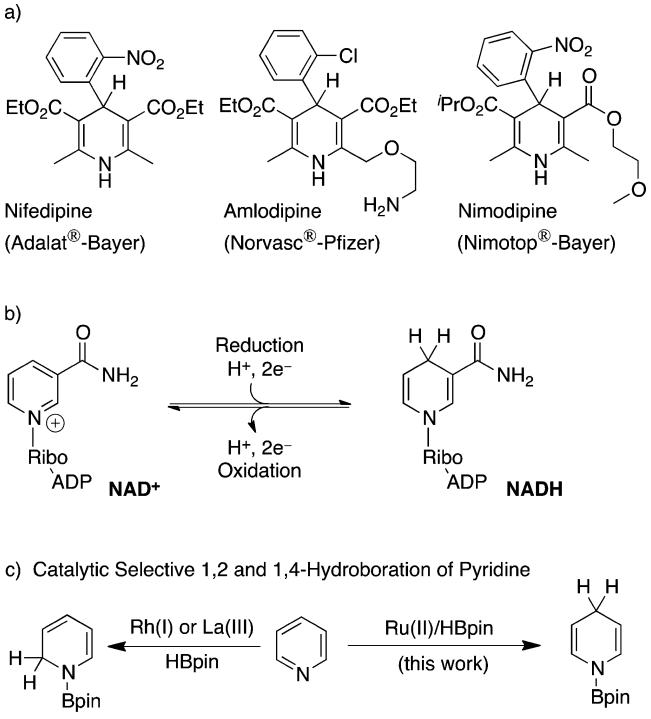
Supporting Information

ABSTRACT: Simple ruthenium precursor $[Ru(p\text{-cymene})Cl_2]_2$ **1** catalyzed regioselective 1,4-dearomatization of pyridine derivatives using pinacolborane is reported. Two catalytic intermediates, $[Ru(p\text{-cymene})Cl_2Py]$ **2** and $[Ru(p\text{-cymene})Cl_2(P(Cy)_3)]$ **3**, involved in this process are identified, independently synthesized, characterized, and further used directly as effective catalysts; two more catalytic intermediates $[Ru(p\text{-cymene})Cl_2(Py)(P(Cy)_3)]$ **4** and $[Ru(p\text{-cymene})(H)Cl(Py)(P(Cy)_3)]$ **5** are identified in solution. Complex **5** is the active catalytic intermediate. An intramolecular selective 1,5-hydride transfer in **5** leading to the regioselective 1,4-hydroboration of pyridine compounds is proposed.



1,4-Dihydropyridines are prevalent in nature and are also commercially available, as they possess pharmacological applications such as Ca^{2+} channel blockers, and for cardiovascular diseases they are the most used drugs. For example, niphedipine, amlodipine, and nimodipine are essential medicines and used for the treatment of various ailments (Scheme 1a).[1] In general, around 92% of the drug candidates possesses nitrogen-containing cycles. The NAD^+/NADH redox couple undergoes dearomatization/aromatization of pyridine motifs and plays an important role in biological systems[2] (Scheme 1b), and 1,4-dihydropyridines are also widely used as reducing agents in organocatalysis.[3] Selective synthesis of dihydropyridines from pyridine is a fundamental and challenging transformation,[4] which is conventionally performed using an excessive amount of alkali metals or metal-hydrides leading to a mixture of 1,2- and 1,4-dihydropyridines.[5,6] Strategies toward the selective synthesis of dihydropyridines from pyridines are more limited.[7] While the direct catalytic hydrogenation resulted in over-reduction of pyridines to piperidines,[8] hydrosilylation,[9] silaboration,[10] phosphinoboration,[11] and hydroboration allow their selective synthesis.

Scheme 1. 1,4-Dihydropyridines: Applications, Role in Nature, and Recent Advances in Synthesis of 1,2-Dihydropyridines



Hill reported the pioneering catalytic hydroboration of pyridines using a Mg(II) complex, which led to the formation of both 1,2- and 1,4-hydroboration products.[12] Harder and co-workers found that dinuclear Mg(II) complexes provide selective 1,2-hydroboration of pyridine; however, catalytic hydroboration resulted in regioisomeric mixtures.[13] The same group also demonstrated stoichiometric 1,2-reduction of pyridines using Ca(II) complexes.[14] The groups of Suginome[15] and Marks[16] developed Rh(I) and La(III) catalyzed elegant hydroboration of pyridine in which insertion of the pyridine C═N bond into the M−H bond provided selective 1,2-hydroboration (Scheme 1c). Ru(II)-catalyzed selective 1,4-hydrosilylation of pyridine was reported by the groups of Nikonov[9c] and Oestreich.[9d] However, selective catalytic 1,4-hydroboration of pyridine remains a challenge and limited to a recent report in which a frustrated Lewis pair from bulky organoborane and pyridine resulted in 1,4-hydroboration of pyridines.[17] The above-mentioned lead studies and our interest in developing efficient hydroboration reactions[18] guided us to investigate transition metal catalyzed selective 1,4-hydroboration of pyridines.

Among the complexes tested, $[Ru(p\text{-cymene})Cl_2]_2$ **1** is the best catalyst, as it provided *N*-boryl-1,4-dihydropyridine

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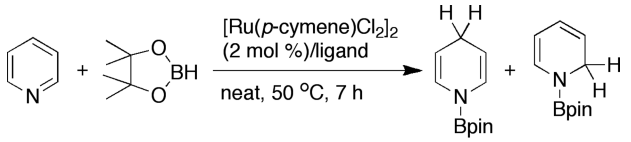
regioselectively in moderate yields (Tables S1 and S2). Further improvement was made possible by the use of phosphine ligands. Tricyclohexyl phosphine (PCy_3) is found to be the most suitable ligand (Table 1). Upon using 2 equiv of ligand PCy_3 (4 mol %, 1 equiv per Ru) with respect to **1** (2 mol %), efficient 1,4-hydroboration was observed (97% yield) with complete regioselectivity (Table 1, entry 4).

Table 1. Optimization of Experimental Conditions for 1,4-Hydroboration of Pyridine



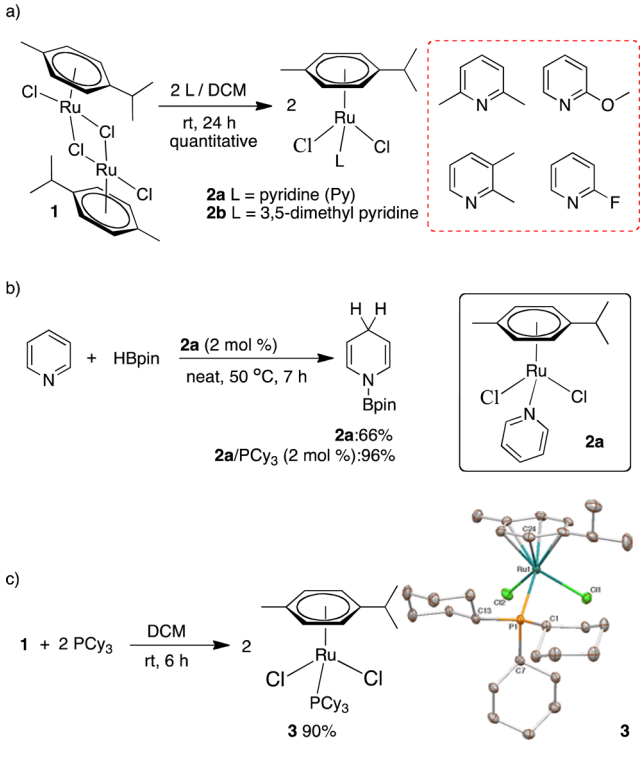
(1.0 equiv) (1.1 equiv) **1,4** **1,2**

entry	cat. load (mol %)	ligand (mol %)	yield (%)[a]	1,4:1,2 ratio[a]
1	1	PPh_3 (2)	28	72:28
2	1	PCy_3 (2)	74	100:0
3	1.5	PCy_3 (3)	82	100:0
4	**2**	**PCy_3 (4)**	**97**	**100:0**
5	2	$(Ad)_2PBn$ (4)	62	100:0

[a]Based on ^1H NMR analysis of the reaction mixture.

In an attempt to identify the intermediates involved in the hydroboration of pyridines, complex **1** was reacted independently with pyridine and 3,5-dimethylpyridine, which resulted in quantitative formation of mononuclear complexes **2a** and **2b** (Scheme 2a). However, when complex **1** was reacted with 2-methoxypyridine, 2-fluoropyridine, 2,6-lutidine, and 2,3-dimethylpyridine, no such mononuclear complexes were formed. Interestingly, when isolated complex **2a** was used as a catalyst (2 mol %), hydroboration of pyridine was observed in 66% yield, indicating the possible involvement of complex **2a** in catalysis (Scheme 2b). Notably, 2, 2,3- and 2,6-substituted pyridines, which failed to provide coordination complexes (Scheme 2a) with **1** were subjected to catalytic hydroboration [**1** (2 mol %)/PCy_3 (4 mol %)] and no reaction was observed in all these substrates emphasizing that *prior pyridine coordination to ruthenium center is an essential requirement for the occurrence of catalysis*.

Scheme 2. Preparation of Intermediates 2 and 3 Involved in the 1,4-Hydroboration of Pyridines



Upon the reaction of complex **2a** (2 mol %) together with PCy_3 (2 mol %) efficient regioselective hydroboration was observed and *N*-boryl-1,4-dihydropyridine was obtained in 96% yield, further eliciting the interest in the phosphine coordinated intermediate complex. When Ru dimer complex **1** was reacted with PCy_3 (2 equiv; 1 equiv per Ru), phosphine-ligated mononuclear ruthenium complex **3** formed (90% yield).[19] Complex **3** exhibited a ^{31}P NMR singlet signal at δ 25.92 ppm, and its structure is unequivocally corroborated by single-crystal X-ray analysis, which displayed pseudo-octahedral geometry around the metal center (Scheme 2c). Complex **3** is a suitable catalyst for the regioselective 1,4-hydroboration of pyridines. Upon using **3** (3 mol %) as a catalyst, regioselectively *N*-boryl-1,4-dihydropyridine was obtained in 97% yield, confirming the potential involvement of complex **3** in catalysis (Scheme 3). Notably, use of added ligand is no longer required.

Using complex **3** as a catalyst, regioselective 1,4-hydroboration was explored for the different pyridines, which indicated that a wide range of 3-substitution on pyridine is tolerated (Scheme 3). An assortment of 3-substituted pyridines undergoes regioselective 1,4-hydroboration with good to excellent yields. Alkyl, aryl, heteroaryl, ester, amine, amide, alkoxy, and acyloxy functional groups are well tolerated in this ruthenium catalyzed reaction. Remarkably, 3,5-dimethylpyridine and 3-methoxypyridine, which were not compatible with an organoborane catalyzed reaction,[17] undergoes ruthenium catalyzed 1,4-hydroboration to provide the corresponding products in moderate yields (Scheme 3), highlighting the potential of this transformation. Moreover, quantitative product formation was observed for several 3-substituted pyridine compounds. Interestingly, with 3-(pyridin-3-ylmethoxy)pyridine successful bis-1,4-hydroboration occurred. As observed in mechanistic studies various 2-substituted pyridines (*vide infra*) do not undergo a hydroboration reaction attributable to steric hindrance and is in agreement with the reactivity of organolanthanides in the catalytic 1,2-hydroboration of pyridines.[16] 4-Methylpyridine also failed to undergo ruthenium catalyzed 1,4-hydroboration.

Mechanistic insights were deciphered by performing a series of elementary reactions and in situ monitoring of both stoichiometric and catalytic reactions. Reaction of **2a** with PCy_3 and HBpin and reaction of **3** with pyridine and HBpin resulted in formation of the same intermediates **4** and **5** in solution, which displayed characteristic singlet signals at δ 50.04 ppm and δ 59.66 ppm in ^{31}P NMR, respectively (Scheme 4a,b). As both reactions progressed, the intensity of complex **4** decreased upon the rise of a singlet signal at δ 59.66 ppm in ^{31}P NMR together with increasing intensity of a doublet at δ −7.88 ppm (J_{PH} = 48.0 Hz) in ^1H NMR confirming the complex **5** is a monohydride ruthenium complex (see Figure S1).[20] ^{11}B NMR of both reaction mixtures confirmed the formation of ClBpin (δ 27.09 ppm).

Further, the equimolar reaction of complex **2a** and HBpin was incomplete after 1 h. Upon use of 5 equiv of HBpin, complete conversion of ligated pyridine on **2a** occurred and resulted in quantitative formations of *N*-boryl-1,4-dihydropyridine and

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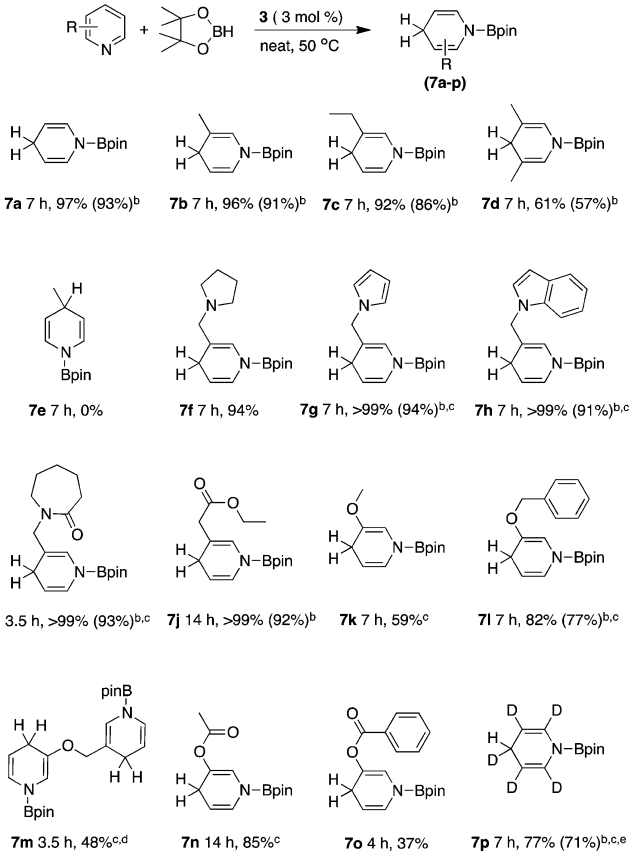
Scheme 3. Ruthenium Catalyzed Regioselective 1,4-Hydroboration of Pyridines[a]

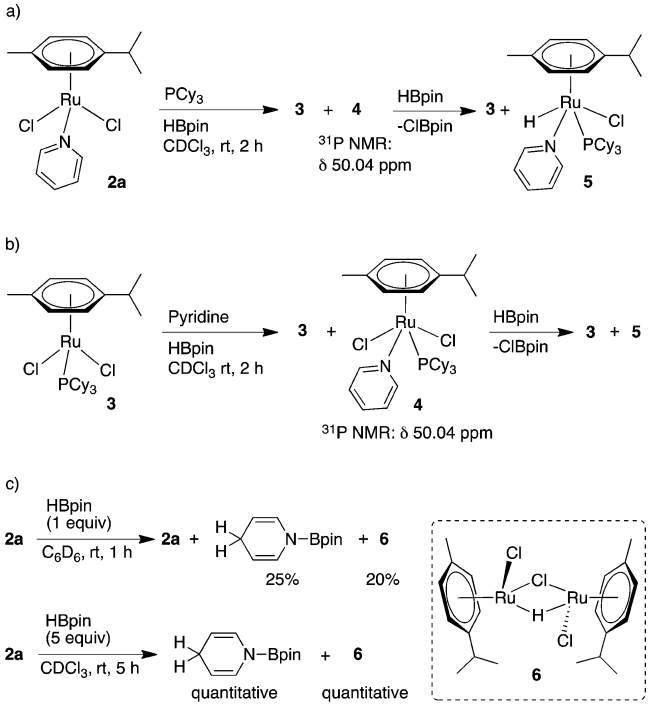


[a]Reaction conditions: substrate (1 mmol), pinacolborane (1.1 mmol), and catalyst **3** (3 mol %) are heated at 50 °C under neat conditions. Yields are based on ^{1}H NMR analysis of the reaction mixture. [b]Isolated yields. [c]DCM (0.5 mL) is added, as neither the substrate or reaction mixture is homogeneous. [d]2.1 equiv of pinacolborane are used. [e]Anisole is used as an internal standard.

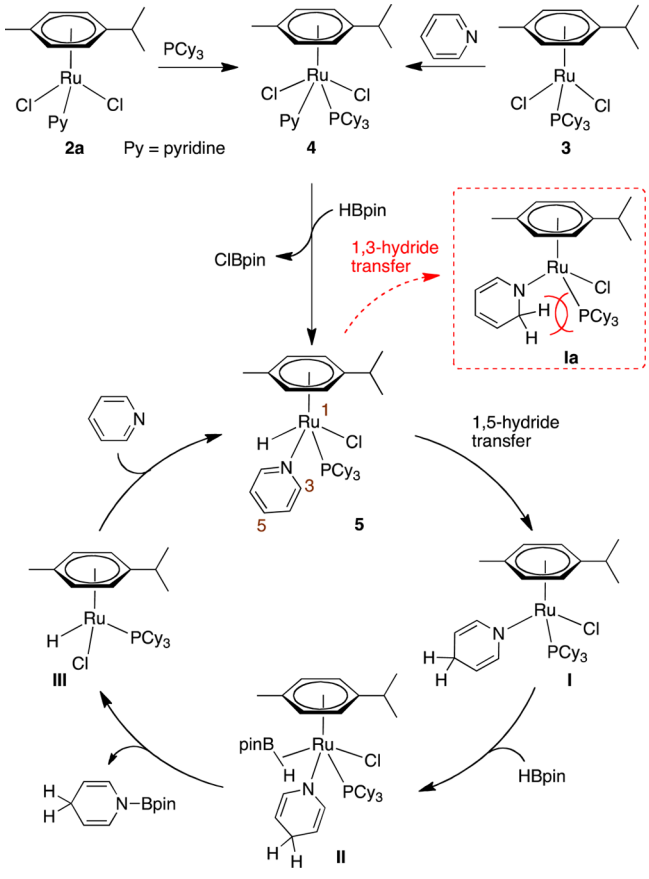
monohydride bridged dinuclear complex [{(η^6-*p*-cymene)-RuCl}$_2$(μ-H-μ-Cl)] **6** (Scheme 4c).[18,21] To ascertain any role of complex **6** in catalysis, the regioselective 1,4-hydroborations of pyridine catalyzed by complexes **2** and **3** (3 mol %)[22] were monitored using ^{1}H NMR, which confirmed the formation and presence of only monohydride complex **5** throughout the catalysis in both experiments.[23]

On the basis of the above-mentioned experimental observations, a catalytic cycle is proposed as depicted in Scheme 5. Reaction of **2a** with PCy_3 or reaction of **3** with pyridine leads to the common intermediate **4**, which upon reaction with HBpin generates Ru−H complex **5** (as observed in Scheme 4a,b). Remarkably, in complex **5**, 1,5-hydride transfer prevails over the 1,3-hydride transfer. Perhaps, the steric hindrance between the "sp^3-CH_2" of the amide ligand at the *ortho*-position in **Ia** that will arise upon 1,2-addition on the pyridine motif and other ligands on the metal center and the electronic factors might be preventing the commonly observed 1,3-hydride transfer.[18,21,24] Notably, no hydroboration reaction was observed with 2-substituted pyridines under these conditions. Thus, intramolecular "1,5-hydride transfer" to the pyridine ligand coordinated at the metal center in **5** leads to the regioselective 1,4-hydroboration of pyridine and amide ligated Ru(II) intermediate **I**. Reaction of HBpin with **I** results in coordination

Scheme 4. Stoichiometric Experiments, *in Situ* Observation of Intermediates and Reaction Progress



Scheme 5. Proposed Reaction Mechanism for the Regioselective 1,4-Hydroboration of Pyridines



complex **II**, and the subsequent transmetalation of amide ligand provides regioselective pyridine 1,4-hydroboration product and

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unobserved intermediate **III**. Coordination of pyridine to **III** regenerates the intermediate complex **5** to close the catalytic cycle. Catalytically active intermediate **5** persisted in the reaction mixture throughout the catalysis as oberved by ^{1}H and ^{31}P NMR analyses.

In summary, efficient regioselective 1,4-hydroboration of pyridine compounds was demonstrated using well-defined transition metal catalysts. Stoichiometric experiments and in situ spectral studies allowed identification of the reaction intermediates **2**–**5**. Intermediates **2** and **3** are independently synthesized, characterized, and further used in catalysis. Phosphine ligated complex **3** turned out to be the optimal catalyst for the regioselective 1,4-hydroboration of pyridines. Solvent is required only when the substrate is solid or the reaction mixture turns inhomogeneous; otherwise catalysis proceeded very well under solventless conditions. Supported by the experimental observations, a mechanism is postulated involving in situ generation of mononuclear Ru–H complex **5**, which undergoes an intramolecular 1,5-hydride transfer leading to the regioselective 1,4-hydroboration of pyridines. Further studies to elucidate the scope of this transformation and the details of the regiochemical discrimination are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01564.

Experimental procedures and spectral data; single-crystal X-ray data of complex **3** CCDC 1444045 (PDF)

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Author Contributions

†A.K. and B.C. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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(22) First-order kinetics is observed for the regioselective 1,4-hydroboration of pyridine using catalyst **3**. See Figure S2.

(23) No hydride signal at δ −10.2 ppm that corresponds to complex **6** was observed. See refs 18 and 21.

(24) ^{1}H NMR kinetic experiments at 50 °C indicated that the rate law is first order with [**3**], [HBpin], and [Py]. However, at a higher concentration (0.8 to 1 equiv) of pyridine, the rate approached being zero order. See ref 20.

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