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Organoborane Catalyzed Regioselective 1,4-Hydroboration of Pyridines

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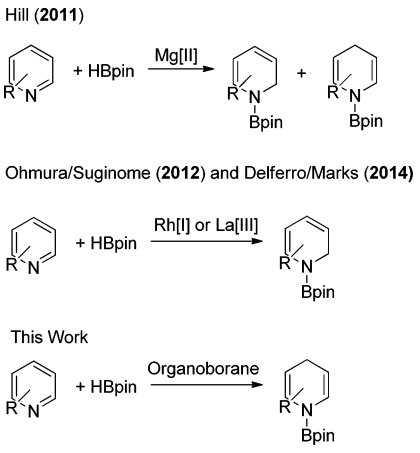
Supporting Information

ABSTRACT: A bulky organoborane $Ar^F{}_2BMe$ (Ar^F = 2,4,6-tris(trifluoromethyl)phenyl, **1**) has been synthesized. In C_6D_6 solution this organoborane and pyridine form a frustrated Lewis pair. Under mild conditions, **1** can efficiently catalyze 1,4-hydroboration of a series of pyridines. This reaction is highly chemo- and regioselective. The reaction intermediate, a boronium complex $[Py_2Bpin][Ar^F{}_2B(H)Me]$ (**3**), was characterized in solution by NMR spectroscopy, which was also confirmed by DFT calculation.

1,4-Dihydropyridines represent an important class of bioactive molecules.[1,2] In addition, its derivatives are widely applied as reducing reagents for organic synthesis.[3] One of the common routes to the synthesis of 1,4-dihydropyridines consists of stoichiometric nucleophilic addition to pyridines or pyridinium salts. However, such a method requires preactivating pyridines and often leads to regioisomeric mixtures.[1] As an alternative, catalyzed reduction of pyridines could provide a straightforward approach for the synthesis of 1,4-dihydropyridines. Whereas hydrogenation of pyridines needs to overcome the problem of overreduction,[4] the approaches employing milder reducing reagents, such as silanes and boranes, have been recently introduced. The Nikonov[5] and Oesterich[6] groups reported that Ru(II) complexes can selectively catalyze 1,4-hydrosilylation of pyridines. On the other hand, effective 1,4-hydroboration of pyridines still remains elusive (Scheme 1). In an earlier report, Hill et al. investigated the hydroboration of pyridines catalyzed by a Mg(II) complex, which affords mixtures of 1,2- and 1,4-dihydropyridine derivatives.[7] Subsequently, the groups of Suginome[8] and Marks[9] discovered that 1,2-hydroboration products can be obtained when Rh(I) or La(III) complexes are used as a catalyst. It is believed that the metal-hydride species are involved in these metal-catalyzed pyridine hydroborations and the facile insertion of the pyridine C═N bond into the M−H bond is responsible for the observed 1,2-selectivity.

Scheme 1. Recent Advances in Hydroboration of Pyridines



The recent emerging chemistry of frustrated Lewis pairs (FLPs) provides a conceptually different strategy for reduction of unsaturated organic substrates.[10−12] Noticeably, the group of Du stereoselectively hydrogenated substituted pyridines to piperidines with $C_6F_5CH_2CH_2B(C_6F_5)_2$ as the catalyst.[13] The Stephan group also described the 1,4-hydrosilylation of 2-phenylquinoline catalyzed by $B(C_6F_5)_3$.[14] Furthermore, the Crudden group reported that borenium complexes can catalyze the 1,4-hydroboration of acridine.[15] Nevertheless, the reduction of unsubstituted pyridine with FLPs has not been achieved.[16] This could be due to the lack of steric protection around the nitrogen atom of pyridine, which can coordinate to the Lewis acid of FLPs and deactivate the catalysts. Apparently, employing a bulky organoborane would hinder such an interaction, thus keeping the FLP reactivity in the reaction system. In our recent report,[17] we have demonstrated that bulky 2,4,6-tris(trifluoromethyl)phenyl (Ar^F) substituted organoborane $HBAr^F{}_2$ can form FLPs with a series of amines, such as NEt_3 and 1,4-diazabicyclo[2.2.2]octane (DABCO), which can effectively activate H_2, alkynes, and CO_2. Thus, we decided to investigate the reactivity of Ar^F substituted organoboranes in pyridine hydroboration reactions.

First we examined $HBAr^F{}_2$ as the catalyst for pyridine hydroboration. Pinacolborane (HBpin) was chosen as the hydroboration reagent. When 10 mol % of $HBAr^F{}_2$ was added to a 1:1 mixture of HBpin and pyridine in C_6D_6 at room temperature, no hydroboration product was observed after 24 h. ^1H and ^{11}B NMR analysis revealed that $HBAr^F{}_2$ and pyridine form a classical Lewis adduct in the reaction mixture, suggesting that the steric protection of the boron center in $HBAr^F{}_2$ is not enough to prohibit the coordination of pyridine. Therefore, we decided to replace the hydride substituent with a methyl group, which would increase the steric bulkiness of the organoborane. Additionally, the decreased Lewis acidity of such an organoborane could also disfavor the coordination of pyridine. $Ar^F{}_2BMe$

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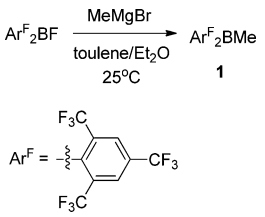
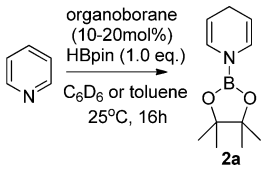
(**1**) was synthesized by treating Ar^F_2BF with MeMgBr in toluene/ether solution at room temperature (Scheme 2). After

Scheme 2. Synthesis of 1



recrystallization, the organoborane **1** could be obtained in 63% yield and was fully characterized by NMR and elemental analysis. Upon mixing **1** with 10 equiv of pyridine, the ^{1}H, ^{19}F and ^{11}B NMR spectra obtained in C_6D_6 at rt remained unchanged, which indicates an FLP is formed between **1** and pyridine. When 10 mol % of **1** was employed as the catalyst, pyridine readily reacts with an equimolar amount of HBpin in C_6D_6, quantitatively yielding 1,4-dihydropyridine **2a** as the only regioisomer within 16 h (Table 1). Two other highly Lewis acidic organoboranes,

Table 1. Screening of Organoborane Catalysts



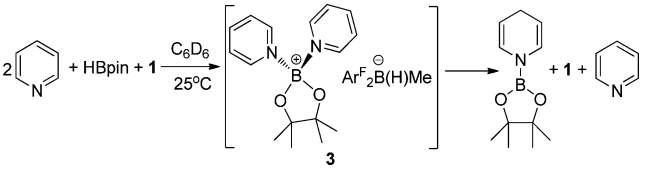
entry	organoborane	yield [%][a]
1	none	0[b]
2	Ar^F_2BH	0[b]
3	**1**	99(87)[b]
4	$B(C_6F_5)_3$	0[b]
5	$B(C_6Cl_5)_3$	40[c]

[a]Yields were determined by ^{1}H NMR analysis (C_6D_6 as solvent), and isolated yields for preparative scale syntheses (toluene as solvent) are given in parentheses. [b]10 mol % of catalyst was employed. [c]20 mol % of catalyst was employed.

$B(C_6F_5)_3$ and $B(C_6Cl_5)_3$,[18] were also tested as the catalyst. The former yielded no hydroboration product, and the latter only provided a moderate yield even with 20 mol % loading of the catalyst.

While monitoring the hydroboration of pyridine by ^{1}H NMR spectroscopy, we observed that catalyst **1** was converted to an intermediate **3** during the reaction process. A set of resonances (8.12(d), 6.88(t), 6.68(t) ppm) from the pyridine moiety, a singlet signal (0.84 ppm) corresponding to the Bpin fragment, and two singlets at 8.17 and 0.58 ppm from the Ar^F_2BMe moiety were observed in the ^{1}H NMR spectrum. Integration of these signals revealed that the molar ratio of the pyridine, Bpin, and Ar^F_2BMe moieties is 2:1:1. The ^{11}B NMR spectrum of the reaction showed two signals (one singlet at 6.8 ppm and one doublet at −15.6 ppm (J_{HB} = 77 Hz)) besides the signals from HBpin and **2a**. While the singlet signal is consistent with the formation of a boronium cation,[15] the doublet signal suggests the existence of a hydridoborate anion. Based on this NMR analysis, the intermediate **3** is assigned as $[Py_2Bpin][Ar^F_2B(H)Me]$, which possibly arises from the activation of HBpin by the pyridine/**1** pair and the subsequent coordination of another molecule of pyridine.[15,19] Indeed, mixing an equimolar amount of **1** and HBpin with 2 equiv of pyridine in C_6D_6 at rt resulted in the formation of **3** (Scheme 3).[20] Attempts to isolate pure **3** have

Scheme 3. Reaction of Pyridine, 1, and HBpin in 2:1:1 Ratio



so far met with failure. **3** decomposed in C_6D_6 at rt to yield pyridine, **1**, and **2a**. Kinetic studies of the decomposition of **3** in C_6D_6 by monitoring ^{1}H NMR revealed that this reaction is a first-order reaction. The activation parameters $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta G^{\ddagger}$ at 298 K are estimated to be 22.9 ± 1.3 kcal mol^{-1}, 5.6 ± 4.4 cal K^{-1} mol^{-1}, and 21.2 ± 2.6 kcal mol^{-1}, respectively. The slight positive value of $\Delta S^{\ddagger}$ implies that the pyridine molecule does not completely dissociate from the boron center in the transition state.

The hydroboration of pyridine was further investigated by DFT(M06-2X) calculations (Figure 1).[21] Initially, HBpin and

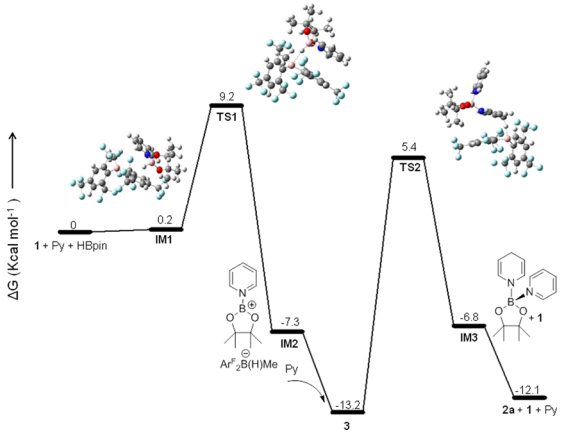


Figure 1. Gibbs free energy profile at 298 K for the reaction between pyridine, HBpin, and **1**.

pyridine form a loosely coordinating complex,[22] which also interacts with the Ar^F moiety of **1** through a weak van der Waals interaction. Subsequently, the B−H bond of HBpin is activated through synergetic interaction of both pyridine and **1** to afford the borenium $[PyBpin][Ar^F_2B(H)Me]$ (**IM2**), which needs to overcome a free energy barrier of 9.2 kcal mol^{-1}. Then a molecule of pyridine coordinates to the borenium **IM2** to generate the boronium **3**, and this step is almost barrierless.[23] The next step is hydride transfer from the $[Ar^F_2B(H)Me]^-$ anion to the 4-position of the pyridine ring of **3**, followed by decoordination of pyridine to form **2a** and **1**. In agreement with the experimental observation, the hydride-transfer step is found to be the rate-determining step and proceeds via the transition state **TS2** with a 18.6 kcal mol^{-1} free energy barrier, which is comparable with the experimental value. We also calculated the free energy barrier for the formation of the 1,2-dihydropyridine derivative from **3**, which is 3.9 kcal mol^{-1} higher than **TS2**. This is possibly due to the large steric repulsion between Bpin and Ar^F moieties.

To investigate the scope and limitation of this novel metal-free catalytic system, we tested a variety of substituted pyridines

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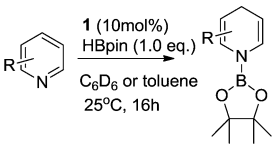
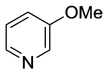
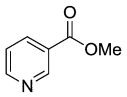
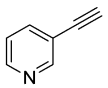
(Table 2).[24] For 3-substitued pyridines, we noticed that electron-donating substituents decrease the activity of the catalyst (entries 1 and 2). 3-Picoline requires an elevated temperature to obtain a moderate yield, and the 3-methoxylpyridine is completely unreactive. When the substituents at the 3-position are electron-withdrawing functionalities, 1,4-hydroborated products can be obtained in good to excellent yields (entries 4–7). For example, bromo and iodo substituents, which are often sensitive to dehalogenation by transition metal catalysts, were found to be compatible with the catalytic system (entries 4 and 5). Moreover, Lewis basic substituents, including the strongly coordinating cyano group, did not inhibit the reaction at all and no reduction of the C═O or C≡N bond was observed (entries 6 and 7). Remarkably, the ethynyl moiety, which is prone to reduction[25] or deprotonation[26] by transition metal or lanthanide complexes, remained untouched under the reaction conditions (entry 8), highlighting the excellent chemoselectivity of this metal-free catalyst system. For 2-substituted pyridines, only 2-picoline can be quantitatively hydroborated (entry 9). Both phenyl and bromo substitution at the 2-position suppressed the reaction completely (entries 10 and 11). Whereas the former might be too sterically demanding for effective B–H activation,[27] the latter could be attributed to the substantially decreased basicity of 2-bromopyridine, which is not basic enough to activate the H–B bond of HBpin.[28] An attempt to extend this catalyst system to 4-substituted pyridines was not successful. No hydroboration product was observed for 4-picoline (entry 12). We also examined a few lutidines and found that only 2,3-lutidine can be reduced to the corresponding dihydropyridine (entries 13–15).

Table 2. Substrate Scope of 1 Catalyzed Hydroboration of Pyridines with HBpin

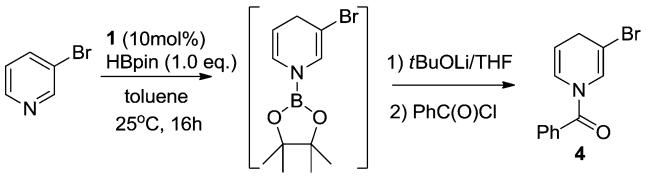


Entry	Substrate	Yield[%][a]	Entry	Substrate	Yield[%][a]
1		41(40)[b]	9		99(93)
2		0	10		0
3		75(71)	11		0
4		99(90)	12		0
5		77(59)	13		77(75)
6		99(89)	14		0
7		99(61)	15		0
8		99(93)			

[a]Yields were determined by ^{1}H NMR analysis (C_6D_6 as solvent), and isolated yields for preparative scale syntheses (toluene as solvent) are given in parentheses. [b]Reaction was carried out at 60 °C.

To demonstrate the synthetic application of *N*-boryl-1,4-dihydropyridines, we converted 3-bromopyridine to the corresponding *N*-benzoyl-1,4-dihydropyridine **4** in a one-pot manner (Scheme 4). Treatment of *in situ* formed *N*-boryl-3-bromo-1,4-dihydropyridine with *t*BuOLi[29] and subsequently with benzoyl chloride resulted in the formation of **4** in 64% yield. It is noteworthy that **4** could not be accessed through common methods, such as Birch reduction[30] or Hantzsch synthesis.[31] Fowler reduction, which involves direct reduction of pyridinium salts with $NaBH_4$, can only provide 1,4-dihydropyridine adducts as a minor product.[32]

Scheme 4. Synthesis of 4



In conclusion, we have developed an efficient regioselective 1,4-hydroboration of pyridines catalyzed by a bulky organoborane **1**. This reaction is metal-free and shows excellent chemo- and regioselectivity under mild conditions. The key to this hydroboration reaction is that **1** is bulky enough to form FLP with pyridine. Experimental and theoretical mechanism studies reveal that the reaction pathway is different from those catalyzed by transition or lanthanide metal complexes and the key intermediate is a boronium complex **3**, which has been observed by NMR spectroscopy. Efforts to extend the application of bulky organoboranes in FLP chemistry are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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(20) When equimolar amounts of **1**, pyridine, and HBpin were combined in C_6D_6, **3** was the only major product with unreacted **1** and HBpin remaining in the solution.

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(22) When HBpin and pyrdine were stoichiometrically mixed in C_6D_6, the ^1H and ^{11}B NMR spectra remained unchanged. See also refs 7and 9.

(23) The free energy barrier for direct hydride transfer in **IM2** to afford **1** and **2a** was calculated to be 10.9 kcal mol^{-1}. Therefore, the formation of the boronium intermediate **3** is favored, which is in agreement with our experimental observation.

(24) Blank experiments, which were carried out without catalyst in C_6D_6 solution at 80 °C, showed no reduction of pyridines. When equimolar of HBpin and pyridines were heated at 80 °C under neat conditions, mixtures of 1,4- and 1,2-dihydropyridine derivatives were observed after 16 h (see Table S1).

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