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Iron-Catalyzed Silylation of (Hetero)aryl Chlorides with $Et_3SiBpin$

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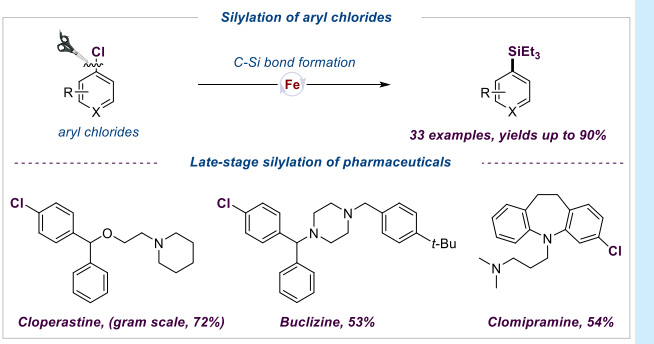
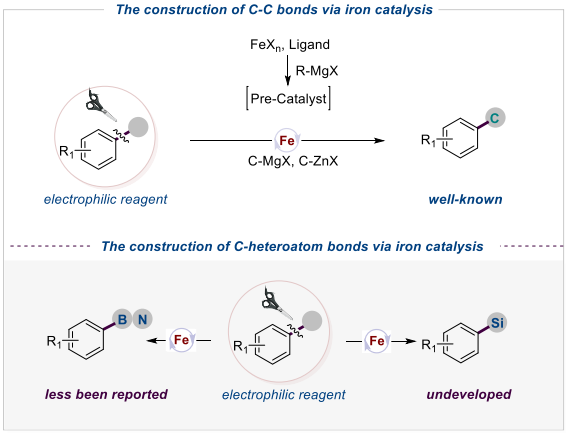
ABSTRACT: To date, the iron-catalyzed construction of C−heteroatom bonds has been less developed due to the difficulty of transmetalation with heteroatom anions and the sluggish reductive elimination. Herein we report an iron-catalyzed method for the silylation of (hetero)aromatic chlorides. It features high efficiency, a broad substrate scope, and excellent functional group compatibility. Moreover, this protocol enables the late-stage silylation of some pharmaceuticals, thus providing an excellent method to access valuable intermediates in medicinal chemistry.



The development of efficient methods for the construction of carbon−heteroatom bonds is an essential objective in organic synthesis.[1] Tremendous achievements have been made in the transition-metal-catalyzed construction of C(aryl)−heteroatom bonds in the past several decades.[2] Compared with noble metals, iron catalysis has become more and more attractive due to its nontoxicity and cheapness.[3] To date, iron catalysis has been widely employed in cross-coupling reactions for the construction of C−C bonds using organometallics as reaction partners (Scheme 1).[4] However, advances in the development of iron-catalyzed C−heteroatom bonds formation have been rather limited,[5] especially through cross-coupling reactions, which might be due to the difficulty of transmetalation with heteroatom anions as well as the sluggish reductive elimination from the iron center (Scheme 1). For instance, to facilitate the transmetalation process, reactive magnesium phenylamides were employed in the iron-catalyzed C−N bond formation cross-coupling reaction.[6] Recently, the Nakamura group disclosed an important work on the iron-catalyzed borylation of aryl chlorides,[7] but the substrate scope was restricted to the reactive aryl chlorides.

Scheme 1. Iron-Catalyzed Formation of C−Heteroatom Bonds



Organosilanes are very important synthons in organic synthesis due to their wide applications in medicinal chemistry and material science.[8] To our knowledge, the iron-catalyzed silylation of electrophilic reagents, such as aryl halides, has scarcely been reported,[9] even though great progress has been achieved in the iron-catalyzed hydrosilylation of alkenes and alkynes.[10] Aryl chlorides are cheap and commercially available and have been extensively used as coupling partners in transition-metal-catalyzed reactions.[11] However, the transition-metal-catalyzed silylation of aryl chlorides has been less documented. This is because of the relatively strong dissociation energy of the C−Cl bond, which requires the use of electron-rich ligands to facilitate the oxidative addition process (Scheme 2).[12] For instance, the Buchwald group reported the palladium-catalyzed silylation of aryl chlorides using a disilane reagent with the aid of electron-rich phosphine ligands.[12a] The reaction of hydrosilane starting materials with aryl chlorides has also been explored with noble metals, palladium, and rhodium, but this transformation has proceeded

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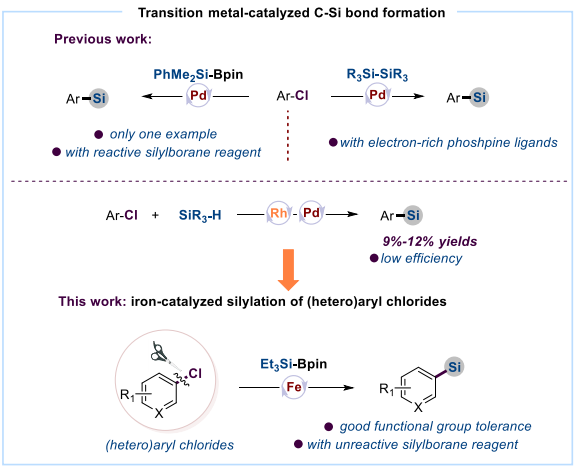
Scheme 2. Iron-Catalyzed Silylation of Aryl Chlorides

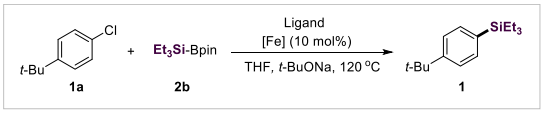


with low efficiency, even in the presence of electron-rich ligands.[13] In 2015, He and coworkers reported the palladium-catalyzed silylation of aryl halides, in which only one example of aryl chloride, 4-chloroanisole, was studied using a reactive silylborane reagent.[14] Therefore, the development of an efficient and economical method for the synthesis of aryl silane is highly appealing. With our continuing interest in transition-metal catalysis,[15] we herein report the first example of the iron-catalyzed silylation of aryl chlorides using a nitrogen ligand.

With these considerations in mind, we began our initial studies on the silylation of the relatively reactive 4-biphenyl chloride **15a** with silylborane reagent **2b**.[9a] To our delight, the corresponding silylated product **15** could be obtained in moderate to excellent yield (90% yield upon isolation) when this reaction proceeded in the presence of FeI_2 and nitrogen ligands or phosphine ligands. (For details, see the Supporting Information.) Encouraged by these results, we started to investigate the silylation of the more inert substrate, which exhibited poor efficiency in the previous report.[7] After testing various ligands, we found that the phosphine ligands and nitrogen ligands could both promote this transformation using **1a** as a substrate (Table 1, entries 1−5). The dinitrogen ligand, 3,4,7,8-*tetra*-Me-phen, stood out, providing the desired product in 65% yield (Table 1, entry 5). Additionally, other iron sources were evaluated as well, and FeI_2 gave the best result (Table 1, entries 5−7; for details, see the Supporting Information). Interestingly, when the highly pure iron catalyst was employed, a higher yield was obtained (Table 1, entry 8, 75% yield upon isolation). Control experiments revealed the necessity for a iron catalyst and ligand. No silylated product was observed in the absence of the iron catalyst, and only a 21% yield of **1** was afforded without the use of a ligand (Table 1, entries 9 and 10). To evaluate the trace-metal effect in this transformation, some transition metals were tested. Copper, palladium, and nickel sources could promote this reaction as well, but lower yields were presented (Table 1, entries 11−13). These results suggest that this reaction was catalyzed by the iron catalyst not other transition metals.

With the optimized reaction conditions established, various aryl chlorides were examined. As shown in Table 2, the monoaryl chlorides and biphenyl chlorides could both undergo this transformation smoothly, providing the corresponding products in moderate to good yield. This reaction exhibited good functional group tolerance. Functional groups, such as BnO, hydroxyl, morpholinyl, amine, Boc, CF_3, Bpin, and alkenyl, could be well-tolerated (**5**, **8**−**14**). Electron-rich substrates reacted well, affording silylated products in moderate to good yield (**4**−**7**, **11**; 5−83%). Electron-deficient aryl chloride **12a** underwent this transformation smoothly, and a moderate yield was obtained. The alkenyl group could not always be tolerated in hydrosilylation reactions, but substrate **14a** could react well and generated the desired product **14** in 76% yield. Importantly, substrate **24a** with a bulky steric hindrance could also undergo this transformation, affording the silylated product **24** in 70% yield. The heteroaromatic chlorides were also suitable for this catalytic system. The

Table 1. Representative Results for the Optimization of the Iron-Catalyzed Silylation of Aryl Chloride 1a[a]



entry	[Fe]	ligand	yield (%)[b]
1	FeI_2	XantPhos (10 mol %)	20
2	FeI_2	XPhos (10 mol %)	28
3	FeI_2	PCy_3 (20 mol %)	38
4	FeI_2	2,9-*di*-Me-phen (10 mol %)	35
5	FeI_2	3,4,7,8-*tetra*-Me-phen (10 mol %)	65
6	$FeBr_2$	3,4,7,8-*tetra*-Me-phen (10 mol %)	43
7	$Fe(OAc)_2$	3,4,7,8-*tetra*-Me-phen (10 mol %)	33
8[c]	FeI_2	3,4,7,8-*tetra*-Me-phen (10 mol %)	77 (75)
9[c]	FeI_2		21
10		3,4,7,8-*tetra*-Me-phen (10 mol %)	0
11	CuI (5 mol %)	3,4,7,8-*tetra*-Me-phen (10 mol %)	28
12	PdI_2 (0.1 mol %)	3,4,7,8-*tetra*-Me-phen (10 mol %)	24
13	$Ni(OAc)_2{\cdot}4H_2O$ (0.1 mol %)	3,4,7,8-*tetra*-Me-phen (10 mol %)	44

[a]Reaction conditions (unless otherwise specified): **1a** (0.2 mmol, 1.0 equiv), silylborane **2b** (0.7 mmol, 3.5 equiv), [Fe] (0.02 mmol, 0.1 equiv), Ligand (0.1 to 0.2 equiv), *t*-BuONa (0.5 mmol, 2.5 equiv), THF (1.5 mL), 120 °C, 12 h. [b]Determined by ^{1}H NMR using mesitylene as an internal standard. The isolated yield is shown in parentheses. [c]FeI_2(99.99%) was used.

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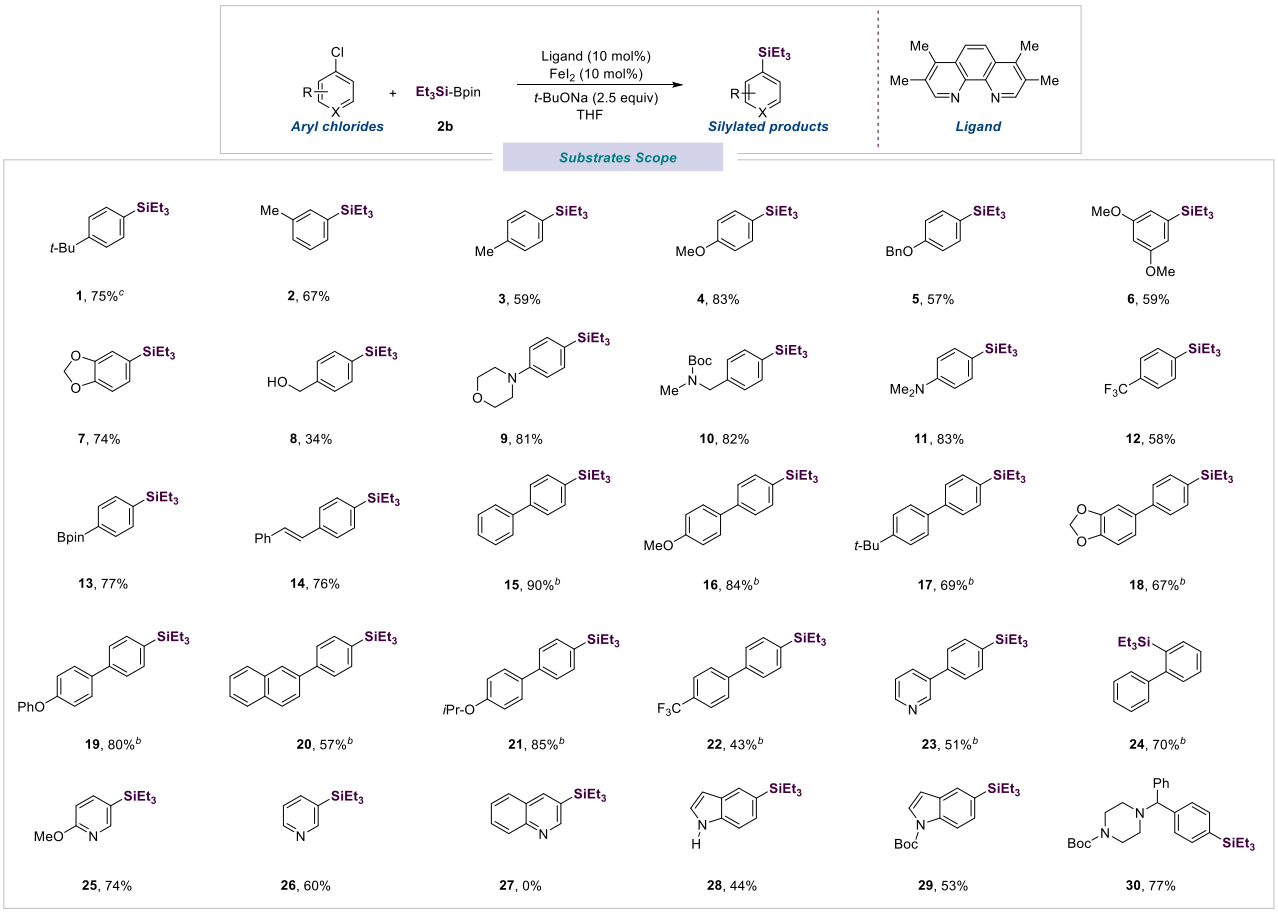
Table 2. Scope of the Iron-Catalyzed Silylation of (Hetero)aryl Chlorides[a]

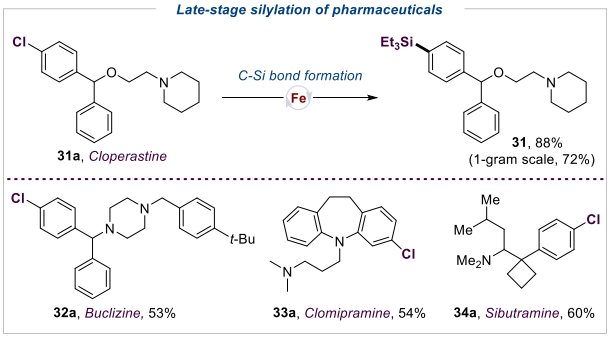


[a]Reaction conditions (unless otherwise specified): aryl chlorides (0.2 mmol, 1.0 equiv), silylborane **2b** (0.7 mmol, 3.5 equiv), FeI_2 (0.02 mmol, 0.1 equiv), 3,4,7,8-*tetra*-Me-phen (0.02 mmol, 0.1 equiv), *t*-BuONa (0.5 mmol, 2.5 equiv), THF (1.5 mL), 120 °C, 12 h. [b]Aryl chlorides (0.2 mmol, 1.0 equiv), silylborane **2b** (0.74 mmol, 3.7 equiv), FeI_2 (0.02 mmol, 0.1 equiv), 3,4,7,8-*tetra*-Me-phen (0.02 mmol, 0.1 equiv), *t*-BuONa (0.5 mmol, 2.5 equiv), THF (1.5 mL), 135 °C, 12 h. [c]FeI_2(99.99%) was used.

chloropyridines and chloroindoles could react well, furnishing the corresponding products in moderate yield (**25**, **26**, **28**, and **29**). However, to our surprise, the chloroquinolone could not undergo this transformation (**27**, 0%). It is worth mentioning that the substrates containing an unprotected hydroxyl or amine group could undergo this silylation smoothly, albeit in low yield (**8**, 34%; **28**, 44%). We found that this transformation is very sensitive to substrates, and the side reactions, such as protonation and dimerization, were always observed. The more reactive substrates, 1-bromo-4-*tert*-butylbenzene and 4-*tert*-butyliodobenzene, prefer to generate the protonated byproducts, not the silylated products. Moreover, other silylation reagents were also evaluated, such as $PhMe_2Si$-Bpin and Ph_3Si-$SiPh_3$, but no desired products were found.

The iron-catalyzed silylation reaction was further demonstrated by its applicability in the late-stage functionalization of pharmaceuticals (Scheme 3). Cloperastine, an antitussive and antihistamine, could undergo this silylation with high efficiency, affording the corresponding product **31** in 88% yield. In addition, this reaction could be conducted on a 1 g scale, and a 72% yield was provided. Buclizine **32a** is considered as an antiemetic and could also be silylated under standard conditions. Clomipramine **33a**, which is used for the treatment of obsessive-compulsive disorder and for decreasing the risk of suicide, could react well, providing the silylated

Scheme 3. Late-Stage Functionalization of Pharmaceuticals



product in 54% yield. Moreover, sibutramine **34a**, an appetite suppressant that is widely employed as an adjunct in the treatment of obesity along with diet and exercise, furnished the silylated product in 60% yield. Thus this protocol offers an excellent synthetic route for the diversification of some pharmaceuticals.

To gain insight into the mechanism of this silylation reaction, radical inhibition experiments were carried out. Drastically decreased yields of **1** were observed when a radical scavenger **TEMPO** (100 mol %) or a radical inhibitor **BHT** (100 mol %) was added as an additive under the standard

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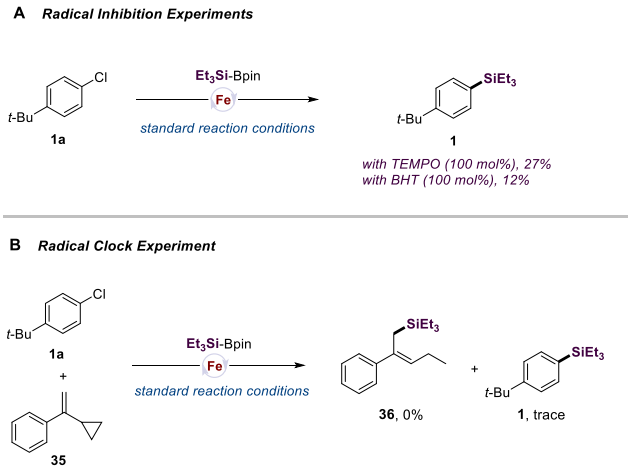
reaction conditions (Scheme 4A). Furthermore, a radical clock experiment was conducted, but no standard radical ring-opening product **36** was observed, and a trace amount of **1** was obtained (Scheme 4B). These results indicated that the silane radical might not be involved in this transformation. On the basis of these results and the radical nature of iron-catalyzed cross-coupling reactions,[7,16] we decided that the radical pathway could not be ruled out in this catalytic system.

Scheme 4. Mechanistic Studies



In conclusion, we have developed an efficient iron-catalyzed method for the silylation of (hetero)aryl chlorides. This reaction features a broad substrate scope and good functional group tolerance. Moreover, this transformation has exhibited the possibility of the late-stage functionalization of some pharmaceuticals, thus providing excellent opportunities for applications in drug discovery and development. Further mechanistic studies to explain this silylation reaction are ongoing in our lab.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00809.

Experimental data and copies of ^{1}H NMR and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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