C–H Activation

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Rhodium(III)-Catalyzed C–C Coupling between Arenes and Aziridines by C–H Activation**

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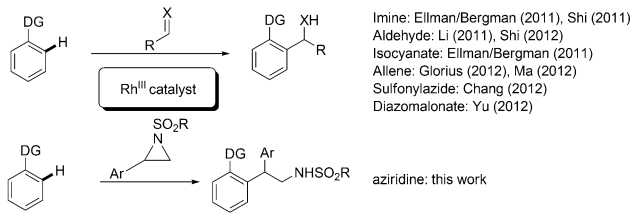
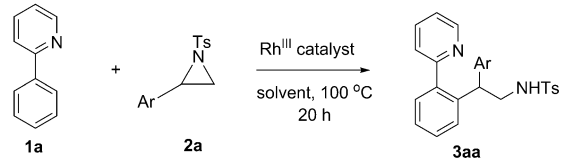
Metal-catalyzed C–H activation has been increasingly explored and has been widely recognized as an efficient and step- and atom-economic strategy for the construction of C–C bonds. Although palladium[1] and ruthenium[2] catalysts have served this purpose with tremendous success over the past years, some of these systems have limitations in substrate scope, high catalyst loading, functional group compatibility, and harsh conditions. Very recently, Rh^{III} complexes have stood out as efficient catalysts for the C–H activation of a large array of C–H bonds.[3] Along with the extensively studied rhodium(III)-catalyzed functionalization of C–H bonds with alkynes[4] and alkenes,[5] the coupling partners have been extended to other substrates, such as imines,[6] aldehydes,[7] isocyanates,[8] allenes,[9] sulfonyl azides,[10] chloroamines, and *N*-halosuccinimides,[11] and carbene precursors such as diazomalonates[12] in redox-neutral reactions (Scheme 1). These coupling partners are electrophiles that typically react with Grignard reagents to allow C–C and C–N couplings starting from arenes. In this sense, the incipient Rh^{III}–C(aryl) bond gives intrinsic reactivity that parallels Grignard reactions. Despite these successes, it is necessary to explore new categories of coupling partners to broaden the scope and applications of rhodium(III)-catalyzed C–C coupling. Aziridines[13] are readily available C-centered electrophiles and may couple with arenes under Rh^{III}-catalyzed C–H activation. Herein we present the selective coupling of aziridines with arenes under chelation assistance for the synthesis of β-branched amines.



Scheme 1. Examples of Rh^{III}-catalyzed C–H insertion into unsaturated substrates. DG = directing group.

Although the coupling between arenes and aziridines can be catalyzed by various Lewis acidic metals,[14] only electron-rich arenes are applicable, because the Friedel–Crafts mechanism is followed. Such reactions for electron-poor arenes are unprecedented. We commenced our studies with the coupling of 2-phenylpyridine (**1a**) and aziridine **2a**. Using $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (**A**) as a catalyst, the desired coupling did occur, but **3aa** was isolated in only 12% yield (Table 1, entry 1). The MeCN in this system may have an inhibitive effect. Indeed, moving to a $[\{Cp^*RhCl_2\}_2]/AgSbF_6$ (5 mol%/20 mol%) system improved the yield to 24% (entry 2). The yield of isolated **3aa** was dramatically improved to 80% when the ratio of $AgSbF_6$ to $[\{Cp^*RhCl_2\}_2]$ was increased to 6:1 (entry 3), where an excess of $AgSbF_6$ likely activates the aziridine substrate.[13f,14e,15] Screening of the counteranion of the silver salt revealed that a less-coordinating anion is more favorable (entries 3–8). Further screening using different solvents gave PhCl as the best choice (entries 9–11), where product **3aa** was isolated in 86% yield (entry 11). Lowering the rhodium catalyst loading to 3 mol% gave rise to a much lower yield (entry 13), and no such coupling occurred when it was omitted.

Table 1: Optimization of the reaction conditions.[a]



Entry	Catalyst	Loading [mol%]	Additive [mol%]	Solvent	Yield[b] [%]
1	**A**[c]	10	–	CH_2Cl_2	12
2	$[\{Cp^*RhCl_2\}_2]$	5	$AgSbF_6$/20	CH_2Cl_2	24
3	$[\{Cp^*RhCl_2\}_2]$	5	$AgSbF_6$/30	CH_2Cl_2	80
4	$[\{Cp^*RhCl_2\}_2]$	5	AgOTf/30	CH_2Cl_2	75
5	$[\{Cp^*RhCl_2\}_2]$	5	AgOAc/30	CH_2Cl_2	< 5
6	$[\{Cp^*RhCl_2\}_2]$	5	$AgPF_6$/30	CH_2Cl_2	39
7	$[\{Cp^*RhCl_2\}_2]$	5	$AgBF_4$/30	CH_2Cl_2	47
8	$[\{Cp^*RhCl_2\}_2]$	5	$AgNTf_2$/30	CH_2Cl_2	34
9	$[\{Cp^*RhCl_2\}_2]$	5	$AgSbF_6$/30	DCE[e]	76
10	$[\{Cp^*RhCl_2\}_2]$	5	$AgSbF_6$/30	$CHCl_3$	78
11	$[Cp^*RhCl_2\}_2]$	5	$AgSbF_6$/30	PhCl	86
12[d]	$[\{Cp^*RhCl_2\}_2]$	5	$AgSbF_6$/30	PhCl	77
13	$[\{Cp^*RhCl_2\}_2]$	3	$AgSbF_6$/30	PhCl	54

[a] Conditions: 2-phenylpyridine (0.2 mmol), aziridine **2a** (0.4 mmol), rhodium catalyst (3–10 mol%), solvent (3 mL), 100°C, sealed tube under N_2, 20 h. [b] Yield of isolated product. [c] **A** = $[Cp^*Rh(MeCN)_3](SbF_6)_2$. [d] The reaction was conducted at 80°C. [e] DCE = 1,2-dichloroethane.

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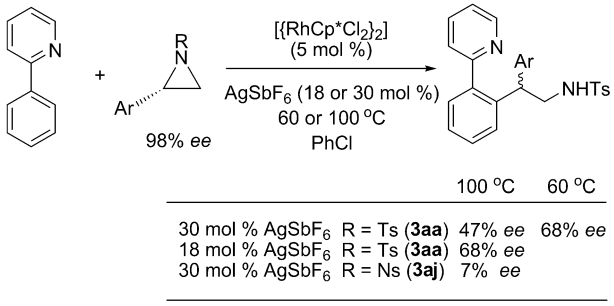
With the optimized conditions in hand, we next examined the generality and limitations of this reaction (Scheme 2). 2-Phenylpyridines bearing donating as well as withdrawing groups in the pyridine ring coupled smoothly with **2a** to give β-branched amine **3aa**–**3fa** in 60–90% yield (**3ga**–**3la**). Selective C–H functionalization was observed at the less-hindered site for susbstrate **1h** bearing a *meta* methyl group, as only product **3ha** was isolated. In contrast, C–H functionalization of 2-(3-fluorophenyl)pyridine (**1j**) occurred predominantly (78% yield) at the more hindered *ortho* position (**3ja**), which is most likely due to the ligating effect of the F atom with its reduced steric bulk.[16] This coupling seems strongly affected by the steric effects of the phenyl ring, and poor conversion was observed when an *o*-Me or *o*-Cl group was introduced to this ring. Heteroarenes are also applicable and the coupling of a thiophene or an indole with **2a** proceeded smoothly with comparable efficiency (**3ma** and **3na**). Furthermore, the directing group is not restricted to a 2-pyridyl group; *N*-pyrazyl and 2-pyrimidyl groups can also effect the C–H activation (**3oa** and **3pa**).

The scope of aziridine was next explored. Aziridines bearing various *N*-alkyl and -aryl substituted sulfonyl groups and different 2-aryl groups are viable substrates, and products **3ab**–**3aj** were isolated in good yields. However, this coupling is limited to 2-aryl substituted aziridines, as essentially no coupling occurred for 2-benzyl and 2-*i*Pr substituted moieties.

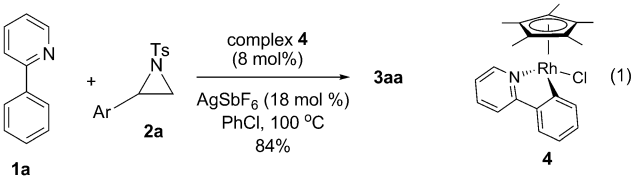
The cleavage of the N–C bond at the more hindered position and the necessity of a 2-aryl substituted aziridines may suggest the involvement of a carbocation intermediate. To explore this possibility, highly enantioenriched **2a** (98% *ee*) was used to give **3aa** with a significant loss of stereochemistry (47% *ee*; Scheme 3). Clearly, the intermediacy of a full-fledged carbocation is not relevant. The enantiopurity of **3aa** was increased to 68% *ee* when the reaction was conducted at 60 °C.[17] By switching to *N*-Ns substituted aziridine, the enantiopurity of the product dropped significantly to 7% *ee*.

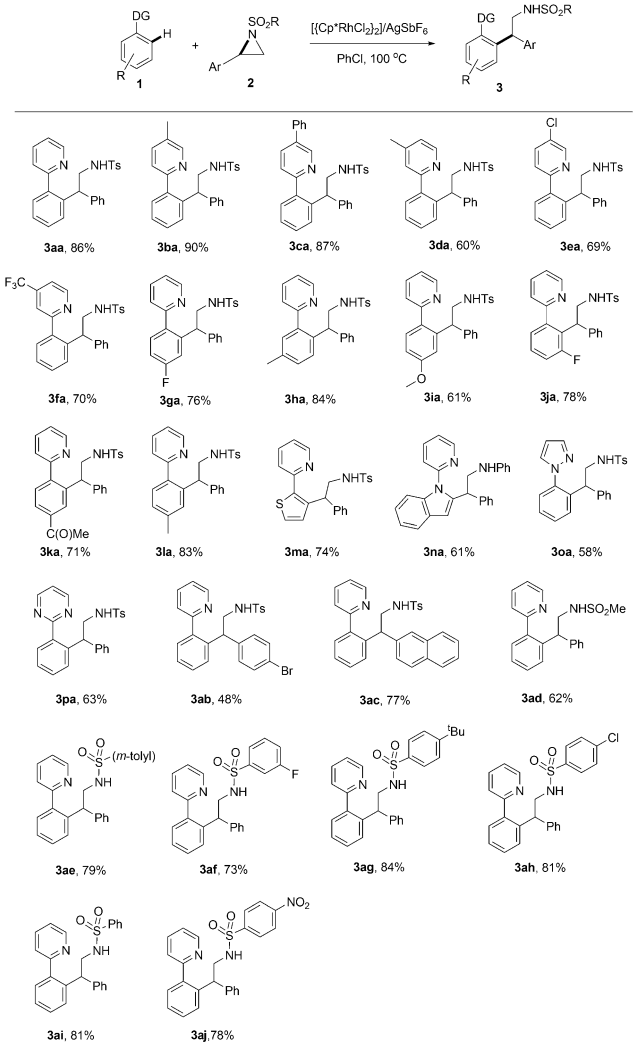


Scheme 3. Coupling of highly enantioenriched aziridines.

The effect of $AgSbF_6$ on the enantioselectivity was examined. Thus using a lower ratio of $AgSbF_6$ (18 mol%) to $[\{Cp^*RhCl_2\}_2]$ (5 mol%) for the coupling of **1a** with **2a** gave **3aa** in 68% *ee* and 30% yield at 100 °C (PhCl). Clearly, the $AgSbF_6$ enhanced the reactivity but decreased the steroselectivity. We also performed a competitive coupling between **1a** and an equimolar mixture of aziridines **2a** and **2j**. ^1H NMR analysis of the mixture product gave a ratio of **3aa** to **3aj** = 1:2.6, and a more-withdrawing *N*-sulfonyl group gives higher reactivity. This observation may suggest cleavage/elongation of the C–N bond to give a tight ion pair with buildup of positive charge at the benzylic position, and this is favored for a better *N*-sulfonyl leaving group.

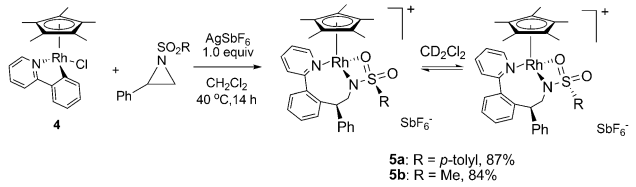
To cast light on the mechanism of this transformation, the kinetic isotope effect (KIE) has been measured. The competitive coupling of **1a** and [D_5]-**1a** with **2a** at low conversion gives $k_H/k_D = 2.1$.[18] This value indicates that real C–H





Scheme 2. C–C coupling between arenes and aziridines. Conditions: arene (0.2 mmol), aziridine (0.4 mmol), $[\{Cp^*RhCl_2\}_2]$ (5 mol%), $AgSbF_6$ (30 mol%), PhCl (2 mL), 100 °C, 20 h. Yield of isolated products are shown.

activation occurred and is likely to be rate-determining.[19] We then studied several intermediates in this reaction. Cyclometalated rhodium chloride complex **4** was prepared and was used as a catalyst precursor (8 mol%) for the coupling of **1a** and **2a** in the presence of $AgSbF_6$ [Eq. (1)]. Product **3aa** was isolated in comparably high yield (84%), suggesting the intermediacy of a cationic Cp*Rh(NC) complex. To gain further insight into the interactions between the Rh–C bond and the aziridine ring, an equimolar mixture of complex **4**, (*rac*)-**2a**, and $AgSbF_6$ was stirred at 40°C (CH_2Cl_2), from which complex **5a** was isolated as the only isomer in high yield (Scheme 4). Both ^1H and ^{13}C NMR spectroscopy pointed to



Scheme 4. Isolation of a key intermediate.

the incorporation of an aziridine unit. In particular, no signal for Rh–C(aryl) could be detected by ^{13}C NMR spectroscopy, indicating that the Rh–C bond might undergo insertion into the aziridine. Further structural information was obtained from the ^1H NMR spectrum of complex **5b**, where the sulfonyl methyl group resonates as a broad single at room temperature ($\delta = 2.62$ ppm, CD_2Cl_2). This signal sharpens when the spectrum was taken at 40°C. Clearly a dynamic exchange process occurred, which could indicate the ligation of the sulfonyl oxygen because decoordination and recoordination of the two sulfonyl oxygen atoms can afford a mixture of two diastereomers at the NMR timescale (Scheme 4).

The solid-state structure of **5a** was secured by X-ray crystallography (Figure 1).[20] Complex **5a** adopts a three-legged piano stool structure, where the rhodium center is stabilized by an N,N,O chelator. The chelation of the pyridine and the sulfonamide N atoms furnishes a rather rare eight-membered ring, which is generally thermodynamically unfavorable, but is fused with a four-membered ring for further stabilization. Cyclometalated rhodium complexes have been shown to undergo insertion into imines,[15,21] sulfonyl azides,[10a] and carbene precursors,[12] but insertion to give an eight-membered ring has not been reported.

Complex **5a** (8 mol%) is an active catalyst for the coupling of **1a** with **2a** in the presence of $AgSbF_6$ (10 mol%), and product **3aa** was isolated in 82% yield. To gain further insight into the catalytic cycle, complex **5a** was treated with **1a** (2 equiv). NMR analysis revealed that cyclometalated complex **6** was generated as a major organometallic product together with the coupled product **3aa** isolated in 64% yield [Eq. (2)].

On the basis of these stoichiometric reactions, a catalytic cycle is proposed (Scheme 5). Complex **6** is a known product when $[\{RhCp^*Cl_2\}_2]$ is treated with 2-phenylpyridine and $AgSbF_6$.[15] Substitution of the 2-phenylpyridine ligand in **6** by an aziridine generates intermediate **7**. Coordination of the

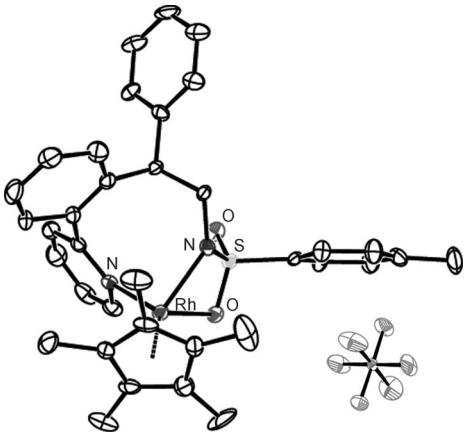
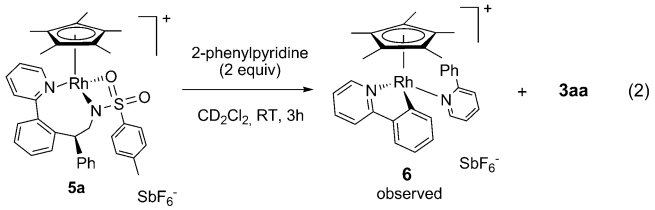
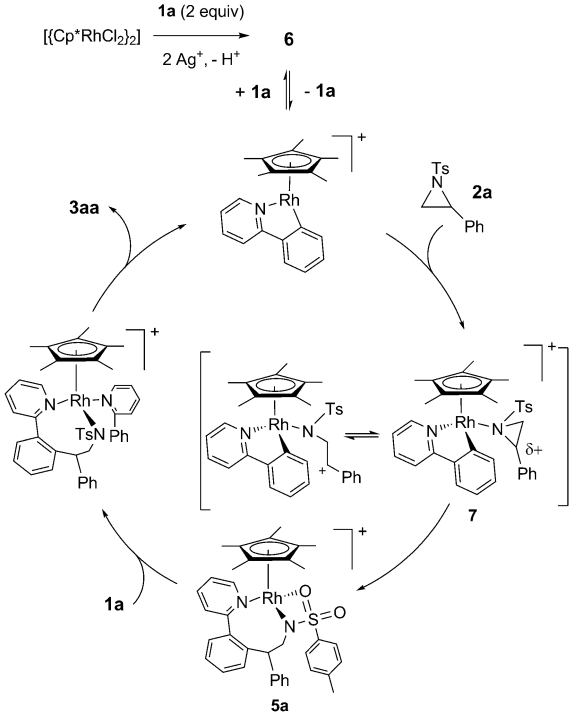


Figure 1. ORTEP diagram of complex **5a**. Ellipsoids are set at a 40% probability; hydrogen atoms are omitted for clarity.[20]



aziridine nitrogen atom to Rh^{III} or Ag^I facilitates elongation of the C–N bond and buildup of positive charge at the benzylic position. We propose that nucleophilic substitution or σ-bond metathesis of **7** leads to complex **5a.** Coordination of a 2-phenylpyridine to **5a** and subsequent C–H activation



Scheme 5. Proposed catalytic cycle.

releases the coupling product with the regeneration of the cyclometalated rhodium complex. The ready isolation of the insertion product **5a** and the KIE of 2.1 strongly argue against a Friedel–Crafts mechanism. We noted that an alternative mechanism can be possible that involves the isomerization of an aziridine to *N*-Ts enamine, followed by insertion of the Rh–C bond into this enamine to give the same product. However, this mechanism can be easily ruled out because a racemic product should be expected for an enatiopure aziridine substrate.

In summary, we have achieved a redox-neutral C–C coupling between aziridines and electron-poor arenes under chelation assistance. This process occurs by a C–H activation pathway, and a series of β-branched amines has been synthesized. The scope of this coupling reaction has been examined and a key intermediate in the catalytic cycle has been isolated. This system expands the applications of rhodium catalysis in C–C coupling reactions and may find applications in the synthesis of complex structures.

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