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Mild Rh(III)-Catalyzed Direct C−H Bond Arylation of (Hetero)Arenes with Arylsilanes in Aqueous Media

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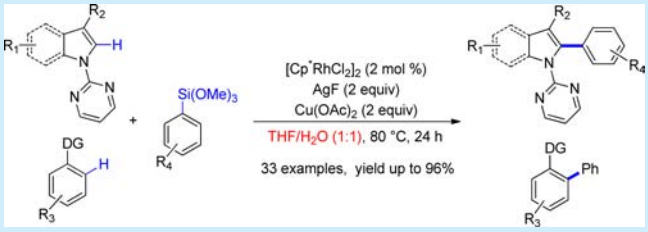
Supporting Information

ABSTRACT: An efficient rhodium(III)-catalyzed C−H bond activation and further direct arylation of (hetero)arenes with organosilanes in aqueous media was developed. This reaction shows good substrate scope and excellent functional group compatibility and gives the products in good yields with excellent regioselectivity.



Transition-metal-catalyzed C−H bond activation or functionalization has emerged rapidly as an efficient and straightforward synthetic protocol employed in the synthesis of complex natural products or functional molecules over the past decade.[1] This strategy obviates prefunctionalization of the starting materials, thus dramatically improving the overall efficiency in an atom- and step-economical manner for carbon−carbon and carbon−heteroatom bond formation. Among many transition-metal catalysts, palladium catalysts are well-known to meet this purpose.[2] Despite significant advances made in recent years, there is still a need to design a new system that has high functional group tolerance and can work for a wide variety of substrates in high selectivity using low catalyst loading. In this context, the development of a novel and efficient catalytic system for C−H bond functionalization is highly desirable. Recently, increased attention has been focused on Rh(III)-catalyzed C−H bond activation because of its high selectivity, broad substrate scope, and excellent functional group tolerance.[3] Many examples of C−H bond direct olefination using various directing groups have been reported.[4] However, direct arylation to form a biaryl structural motif via rhodium-(III)-catalyzed C−H bond functionalization has been seldom explored. Until now, only a few examples under relatively high temperature were reported.[5] Thus, there still remains a major challenge in achieving an efficient and selective direct arylation of aromatic or alkenyl C−H bond under mild conditions.

The Hiyama cross-coupling reaction is one of the most useful and reliable approaches for the formation of C−C bonds and is well utilized by organic chemists.[6,7] Compared with many other organometallic coupling-partners widely used in conventional coupling reactions, organosilicon reagents have many unique advantages, including nontoxicity, high stability, environmental benignity and ease of introduction into substrates. The pioneering work of organosilicon reagents in Pd(II)-catalyzed C−H functionalization reactions was first reported by Shi and co-workers.[8] Shortly after that, our group also developed a direct arylation of cyclic enamide with arylsilanes using $Pd(OAc)_2$ as the catalyst.[9] Zhang and co-workers also reported the regioselective C2-arylation of indoles with arylsilanes in acidic medium by palladium catalyst.[10b] However, there are still very few examples on C−H bond direct arylation using organosilanes as the coupling reagents.[10] Very recently, the Shi group reported an example of direct oxidative coupling with arylsilanes via rhodium(III)-catalyzed C−C bond cleavage.[11] Encouraged by this work and pursuing our continuous interests in Rh(III)-catalyzed C−H bond functionalization,[12] herein, we report an efficient Rh(III)-catalyzed C−H bond direct arylation of (hetero)arenes with arylsilanes under mild reaction conditions.

Indole represents one of the most important structural scaffolds in bioactive products and medicinal reagents.[13] Therefore, we chose indole as the model substrate for this reaction with trimethoxyphenylsilane **2a** in the presence of 2 mol % $[Cp^*RhCl_2]_2$ and 8 mol % $AgSbF_6$ as the catalyst, 2 equiv of AgF as the activator, 2 equiv of $Cu(OAc)_2$ as the oxidant, at 130 °C in dioxane for 48 h. Unfortunately, no desired product was observed. This result prompted us to evaluate the influence of different substituents on the indole nitrogen atom. After extensive screenings, we were pleased to find that the reaction of *N*-(2-pyrimidyl)indole **1a** with trimethoxyphenylsilane **2a** resulted in the formation of the product in 78% yield (Table 1, entry 1). No desired product was detected in the absence of $[Cp^*RhCl_2]_2$ or AgF (Table 1, entry 2 and 3). $Cu(OAc)_2$ was an efficient oxidant to promote this reaction as only 21% yield was obtained without this oxidant (Table 1, entry 4). 80 °C was found to be the optimal

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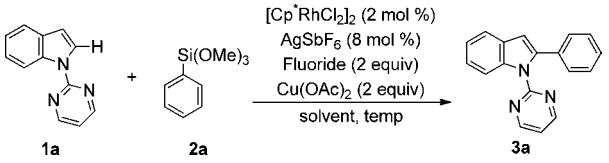
Table 1. Optimization of Reaction Conditions[a]



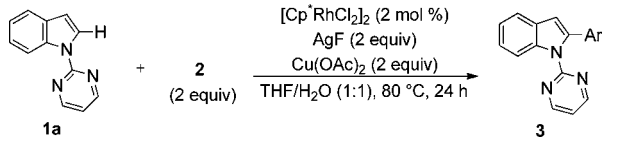
entry	fluoride	solvent	temp (°C)	time (h)	yield[b] (%)
1	AgF	dioxane	130	48	78
2[c]	AgF	dioxane	130	48	0
3		dioxane	130	48	0
4[d]	AgF	dioxane	130	48	21
5	AgF	dioxane	100	48	84
6	AgF	dioxane	80	48	88
7	AgF	dioxane	60	48	69
8	CsF	dioxane	80	48	<5
9	TBAF	dioxane	80	48	<5
10	AgF	toluene	80	48	92
11	AgF	DMF	80	48	83
12	AgF	THF	80	48	95
13	AgF	DCM	80	48	85
14	AgF	THF	80	24	95
15[e]	AgF	THF	80	24	95
16[e]	AgF	H_2O	80	24	65
17[e]	AgF	THF/H_2O[f]	80	24	92

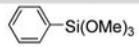
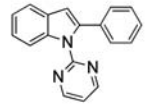
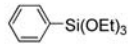
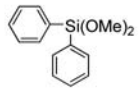
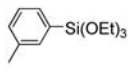
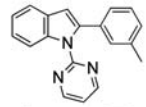
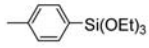
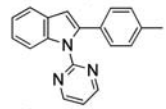
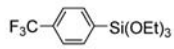
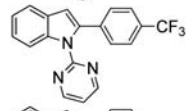
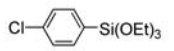
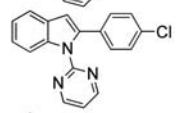
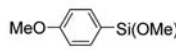
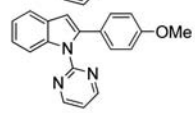
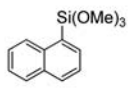
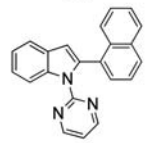
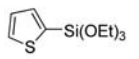
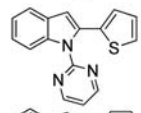
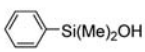
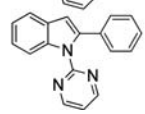
[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), $[Cp^*RhCl_2]_2$ (2 mol %), $AgSbF_6$ (8 mol %), fluoride (2.0 equiv), $Cu(OAc)_2$ (2.0 equiv), solvent (2 mL). [b]Isolated yields. [c]No $[Cp^*RhCl_2]_2$. [d]No $Cu(OAc)_2$. [e]No $AgSbF_6$. [f]THF/H_2O (1 mL/1 mL).

temperature, with the yield 88% (Table 1, entry 6). Other fluoride sources substantially inhibited this transformation (Table 1, entry 8 and 9). Different solvents were subsequently investigated, and THF was found to be the best solvent (Table 1, entry 10−13). Interestingly, this reaction could be conducted in the absence of $AgSbF_6$ in 24 h with the same yield (Table 1, entry 15). Much to our surprise, this reaction could be performed in H_2O in 65% yield (Table 1, entry 16). To the best of our knowledge, this is the first example of transition-metal-catalyzed C−H bond functionalization with organosilicon reagents in water.[14] After many trials, we were delighted to find that the desired product could be achieved in 92% yield when carried out in 1:1 mixture of THF and H_2O as the cosolvent (Table 1, entry 17). With our long-standing interests in developing efficient reactions in aqueous media,[15] we selected this mixture solvent system for this reaction.[16]

With the optimized reaction conditions in hand, we next turned our attention to examine the substrate scope of this process. Various arylsilanes **2** were surveyed under the optimized conditions (Table 2). Triethoxyphenylsilane **2b** showed similar efficiency as with trimethoxyphenylsilane **2a** giving the desired product **3aa** in excellent yield (Table 2, entries 1 and 2). Dimethoxydiphenylsilane **2c** was also applicable for this reaction but with a slight decrease in reactivity than monophenylsilanes (Table 2, entry 3). The different substituents had a negligible electronic effect on this transformation, both the phenylsilanes with electron-donating and electron-withdrawing group on the phenyl ring could furnish the desired products in high to excellent yields. It was worth noting that C−Cl on the phenylsilane could be tolerated under the reaction conditions, enabling further functionalization at the chloro substituted position (Table 2, entry 7). Thienylsilane **2j** could also be employed as the coupling partner

Table 2. Rh(III)-Catalyzed Direct Arylation of 1a with Various Arylsilanes 2[a]



entry	2		3		yield[b] (%)
1		2a		3aa	92
2		2b		3aa	92
3		2c		3aa	78
4		2d		3ad	60
5		2e		3ae	79
6		2f		3af	81
7		2g		3ag	93
8		2h		3ah	92
9		2i		3ai	80
10		2j		3aj	67
11		2k		3aa	78

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), $[Cp^*RhCl_2]_2$ (2 mol %), AgF (2.0 equiv), $Cu(OAc)_2$ (2.0 equiv) in THF/H_2O (1 mL/1 mL). [b]Isolated yields.

and gave the corresponding product in 67% yield, an attractive alternative for aryl−heteroaryl bond formation under mild conditions (Table 2, entry 10). In addition, dimethylphenylsilanol **2k** also showed good efficiency in this transformation under the same reaction conditions and gave the product **3aa** in 78% yield (Table 2, entry 11).

The scope of this transformation with respect to arene substrates was next evaluated under the optimal conditions. The results are summarized in Scheme 1. Much to our delight, a broad scope of substrates bearing various groups at 3−7-positions proved to be favorable in the reaction and gave the corresponding products in excellent yields. Notably, both electron-donating and electron-withdrawing groups, including

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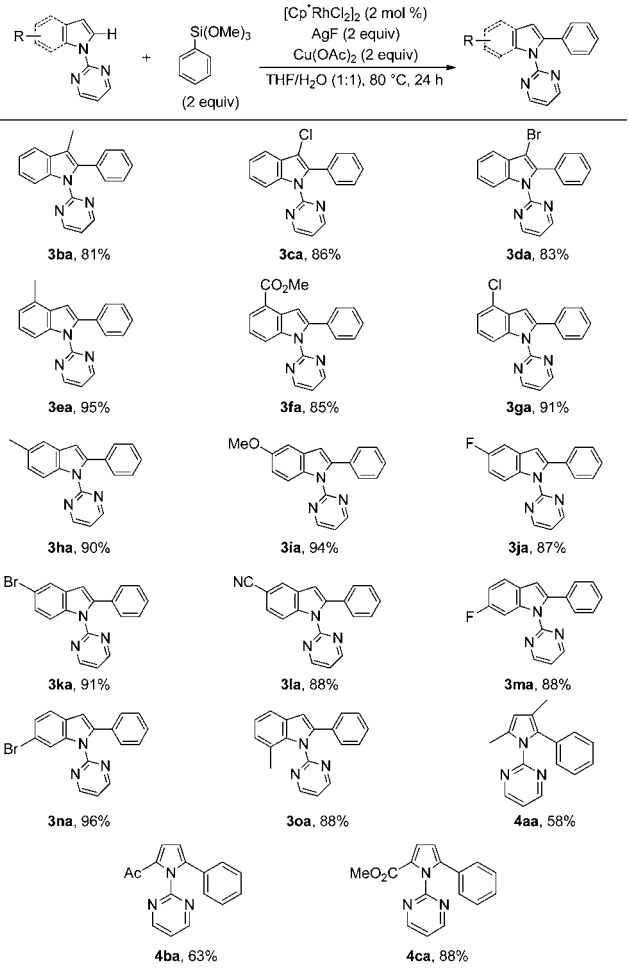
Scheme 1. Rh(III)-Catalyzed Direct Arylation of Various Indoles and Pyrroles with Trimethoxyphenylsilane 2a[a,b]



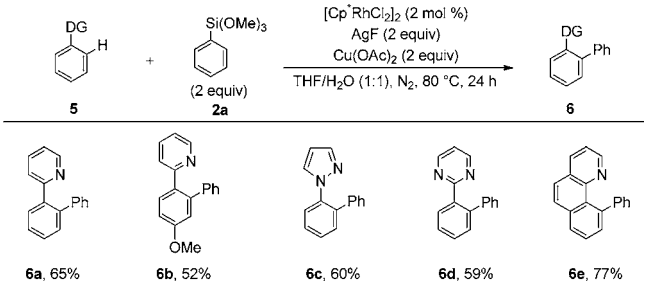
[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), $[Cp^*RhCl_2]_2$ (2 mol %), AgF (2.0 equiv), $Cu(OAc)_2$ (2.0 equiv) in THF/H_2O (1 mL/1 mL). [b]Isolated yields.

fluoro (**3ja** and **3ma**), chloro (**3ca** and **3ga**), bromo (**3da**, **3ka** and **3na**), methoxy (**3ia**), and in particular, cyano (**3la**) and ester group (**3fa** and **4ba**), were well tolerated under the conditions. Moreover, substituents at the 3- and 7-positions of indole did not cause obvious steric inhibition on this reaction. In addition, this protocol was not limited to indole substrates. The pyrrole substrates **4a**–**4c** were also found to react with **2a** smoothly and provided the products in 58, 63, and 88% yields, respectively.

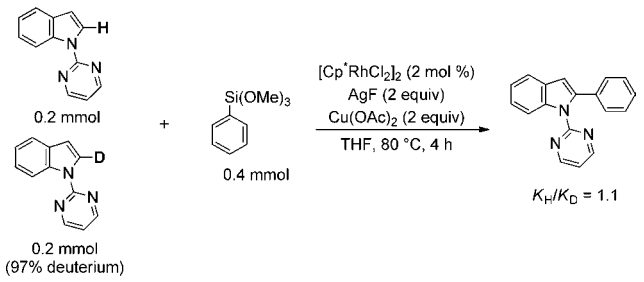
To explore the utility of this transformation, other N-containing heterocycles were also examined (Scheme 2). Benzo[*h*]quinolone, pyridinyl, pyrazolyl, and pyrimidyl groups demonstrated good reactivity, and the desired products were obtained in good to excellent yields (52–77%).[17]

Preliminary isotope experiments were conducted to obtain more insights into the mechanism of this process. Intermolecular competition experiments between *N*-(2-pyrimidyl)-indole **1a** and its deuterated analogue **1a**-*d* exhibited a kinetic isotopic effect (KIE) of 1.1 (Scheme 3), which suggested that the C–H cleavage was not the rate-determining step in the catalytic cycle. On the basis of previous reports,[8−11] we proposed the plausible mechanism to account for this reaction (Scheme 4). The process is likely to be initiated by the

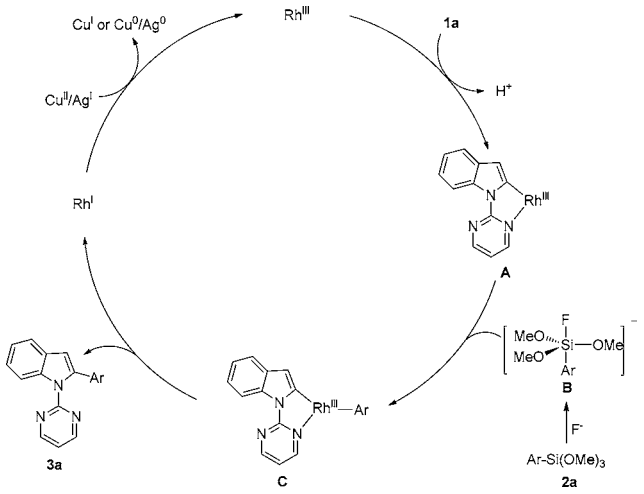
Scheme 2. Rh(III)-Catalyzed Direct Drylation of Heteroarenes 5 with Trimethoxyphenylsilane2a



Scheme 3. Kinetic Isotope Effect



Scheme 4. Proposed Catalytic Mechanism



coordination of the nitrogen atom of 2-pyrimidyl group of **1a** to the rhodium catalyst and subsequent cyclometalation process via C–H bond cleavage gives the five-membered rhodacycle **A**. Next, the intermediate reacts with the pentavalent arylsilicate **B** to afford the Rh(III) intermediate **C**, which is generated in situ with fluoride. Finally, reductive elimination provides the product **3a** and Rh(I) species, which is reoxidized to Rh(III) species by AgF or $Cu(OAc)_2$ to complete the catalytic cycle.

In conclusion, we have demonstrated a versatile rhodium-(III)-catalyzed C–H bond activation and further direct arylation of (hetero)arenes with organosilicon reagents in aqueous media. This transformation exhibits excellent reactivity and broad substrate scopes, which provides the coupling products in good to excellent yields. Various functional groups are well tolerated under the mild reaction conditions. Further investigation to extend this reaction is now ongoing in our laboratory and will be reported in due course.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, HRMS). 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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