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C-H and C-N Activation at Redox-Active Pyridine Complexes of Iron

K. Cory MacLeod^a, Richard A. Lewis^a, Daniel E. DeRosha, Brandon Q. Mercado, and Patrick L. Holland

Department of Chemistry, Yale University, New Haven, Connecticut 06520 (USA)

Abstract

Pyridine activation by inexpensive iron catalysts has great utility, but the steps through which iron species can break the strong (105–111 kcal/mol) C-H bonds of pyridine substrates are unknown. In this work, we report the rapid room-temperature cleavage of C-H bonds in pyridine, 4-tert-butylpyridine, and 2-phenylpyridine by an iron(I) species, to give well-characterized iron(II) products. In addition, 4-dimethylaminopyridine (DMAP) undergoes room-temperature C-N bond cleavage, which forms a dimethylamidoiron(II) complex and a pyridyl-bridged tetrairon(II) square. These facile bond-cleaving reactions are proposed to occur through intermediates having a two-electron reduced pyridine that bridges two iron centers. Thus, the redox non-innocence of the pyridine can play a key role in enabling high regioselectivity for difficult reactions.

Graphical abstract

An iron(I) complex can activate C-H and C-N bonds in pyridines, using a mechanism that takes advantage of pyridine's redox activity.

Keywords

Pyridine; Iron; Redox-Active; Bond Cleavage

Pyridines are widespread in pharmaceuticals, natural products, and polymers, and therefore their expedient synthesis is crucial.^[1] However, pyridines are relatively unreactive in the absence of prior activation.^[2] Direct cleavage of C-H bonds in unfunctionalized pyridines is uncommon, but has made substantial progress recently.^[3] A recent exciting development has been the C-H arylation of pyridines using catalytic mixtures generated *in situ* from simple iron salts and an excess of Grignard reagent.^[4] This recipe presumably generates reduced

Correspondence to: Patrick L. Holland.

^aThese authors contributed to this work equally, and should be considered co-first authors.

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iron species that are the catalysts, but little is known about reduced iron-pyridine compounds and what stoichiometric steps to expect under these conditions. In this communication, we report well-characterized iron products that result from pyridine C-H bond cleavage. We also show an unprecedented C-N bond cleavage of 4-dimethylaminopyridine (DMAP) and construct a reasonable mechanistic scaffold that is based on the ability of pyridines to accept charge from low-valent iron.

Pyridines are well-known redox-active ligands.^[5] We have shown that the addition of one or more equiv of pyridine to the iron(I) complex $\text{LFe}(\text{C}_6\text{H}_6)$ ($\text{L} = \beta$ -diketiminate ligand, shown in Scheme 1) yields products in which the pyridine ligands are reduced by 1–2 electrons.^[6] However, we have now discovered that addition of smaller amounts of pyridine leads to formation of a surprising new compound (**1**). Solutions of **1** are in equilibrium with the previously characterized pyridine-bound complexes and with $\text{LFe}(\text{C}_6\text{H}_6)$, as shown by ^1H NMR spectra of C_6D_6 solutions of **1** with various amounts of pyridine (Figure S5). Compound **1** can be isolated by adding 0.5 equiv of pyridine to $\text{LFe}(\text{C}_6\text{H}_6)$ in pentane, from which **1** precipitates in 51% yield. An analogue with 4-*tert*-butylpyridine (**2**) can be isolated similarly in 76% yield.

X-ray diffraction studies^[b] show that **1** and **2** have similar bimetallic structures, in which two diketiminate-supported iron atoms are bridged by an ortho-metallated pyridine and by a bridging hydride that is visible in the Fourier difference map (Figure 1). This structure clearly shows C-H activation of the pyridine. The ^1H NMR spectra of **1** and **2** are consistent with a single mirror plane that contains both iron atoms, the 2-pyridyl bridge, and the hydride.

In **1** and **2**, the Fe-N_{py} bond lengths are 2.05 Å (Table 1), which is shorter than the analogous bonds to dative pyridines (2.10–2.11 Å) but longer than pyridine-derived amido ligands (1.94–2.00 Å) in other iron β -diketiminate complexes.^[6–7] The Fe-C bond lengths are similar to those in diketiminate-iron alkyl complexes.^[8] These data indicate that the pyridine-derived ligand is a monoanion, implying that each tetrahedral iron site is in the +2 oxidation state as shown in Scheme 1. The solid state Mössbauer spectra of **1** and **2** each have two doublets of equal intensity that corroborate the presence of inequivalent high-spin iron(II) sites.

The presence of the hydride bridge was verified by adding 1 equiv of diphenylacetonitrile to **2**, which affords a bridging iminyl complex (**3**) from formal [1,2]-addition of the Fe-H bond to the C-N triple bond. This reaction demonstrates that the hydride generated by the C-H activation is still reactive.^[3i] X-ray crystallographic analysis of **3** shows the new C-bound hydrogen atom in the difference map, and its solid state IR spectrum shows a new C-N stretching vibration at 1597 cm^{-1} .

Thus, **1** and **2** arise from a bimetallic pathway that uses one electron from each iron(I) center of $\text{LFe}(\text{C}_6\text{H}_6)$ to break the strong (106 kcal/mol) ortho C-H bond of pyridine. Most surprising is the rapid rate of this C-H activation reaction, which occurs within a few

^[b]The crystallographic structures for this paper have been deposited with the CCDC with deposition numbers 1513726–1513731.

minutes at room temperature. In contrast, the pyridine C-H activation reactions of bimetallic Zr-Ir complexes and late-metal carbonyl clusters require high temperatures and/or photolysis.^[3a, 3i]

More distant C-H bonds in pyridines are also susceptible to activation. The addition of 2-phenylpyridine to a solution of $\text{LFe}(\text{C}_6\text{H}_6)$ at room temperature for 1 h results in a deep red solution, from which two products can be isolated. One of the products is the known hydride complex $[\text{LFe}(\mu\text{-H})_2]$ (63% spectroscopic yield).^[9] The other product (**4**, 92% isolated yield) is shown by X-ray diffraction to be a mononuclear iron(II) complex with an ortho-metallated phenyl ring (Scheme 2, Figure 2). The ^1H NMR spectrum of **4** consists of fifteen resonances as expected for C_s symmetry. The Mössbauer spectrum of **4** indicates high-spin iron(II) (Table 1), which is also consistent with the solution magnetic moment of $5.0(1) \mu_B$.

The ability of iron to oxidatively add this C-H bond is particularly impressive because the bond dissociation energy is even stronger at 111 kcal/mol.^[10] Thus, the proximity of the low valent iron to this C-H bond enables more difficult transformations. This C-H activation was not observed with bulkier diketiminate ligands in earlier studies.^[11] No intermediates are observed, but we favor a monometallic mechanism, since a bimetallic mechanism (like the one observed in **1** and **2** above) does not explain the ortho selectivity.

An even more intriguing reaction is observed with 4-dimethylaminopyridine (DMAP). DMAP reacts rapidly with $\text{LFe}(\text{C}_6\text{H}_6)$ at room temperature to give soluble **5** in 71% spectroscopic yield, and precipitated **6** in 76% isolated yield, which together account for the consumption of 1 equiv of DMAP per iron (Scheme 3). Compounds **5** and **6** can be separated based on solubility, and thermal ellipsoid plots of their crystallographic structures are shown in Figure S24 and Figure 3. The red ether-soluble product **5** is the mononuclear complex $\text{LFe}(\text{NMe}_2)(\text{DMAP})$, which can also be independently synthesized in 75% yield from $[\text{LFe}(\mu\text{-Cl})_2]$,^[12] DMAP, and lithium dimethylamide (see Supporting Information). The sparingly soluble orange product **6** is a tetrametallic iron cluster that is bridged by four pyridyl ligands in a square (Figure 3). Reaction of $\text{LFe}(\text{C}_6\text{H}_6)$ with 4-chloropyridine in Et_2O solution also gives **6** (70%) and $[\text{LFe}(\mu\text{-Cl})_2]$ (84%).

The ^1H NMR spectrum of **6** has only five peaks, indicating a single type of diketiminate ligand environment that in turn suggests idealized C_{4h} symmetry with pseudotetrahedral iron sites. Therefore, we conclude that the bridging pyridyl ligands in **6** have alternating N and C binding, as shown in Scheme 3 and Figure 3, rather than other possible isomers. Interestingly, in the solid state, the iron sites are distorted toward trigonal pyramidal, which breaks the C_{4h} symmetry and gives the tetrametallic cluster a symmetry that is closer to C_{2h} . This reduction of symmetry is reflected in the solid-state Mössbauer spectrum of **6** at 80 K, which consists of *two* doublets with equal intensity, having similar isomer shifts but different quadrupole splittings (see Table 1). The difference is attributable to the solid-state geometry difference between Fe1/Fe3, which have N in the axial position, from Fe2/Fe4, which have C in the axial position. The fluxional motion that leads to higher symmetry in solution NMR measurements could be a shift in the geometries, or reversible Fe-N bond cleavage.

The formation of **5** and **6** clearly shows the cleavage of the C-N bond in DMAP. There are examples of metal-catalyzed functionalization of pyridines in the para position,^[13] but to our knowledge this is the first example of C-N cleavage in DMAP. C-N cleavage is a difficult reaction with numerous potential catalytic applications,^[14] and so the observation of room-temperature C(aryl)-N cleavage is particularly interesting.^[13e, 15]

The C-H and C-N activation products from reactions of $\text{LFe}(\text{C}_6\text{H}_6)$ with pyridine, *tert*-butylpyridine, and DMAP can be explained using a mechanistic scaffold (Scheme 4) that conceptually derives from the previously reported reaction of $\text{LFe}(\text{C}_6\text{H}_6)$ with 1 equiv of pyridine to give $\text{LFe}(\text{py})(\mu\text{-}\kappa^1\text{:}\eta^3\text{-py})\text{FeL}$ (**7**; downward in Scheme 4).^[6] In **7**, the bridging pyridine is reduced by two electrons to a form that has one formal negative charge on the N atom, and a formal negative charge on an η^3 -allyl that spans the ortho to the para positions of the ring. This η^3 -allyl could isomerize to two different η^1 -allyl isomers, with the iron attached to the ortho or the para carbon. If Fe moves to the ortho position (leftward in Scheme 4), the change of the ortho carbon from sp^2 to sp^3 hybridization would bring the β -hydride close enough to the N-bound iron for β -hydride elimination to re-aromatize the ring and give the ortho-metallated pyridine, and the new hydride could form a bridge to result in **1** (or **2**, if $\text{X} = \text{tBu}$). If Fe moves to the para position (rightward in Scheme 4), then abstraction of the NMe_2 group by an iron(I) species could give the *N,C*-bridging unit of **6** in one product, as well as a dimethylaminoiron(II) complex. The re-aromatized *N,C*-bridging pyridyl would be coordinated to a formally iron(I) species, which could activate another NMe_2 group and continue until the four bridging groups give the thermodynamically stable square **6**. This would produce 4 equiv of $\text{LFe}(\text{NMe}_2)$ per square, each of which could attract another molecule of DMAP to form the stable product **5**.

Definitive mechanistic experiments are difficult because of previously described equilibria^[6] that interconvert $\text{LFe}(\text{C}_6\text{H}_6)$, **1**, **7**, $\text{LFe}(\text{py})_2$, and $[\text{LFe}(\text{py})_2]_2$. However, we gained some insight into the mechanism of *ortho*-activation of pyridine (lower left of Scheme 4). First, the addition of equimolar pyridine and pyridine- d_5 to $\text{LFe}(\text{C}_6\text{H}_6)$ showed no evidence of H/D exchange, supporting an intramolecular reaction. More importantly, we were able to avoid the problematic pyridine equilibria by monitoring the kinetics of the reverse reaction, the conversion of **1** into $\text{LFe}(\text{C}_6\text{H}_6)$ in the presence of excess benzene, which should follow the same mechanism as the forward C-H activation. The kinetic experiments indicate the rate law $v = k[\mathbf{1}]$, with a zero-order dependence on $[\text{C}_6\text{H}_6]$ (see Supporting Information). We observed slower rates with the deuteride isotopologue of **1**, showing a kinetic isotope effect (KIE) of $k_{\text{H}}/k_{\text{D}} = 1.31 \pm 0.01$. This value shows that Fe-H/Fe-D bond cleavage occurs during the rate-determining step.^[16] This KIE is similar to some reported values for insertion of unsaturated substrates into metal hydride bonds.^[17] A normal KIE of 3.0 was observed in a Rh-based C-H activation that was proposed to use a similar bimetallic mechanism.^[18] Overall, we conclude that the rate-determining step is intramolecular addition of the Fe-H bond across the N=C bond, as depicted in the lower left of Scheme 4. The ability to explain the kinetics using the mechanistic model in Scheme 4 also supports its applicability to the reverse reaction: that is, β -hydride elimination as the step that breaks the C-H bond of pyridine. Additional studies will be needed to verify the proposed mechanism for C-N cleavage that forms **5** and **6**.

In conclusion, we have characterized stoichiometric C-H and C-N activation reactions by a low-coordinate iron(I) fragment, demonstrating the feasibility of oxidative addition steps in catalytic reactions of iron and pyridines. Each C-H activation is rapid at room temperature, even though all the species have high-spin electronic configurations and weak-field ligands. Moreover, the redox-active pyridine ligand can play a key role, as two-electron reduction of the pyridine by iron(I) activates it toward regioselective bond breaking at the ortho and para positions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. The molecular structures of **1** (left) and **2** (right), with thermal ellipsoids shown at 50% probability. H atoms (except for the hydride) and the ortho-methyl groups on the supporting ligands are omitted for clarity.

Figure 2.

The molecular structure of **4**, with thermal ellipsoids shown at 50% probability. Only one of two independent molecules in the asymmetric unit is shown. The hydrogen atoms have been omitted for clarity.

Figure 3.

The molecular structure of **6**, with thermal ellipsoids shown at 50% probability. One of the two possible orientations is shown for the bridging pyridinyl ligands. Hydrogen atoms and 2,6-Me₂C₆H₃ groups omitted for clarity.

Scheme 1.

C-H activation of *tert*-butylpyridine, and functionalization of the hydride product.

Scheme 2.
C-H activation of 2-phenylpyridine.

Scheme 3.
C-N activation in DMAP.

Scheme 4.
Proposed mechanism for C-H and C-N activation.

Table 1

Metrical and Mössbauer parameters.

Compound	Fe-N _{py} (Å)	Fe-C (Å)	δ (mm s ⁻¹) ^[a]	E _Q (mm s ⁻¹)
1	2.048(3)	2.065(3)	0.82, 0.53	2.02, 1.79
2	2.054(4)	2.077(5)	0.77, 0.59	1.73, 1.58
3	2.066(3)	2.084(3)	0.76, 0.63	2.28, 2.25
4	2.131 ^[b]	2.054 ^[b]	0.61	1.05
5	na	na	0.73	1.29
6	2.063 ^[b]	2.063 ^[b]	0.64, 0.66	2.38, 1.63

^[a]In **1**, **2**, **3**, and **6**, there are two ways of modeling the four peaks that fit the data equally well. The parameters here are based on the expectation of different δ for different coordination environments.

^[b]Average value.