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Atom-Economical Route to Substituted Pyridines via a Scandium Imide

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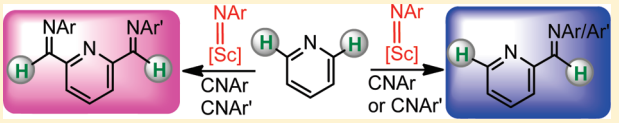
Supporting Information

ABSTRACT: Taking advantage of a tautomerization process between (PNP)Sc═N(DIPP)(NC_5H_5) (PNP = N[2-P($CHMe_2$)$_2$-4-methylphenyl]$_2^-$, DIPP = 2,6-*i*$Pr_2C_6H_3$) and (PNP)Sc(NH-(DIPP))(η^2-NC_5H_4) (**1**), we demonstrate in this work that pyridine can be both activated and functionalized with isonitriles (in one case catalytically) to ultimately afford mono- and bis-imino-substituted pyridines. Several intermediates in the cycle have been isolated and characterized.



Selectively activating and functionalizing C−H bonds is a never-ending endeavor in organometallic chemistry, because this route can provide direct entry to commodity reagents while avoiding the more conventional, often more difficult/expensive steps needed to achieve similar targets in a non-atom-economical fashion. In this regard, ortho functionalization of pyridine (Py) is particularly attractive, due to the importance of this moiety as a building block in N-heterocyclic chemistry, as well as its role as a backbone skeleton in the construction of robust ligands. One particular class of ligands that deserve special recognition are the mono- and bis-imino-substituted pyridines (IMPy and BIMPy), given their role as popular ancillary supports for mid- to late-transition-metal catalysts and more recently (in the case of bis-imino-substituted pyridines), their involvement as electron reservoirs in low-valent mid- to late-transition-metal complexes and the lanthanides.[1] Although the synthesis of the these ligands from their respective aldehydes or ketones[2] is rather straightforward, a system capable of generating such scaffolds directly from pyridine, stoichiometrically or catalytically, in one step, has not been reported. The work by Jordan and co-workers, using [$Cp_2Zr(CH_3)(THF)$][BPh_4], represents the first example of a cyclic and catalytic system capable of activating pyridine and functionalizing one ortho position via a series of steps such as σ-bond metathesis, migratory insertion, and hydrogenation (for product release).[3] Another example includes the work of Teuben and co-workers.[4]

In this work, we demonstrate that a transient scandium imide, (PNP)Sc═N[DIPP] (PNP = N[2-P($CHMe_2$)$_2$-4-methylphenyl]$_2^-$, DIPP = 2,6-*i*$Pr_2C_6H_3$),[5] can cleanly activate and functionalize Py with isonitriles in both the 2- and 2,6-positions to afford mono- and bis-imino-substituted pyridines via a combination of steps such as 1,2-CH bond addition, insertion, and 1,3-hydrogen migrations. In addition to isolating some intermediates formed along the C−H activation and functionalization cycle, the reactions reported herein are not only atom-economical and in one case catalytic but also provide access to asymmetric bis-imino-substituted pyridines directly from a feedstock such as Py.

Recently we demonstrated that the pyridyl-anilide complex (PNP)Sc(NH[DIPP])(η^2-NC_5H_4) (**1**), prepared cleanly from addition of Py to (PNP)Sc(NH[DIPP])(CH_3) or the zwitterion (PNP)Sc(μ_2-N[DIPP])(μ_2-CH_3)[$Al(CH_3)_2$], can undergo smooth exchange with d_5-Py, at 90 °C over 8 h, to form the isotopologue (PNP)Sc(ND[DIPP])(η^2-NC_5D_4) (d_5-**1**).[5] Realizing that the scandium imide tautomer (PNP)Sc═N[DIPP]-(Py) (**A**) is the active form while **1** is the resting state, we speculated whether the former species could activate C−H bonds while taking advantage of the 1,3-hydrogen migration process for the purpose of product release. When complex **1** is treated with 1 equiv of CN[DMeP] ([DMeP] = 2,6-$(CH_3)_2C_6H_3$), the iminoacyl complex (PNP)Sc(NH[DIPP])(η^2-[DMeP]N═C[NC_5H_4]) (**2a**) is formed quantitatively and isolated in 78% yield (Scheme 1).

Complex **2a** originates via insertion of the isonitrile into the Sc−C bond of the pyridyl ligand in precursor **1**, and diagnostic features include the observation of an intact anilide N−H resonance (6.15 ppm) as well as inequivalent aryl C−H resonances for the 2-substituted pyridine moiety, as inferred by ^{1}H NMR spectroscopy. ^{13}C NMR spectroscopic data also corroborate formation of an iminoacyl carbon group (258.6 ppm), which is comparable to other examples known in the literature for d^0 early-transition-metal complexes (Ti(IV), 212−256 ppm; Zr-(IV), 240−244 ppm).[6] In addition to NMR spectroscopic data, single-crystal X-ray diffraction studies (XRD) confirm the proposed connectivity by showing a coordinately saturated scandium anilide complex having an η^2-bound iminoacyl ligand (Figure 1). Due to strain, the side-on coordination of the iminoacyl group forbids chelation of the pendant pyridine group (Sc1···N4, 4.242 Å). Location and isotropic refinement of the anilide hydrogen reveals it to be pointing away from the

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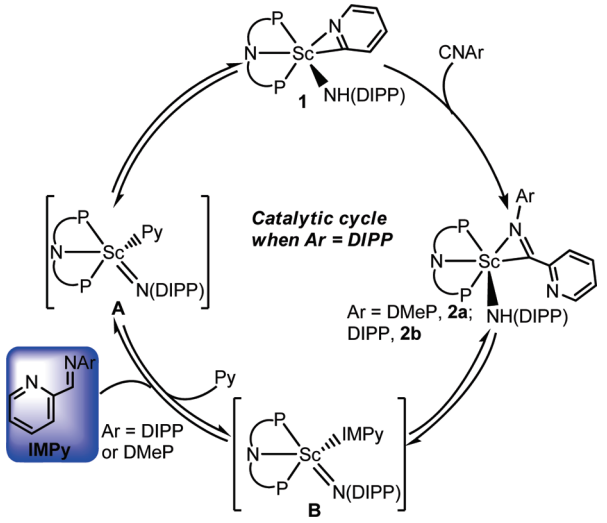
Scheme 1. Synthetic Cycle for C−H Activation and Functionalization of Pyridine to Monosubstituted (Blue Product) Imino Pyridines



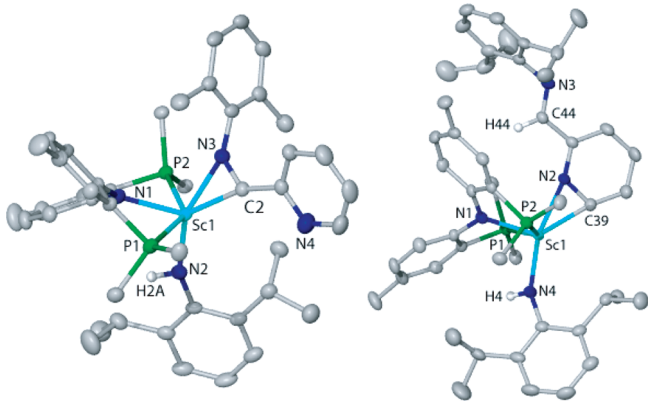
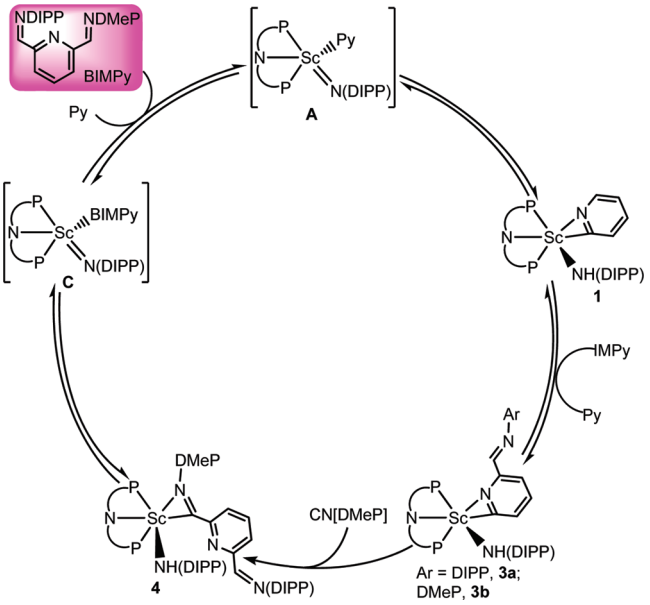


Figure 1. Perspective views of the molecular structures of complexes **2a** (left) and **3a** (right). *i*Pr groups on P and hydrogens (excluding the α-hydrogens on N2 and N4 and the aldimine carbons, C44 and C53) have been omitted for the purpose of clarity. Distances are reported in angstroms (Å) and angles in degrees (deg). Data for **2a**: Sc1−C2, 2.2279(19); Sc1−N3, 2.2111(15); Sc1−N1, 2.1613(16); Sc1−N2, 2.0761(16); Sc1−P1, 2.7679(6); Sc1−P2, 2.7808(6); N3−C39, 1.291(3); P1−Sc1−P2, 143.802(19); N3−Sc1−C2, 33.82(6). Data for **3a**: Sc1−C39, 2.212(4); Sc1−N2, 2.235(3); Sc1−N4, 2.073(3); Sc1−N1, 2.155(3); Sc1−P1, 2.7415(11); Sc1−P2, 2.7604(12); N2−C39, 1.363(4); C44−N3, 1.267(4); P1−Sc1−P2, 142.87(4); N2−Sc1−C39, 35.69(11).

iminoacyl carbon (Sc1−C39, 2.2279(19) Å; Sc1−N3, 2.1613(16) Å; N3−Sc1−C39, 33.82(6)°), which is an orientation analogously observed for precursor **1**.[4] When CN[DIPP][7] (DIPP = 2,6-*i*Pr$_2$C$_6$H$_3$) is treated with **1**, the product is not as easy to spectroscopically elucidate. The ^{31}P NMR chemical shifts of this new complex are, however, more akin to those of **1** than to those of **2a** (6.5 and 3.8 ppm vs 5.1 and 4.5 ppm for **1** and 8.6 and 0.1 ppm for **2a**), suggesting that the iminoacyl group likely coordinates thru the iminoacyl carbon and pyridine nitrogen. The ^{1}H NMR spectra of this new complex also exhibited broad

Scheme 2. Synthetic Cycle for C−H Activation and Functionalization of a Monosubstituted Pyridine to Disubstituted (Pink Product) Imino Pyridine



resonances in the aryl region as well as in the region associated with the PNP isopropyl groups, although the anilide N−H resonance was observed (6.19 ppm). As a consequence, we tentatively assign this complex as (PNP)Sc(NH[DIPP])([DIPP]N=C[NC$_5$H$_4$]) (**2b**), but without specifying too much about the coordination mode of the [DIPP]N=C[NC$_5$H$_4$] ligand.

Complexes **2a**,**b** react cleanly at 90 °C with Py to close the cycle and re-form **1**, concurrent with ejection of the monosubstituted iminopyridines (IMPy) ArN=CH[NC$_5$H$_4$] (Ar = DMeP, DIPP), confirmed by ^{1}H NMR spectroscopy, GC-MS, or comparison with authentic samples prepared independently (Scheme 1).[8] The capacity of Py to promote imine ejection implies that **2a**,**b** tautomerize via an imide-IMPy adduct intermediate, **B**, which is then susceptible to exchange IMPy with Py via a scandium imido[5,9] intermediate, **A** (Scheme 1). 1,2-CH bond addition of the coordinated pyridine across the Sc=N bond in **A** results in cyclometalation and closure of the cycle to re-form **1** (Scheme 1). To confirm that the aldimine proton of the product originates from the 1,3-transfer of the anilide proton, **2a**,**b** were both thermolyzed in the presence of d_5-Py. High-resolution mass spectrometry, as well as deuterium NMR, confirmed that the only products were the fully protonated iminopyridine and d_5-**1**.[7]

The ortho C−H bond of the pyridine group in IMPy is also amenable to activation by transient **A**. Accordingly, the complex (PNP)Sc(NH[DIPP])(η^2-[NC$_5$H$_3$]CH=N[DIPP]) (**3a**) can be prepared by thermolyzing **1** in the presence of IMPy (Ar = DIPP, Scheme 2). However, such an exchange is not complete without an excess of IMPy, which makes separation of **3a** difficult. Independently, treatment of the previously reported complex (PNP)Sc(NH[DIPP])(CH$_3$)[5] with 1 equiv of IMPy (Ar = DIPP) results in formation of **3a** and CH$_4$ quantitatively, as established by ^{1}H and ^{31}P NMR spectroscopy and comparison with the reaction mixture formed from **1** and IMPy. Diagnostic spectroscopic features for **3a** are similar to those of **1**: the anilide proton (6.34) and anilide isopropyl methyl proton resonances (1.57 and 1.41 ppm, $\Delta\nu_{1/2}$ = 41 Hz) are comparable. When 1 equiv of IMPy

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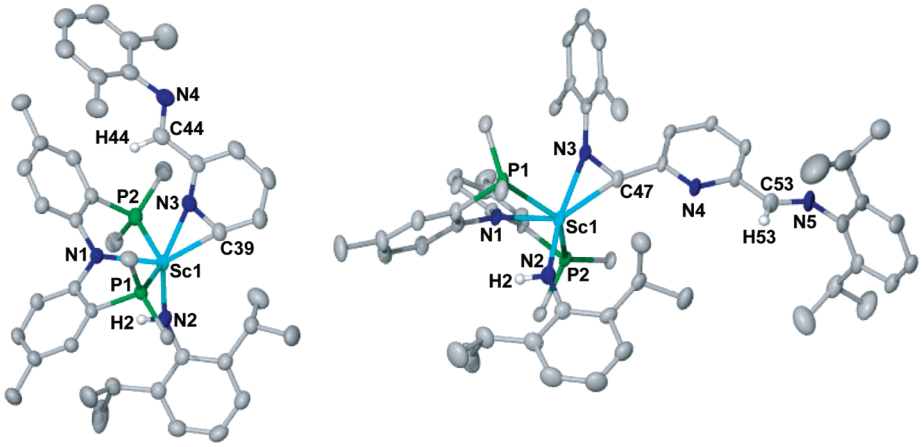

Figure 2. Perspective views of the molecular structures of complexes **3b** (left) and **4** (right). *i*Pr groups on P and hydrogens (excluding the α-hydrogens on N2 and N4 and the aldimine carbons, C44 and C53) have been omitted for the purpose of clarity. Distances are reported in angstroms (Å) and angles in degrees (deg). Data for **3b**: Sc1−C39, 2.2127(19); Sc1−N3, 2.2422(16); Sc1−N1, 2.1750(14); Sc1−N2, 2.0512(17); Sc1−P1, 2.7340(7); Sc1−P2, 2.7404(6); N3−C39, 1.356(2); P1−Sc1−P2, 143.181(9); N3−Sc1−C39, 35.43(6). Data for **4**: Sc1−C47, 2.239(4); Sc1−N3, 2.220(3); Sc1−N1, 2.157(3); Sc1−N2, 2.058(3); Sc1−P1, 2.7982(13); Sc1−P2, 2.7617(12); C47−N3, 1.304(5); C53−N5, 1.257(5); P1−Sc1−P2, 145.01(4); N3−Sc1−C47, 34.01(12).

(Ar = DMeP) is treated with **1**, analogously to the reaction to generate **3a**, the result is a mixture of products from which the major product, the iminoacyl derivative (PNP)Sc(NH[DIPP])-(η^2-[NC_5H_3]CH═N[DMeP]) (**3b**), could be crystallized.[7]

However, some resonances for **3a** are broader than for **3b**, implying a more hindered environment. The ^{31}P NMR spectrum of **3a** also displays two inequivalent phosphorus resonances (6.1 and 4.8 ppm), similar to but more well resolved than the resonances observed for **1**.[5] The pyridyl ^{13}C NMR resonance (215.4 ppm) and ^{31}P resonances (5.9 and 4.0 ppm) are indicative of a C−H activated pyridyl complex, similar to **3a**. Pyridyl formation, attributed to the diagnostic Sc−C resonance, was unambiguously confirmed via ^{13}C NMR spectroscopy (216.0 ppm), which is also similar to the resonance for **1** (217.2 ppm).[5]

To conclusively establish where C−H bond activation took place in complex **3a**, as well as assess the coordination environment about the Sc(III) center, we relied on XRD studies. Figure 1 depicts a six-coordinate Sc(III) center having an anilide ligand as well as an η^2-pyridyl group (Sc1−N2, 2.155(3) Å; Sc1−C39, 2.212(4) Å; N2−Sc1−C39, 35.69(11)°) with a pendant imino group in the 6-position (N3−C44, 1.267(4) Å) that does not coordinate to the metal center (Sc1···N3, 5.538 Å) and is oriented anti with respect to the pyridyl nitrogen. No α-H agostic interaction of the anilide hydrogen (Sc1···H4, 2.410 Å) is observed, and the hydrogen is pointing away from the pyridyl α-C. Overall, the gross geometry about the Sc center in **3a** is reminiscent of the parent pyridyl derivative **1**.[5] We were also able to obtain single-crystal diffraction data of **3b**, and the structure displays an imino group oriented akin to **3a**, as well as similar bond lengths and angles (Figure 2).[7]

To determine whether a BIMPy could be derived from pyridine, we treated complex **3a** with CN[DMeP], resulting in the formation of a new product (65% isolated yield) having diagnostic ^{1}H and ^{31}P NMR spectroscopic features similar to those of **2a**. The NMR spectroscopic data of this new complex is consistent with generation of the iminoacyl complex (PNP)-Sc(NH[DIPP])(η^2-[DMeP]N═C[NC_5H_3]HC═N[DIPP]) (**4**, Scheme 2).[7] XRD confirms the insertion of the isonitrile into the pyridyl moiety of **3a** to form an extended η^2-iminoacyl motif, where both the noncoordinating pyridine and aldimine groups branch away from the metal center (Figure 2).[7] Overall, metrical parameters for **4** are similar to those of **2a** by having comparable iminoacyl C−N bond lengths. What is more significant is that when Py is added to **4** and the mixture heated to 70 °C over 6 days, a novel, asymmetric BIMPy ([DIPP]N═CH)NC_5H_3-(HC═N[DMeP]) and **1** (Scheme 2) are formed quantitatively. BIMPy can be isolated in 32% yield from the reaction mixture, and characterization of this novel organic product has been established by a combination of ^{1}H and ^{13}C NMR spectroscopy as well as high-resolution GC-MS.[7] We propose formation of **1** from **4** to follow a similar sequence of events analogous to the conversion of **2a** to **1** in Py: by forming the tautomer, **C**, followed by exchange with Py to produce intermediate **A** and BIMPy, and finally C−H bond activation to re-form **1** (Scheme 2).

Unfortunately, complex **2a** reacts with 1 equiv of CN[DMeP] to give a mixture of products, therefore preventing this substrate from entering a catalytic cycle.[10] However, complex **2b** does not react with CN[DIPP] under similar conditions, therefore implying that an IMPy with the group Ar = DIPP could in principle be prepared catalytically using pyridine as our substrate. Accordingly, when 20 mol % of **1** is thermolyzed at 90 °C with CN[DIPP] (0.08 mol) and Py (0.24 mol) in C_6D_6, formation of IMPy can be observed by ^{1}H NMR, with complete conversion observed after 45 h (Scheme 1) to give a TOF of 0.11/h (~5.5 turnovers).[7] Interestingly, there is no observation of BIMPy in this reaction, implying that the IMPy formed is not able to re-enter the catalytic cycle and be further functionalized. We propose that sterics, and not electronic effects, forbid the entry of IMPy into the cycle.

In summary, the present work has established for the first time an atom-economical route to mono- and bis-imino-substituted pyridines by taking advantage of the reversible tautomerization process between a scandium pyridyl-anilide complex and a putative scandium pyridine-imido species.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Text and figures giving synthetic details for all the compounds prepared in this paper and a

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table and CIF files giving crystallographic data for **2a**, **3a**,**b**, and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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