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Iridium-Catalyzed *ortho*-Selective C−H Silylation of Aromatic Compounds Directed toward the Synthesis of π-Conjugated Molecules with Lewis Acid−Base Interaction

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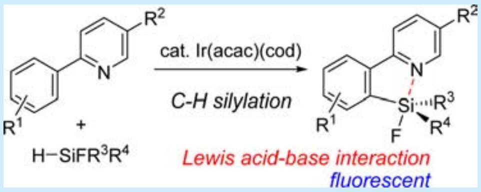
S *Supporting Information*

ABSTRACT: We successfully developed an iridium-catalyzed *ortho*-selective C−H silylation of aromatic compounds. The reaction exhibited a wide substrate scope, and a variety of π-conjugated molecules were synthesized in good to excellent yields, even in gram scale. Several silyl groups could also be introduced into the products. The experimental results indicated that the regioselectivity could be controlled by a Lewis acid−base interaction between the Lewis acidic silicon atoms of fluorinated hydrosilanes and the Lewis basic nitrogen atoms of aromatic compounds.



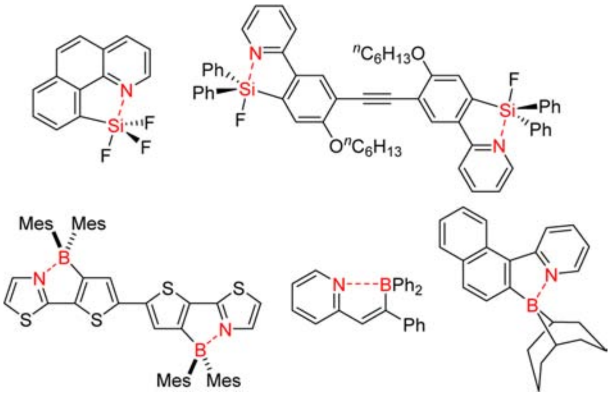


Figure 1. Several examples of π-conjugated molecules with a Lewis acid−base interaction.

π-Conjugated molecules with a Lewis acid−base interaction have recently attracted attention due to the special properties of such molecules compared with π-conjugated molecules bearing only covalent bonds (Figure 1).[1−4] It is expected that the Lewis acid−base interaction increases the efficiency of the π-conjugation by constraining the π-conjugated system in a planar fashion, and the electronegativity of Lewis acidic heteroatoms decreases the LUMO level of π-conjugated molecules.[3a] We recently reported the synthesis of silylated 2-phenylpyridines (silafluorene equivalent) with a Lewis acid−base interaction between the Lewis acidic silicon atoms of fluorinated silyl groups and the Lewis basic nitrogen atoms of 2-phenylpyridines, and the silafluorene equivalent has a fluorescent quantum yield higher than that of the corresponding silafluorene.[1c] We also reported palladium-catalyzed C−H borylation at the *ortho*-position of aromatic compounds.[3g] In this reaction, regioselectivity was controlled by the Lewis acid−base interaction between a boron atom of hydroboranes and a nitrogen atom of aromatic compounds. The Lewis acidity of a boron atom results from an unoccupied orbital of the boron atom. On the other hand, dispersion of electrons from the silicon atom to the electron-withdrawing group(s) causes the Lewis acidity of the silicon atom, and the silicon atom can thus form a five-coordinated silicon species. Therefore, hydrosilanes with electron-withdrawing group(s) are desirable candidate Lewis acidic reagents for *ortho*-selective C−H functionalization. We report herein iridium-catalyzed C(sp^2)−H silylation of aromatic compounds at the *ortho*-position, in which the regioselectivity could be controlled by the Lewis acid−base interaction.[5−8] In this reaction, fluorinated hydrosilanes were used as silylation reagents.

First, we investigated palladium complex $[\mathrm{Pd(NCCH_3)_4}](\mathrm{BF_4})_2$ and a $\mathrm{Pd(OAc)_2}$ salt as a catalyst using 2-phenylpyridine (**1a**) and fluorodiphenylsilane (**2a**) as substrates because the two above-mentioned reactions proceeded using palladium catalysts (Table 1, entries 1 and 2).[1c,3g] The desired *ortho*-C−H silylation reaction, however, did not proceed at all. Therefore, we next investigated several other transition metal complexes. Although carbonyl complexes $\mathrm{W(CO)_6}$ and $\mathrm{Ru_3(CO)_{12}}$ did not produce the desired product (Table 1, entries 3 and 5), a rhenium complex, $[\mathrm{ReBr(CO)_3(thf)}]_2$, afforded silylated product **3a** in 37% yield (Table 1, entry 4). Ruthenium and cobalt complexes, $[\mathrm{RuCl}(p\text{-cymene})]_2$ and $\mathrm{CoCl(PPh_3)_3}$, also did not produce good results (Table 1, entries 6 and 7). In contrast, rhodium and iridium complexes exhibited catalytic activities and gave the desired product **3a** in 35−48% yield (Table 1, entries 8−11). To

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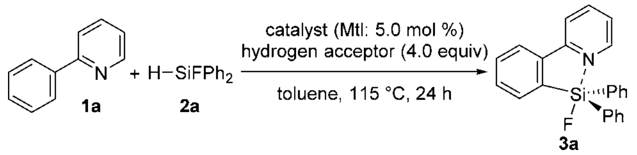
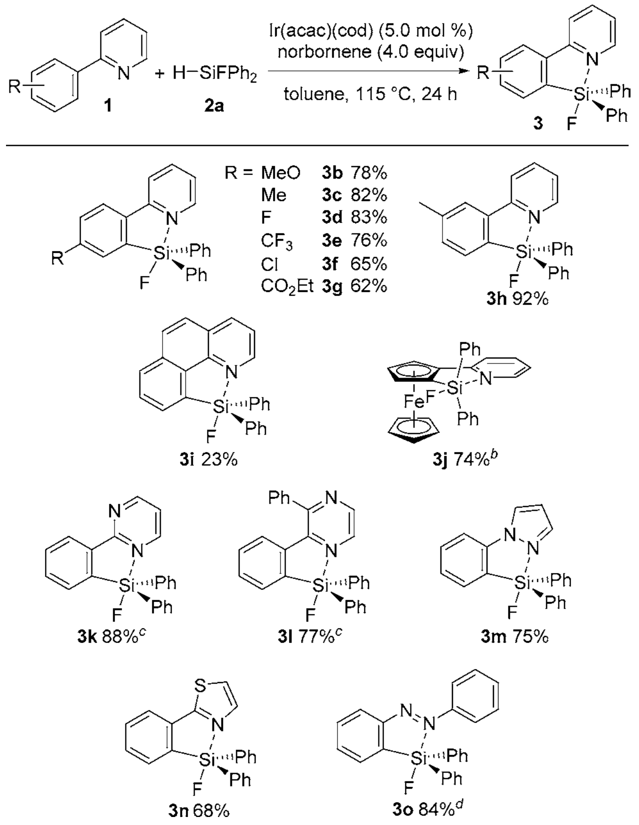
Table 1. Investigation of Several Transition Metal Compounds and Hydrogen Acceptors[a]



entry	catalyst	hydrogen acceptor	yield (%)
1	$[Pd(NCCH_3)_4](BF_4)_2$		<1
2	$Pd(OAc)_2$		<1
3	$W(CO)_6$		<1
4	$[ReBr(CO)_3(thf)]_2$		37
5	$Ru_3(CO)_{12}$		<1
6	$[RuCl(p\text{-cymene})]_2$		9
7	$CoCl(PPh_3)_3$		<1
8	$RhCl(PPh_3)_3$		35
9	$[RhCl(cod)]_2$		45
10	$[IrCl(cod)]_2$		42
11	Ir(acac)(cod)		48
12	$[RhCl(cod)]_2$	3,3-dimethyl-1-butene	13
13	$[IrCl(cod)]_2$	3,3-dimethyl-1-butene	84
14	$[IrCl(cod)]_2$	norbornene	95
15	Ir(acac)(cod)	norbornene	97 (93)[b]

[a] **2a** (1.4 equiv). [b] Isolated yield.

Scheme 1. Reactions between Aromatic Compounds 1 and Hydrosilane 2a[a]



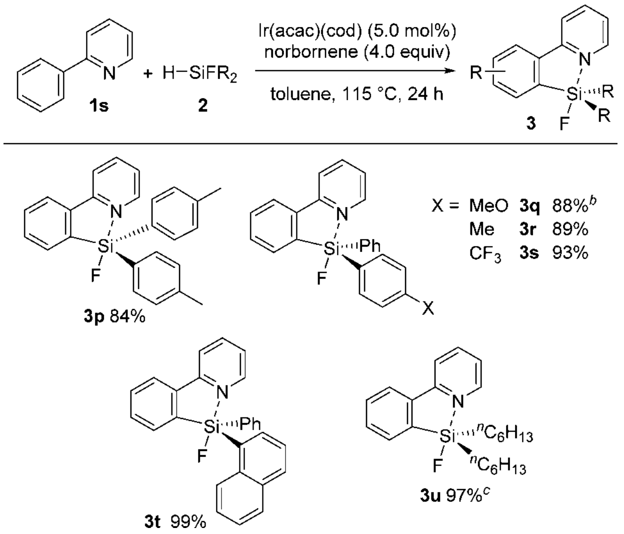
[a] **2a** (1.4 equiv). [b] Yield was determined by converting a fluorine atom of **3j** to a methyl group. [c] Norbornene (2.0 equiv), chlorobenzene, 100 °C. [d] *E*/*Z* = 1:1.

improve the yield of **3a**, hydrogen acceptors were investigated. Unfortunately, the yield of **3a** decreased when $[RhCl(cod)]_2$ was used as a catalyst (Table 1, entry 12). On the other hand, the yield of **3a** was dramatically improved in the case of iridium complexes $[IrCl(cod)]_2$ and Ir(acac)(cod) (Table 1, entries 13−15), and a combination of Ir(acac)(cod) and norbornene gave **3a** in 97% yield (93% isolated yield) (Table 1, entry 15). In this reaction, a fluorine atom of hydrosilanes was indispensable for promoting the silylation reaction. In fact, the silylation reaction did not proceed under the reaction conditions even with the use of several hydrosilanes, such as $HSiPh_3$, $HSiEt_3$, and H_2SiPh_2. This reactivity is quite different from the previous *ortho*-selective C−H silylation of aromatic compounds with a directing group, in which $HSiPh_3$, $HSiEt_3$, and H_2SiPh_2 were good silylation reagents.[6b−d] There are several reports of transition-catalyzed *meta*- (or *meta*- and *para*-) selective $C(sp^2)$−H silylations, in which the regioselectivity is controlled by steric hindrance,[7] but the present silylation did not occur at the *meta*- and *para*-positions. The silylated product **3a** had a Lewis acid−base interaction between the silicon and nitrogen atoms, as previously reported.[1c] In this reaction, the double *ortho*-silylation reaction did not proceed at all, likely due to the Lewis acid−base interaction between the silyl and pyridyl groups.

We investigated the substrate scope of aromatic compounds (Scheme 1). The silylation reaction was not affected by the electronic properties of an electron-donating or electron-withdrawing group at the *para*-position of aromatic compounds, and the desired silylated compounds **3b**−**3e** were obtained in 76−83% yields. Functional groups, such as a chlorine atom and ethoxycarbonyl group, remained unchanged, and the corresponding silylated products **3f** and **3g** were obtained in good yields. The silylation reaction proceeded regioselectively at the *ortho*-position with less steric hindrance, and only **3h** was obtained. The yield of silylated product **3i** was low when a substrate with a rigid structure (benzo[*h*]quinoline, **1i**) was used. Silylation also occurred at the C−H bond of pyridylferrocene, which is a rare example of C−H functionalization of ferrocene derivatives.[9] Silylated products **3k**−**3n** were also obtained using aromatic compounds with other heterocyclic rings, such as pyrimidinyl, pyrazinyl, pyrazolyl, and thiazolyl groups. (*E*)-1,2-Diphenyldiazene also produced the corresponding silylated product **3o** in 84% yield.[10] Based on the chemical shifts of ^{29}Si NMR spectra, all the products in Scheme 1 had Lewis acid−base interactions between the silicon and nitrogen atoms (for details, see Supporting Information).

We then investigated several fluorinated hydrosilanes (Scheme 2). Compared with our previous report using borylated silanamines as a silicon source,[1c] the preparation of silylation reagents was easier, and many types of silylation reagents were efficiently realized. Fluorinated hydrosilanes with an electron-donating or electron-withdrawing group on the aromatic ring(s) produced the corresponding silylated products **3p**−**3s** in 84−93% yields. In these reactions, silyl groups with two different aryl groups could be introduced into the structures of products **3q**−**3s**. Based on the chemical shifts of ^{29}Si NMR spectra, the Lewis acid−base interaction between the silicon and nitrogen atoms of the silylated product with an electron-withdrawing group on the aromatic ring (**3s**, ^{29}Si NMR δ −66.7 ppm) was stronger than that of a silylated product bearing an electron-donating group (**3q**, ^{29}Si NMR δ −62.2 ppm). Silylated product **3t** was also obtained quantitatively using a fluorinated hydrosilane bearing a naphthyl group. The silylation reaction using a fluorinated hydrosilane with alkyl groups proceeded in excellent yield; however, product **3u** could not be isolated by column

Scheme 2. Reactions between 2-Phenylpyridine 1a and Hydrosilanes 2[a]

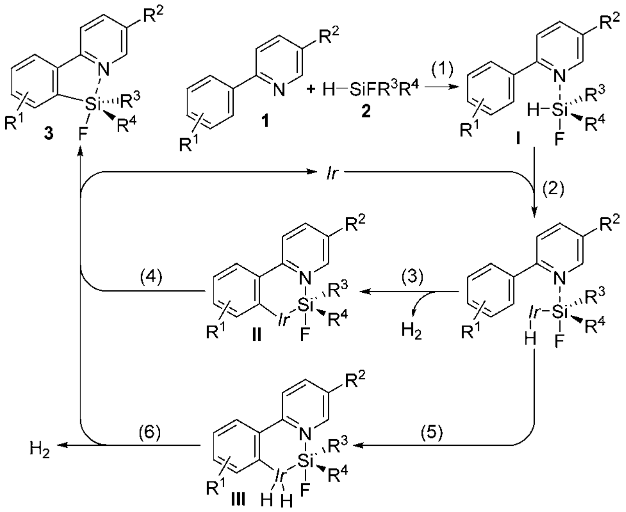


[a]**2** (1.4 equiv). [b]Norbornene (2.0 equiv), chlorobenzene, 100 °C. [c]^{1}H NMR yield using 1,1,2,2-tetrachloroethane as an internal standard.

chromatography on silica gel due to the instability of **3u**, probably a result of the weak Lewis acid−base interaction (^{29}Si NMR δ −31.9). Therefore, the product was isolated in 89% total yield by converting the fluorine atom to a methyl group through the reaction of **3u** with methyllithium.

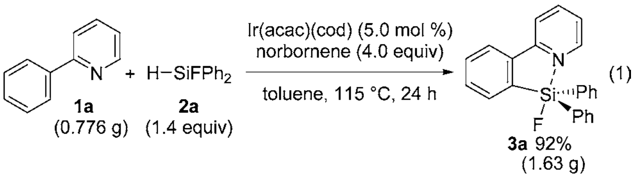
The reaction mechanism remains unclear; the silylation reaction may, however, proceed via Lewis acid−base interaction based on the following experimental results:[11] (1) Formation of a complex between 2-phenylpyridine (**1a**) and fluorinated hydrosilane **2a** (intermediate **I** in Scheme 3) was observed by ^{29}Si NMR. (2) As mentioned above, the silylation reaction did not proceed using several hydrosilanes, such as $HSiPh_3$, $HSiEt_3$, and H_2SiPh_2. These results suggested that Lewis acidity of a silicon atom caused by the electronegativity of the fluorine atom was important to promote the silylation reaction.[12] (3) One of the authors reported Lewis acid−base interaction-controlled *ortho*-selective C−H borylation of aromatic compounds as a related reaction.[3g] The proposed mechanism for the silylation is as follows (Scheme 3): (1) Lewis acid−base interaction between 2-phenylpyridine derivative **1** and hydrosilane **2**; (2) oxidative addition of the formed complex **I** to the iridium catalyst; (3) σ-bond metathesis via elimination of H_2 to give intermediate **II** (C−H bond activation); and (4) reductive elimination to give silylated product **3** and regenerate the iridium catalyst. Another possible pathway is (5) oxidative addition of the aromatic C−H bond to the iridium center and (6) reductive elimination of the formed intermediate **III** to give the desired silylated product **3** and regenerate the iridium catalyst via the formation of H_2.

Scheme 3. Proposed Mechanism for the Silylation of 2-Phenylpyridines via Lewis Acid−Base Interaction



Kinetic isotope effect experiments revealed that the value of the kinetic isotope effect, k_H/k_D, was 3.6 (for details, see Supporting Information). This result indicates that C−H bond activation was the rate-determining step of the reaction.

The silylation reaction proceeded in excellent yield, even on gram scale (eq 1). Treatment of 0.776 g of **1a** with **2a** in the presence of an iridium catalyst, Ir(acac)(cod), and norbornene gave 1.63 g of *ortho*-silylated product **3a** in 92% yield (eq 1). The yield of **3a** was comparable to that of **3a** in a smaller scale (Table 1, entry 15, **1a**: 66.2 mg).



In summary, we achieved an *ortho*-selective C(sp^2)−H silylation of aromatic compounds under iridium catalysis. The reaction proceeded in good to excellent yields using a variety of aromatic compounds, such as 2-phenylpyridines, benzo[*h*]-quinoline, pyridylferrocene, 2-phenylpyrimidine, 2-phenylpyrazine, 1-phenyl-1*H*-pyrazole, 2-phenylthiazole, 2-phenylimidazole, and azobenzene, even in gram scale. In addition, several fluorinated silyl groups could be introduced into the products. The experimental results suggested that the regioselectivity could be controlled by Lewis acid−base interaction between Lewis acidic fluorinated silicon atoms of hydrosilanes and Lewis basic nitrogen atoms of aromatic compounds. We believe that the present results will contribute to synthetic organic chemistry, especially C−H bond transformations, and organic materials chemistry dealing with π-conjugated molecules.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedure and characterization data. 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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■ REFERENCES

(1) There are several reports on π-conjugated molecules with a Lewis acid—base interaction between the Lewis acidic silicon atom and Lewis basic nitrogen atom. For examples, see: (a) Tokoro, Y.; Yeo, H.; Tanaka, K.; Chujo, Y. *Chem. Commun.* **2012**, *48*, 8541. (b) Tokoro, Y.; Tanaka, K.; Chujo, Y. *Org. Lett.* **2013**, *15*, 2366. (c) Xiao, Q.; Meng, X.; Kanai, M.; Kuninobu, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 3168.

(2) There are several reports on organic molecules with a Lewis acid—base interaction between the Lewis acidic silicon atom and Lewis basic nitrogen atom. For examples, see: (a) Kano, N.; Komatsu, F.; Kawashima, T. *J. Am. Chem. Soc.* **2001**, *123*, 10778. (b) Kano, N.; Yamamura, M.; Kawashima, T. *J. Am. Chem. Soc.* **2004**, *126*, 6250. (c) Kano, N.; Komatsu, F.; Yamamura, M.; Kawashima, T. *J. Am. Chem. Soc.* **2006**, *128*, 7097.

(3) There are several reports on π-conjugated molecules with a Lewis acid—base interaction between the Lewis acidic boron atom and Lewis basic nitrogen atom. For examples, see: (a) Wakamiya, A.; Taniguchi, T.; Yamaguchi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 3170. (b) Bosdet, M. J. D.; Piers, W. E.; Sorensen, T. S.; Parvez, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 4940. (c) Jaska, C. A.; Piers, W. E.; McDonald, R.; Parvez, M. *J. Org. Chem.* **2007**, *72*, 5234. (d) Ishida, N.; Narumi, M.; Murakami, M. *Org. Lett.* **2008**, *10*, 1279. (e) Ishida, N.; Moriya, T.; Goya, T.; Murakami, M. *J. Org. Chem.* **2010**, *75*, 8709. (f) Ishida, N.; Narumi, M.; Murakami, M. *Helv. Chim. Acta* **2012**, *95*, 2474. (g) Kuninobu, Y.; Iwanaga, T.; Omura, T.; Takai, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 4431.

(4) There are several reports on organic molecules with a Lewis acid—base interaction between the Lewis acidic boron atom and Lewis basic nitrogen atom. For examples, see: (a) Kano, N.; Yoshino, J.; Kawashima, T. *Org. Lett.* **2005**, *7*, 3909. (b) Yoshino, J.; Kano, N.; Kawashima, T. *Chem. Commun.* **2007**, 559. (c) Yoshino, J.; Kano, N.; Kawashima, T. *Tetrahedron* **2008**, *64*, 7774. (d) Yoshino, J.; Furuta, A.; Kambe, T.; Itoi, H.; Kano, N.; Kawashima, T.; Ito, Y.; Asashima, M. *Chem.—Eur. J.* **2010**, *16*, 5026. (e) Kano, N.; Furuta, A.; Kambe, T.; Yoshino, J.; Shibata, Y.; Kawashima, T.; Mizorogi, N.; Nagase, S. *Eur. J. Inorg. Chem.* **2012**, 1584. (f) Yoshino, J.; Kano, N.; Kawashima, T. *Dalton Trans.* **2013**, *42*, 15826.

(5) For an example of C(sp^2)—H silylation of benzene, see: (a) Sakakura, T.; Tokunaga, Y.; Sodeyama, T.; Tanaka, M. *Chem. Lett.* **1987**, 2375. (b) Uchimaru, Y.; El Sayed, A. M. M.; Tanaka, M. *Organometallics* **1993**, *12*, 2065. (c) Tsukada, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 5022.

(6) For several examples of *ortho*-position-selective C(sp^2)—H silylation using a directing group, see: (a) Williams, N. A.; Uchimaru, Y.; Tanaka, M. *J. Chem. Soc., Chem. Commun.* **1995**, 1129. (b) Kakiuchi, F.; Igi, K.; Matsumoto, M.; Chatani, N.; Murai, S. *Chem. Lett.* **2001**, 422. (c) Kakiuchi, F.; Igi, K.; Matsumoto, M.; Hayamizu, T.; Chatani, N.; Murai, S. *Chem. Lett.* **2002**, 396. (d) Kakiuchi, F.; Matsumoto, M.; Tsuchiya, K.; Igi, K.; Hayamizu, T.; Chatani, N.; Murai, S. *J. Organomet. Chem.* **2003**, *686*, 134. (e) Tobisu, M.; Ano, Y.; Chatani, N. *Chem.—Asian J.* **2008**, *3*, 1585. (f) Ihara, H.; Suginome, M. *J. Am. Chem. Soc.* **2009**, *131*, 7502. (g) Kanyiva, K. S.; Kuninobu, Y.; Kanai, M. *Org. Lett.* **2014**, *16*, 1968.

(7) For several examples of *meta*- and *para*-position-selective C(sp^2)—H silylation, see: (a) Ishiyama, T.; Sato, K.; Nishio, Y.; Miyaura, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 5346. (b) Saiki, T.; Nishio, Y.; Ishiyama, T.; Miyaura, N. *Organometallics* **2006**, *25*, 6068. (c) Murata, M.; Fukuyama, N.; Wada, J.-i.; Watanabe, S.; Masuda, Y. *Chem. Lett.* **2007**, 910. (d) Cheng, C.; Hartwig, J. F. *Science* **2014**, *343*, 853.

(8) For several examples of intramolecular C(sp^2)—H silylation, see: (a) Ureshino, T.; Yoshida, T.; Kuninobu, Y.; Takai, K. *J. Am. Chem. Soc.* **2010**, *132*, 14324. (b) Simmons, E. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 17092. (c) Kuninobu, Y.; Yamauchi, K.; Tamura, N.; Seiki, T.; Takai, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 1520.

(9) For several examples of C—H bond transformations of ferrocene derivatives, see: (a) Siegel, S.; Schmalz, H.-G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2456. (b) Gao, D.-W.; Shi, Y.-C.; Gu, Q.; Zhao, Z.-L.; You, S.-L. *J. Am. Chem. Soc.* **2013**, *135*, 86. (c) Deng, R.; Huang, Y.; Ma, X.; Li, G.; Zhu, R.; Wang, B.; Kang, Y.-B.; Gu, Z. *J. Am. Chem. Soc.* **2014**, *136*, 4472. (d) Gao, D.-W.; Yin, Q.; Gu, Q.; You, S.-L. *J. Am. Chem. Soc.* **2014**, *136*, 4841. (e) Liu, L.; Zhang, A.-A.; Zhao, R.-J.; Li, F.; Meng, T.-J.; Ishida, N.; Murakami, M.; Zhao, W.-X. *Org. Lett.* **2014**, *16*, 5336. (f) Shibata, T.; Shizuno, T. *Angew. Chem., Int. Ed.* **2014**, *53*, 5410.

(10) 2-Silylazobenzenes with fluorine atoms on the silicon atom have a reversible photoswitching ability. See ref 2c.

(11) At present, we cannot rule out the following or their related mechanisms: (1) coordination of a pyridyl directing group of 2-phenylpyridine derivative **1** to an iridium catalyst; (2) oxidative addition of a C—H bond to the iridium catalyst (C—H bond activation); (3) oxidative addition of hydrosilane **2** to an iridium center; and (4) reductive elimination to give silylated product **3** and regenerate the iridium catalyst via the elimination of H_2.

(12) Lewis acid—base interaction can control *ortho*-selectivity of C(sp^2)—H transformation. See ref 3g.