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An effective and versatile strategy for the synthesis of structurally diverse heteroarylsilanes *via* Ir(III)-catalyzed C–H silylation†

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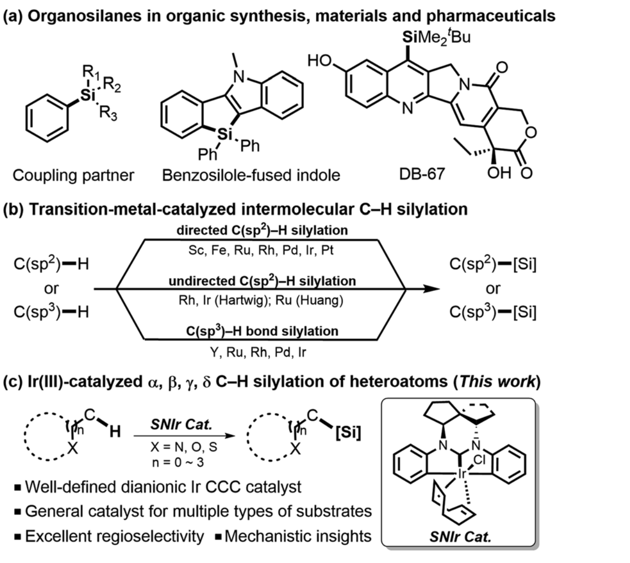
A versatile silylation of heteroaryl C–H bonds is accomplished under the catalysis of a well-defined spirocyclic NHC Ir(III) complex (SNIr), generating a variety of heteroarylsilanes. A significant advantage of this catalytic system is that multiple types of intermolecular C–H silylation can be achieved using one catalytic system at α, β, γ, or δ positions of heteroatoms with excellent regioselectivities. Mechanistic experiments and DFT calculations indicate that the polycyclic ligand of SNIr can form an isolable cyclometalated intermediate, which leaves a phenyl dentate free and provides a hemi-open space for activating substrates. In general, favorable silylations occur at γ or δ positions of chelating heteroatoms, forming 5- or 6-membered C–Ir–N cyclic intermediates. If such an activation mode is prohibited sterically, silylations would take place at the α or β positions. The mechanistic studies would be helpful for further explaining the reactivity of the SNIr system.

Introduction

Organosilanes have emerged as an important class of compounds with diverse utilities,[1] serving as versatile organic reagents to mediate many novel organic reactions,[1a,2] functional materials,[3] therapeutic pharmaceuticals, and bioactive chemicals (Scheme 1).[4] Traditionally, silicon-containing molecules have been prepared through the reactions of equivalent organometallic species with electrophilic silicon reagents,[5] which suffer from inferior atom-economy and low functional-group tolerance. For several decades, transition-metal-catalyzed intermolecular direct C–H silylation has been developed as a more efficient and attractive strategy.[1c–e] Among them, C(sp^2)–H silylation can generally be promoted with a directing group, which could coordinate with the metal center to form cyclometalated species and thus improve the regioselectivity of reaction. In this field, a range of directing groups have been developed,[6] which include strongly coordinating pyridines and various azoles, and more weakly coordinating imines, amides, esters, and ketones. In particular, Hou reported an alkoxyl-directed Sc-catalyzed silylation of various anisole derivatives.[6a] In 2009, a distinctive strategy of using easily-installed and -removed 2-pyrazol-5-ylaniline as a directing group for *o*-silylation of arylboronic acids has been developed by Suginome.[6b]

In comparison, undirected C(sp^2)–H silylation[7] is more challenging due to the loss of interaction between the coordinating group and the catalyst. A breakthrough in undirected silylation was established by Hartwig,[7a] which takes advantage



Scheme 1 Representative organosilanes and intermolecular C–H silylation.

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of steric effects in controlling regioselectivities. In addition, C(sp^3)–H bond silylation at the benzylic position[8] of the aromatic ring or next to the heteroatom such as nitrogen[9] or sulfur[10] was also reported, which has expanded the substrate scope and applicability of silylation reaction. Despite those precedent achievements on either directed or undirected C–H silylation reactions, a certain catalytic system could usually be used to activate a specific type of substrate. Therefore, development of a more general catalytic system for C–H silylation of multiple types of substrates with high regioselectivities for each type of reaction would be in high demand, considering the versatility of this strategy.

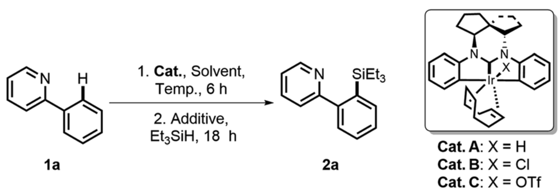
Results and discussion

In our previous work, we have developed a well-defined dianionic Ir(III) CCC pincer catalyst (SNIr),[11] which features unique double C(sp^2)–H bond activation in a polycyclic ligand framework. This unexpected chelation mode reminds us that the central Ir may potentially enable C–H activation upon cleavage of the phenyl Ir–C bond to provide a hemi-open space for substrate activation under certain conditions. Base on this hypothesis, we have developed a versatile strategy for Ir(III)-catalyzed C–H silylation of diverse heteroarylsilanes. Herein we present our research results.

We started our investigation with 2-phenylpyridine **1a** as the model substrate and Et_3SiH as the silane source to screen the catalysts **A–C**. A mixture of **1a** and **A–C** (2.5–5 mol%) was first stirred at 100 °C for 6 h. Then a hydrogen acceptor (3 equiv.) and Et_3SiH (2 equiv.) were added for further reaction. The results are summarized in Table 1. To our delight, the chloride catalyst **B** could give the highest yield of the desired silylation product **2a** (entries 2 *vs.* 1 and 3), and no reaction was observed in the absence of Ir catalysts or hydrogen acceptors (entries 4 and 5). Further investigation found that *tert*-butylethylene (*t*be) was the most effective hydrogen acceptor (entries 7 *vs.* 2 and 6). When an increased loading (5 mol%) of **B** was used in *o*-xylene solvent, the yield was improved to 85% (entries 9 *vs.* 7 and 8). Notably, when all reactants and catalysts were added to the reaction simultaneously, the system would become complicated and give a relatively low yield (entry 11).

With the optimized conditions in hand,[12] the substrate scope of γ silylations with a series of 2-phenylpyridine substrates was first explored. As shown in Table 2, high yields and regioselectivities were obtained in most cases, while the reaction efficiency could be influenced with the variation of the substitution pattern of substrates. Specifically, for substituted 2-phenylpyridine (**1a–1j**), the *o*- or *p*-methyl substitution on the benzene ring gave better product yields (83% for **2b**, 87% for **2d**) compared with the *m*-substitution (51% for **2c**). The substrates with the *p*-EDG substituted phenyl group could give much higher yields than those with *p*-EWD substitution (**2d** and **2g** *vs.* **2e** and **2f**). A significant substituent effect was also observed on

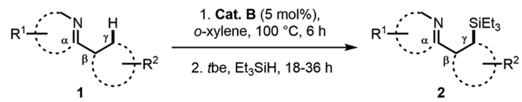
Table 1 Optimization of the reaction conditions^a

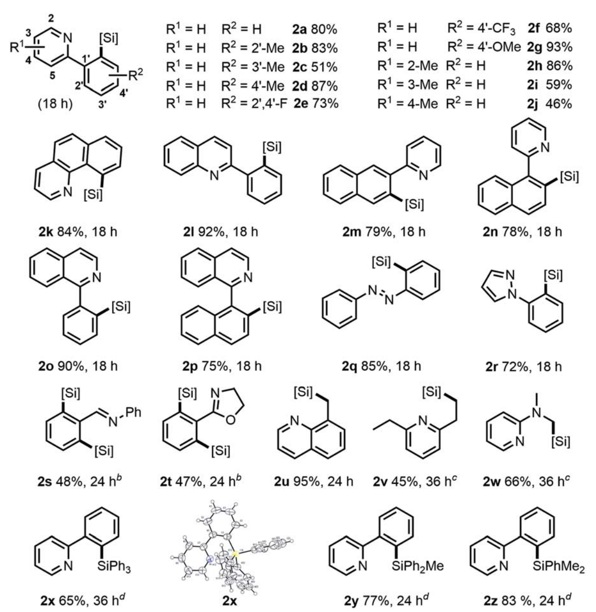


Entry	Cat. (mol%)	Additive	Solvent	Temp. (°C)	Yield^b (%)
1	**A** (2.5)	Cyclohexene	Toluene	100	22
2	**B** (2.5)	Cyclohexene	Toluene	100	46
3	**C** (2.5)	Cyclohexene	Toluene	100	<5
4	None	Cyclohexene	Toluene	150	0
5	**B** (2.5)	None	Toluene	150	0
6	**B** (2.5)	nbe	Toluene	100	26
7	**B** (2.5)	*t*be	Toluene	100	60
8	**B** (5.0)	*t*be	Toluene	100	78
9	**B** (5.0)	*t*be	*o*-Xylene	100	85 (80)^c
10	**B** (5.0)	*t*be	*o*-Xylene	80	63
11^d	**B** (5.0)	*t*be	*o*-Xylene	100	66

^{a} Unless otherwise specified, reactions were conducted by pretreatment of a solution of **1a** (0.5 mmol), cat. (2.5–5 mol%) and solvent (2 mL) at a given temperature for 6 h, and then the additive (3 equiv.) and Et_3SiH (2 equiv.) were added for further reaction. ^{b} Determined by GC-MS (internal standard: dodecane). ^{c} Isolated yield in parentheses. ^{d} No pretreatment. nbe = 2-norbornene, *t*be = *tert*-butylethylene.

Table 2 Dehydrogenative silylation of γ C–H bonds of heteroarenes^a





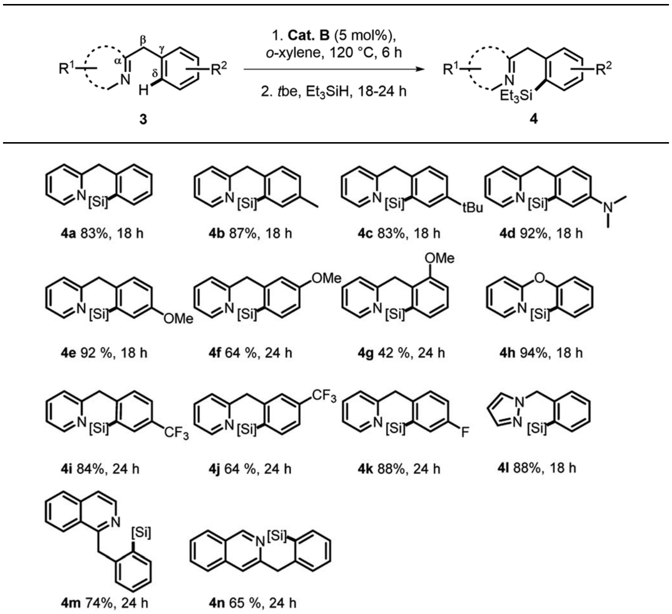
^{a} Unless otherwise specified, reactions were conducted by pretreatment of a solution of **1** (0.5 mmol) and cat. **B** (5 mol%) in *o*-xylene (2 mL) at 100 °C for 6 h, and then *t*be (3 equiv.) and Et_3SiH (2 equiv.) were added for further reaction. ^{b} Trace amount (<5%) of monosilylation product could be detected by GC-MS. ^{c} At 140 °C, starting materials recycled. ^{d} Ph_3SiH, Ph_2MeSiH, or $PhMe_2SiH$ was used instead of Et_3SiH.

different positions of the pyridine ring. For example, 2-methyl substitution afforded a higher yield than 3,4-substitutions (**2h** *vs.* **2i** and **2j**). The scope could be further extended to benzo-fused substrates (**1k–1p**), whose reactions could generally afford the desired products in good to high yields (75–92%). Notably, 2-phenylquinoline and 1-phenylisoquinoline could give excellent higher yields (92% for **2l**, 90% for **2o**). Moreover, for other *N*-heteroarenes, such as azo-, pyrazolyl-, and iminyl-arenes (**1q–1t**), they were also amenable in the reaction, affording the corresponding products with high efficiency. In particular, substrates **1s** and **1t** could mainly give disilylation products in moderate yields along with a trace amount of monosilylation product. Besides, our catalytic system was also well effective toward more inert γ C(sp^3)–H bonds linked to heteroarenes. As a representative example, 8-methylquinoline could afford the γ-silylation product **2u** in 95% yield. The reactions of 2,6-diethylpyridine (**1v**) and 2-dimethylaminopyridine (**1w**) were also feasible, giving products in moderate yields under conditions with elevated temperature. Remarkably, our catalytic system also accommodated the silylation of **1a** with other hydrosilanes, such as Ph_3SiH, Ph_2MeSiH, or $PhMe_2SiH$ with good regioselectivities (**2x–2z**). It is worth nothing that in all cases we were not able to detect other α, β or δ silylation products.

Subsequent investigation was carried out toward the δ-silylation of 2-benzylpyridine **3**,[13] and the desired products could be generated in good to high yields in most cases (Table 3). Generally, a higher reaction temperature (120 °C) was required than the corresponding γ C–H silylation, possibly due to a higher activation energy for the formation of the 6-membered cyclometalated intermediates. Similarly, both electron and steric effects of the benzyl group showed significant influence on the reaction outcome. For example, *p*-EDG substituted substrates gave higher yields than the *p*-EWG substituted ones in general sense (**4d** and **4e** *vs.* **4i** and **4k**). However, for the *o*- or *m*-substitutions, both reactions were sluggish and gave poor to moderate yields regardless of either EDG or EWG substituents (**4f**, **4g** and **4j**). Delightedly, 2-phenoxypyridine afforded the best result (94% for **4h**), probably because of the double activation of the same C–H bond (N to δ-C and O to β-C) and electro-donating effect of the ether group. Compared with γ C–H silylations of benzo-phenyl pyridines (92% for **2l**, 90% for **2o**, Table 2), a slow reaction rate and decreased product yields were observed for these δ-silylations (74% for **4m**, 65% for **4n**).

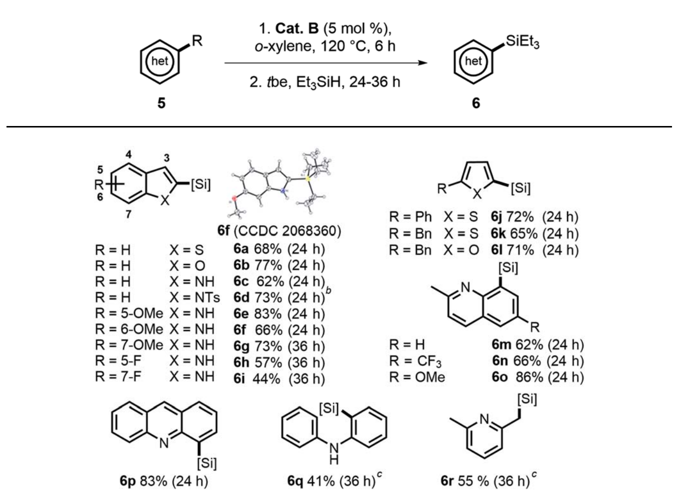
Finally, we investigated more universal and practically useful heteroarenes (Table 4), and these silylation reactions showed extremely good regioselectivities and broad substrate scope. For thiophene (**5a**, **5j** and **5k**) and furan (**5b** and **5l**) derivatives, silylations generally took place at α positions with good yields, which complemented the normal electrophilic Friedel–Crafts silylation reactions.[1e,14] Further investigation was focused on the derivatives of indole **5c–5i** as they have practical utilities in the fields of natural products and drug discovery.[15] In general, silylation always occurred at C-2 positions of indoles except for *N*-tosyl substituted indole, which directed the silylation to an unusual β-position (**6d**).[7d] The results of α-silylations of indoles indicated that EDG substitutions would give better outcomes than the EWG substitutions (**6e–6g** *vs.* **6h** and **6i**). As for the substituted 2-methyl quinolines and benzo(*b*)quinoline, β-silylation would occur to afford **6m–6p** in moderate to good yields. Moreover, this catalytic mode was also well effective toward the

Table 3 Dehydrogenative silylation of δ C–H bonds of heteroarenes[a]



[a] Unless otherwise specified, reactions were conducted by pretreatment of a solution of **3** (0.5 mmol) and cat. **B** (5 mol%) in *o*-xylene (0.5 mL) at 120 °C for 6 h, and then *t*be (1.5 equiv.) and Et_3SiH (3 equiv.) were added for further reaction.

Table 4 Regioselective dehydrogenative silylation of α, β C–H bonds of *N,O,S*-heteroarenes[a]



[a] Unless otherwise specified, reactions were conducted by pretreatment of a solution of **5** (0.5 mmol) and cat. **B** (5 mol%) in *o*-xylene (0.5 mL) at 120 °C for 6 h, and then *t*be (3 equiv.) and Et_3SiH (2 equiv.) were added for further reaction. [b] β-silylation was observed. [c] At 140 °C, starting materials recycled.

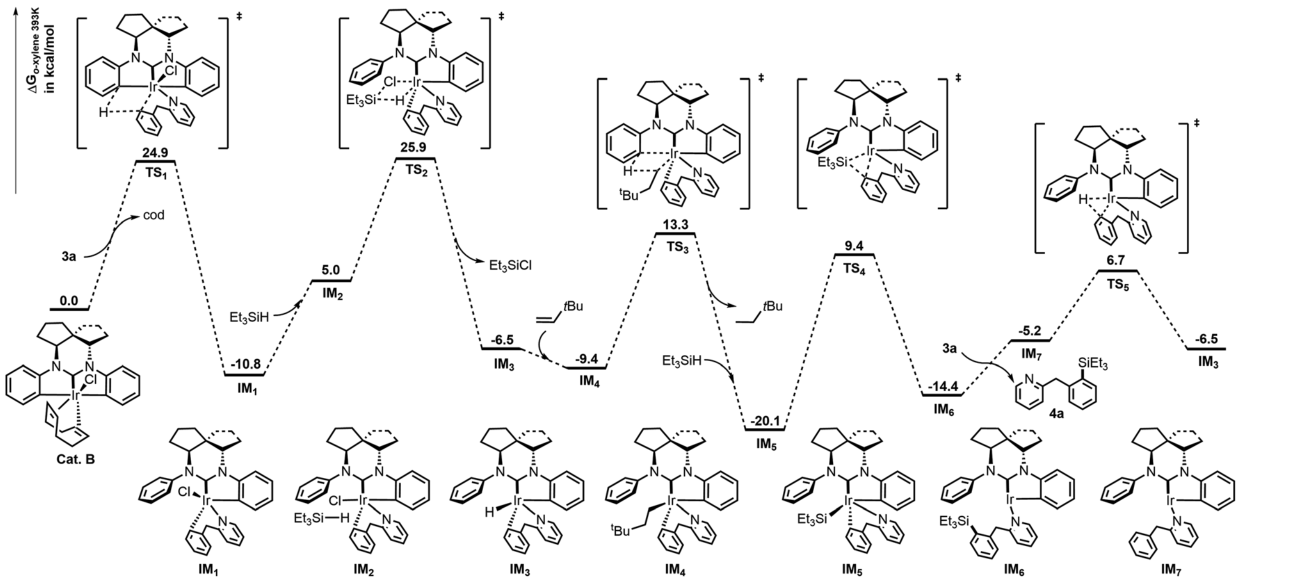


Fig. 1 Energy profiles of the Ir-catalyzed silylation of **3a** at 120 °C.

β C–H silylation of arene directed by sp^3-N (**5q**) or the more inert β C(sp^3)–H bond (**5r**).

Computational studies were next conducted to explore the mechanism using **3a** (2-BnPy) as a model (Fig. 1).[6f,16,17] Initially, the cod ligand of cat. **B** was dissociated from Ir before coordination of the N atom of 2-BnPy. Next, σ-metathesis between the phenyl C–Ir and δ C–H bonds of the 2-BnPy moiety easily took place through **TS$_1$** to form a stable 6-membered intermediate **IM$_1$**, which then reacted with Et_3SiH to give the Ir–H species **IM$_3$** with the formation of Et_3SiCl. As the catalytic cycle begins, the hydride of **IM$_3$** was captured by the hydrogen acceptor (*t*be) in the system to give Ir-alkyl species **IM$_4$**. Then the *o*-C–H activation of the side-phenyl occurred through **TS$_3$** with the release of neohexane and formation of the Ir–Si intermediate **IM$_5$** in the presence of Et_3SiH. Thereafter, Ir(I) species **IM$_6$** was generated by reductive elimination of **IM$_5$** through **TS$_4$**. Finally, exchange of the silylation products **4a** to 2-BnPy followed by oxidative addition of Ir to the δ C–H bond of intramolecular 2-BnPy regenerated the active Ir–H species **IM$_3$** and completed the catalytic cycle.

To further probe the mechanism, several control experiments were conducted (Fig. 2). First, reactions of **1b** or **3d** and catalyst **B** without Et_3SiH at 120 °C for 6 h could generate two brown complexes **1bB** and **3dB** in 88% and 92% yields, respectively. ^{1}H NMR, high resolution mass spectroscopy (HRMS) and X-ray analysis confirmed that these complexes contained either a 5- or 6-membered C–Ir–N ring formed from the substrates and catalyst, and both intermediates had a free phenyl group dissociated with Ir.[18] Furthermore, the silylation products **2b** and **4d** could be generated in 65% and 77% yields, respectively, when 5 mol% **1bB** or **3dB** was directly used as a catalyst under standard conditions. These results suggested that the iridacycle intermediates might serve as the pre-catalysts during the reaction process. Next, the H/D exchange experiment indicated that the C–H bond activation step might be irreversible (Fig. 2b). The kinetic isotope effect experiment showed a value of 3.1 from two parallel reactions and a KIE of 2.4 from intermolecular competition, which indicated that the C–H bond cleavage process was likely involved in the rate-determining step (Fig. 2c).

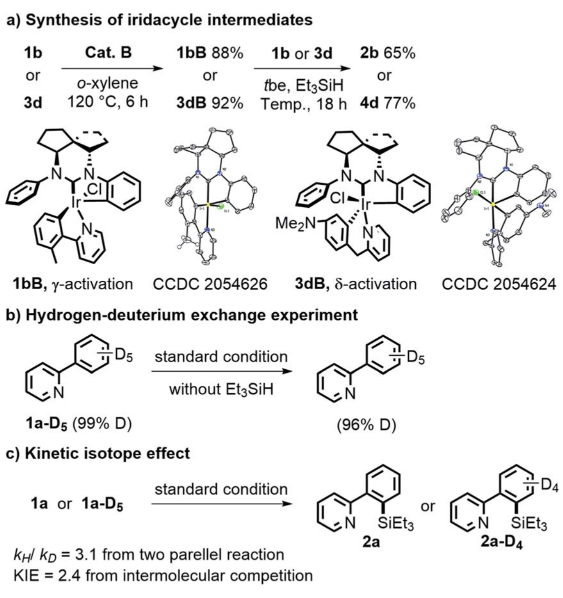


Fig. 2 Mechanistic experiments.

Conclusions

In summary, we have developed a general catalyst system based on SNIr for intermolecular C–H silylation of a wide range of substrate types with excellent regioselectivities and good to high yields. In all examples, single silylation products can be obtained in high regioselectivities. Mechanistic experiments and

DFT calculations indicated the intermediate species and an Ir(III)/Ir(I) mechanism in the catalytic cycle. This methodology we established here would probably shed some new light on dianionic pincer complexes both in academic and applied research.

Data availability

The datasets supporting this article have been uploaded as part of the ESI.†

Author contributions

Z.-B. Yan performed all of the experiments and prepared the ESI;† M. Peng prepared materials and catalysts for silylation reactions; K. Lu performed the computational studies; Y.-Q. Tu and Z.-B. Yan wrote the manuscript; all authors provided input on the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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18 For details of ^{1}H NMR, mass spectroscopy, infrared spectrum and X-ray data of complexes **1bB** and **3dB**, see ESI, Sections 6.1 and 8.†