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, serving as versatile organic reagents to mediate many novel organic reactions, functional materials, therapeutic pharmaceuticals, and bioactive chemicals (Scheme 1). Traditionally, silicon-containing molecules have been prepared through the reactions of equivalent organometallic species with electrophilic silicon reagents, 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. Among them, C(sp²)–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, 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. 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. In comparison, undirected C(sp²)–H silylation 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, which takes advantage of a well-defined diaminic iridium (III) catalyst.
of steric effects in controlling regioselectivities. In addition, C(sp^3)–H bond silylation at the benzylic position\(^a\) of the aromatic ring or next to the heteroatom such as nitrogen\(^a\) or sulfur\(^b\) 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),\(^1\) which features unique double C(sp^3)–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 semi-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 heteroaryl silanes. Herein we present our research results.

We started our investigation with 2-phenylpyridine 1a as the model substrate and Et₃SiH 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 Et₃SiH (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 (tbe) 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,\(^2\) the substrate scope of \(\gamma\) 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 phenylpyridine (1a–i), 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 \(p-\)EWG 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 (%) |
| 1 | A (2.5) | Cyclohexene | Toluene | 100 | 22 |
| 2 | B (2.5) | None | 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) | tbe | Toluene | 100 | 26 |
| 7 | B (2.5) | tbe | Toluene | 100 | 60 |
| 8 | B (5.0) | tbe | Toluene | 100 | 78 |
| 9 | B (5.0) | tbe | o-Xylene | 100 | 85 (80)\(^e\) |
| 10 | B (5.0) | tbe | o-Xylene | 80 | 63 |
| 11\(^f\) | B (5.0) | tbe | 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 Et₃SiH (2 equiv.) were added for further reaction.\(^b\) Determined by GC-MS (internal standard: dodecane).\(^c\) Isolated yield in parentheses.\(^d\) No pretreatment. tbe = 2-norbornene, tbe = tert-butylethylene.

| Table 2 Dehydrogenative silylation of \(\gamma\) C–H bonds of heteroarenes\(^d\) |
|---|---|
| 1. Cat. B (5 mol%), o-xylene, 100 °C, 8 h |
| 2. B, Et₃SiH, 18-36 h |

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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 C(sp3)-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 Ph₃SiH, Ph₂MeSiH, or PhMe₂SiH with good regioselectivities (2x-2z). It is worth noting 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, 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 C and O to 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. Further investigation was focused on the derivatives of indole 5e-5i as they have practical utilities in the fields of natural products and drug discovery. 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). 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

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Table 3  Dehydrogenative silylation of δ C-H bonds of heteroarenes

| R₁ | R₂ | 1. Cat. B (5 mol%), o-xylene, 120 ºC, 6 h | 2. b.e., Et₃SiH, 18-24 h |
|----|----|-----------------------------------|-----------------------------|
| R₁ | R₂ | 4a 83%, 18 h | 4b 87%, 18 h | 4c 83%, 18 h | 4d 92%, 18 h |
| 4e 92%, 18 h | 4f 64%, 24 h | 4g 42%, 24 h | 4h 94%, 18 h |
| 4i 84%, 24 h | 4j 64%, 24 h | 4k 88%, 18 h | 4l 88%, 18 h |
| 4m 74%, 24 h | 4n 65%, 24 h |

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Table 4  Regioselective dehydrogenative silylation of α, β C-H bonds of N,O,S-heteroarenes

| R | 1. Cat. B (5 mol %), o-xylene, 120 ºC, 6 h | 2. b.e., Et₃SiH, 24-38 h |
|----|-----------------------------------|-----------------------------|
| 5a | 5b | 5c |
| 6a 83% (24 h) | 6b 72% (24 h) | 6c 72% (24 h) |
| 6d 62% (24 h) | 6e 66% (24 h) | 6f 76% (24 h) |
| 6g 65% (24 h) | 6h 60% (24 h) | 6i 77% (24 h) |
| 6j 64% (24 h) | 6k 62% (24 h) | 6l 64% (24 h) |
| 6m 83% (24 h) | 6n 41% (24 h) |
| 6o 55% (26 h) |

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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 ºC for 6 h, and then b.e. (1.5 equiv.) and Et₃SiH (3 equiv.) were added for further reaction.

b 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 ºC for 6 h, and then b.e. (3 equiv.) and Et₃SiH (2 equiv.) were added for further reaction. β-silylation was observed. c At 140 ºC, starting materials recycled.
β C–H silylation of arene directed by sp3-N (5q) or the more inert β C(sp3)–H bond (5r).

Computational studies were next conducted to explore the mechanism using 3a (2-BnPy) as a model (Fig. 1). 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 TS1 to form a stable 6-membered intermediate IM1, which then reacted with Et3SiH to give the Ir–H species IM3 with the formation of Et3SiCl. As the catalytic cycle begins, the hydride of IM3 was captured by the hydrogen acceptor (te) in the system to give Ir-alkyl species IM4. Then the o-C–H activation of the side-phenyl occurred through TS3 with the release of neohexane and formation of the Ir–Si intermediate IM5 in the presence of Et3SiH. Thereafter, Ir(i) species IM6 was generated by reductive elimination of IM5 through TS4. 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 IM3 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 Et3SiH at 120 °C for 6 h could generate two brown complexes 1bB and 3dB in 88% and 92% yields, respectively. 1H 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. 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).

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(ni)/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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