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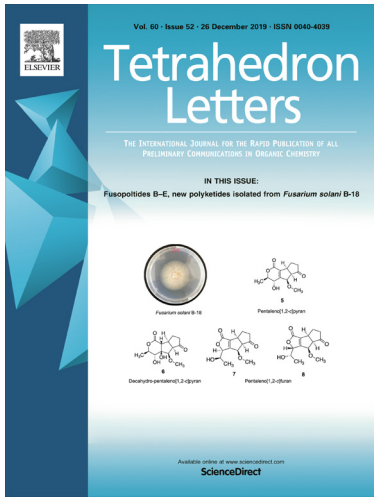

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Rhodium-Catalyzed Regioselective C(sp^2)−H Bond Activation Reactions of *N*-(Hetero)aryl-7-azaindoles and Cross-Coupling with α-Carbonyl Sulfoxonium Ylides

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ABSTRACT

We described a protocol for rhodium-catalyzed C(sp^2)−H bond activation reactions of *N*-(hetero)aryl-7-azaindoles and cross-coupling with α-carbonyl sulfoxonium ylides. In the C−H activation reaction, the 7-azaindole moiety acts as a directing group, which results in high regioselectivity. The protocol features excellent chemical yields and good functional group tolerance.

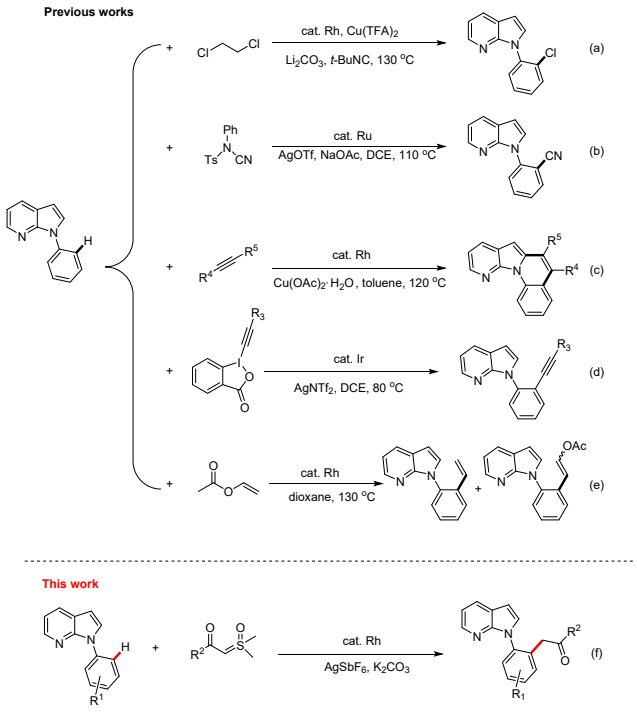
Azaindole is one of the most attractive frameworks with a wide range of biological and pharmacological activities, present in various biologically active molecules[1] and new synthetic materials.[2] Compared with indole, 7-azaindole ring system has an additional nitrogen atom, they can act both as hydrogen donors and as hydrogen acceptors, and this feature endows azaindole-containing molecules exhibiting a broad spectrum of biological activities such as antitumor, antibacterial, and anti-inflammatory activity. Many marketed drugs contain a 7-azaindole skeleton,[3] such as anticancer drug Vemurafenib, potent anti-melanoma agent PLX4720.[4]

Despite the importance of 7-azaindoles in medicinal and materials chemistry, only a few methods for metal-catalyzed functionalization of the 7-azaindole skeleton have been developed. The reported methods have been developed：palladium-catalyzed amination,[5] C2−C3 arylation,[6] C3-alkenylation,[7] and selective C6 arylation.[8] Reports of activation of the C(sp^2)−H bonds of the aryl groups of *N*-aryl-7-azaindoles with the azaindole moiety acting as a directing group are even rarer. The few examples include C−H chlorination,[9] C−H cyanation,[10] alkynylation,[11] and C−C coupling reactions with vinyl and allyl acetates,[12] with catalysis by expensive rhodium or iridium complexes (Scheme 1a–e). However, 7-azaindole-directed C(sp^2)−C bond-forming cross-coupling reactions involving sulfoxonium ylides have not been reported.

Metal-catalyzed reactions of sulfoxonium ylides have been used for the construction of C–C, C–N, and C–O bonds.[13] For example, α-carbonyl sulfoxonium ylides undergo efficient rhodium-catalyzed cross-coupling reactions with C(sp^2)–H bonds of both arenes and heteroarenes[14a-d] without the need for a sacrificial oxidizing reagent.[14e-f] Notably, the use of sulfoxonium ylides can avoid the potential hazards of the recently reported C(sp^2)–H functionalization reactions involving diazo compounds.[15]

Herein, we report the development of a protocol for rhodium-catalyzed regioselective C(sp^2)−H bond activation reactions of *N*-(hetero)aryl-7-azaindoles and cross-coupling with α-carbonyl sulfoxonium ylides, which generates the corresponding derivative ketones of *N*-(hetero)aryl-7-azaindoles in high chemical yields, has broad functional group tolerance, and does not require a sacrificial oxidizing reagent (Scheme 1f).

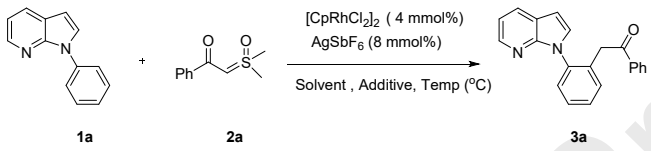
Scheme 1: 7-Azaindole-directed C(sp^2)−H bond functionalization



We began our investigation by carrying out C(sp^2)−C cross-coupling reactions between 1-phenyl-7-azaindole (**1a**) and α-

the reaction conditions (Table 1). Because $[CpRhCl_2]_2$ is known to catalyze cross-coupling of α-carbonyl sulfoxonium ylides with C–H bonds,[14f] we started with a catalyst system comprising $[CpRhCl_2]_2$ and $AgSbF_6$. However, in DCE at 100 °C, the yield of desired product **3a** was only 9% (entry 1). Exploration of various nonpolar and polar solvents (entries 2–7) revealed that HFIP (1,1,1,3,3,3-hexafluoro-2-propanol) produced the best results, giving a 23% yield of **3a** (entry 6). In attempts to increase the yield, we tested various additives (CsOAc, K_2CO_3, KOAc, and NaOAc) and found that neither NaOAc and KOAc improved the yield (entries 10 and 11). However, the addition of CsOAc increased the yield to 54% (entry 8), and when we used K_2CO_3 as an additive, **3a** was obtained in 83% yield (entry 9). Variation of the reaction temperature from 80 to 110 °C failed to produce any additional improvements (entries 12–14). Shortening the reaction time to 7 h decreased the yield of **3a** to 72% (entry 9). The reaction did not proceed at all in the absence of $[CpRhCl_2]_2$ (entry 15), and although the reaction worked without $AgSbF_6$, the yield was only 23% (entry 16). In summary, the $[CpRhCl_2]_2$ catalyst was indispensable, and $AgSbF_6$ and K_2CO_3 played supporting roles in increasing the yield. Also, HFIP, which has been shown to play a unique role in the activation of C(sp^2)–H bonds,[16] was essential for efficient protodemetallation leading to catalyst turnover and product formation.

Table 1. Optimization of reaction conditions.[a]



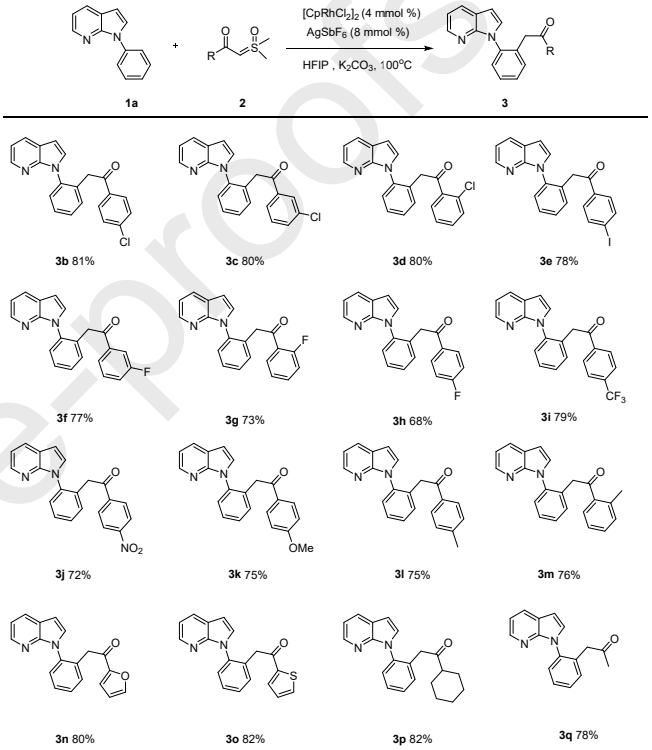
1a **2a** **3a**

Entry	Solvent	Additive	Temp (°C)	Yield[b]
1	DCE	—	100	9%
2	DCM	—	100	13%
3	1,4-dioxane	—	100	5%
4	MeOH	—	100	trace
5	*t*-AmOH	—	100	17%
6	HFIP	—	100	23%
7	CF_3CH_2OH	—	100	Trace
8	HFIP	CsOAc	100	54**%**
9	**HFIP**	**K_2CO_3**	**100**	**83% (72%[c])**
10	HFIP	KOAc	100	22%
11	HFIP	NaOAc	100	12%
12	HFIP	K_2CO_3	110	81%
13	HFIP	K_2CO_3	90	75%
14	HFIP	K_2CO_3	80	66%
15[d]	HFIP	K_2CO_3	100	NR
16[e]	HFIP	K_2CO_3	100	23%

[a] Reaction conditions, unless otherwise noted: **1a** (0.2 mmol), **2a** (0.4 mmol), $[CpRhCl_2]_2$ (4 mmol %), $AgSbF_6$ (8 mmol %), and additive (0.2 mmol) were gradually added to the solvent (2 mL) with stirring under N_2, and then the reaction mixture was heated at 100 °C for 12 h. [b] Isolated yields are provided. [c] Reaction time, 7 h. [d] $[CpRhCl_2]_2$ was omitted. [e] $AgSbF_6$ was not used.

With the optimized conditions in hand (Table 1, entry 9), we explored the substrate scope and functional group tolerance of the rhodium(III)-catalyzed C–C cross-coupling reactions between *N*-(hetero)aryl-7-azaindoles and α-carbonyl sulfoxonium ylides **2** with 1-phenyl-7-azaindole **1a** (Table 2). Aryl-group-bearing ylides with an *ortho, meta, or para* chlorine atom on the aromatic ring afforded good yields of the corresponding products (**3b**–**3d**), regardless of the position of the chlorine atom. The analogous fluorine-substituted compounds gave lower yields (**3f–3h**, 68%–77%). Both electron-deficient (–CF_3, NO_2) and electron-rich (–OMe, Me) aryl substituents were well-tolerated, giving excellent yields of the corresponding products (**3i**–**3m**). Replacement of the phenyl ring on the α-carbonyl sulfoxonium ylide with a furan, thiophene or aliphatic (cyclohexyl or methyl) ring also resulted in excellent yields of the target products (**3n**, **3o, 3p,** and **3q**, respectively).

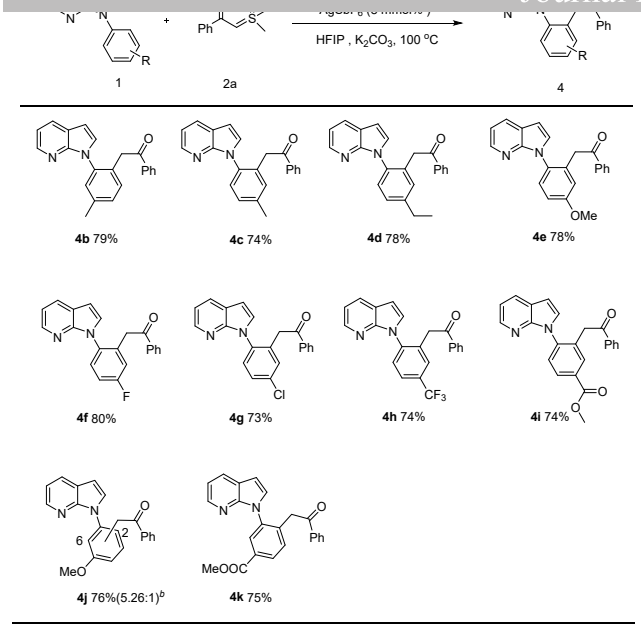
Table 2. Scope for α-Carbonyl Sulfoxonium Ylides[a]



[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), $[CpRhCl_2]_2$ (4 mmol %), $AgSbF_6$ (8 mmol %), and K_2CO_3 (0.2 mmol) were gradually added to the HFIP (2 mL) with stirring under N_2, and then the reaction mixture was heated at 100 °C for 12 h. Isolated yields are provided.

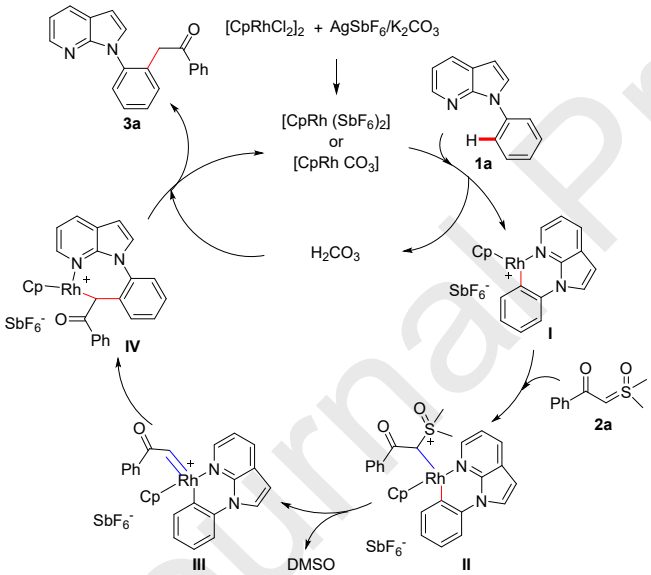
Next, we explored how various substituents on the *N*-phenyl ring of *N*-(hetero)aryl-7-azaindoles **1** affected their reactions with **2a** (Table 3). Neither the position of the substituent (*meta, para*) nor its electronic properties played a major role; good yields were obtained in all cases. Specifically, alkyl groups (**4b**–**4d**), ethers (**4e**), halides (**4f** and **4g**), a trifluoromethyl group (**4h**), and an ester group (**4i**) were all well-tolerated. To further evaluate the regioselectivity of the reaction, we changed the meta-substituents from methyl(**4b**) to other groups, such as methoxy(**4j**) and ester(**4k**). Only a few of the methoxy-substituted products(**4j**) are 6-substituted regioisomers. Ester-substituted products(**4k**) have a single configuration.

Table 3. Scope for *N*-(hetero)aryl-7-Azaindoles[a]



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $[CpRhCl_2]_2$ (4 mmol %), $AgSbF_6$ (8 mmol %), and K_2CO_3 (0.2 mmol) were gradually added to HFIP (2 mL) with stirring under N_2, and then the reaction mixture was heated at 100 °C for 12 h. Isolated yields are provided. [b] Ratio of regioisomers.

Scheme 2. Proposed reaction mechanism



On the basis of previous reports,[17] we propose the mechanism outlined in Scheme 2 for the reaction between 1-phenyl-7-azaindole (**1a**) and α-carbonyl sulfoxonium ylides **2a**. The catalytic cycle begins with generation of the active catalyst, $[CpRh(SbF_6)_2]$ or $[CpRhCO_3]$, by reaction of $[CpRhCl_2]_2$ with $AgSbF_6/K_2CO_3$. Then $[CpRh(SbF_6)_2]$ or $[CpRhCO_3]$, activates the C(sp^2)–H bond of **1a** to generate intermediate **I**, and subsequent coordination with **2a** leads to the formation of **II**. In the C–H activation reaction, the nitrogen atom of 7-azaindole moiety complexes with metal Rh, acting as a directing group. α-Elimination of DMSO produces key intermediate carbene species **III**, which undergoes migratory insertion to give **IV**. Finally, in the presence of H_2CO_3, this intermediate **IV** liberates cross-coupling product **3a** upon protodemetallation, and release of the rhodium catalyst completes the catalytic cycle.

ient rhodium-catalyzed C(sp^2)–H bond activation reactions of *N*-(hetero)aryl-7-azaindoles and cross-coupling with α-carbonyl sulfoxonium ylides. This protocol, which shows high regioselectivity and broad functional group tolerance, provides a new method for derivatizing 7-azaindoles and represents a novel application of sulfoxonium ylides. Investigation of other metal-catalyzed C(sp^2)–H activation systems is currently underway in our laboratories.

Acknowledgments

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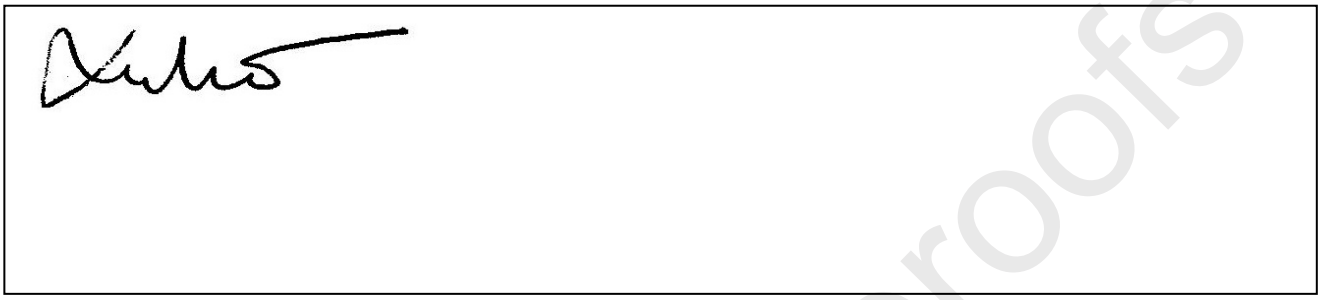

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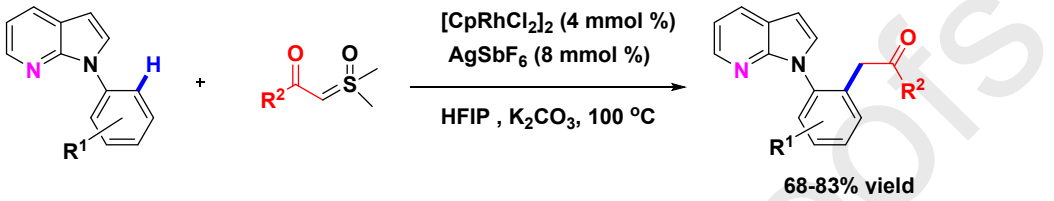

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