ChemComm

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Journal:	*ChemComm*
Manuscript ID	CC-COM-01-2021-000278.R1
Article Type:	Communication

COMMUNICATION

C2-Selective Silylation of Pyridines by a Rhodium–Aluminum Complex

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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We have developed a C2-selective mono-silylation of a variety of pyridines using a Rh–Al complex. Both the site- and mono-selectivity are controlled via the pyridine coordination to the Lewis-acidic Al center prior to the activation of the pyridine C(2)–H bond at the proximal Rh center. A reaction mechanism is proposed based on several mechanistic studies, including the isolation of a (2-pyridyl)silylrhodium intermediate.

Pyridine is an important substructure widely found in numerous important agrochemicals and pharmaceuticals,[1] and methods for the functionalization of pyridine are thus widely sought after and highly valuable.[2] Substituents at the C2-position of pyridine strongly affect the electronic and steric properties around the pyridine nitrogen atom, which often allows improving the pharmacological activity of molecules containing such C2-substituted pyridine moieties.[1b] Conventionally, halogenation followed by metalation or directed metalation is employed for the functionalization of pyridine at the C2-position,[3] albeit that this approach usually generates inorganic waste and shows low functional-group tolerance due to the high reactivity of the metalated pyridines. Borylpyridines represent useful alternatives that enable access to versatile functionalized pyridines via various chemoselective transformations such as the Suzuki-Miyaura cross-coupling.[4] Indeed, 3- and 4-pyridyl-B(pin) (pin = pinacolate) have been synthesized by C–H borylation, and these can subsequently be converted into other functional groups.[4,5] However, 2-borylpyridines are usually not synthetically useful given their high propensity toward protodeboronation.[6] Therefore, stable B(aam) (aam = anthranilamide), B(MIDA) (MIDA = *N*-methyliminodiacetic acid), and triolborate groups have been developed to provide more reliable reagents for the functionalization of 2-pyridyl moieties.[7]

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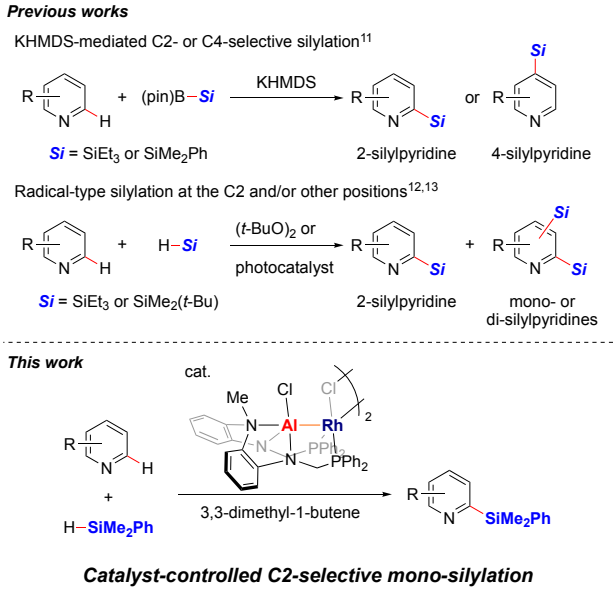
Electronic Supplementary Information (ESI) available: details of any supplementary information available should be included here. See DOI: 10.1039/x0xx00000x

Pyridines with a 2-silyl group can also be used to access C2-functionalized pyridines as silyl groups are generally stable and can be converted into various functional groups.[8] However, the synthesis of 2-silylpyridines has so far relied on multi-step *ortho*-halogenation/metalation/silylation or directed metalation/silylation processes,[3] whereas the direct C2-selective C–H silylation would be a more efficient way to access 2-silylpyridines.[8f,9,10] Although there are several reports on the direct C–H silylation of pyridines using late transition metal catalysis,[10] the site-selectivity of these processes usually depends on the electronic and steric properties of the substrate, i.e., the C2-selectivity is hard to control. In 2019, Martin demonstrated a potassium hexamethyldisilazide (KHMDS)-mediated C2- or C4-selective direct silylation of pyridine derivatives with Et_3Si–B(pin). However, it focused on the C4-selectivity and limited cases of the C2-selectivity was demonstrated (Scheme 1).[11] While silylation using silyl radical intermediates, reported by Maruoka and Zhang/Wang, affords 2-silylpyridines bearing C4-substituents (Scheme 1),[12,13] these radical-based approaches suffer from poor site-selectivity with other substituted pyridines and/or contamination of disilylpyridine products. Accordingly, a C2- *and* mono-selective silylation of pyridines remains, to the best of our knowledge, elusive.

We have recently reported the activation of the pyridine C(2)–H bond using a rhodium complex that bears an X-type aluminyl ligand.[14,15] This was independently observed by Ozerov, who employed an iridium complex that bears an X-type boryl ligand.[16] In both cases, pyridine coordinates to the Lewis-acidic metal in the ligand to activate the C(2)–H bond at the proximal transition metal. In contrast, the catalytic cycle of the Rh-catalyzed C–H silylation includes the oxidative addition of a hydrosilane to a Rh^{I}–H species, the hydrogenation of an olefin, arene C(sp^2)–H activation by a Rh^{I}–Si species, and C–Si bond formation via reductive elimination to regenerate the Rh^{I}–H species.[17] On the basis of these studies, we envisioned that a Rh–Al complex could accomplish the C2-selective silylation of pyridine with an appropriate silylating agent and a hydrogen

acceptor. Herein, we report the C2-selective mono-silylation of pyridines with a hydrosilane using a Rh–Al catalyst (Scheme 1, this work). The site- and mono-selectivity are exclusively controlled by the catalyst, and only 2-monosilylpyridines are produced. We conducted experimental mechanistic studies, including the characterization of a key (2-pyridyl)silylrhodium intermediate that likely produces the 2-silylpyridine products upon reductive elimination, and propose a reaction mechanism based on these results.

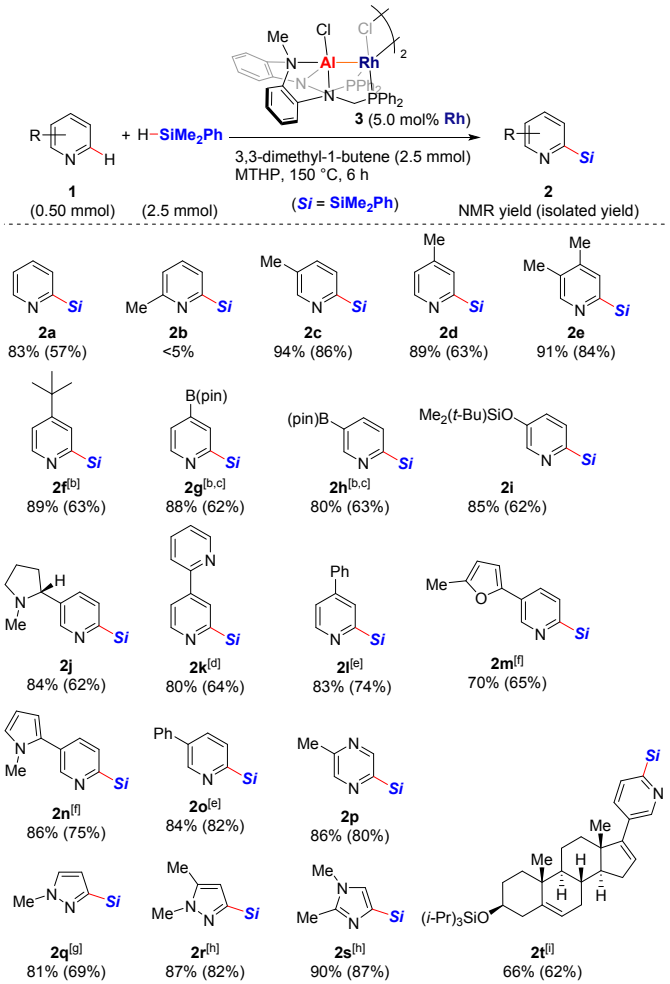
Scheme 1. Previous works and this work.



Catalyst-controlled C2-selective mono-silylation

After the optimization of the reaction conditions (see the Supporting Information for details), we investigated the scope of the reaction with respect to the pyridine substrates in the presence of Z-type PAlP–Rh complex **3** (Table 1). Under the standard conditions, various pyridines can be applied to the silylation and the desired 2-silylpyridines are obtained in good to excellent yield with the generation of a little amount of 2-alkylpyridines. Pyridine (**1a**), 3-picoline (**1c**), 4-picoline (**1d**), 3,4-dimethylpyridine (**1e**), and 4-*tert*-butylpyridine (**1f**) all afforded the corresponding 2-silylpyridines in excellent yield, suggesting that the site-selectivity of the reaction can be controlled by the catalyst. 2-Picoline (**1b**) did not provide the corresponding product and this is probably due to inefficient coordination of 2-picoline to the Al center on account of the steric repulsion. This could be supported by the fact that the silylation of **1a** in the presence of **1b** proceeded well only with **1a**. Pyridines that bear a pinacolatoboryl group, which can be converted into various functional groups, at the C4 or C3 position (**1g** and **1h**) participated in the silylation reaction as did the silyl-protected 3-hydroxypyridine (**1i**) and nicotine (**1j**). Notably, 2,4'-bipyridine (**1k**) preferentially afforded 2'-(dimethylphenylsilyl)-2,4'-bipyridine (**2k**). Therefore, the catalyst-controlled C2-selectivity overrides the conventional substrate-controlled C–H functionalization at the C3 position of **2k**. The reaction of 4-phenylpyridine (**1l**) generated exclusively **2l** in 74% yield, whereas the photocatalytic silylation reported by Zhang/Wang produced the 2,6-disilylated product and the 2-silylated product in 65% and 5% yield, respectively.[13] 3-(5-Methylfuran-2-yl)pyridine (**1m**) afforded the corresponding C6-silylated product in 65% yield, whereby the furyl group remained intact. It should be noted that the silylation of 3-(1-methyl-1*H*-pyrrol-2-yl)pyridine (**1n**) furnished only the C6-silylated product (**2n**) in 86% NMR yield. Conversely, the KHMDS-mediated silylation

Table 1. Scope of pyridines.

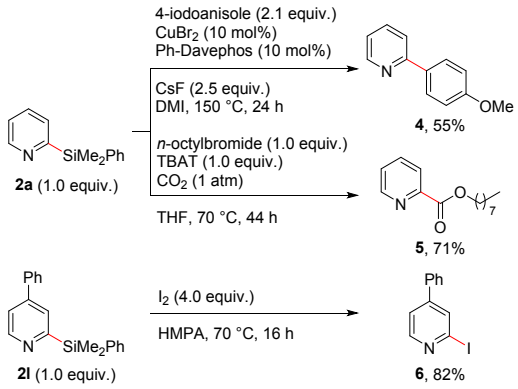


[a] NMR yield determined by ^{1}H NMR spectroscopy using mesitylene as an internal standard. [b] Reaction run for 10 h. [c] The isolated yield was determined after conversion of the B(pin) moiety into a Ph group via the Suzuki-Miyaura coupling. [d] Reaction run for 1 h. [e] Reaction run for 9 h. [f] Reaction run for 8 h. [g] Reaction with norbornene (3.8 mmol) under neat conditions for 24 h. [h] Reaction with 3,3-dimethyl-1-butene (3.8 mmol) under neat conditions for 24 h. [i] Reaction with **1q** (0.20 mmol), H–SiMe$_2$Ph (1.0 mmol), **3** (5.0 mol% Rh), and norbornene (1.0 mmol) in 4-methyltetrahydropyran (MTHP; 0.20 mL) for 24 h.

reported by Martin afforded a mixture of C6-, C4-, and C2-silylated products in 16%, 7%, and 5% NMR yield, respectively.[11] In the case of 3-phenylpyridine (**1o**), the silylation using our system took place exclusively at the C6-position to generate **2o** in 82% yield, whereas in the KHMDS-mediated silylation the C6- and C4-positions were silylated. Overall, the C2-selectivity exhibited by our heterobimetallic catalyst is unique in comparison to other known protocols for the C–H silylation of pyridines. In addition, pyrazine (**1p**), another azine heterocycle commonly found in pharmaceuticals and functional materials, could be silylated in 80% yield. The silylation also proceeded

site-selectively with pyrazoles (**1q** and **1r**) under slightly modified reaction conditions to exclusively afford C3-functionalized products, which had limited accesses through C–H functionalization.[18] Likewise, 1,2-dimethyl-1*H*-imidazole (**1s**) participated in the reaction at the position α to the sp^2-nitrogen atom in 87% yield. The silylation could also be applied to the late-stage functionalization of a silyl-protected abiraterone, whose acetate is a prostate cancer drug commercially available as Zytiga®, to give **2t** in moderate yield. Pyridines that bear chloro or amido groups hamper the silylation, possibly due to the low stability of **3** toward these Lewis-basic substituents and other heterocycles such as thiazole and oxazole were not competent substrates for this system (see the Supporting Information).

Scheme 2. Transformations of 2-silylpyridines.



DMI = 1,3-Dimethyl-2-imidazolidinone; TBAT = tetrabutylammonium difluorotriphenylsilicate; HMPA = hexamethylphosphoramide.

Several possible synthetic transformations of two 2-(dimethylphenylsilyl)pyridines are shown in Scheme 2. For example, **2a** was subjected to a Cu-catalyzed Hiyama cross-coupling[8j] and an esterification,[8i] while **2r** participated in an iodination reaction,[8g] demonstrating the synthetic versatility of these 2-silylpyiridnes and the utility of our C2-selective silylation protocol.

A plausible reaction mechanism for the C2-selective silylation of pyridine substrates is shown in Figure 1. First, the reduction of **3** with H–$SiMe_2Ph$ and 3,3-dimethyl-1-butene affords an active rhodium complex that bears an X-type aluminyl ligand (**7**), which is partly supported by stoichiometric experiments (see the Supporting Information). Next, pyridine coordinates to the Al center (**8**), supported by the isolation of DMAP-coordinated PAlP–Rh complex **8(nbd)-DMAP** (see the Supporting information), before the Rh center selectively activates the C(2)–H bond of the pyridine to afford rhodium hydride (**9**).[14] Then, alkene coordinates to the Rh center and inserts into the Rh–H bond to generate intermediate **10**. Deuterium-labeling experiments demonstrated that the catalyst exclusively activates the C(2)–H bond and, as has been reported previously,[14] that the oxidative addition and the subsequent olefin insertion steps are reversible (for details, see the Supporting Information). The reaction of **10** with $HSiMe_2Ph$ produces intermediate **11**, which reductively eliminates the 2-silylpyridine to complete the catalytic cycle. It should be noted here that, judging from the small amount of 2-alkylpyridine formed, the formation of a C–C bond via reductive elimination from **10** to afford the 2-alkylpyridine is likely to be slower than the reaction of **10** with $HSiMe_2Ph$. It seems plausible that due to the steric repulsion between the 2-silyl group and the ligand backbone, as seen in the reaction of 2-picoline (**1b**), the 2-silylpyridines are only able to weakly coordinate to the aluminum center, which prevents further silylation and subsequent generation of a 2,6-disilylpyridine and leads exclusively to the observed mono-selectivity.

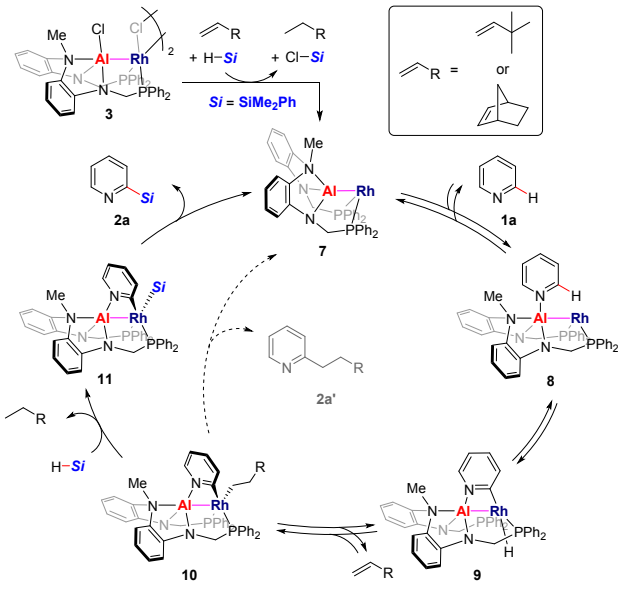
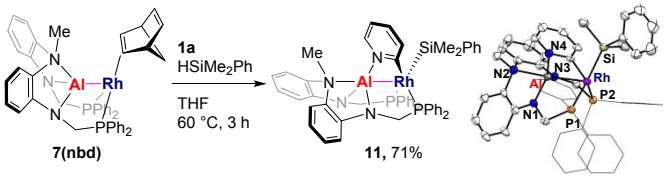


Figure 1. A plausible reaction mechanism for the C2-selective silylation of pyridine substrates.

Scheme 3. Synthesis and crystal structure of complex **11**.



To gain further insight into the reaction mechanism, we also attempted to isolate reaction intermediates. Treatment of X-type PAlP–Rh(nbd) complex **7(nbd)** with **1a** and $HSiMe_2Ph$ at 60 °C produced complex **11**, which is characterized by X-ray diffraction analysis (Scheme 3). In the crystal structure, the Rh center of **11** adopts a square-pyramidal conformation where the base consists of two phosphorous, a silicon, and a carbon atom from the pyridine, while the Al atom serves as the apex of the pyramid. The Al atom itself adopts a trigonal bipyramidal conformation involving three nitrogen atoms from the ligand backbone, a Rh atom, and the nitrogen atom of the pyridine. It should be noted here that the crystallography results show that the Al center is indeed coordinated by the pyridine nitrogen atom, that the C–Rh bond is derived from the activation of the pyridine C(2)–H bond, and that the substitution of the hydride ligand by the silyl group occurs at the Rh center. Based on the obtained crystal structure, **11** appears to be an intermediate that is formed immediately prior to the reductive elimination.

Subsequently, we studied the properties of **11**. Under the previously established standard conditions, **11** serves as a catalyst for the C2-selective silylation to give **2a** in 87% yield. This result is comparable to that obtained when using **3**, which corroborates the notion that **11** is involved in the catalytic cycle. Moreover, stirring **11** at 150 °C afforded **2a** in 47% yield, implying that the C–Si bond-forming reductive elimination can occur directly from **11** without any added reagents. An NMR time-course study revealed the existence of **11** during the reaction, indicating that **11** is likely an intermediate and possibly a resting state. These observations in combination with the formation of **11** from **7(nbd)** at 60 °C (Scheme 3) but no silylation with **7(nbd)** at 60 °C (Table S1) suggest that the C–Si bond-forming reductive elimination would be rate-determining.

In conclusion, we have achieved a C2-selective mono-silylation of a variety of pyridines catalyzed by a Rh–Al complex (**3**). The excellent site- and mono-selectivity are due to the cooperative interaction of the Rh and Al centers in **3**. Our results show that a heterobimetallic complex that bears a transition metal and an additional Lewis-acidic metal allows accomplishing challenging reactions that are not possible using conventional catalysts.

This work was supported by the JST CREST program (JPMJCR14L3) via the "Establishment of Molecular Technology towards the Creation of New Functions" project and by a JSPS KAKENHI grant (JP20H00376). N.H. is grateful for a Research Fellowship of the Japan Society for the Promotion of Science (JSPS) for Young Scientists. The authors would like to thank KURARAY for a generous donation of MTHP.

Conflicts of interest

There are no conflicts to declare.

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