From C-F Activation to Catalytic Regioselective Double Hydrodefluorination of Pyridines with a Nickel Complex

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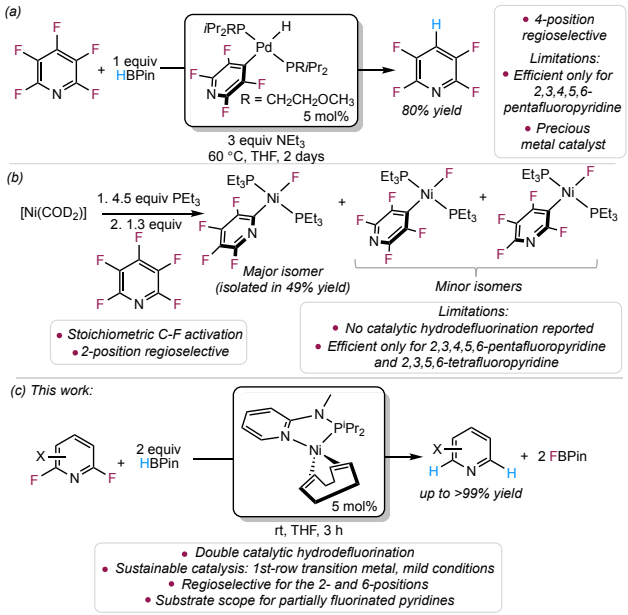
ABSTRACT: The nickel(0) complex [Ni(^{iPr}PN)(COD)] (^{iPr}PN = 2-[(*N*-diisopropylphosphino)methylamino]pyridine, COD = 1,5-cyclooctadiene) has been found an efficient precatalyst for the hydrodefluorination of pyridines employing HBPin. Substituted 2,6-difluoropyridines were doubly hydrodefluorinated selectively at the 2 and 6 positions at room temperature employing 5 mol% of catalyst loading. Mechanistic studies for the hydrodefluorination of 2,6-difluoropyridine allowed to identify COD decoordination followed by C-F activation of the fluorinated pyridine as the catalyst entry pathway to the cycle and the [Ni(^{iPr}PN)(COD)] complex as the catalyst resting-state.

The hydrodefluorination (HDF) of small molecules finds applications in the synthesis of drugs, agrochemicals and materials and is key to the remediation of perfluoroalkyl substances (PFAs).[1] Due to the strong nature of the C-F bonds, their activation by transition metals,[2] as well as their catalytic transformation into C-H bonds[3] has attracted a lot of attention. Since partially fluorinated and non-fluorinated pyridines are common motifs in drugs,[4] their HDF is particularly relevant, as it allows to access valuable motifs for drug synthesis and for the assessment of the impact of fluorine in the physicochemical and metabolic properties of fluorinated drugs.[5] However, catalysts for the HDF of pyridines are scarce,[5,6] most of them being precious-metal complexes[6b-d,7] which require harsh conditions and the use of reactive alkylsilanes as H sources. More importantly, their efficiency is mostly limited to the HDF of *2,3,4,5,6-pentafluoropyridine* at the *4-position*,[6a-c,e] such as the Pd(II) complex shown in Scheme 1a,[6b] with the C-F activation or the HDF of more drug-relevant partially fluorinated pyridines being unknown. Because partially fluorinated pyridines contain C-H and C-F bonds, one of the main challenges relies on discovering chemoselective catalysts capable of activating C-F bonds in the presence of weaker C-H bonds.[2d] Furthermore, the HDF at positions other than the 4 is still challenging, and only a Ru complex has been described capable of the catalytic HDF of 2,3,4,5,6-pentafluoropyridine at the 2-position, although with moderate regioselectivity.[6d]

In this context, nickel(0) complexes emerge as promising catalysts, as they have been found to show a marked preference for C-F bond activation over C-H,[8,2a,d] and to be selective for the 2-position. Seminal work by Perutz and coworkers supported that the *in situ* generated 16-electron Ni(0) species, [Ni(PEt_3)$_2$], was efficient for the stoichiometric C-F activation at the 2-position of pentafluoropyridine and 2,3,5,6-tetrafluoropyridine under mild conditions (Scheme 1b).[8] However, the presence of C-H bonds has been found to slow down the activation of C-F bonds,[2d]

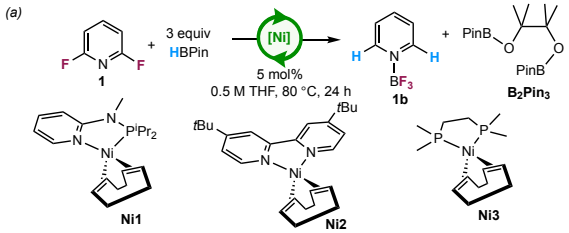


Scheme 1. (a) Pd catalyzed HDF of pentafluoropyridine (reference 6b); (b) stoichiometric C-F bond activation of pentafluoropyridine by an in situ generated Ni(0) complex (reference 8a); (c) This work: Ni-catalyzed 2,6-regioselective double HDF of partially fluorinated pyridines with pinacolborane

with C-F bond activation of pentafluoropyridine proceeding five times faster than that of 2,3,5,6-tetrafluoropyridine with the [Ni(PEt_3)$_2$] species.[8c] Although Ni complexes for the HDF and C-F functionalization of fluorinated arenes have been reported,[9] a Ni catalyst for the HDF of partially fluorinated pyridines remains unknown to date.

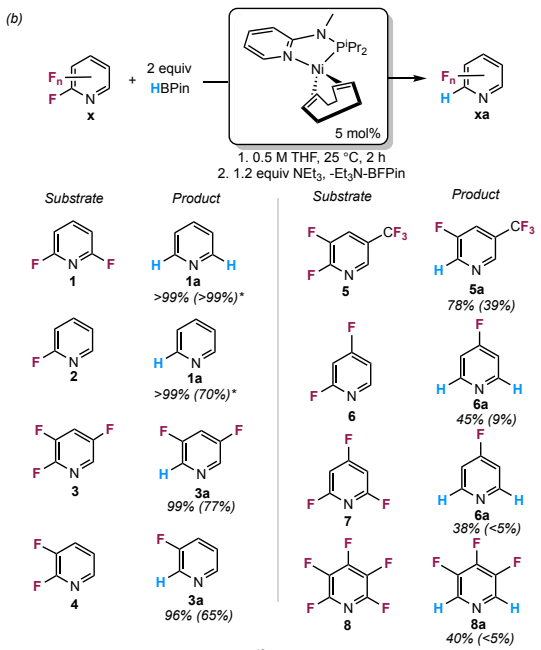
In this work we report the first catalytic double 2,6-regioselective HDF of partially fluorinated pyridines with HBPin employing a Ni catalyst (Scheme 1c). Mechanistic studies provided insights into the precatalyst entry pathway to the cycle, the catalyst resting-state, a catalyst deactivation pathway and the identity of the C-F activating species.

Our research commenced with the assessment of the catalytic efficiency of the Ni(0) complexes [Ni(LL)(COD)] (**Ni1**-**Ni3**, see SI for synthetic details)[10] for the HDF of 2,6-difluoropyridine (**1**) with HBPin (Scheme 2a). Under the conditions described in Scheme 2a, the nickel(0) complex [Ni(^{iPr}PN)(COD)] (**Ni1,** ^{iPr}PN = 2-[(*N*-diisopropylphosphino)methylamino]pyridine, COD = 1,5-cyclooctadiene) afforded full conversion of the starting material yielding pyridine as the BF_3 adduct (**1b**) in 83% yield (Scheme 2a, entry 1 in table). Product **1b** was formed by the double hydrodefluorination of **1** at the 2- and 6-positions to afford pyridine that coordinated to BF_3 *in situ* generated along with B_2Pin_3 from FBPin.[11] The identity of the ^{iPr}PN ligand in **Ni1** was key to enable the HDF of **1**, since the Ni(0) complexes **Ni2** and **Ni3**, containing bidentate ligands with imine or phosphine donors, afforded poor reaction conversions and product yields (Scheme 2a). Control experiments (page S7 in the SI) for the transformation resulted in the recovery of the starting material, supporting **Ni1** as responsible for the HDF of **1**. A preliminary optimization of the reaction conditions for the **Ni1**-catalyzed HDF of **1** (see table S1 in the SI) identified 25 °C, 2 h, 2 equiv of HBPin, a 0.5 M solution of THF and 5 mol% of catalyst loading as the optimum conditions, affording pyridine (**1a**) in >99% yield after treatment with 2 equiv of NEt_3 (see below for mechanistic rationale). The identity of the reducing agent pinacolborane was found to be key for **Ni1** to be efficient, and when $HSiEt_3$ or $HSi(OEt)_3$ were employed as H-sources, the starting material **1** was fully recovered.



Entry	[Ni]	Conversion (%)	Yield(%)
1	**Ni1**	>99	83
2	**Ni2**	21	<5
3	**Ni3**	<5	<5

Conversion and yields were calculated by ^{19}F NMR spectroscopy integration employing fluorobenzene as internal standard

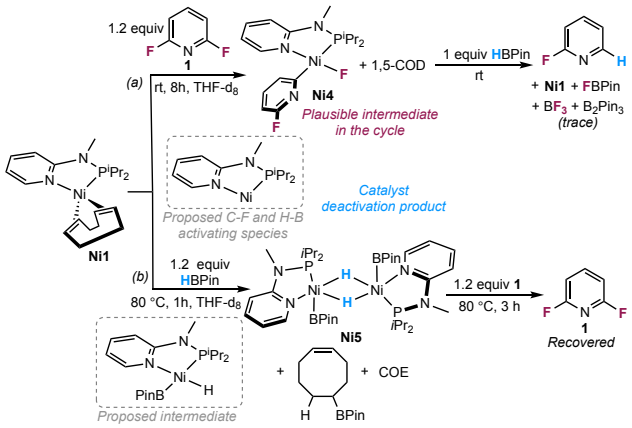


Conversion and yields were calculated by ^{19}F NMR spectroscopy integration employing fluorobenzene as internal standard
**Conversion and yields were calculated by ^{1}H NMR spectroscopy integration employing mesitylene as internal standard*

Scheme 2. C(sp^2)-F HDF of 2,6-difluoropyridine (a) catalyst screening and (b) optimized catalytic conditions and substrate scope for the HDF of fluorinated pyridines.

With a set of optimized conditions in hand, a preliminary substrate scope employing pyridines with different number of fluorines at different positions, was explored (Scheme 2b). Pyridines containing F at positions other than the 2 and 6 (**3**-**8**) were selectively hydrodefluorinated at the 2 and 6 positions, supporting **Ni1** to be regioselective for the C-F activation at these positions. Furthermore, the efficiency of the catalytic system decreased with an increased number of F at the pyridine (*e. g.* **1a** was obtained in >99% yield whereas **3a** was obtained in 77% yield from the HDF of **3**). **Ni1** was inefficient for substrates containing a F at the 4-position (substrates **6**-**8**) which afforded the corresponding HDF products (**6a** and **8a**) in <10% yield. Further evaluation of the substrate scope is currently undergoing in our laboratory.

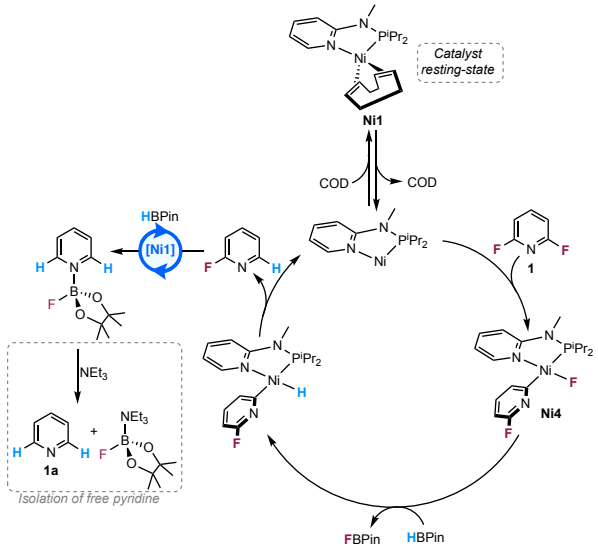
Aiming to gain insights into the intermediates involved in the catalytic cycle, the reaction of **Ni1** with 1.2 equiv of **1** in THF-d_8 at room temperature was monitored by ^{1}H, ^{19}F and ^{31}P NMR spectroscopy. The NMR spectra supported that the reaction reached completion in 8 h and that a single species, **Ni4**, was formed at the expense of **Ni1** and **1** with the concomitant formation of COD as the byproduct (pages S26-S32 in the SI). The NMR characterization of **Ni4** (pages S54-S58 in the SI) supported its identity as the Ni(II) complex *cis*-[NiF(^{iPr}PN)(6-Fpy)] (6-Fpy = 6-fluoro-2-pyridyl) (Scheme 3a). **Ni4** is proposed to form by COD decoordination in **Ni1** to yield the unsaturated 16-electron Ni(0) [Ni(^{iPr}PN)] species followed by the 2-regioselective C-F oxidative addition of **1** which was fast in the NMR timescale, preventing the observation of the [Ni(^{iPr}PN)] species responsible for C-F activation. Consistent with a Ni-F moiety, the ^{19}F NMR spectrum of **Ni4** showed a significantly upfield shifted signal[2a,d] (-258.9 ppm, dd, $^{2}J_{FP}$ = 128.2 Hz, $^{5}J_{FF}$ = 7.7 Hz) attributed to the fluoro ligand, and a signal at -69.9 ppm attributed to the F of the 6-Fpy ligand. Addition of 1 equiv of HBPin to the reaction mixture at room temperature resulted on the disappearance of the signals attributed to **Ni4** in the ^{19}F NMR spectrum and the appearance of a new signal at -66.5 ppm attributed to 2-fluoropyridine as well as on the regeneration of **Ni1** as confirmed by ^{31}P and ^{1}H NMR spectroscopy (Scheme 3a). The ^{19}F and ^{11}B NMR spectrum supported FBPin, BF_3 and B_2Pin_3 formed as byproducts, consistent with B acting as a F acceptor. The instantaneous formation of **Ni1** from **Ni4** upon addition of HBPin supports a reaction of **Ni4** with HBPin fast in the NMR timescale, followed by a fast COD recoordination. Complex **Ni4** was independently synthesized and isolated by reaction of **Ni1** with 1.2 equiv of **1** at rt in THF for 16 h and fully characterized by NMR spectroscopy (see page S3 and pages S54-S58 in the SI).



Scheme 3. Stoichiometric reaction of Ni1 with (a) 1 followed by addition of HBPin, and (b) with HBPin followed by addition of 1.

Aiming to explore the ability of **Ni1** to activate the H-B bond in HBPin, the reaction of **Ni1** with 1 equiv of HBPin was monitored by ^{1}H, ^{11}B and ^{31}P NMR spectroscopy in THF-d_8. After 16 hours at room temperature the NMR spectra showed signals consistent with the presence of a new Ni complex, **Ni5**, and unreacted **Ni1** and HBPin, supporting that the reaction did not reach completion. When the mixture was heated up to 80 °C for 1 h, the ^{31}P NMR spectrum showed the disappearance of the signal attributed to **Ni1** (120.8 ppm, singlet) concomitant with the presence of a new signal attributed to **Ni5** (214 ppm, ddt) and other minor unidentified species (see page S40 in the SI). The fact that the reaction mixture required be heating up to reach completion hints toward a higher barrier for the reaction of **Ni1** with HBPin than that for the reaction of **Ni1** with **1**, which proceeded at room temperature. Furthermore, the ^{1}H NMR spectra supported the disappearance of the signals attributed to HBPin concomitant with the appearance of signals attributed to **Ni5** and an alkylboronate ester from COD hydroboration and cyclooctene (COE) from COD hydrogenation. Based on NMR spectroscopy characterization, **Ni5** was tentatively identified as the Ni(II) complex [Ni(BPin)(μ^2-H)(^{iPr}PN)]$_2$ (Scheme 3b).[12] A plausible reaction pathway that explains the formation of **Ni5** is the hydroboration of the COD ligand in **Ni1** by reaction with HBPin to afford the 16-electron [Ni(^{iPr}PN)] species followed by the oxidative addition of the H-B bond in HBPin to yield the Ni(II) complex [NiH(^{iPr}PN)(BPin)] which dimerizes in the reaction medium. These results support that **Ni1** can activate the H-B bond in HBPin but requires a higher temperature than the activation of the C-F bond in **1**, hinting to a lower barrier for C-F activation and, therefore, a plausible catalyst entry pathway to the cycle. Addition of 1 equiv of **1** to the reaction mixture resulted in no product formation after 48 h at room temperature neither after 3 h at 80 °C supporting **Ni5** as a catalyst deactivation product (Scheme 3b).

To gain insights into the identity of the catalyst resting-state, the HDF of **1** with 3 equiv of HBPin employing 10 mol% of **Ni1** as precatalyst was monitored by ^{1}H, ^{19}F, ^{11}B and ^{31}P NMR spectroscopy in THF-d_8 at room temperature for 8 hours (see pages S8-S16 in the SI). The ^{19}F NMR spectra supported two catalytic cycles operative for the transformation of **1** into **1a**, one involving the HDF of **1** (-67.7 ppm) to yield 2-fluoropyridine (-66.5 ppm) and a subsequent HDF of 2-fluoropyridine to yield pyridine (**1a**). The HDF of **1** was found to be faster (full conversion of **1** in 3 h) than that of 2-fluoropyridine (the full conversion of 2-fluoropyridine required 5 h). The NMR monitoring of the HDF of 2-fluoropyridine (**2**) supported an analogous cycle operative to the second cycle in the HDF of **1** (see pages S17-S25 in the SI). As the reaction progressed, the pyridine product coordinated to FBPin affording the pyridine-BFPin adduct[13] as evidenced by the shift in the pyridine signals in the ^{1}H NMR spectrum and of the signal in the ^{19}F and ^{11}B NMR spectra attributed to FBPin (see pages S9 and S14 in the SI). Addition of NEt$_3$ to the synthetic reaction allowed to isolate the free pyridine with the concomitant formation of the NEt$_3$-BFPin adduct.[14] The ^{31}P NMR spectrum showed one singlet at 120.8 ppm during the catalytic turnover, which was attributed to **Ni1** and allowed to identify **Ni1** as the catalyst resting-state of both catalytic cycles. Three minor unidentified peaks (see page S15 in the SI) were observed after 1 h and 30 min of reaction (98% conversion of **1**) that grew at the expense of **Ni1** at a slow rate (their ratio to **Ni1** was 1(**Ni1**):0.06:0.19:0.12 after 5 h, at full conversion of 2-fluoropyridine) and were tentatively attributed to catalyst deactivation products. Signals attributable to **Ni5** were not identified in the ^{1}H, ^{31}P and ^{11}B NMR spectra of the catalytic reaction, ruling out reaction of **Ni1** with HBPin as a deactivation pathway operative in catalysis. When the reaction of **Ni1** with 10 equiv of pyridine was monitored by ^{1}H and ^{31}P NMR spectroscopy at room temperature for 21 h, the spectra did not show any change in the signals of **Ni1**, supporting that **Ni1** did not react with pyridine under these conditions and allowing to rule out this reaction as a catalyst deactivation pathway. Further experiments are being conducted in our laboratory to identify potential catalyst deactivation pathways.



Scheme 4. Proposed catalytic cycle for the HDF of 2,6-difluoropyridine catalyzed by Ni1.

Based on the experimental evidence presented above, a plausible catalytic cycle for the formation of 2-fluoropyridine from **1** by **Ni1**-catalyzed HDF is depicted in Scheme 4. The **Ni1** precatalyst generates the 16-electron active species [Ni(^{iPr}PN)] by COD decoordination. The unsaturated [Ni(^{iPr}PN)] reacts with **1** affording **Ni4** by C-F oxidative addition at the 2-position, which further reacts with HBPin to generate FBPin and the [NiH(^{iPr}PN)(2-Fpy)] intermediate. Unlike in the Pd-catalyzed HDF of pen-

tafluoropyridine,[6b] this intermediate has not been observed by NMR spectroscopy, presumably because it undergoes fast C-H reductive elimination to afford 2-fluoropyridine and regenerate the active species [Ni(^{iPr}PN)]. Because **Ni1** is the catalyst resting-state, the [Ni(^{iPr}PN)] active species should be in equilibrium with **Ni1** by reversible COD coordination/decoordination. An analogous catalytic cycle to that depicted in Scheme 4 could be proposed for the transformation of 2-fluoropyridine into pyridine (**1a**, see page S59 in the SI for the full mechanistic scenario). The free pyridine product, **1a**, coordinates to the FBPin byproduct to afford the pyridine-BFPin adduct, and treatment of this adduct with NEt_3 during work-up allows to isolate the free pyridine (Scheme 4, bottom left). Additional mechanistic experiments are currently being conducted in our laboratory to gain further insights into the mechanism operative in catalysis.

In conclusion, the first nickel catalyst for the double 2,6-regioselective hydrodefluorination of partially fluorinated pyridines with HBPin has been discovered. The Ni(0) [Ni(^{iPr}PN)(COD)] complex has been found to be an efficient precatalyst for the HDF of 2,6-difluorinated pyridines at room temperature in 2 hours. Mechanistic studies support two consecutive cycles operative for the double HDF of 2,6-difluoropydirine and the Ni(0) complex [Ni(^{iPr}PN)(COD)] as the resting-state for both cycles. The [Ni(^{iPr}PN)(COD)] precatalyst has been found to enter the cycle by reversible COD decoordination to yield the 16-electron active species [Ni(^{iPr}PN)] responsible for C-F activation.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge.
Complete experimental details, characterization data, NMR spectroscopic data (PDF)

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Author Contributions

RA conceived the project, designed the experiments, supervised the experimental work and drafted the manuscript. RN conducted the optimization of the reaction conditions, the control experiments, the evaluation of the substrate scope and the synthesis of **Ni4**. VDA conducted the mechanistic studies, including the NMR monitoring of catalytic and stoichiometric reactions. RN and VDA drafted the SI. The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript. ‡These authors contributed equally.

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Notes

The authors declare no competing financial interest.

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