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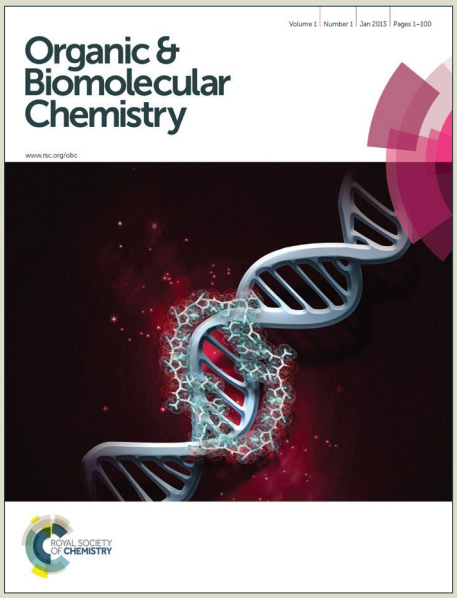

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ARTICLE TYPE

A Unique Annulation of 7-Azaindoles with Alkenyl Esters to Produce π-Conjugated 7-Azaindole Derivatives

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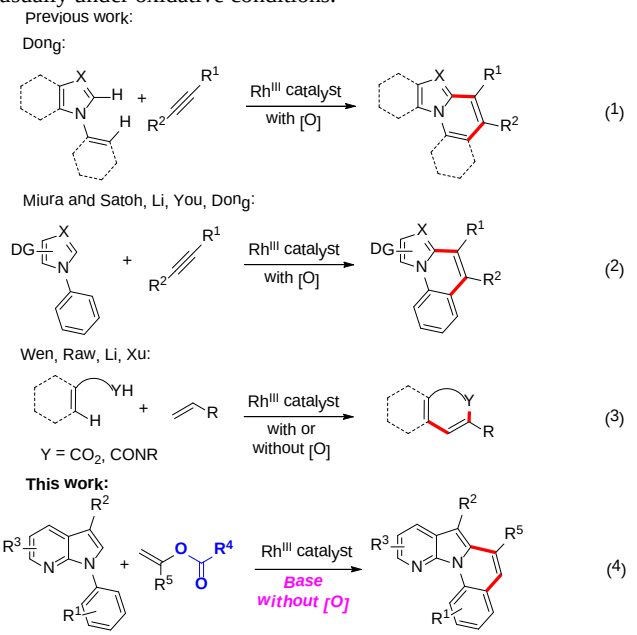
Rhodium(III)-catalyzed *N*-directed *ortho* C-H activation and subsequent *roll-over* C-H activation represents an important strategy to synthesize fused polycyclic compounds. Herein, the novel methodology broadens the scope of the coupling partner to alkenes, which working smoothly with 7-azaindoles has proven to be an efficient and atom-economic strategy to access complex π-conjugated 7-azaindole derivatives.

Fused polycyclic heteroarene compounds as important frameworks have been widely implicated in natural products, organic electronic materials and pharmaceutical molecules.[1] Therefore, the development of versatile and efficient protocols for constructing such π-conjugated molecules from simple precursors are highly desirable.[2] Recently, the rhodium-catalyzed C–H bonds activation has been increasingly explored because of high reactivity, selectivity and functional group compatibility.[3] In particular, the use of rhodium catalysis has tremendously contributed to synthesis of a range of valuable fused heteroaromatics via double C–H activation.[4-6] One of the approaches to access complex aza-fused scaffolds was reported by us via direct rhodium(III)-catalyzed double C–H activation of substituted imidazoles and alkynes (Scheme 1, eq 1).[5] The other tool is oxidative annulation between the heterocyclics and alkynes with assistance of directing groups via double C–H activation to synthesize a different neutral polycyclic system (Scheme 1, eq 2).[6]

Despite the process, the construction of such π-system compounds between alkenes and aromatic rings has been rarely studied, because most of cyclization reactions using alkenes as coupling partners are only limited to C-O and C-N bonds formation (Scheme 1, eq 3).[7] In continuation of our interest in 7-azaindoles as the directing groups,[6d,8] we envisioned that alkenes would be used as coupling partners in annulation reaction to form aza-fused scaffolds. Herein, we described a novel protocol to access complex aza-fused 7-azaindole derivatives via rhodium(III)-catalyzed double C–H activation/annulation between *N*-aryl azaindoles and less-reactive electron-rich alkenyl esters without the need of any oxidizing agent (Scheme 1, eq 4), indeed, most of rhodium(III)-catalyzed annulation reactions are usually under oxidative conditions.[9]



Scheme 1 Rhodium(III)-catalyzed annulation via C–H bonds activation

Results and Discussion

We initiated our studies in annulation of 7-azaindole **1a** and isopropenyl acetate **2a** (Table 1). To our surprise, the unique annulation product **3aa** was isolated in 55% yield when using cationic $Cp^*Rh(CH_3CN)_3(SbF_6)_2$ as the catalyst and NaOAc as a base without extra oxidant (entry 1). This finding is quite different from our previous results in which only olefinated and DHR (Dehydrogenative Heck Reaction) products were afforded

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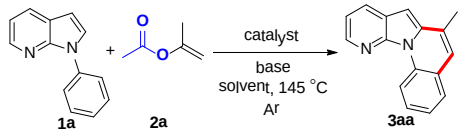
in absence of additive,[8e] which imply that additive might be crucial to this novel annulation. To our delight, $[Cp^*RhCl_2]_2$ could slightly increase the yield of **3aa** (entry 2). Furthermore, the catalyst system was efficient in various solvents such as *t*AmOH, DMF, toluene, and even water (entries 3-8). Notably, the application of an excess of inexpensive isopropenyl acetate **2a** as solvent turned out to be beneficial (entry 9). Decreasing reaction temperature lead to inferior results (entry 10). To investigate the reaction, an evaluation of different additive has been examined in the designed coupling reaction. Gratifyingly, an extensive optimization study enabled KOAc to be identified as the most compatible base, while the 2 equiv loading of KOAc was good for the conversion which indicates that the appropriate amount base might be important to the catalytic system (entries 11-15). However, decreasing the loading of $[Cp^*RhCl_2]_2$ catalyst gave rise to a lower yield (entry 16). Additionally, only 65% yield of product **3aa** was obtained when 10 equiv of **2a** was used (entry 17).

Table 1 Optimization of the reaction conditions[a]

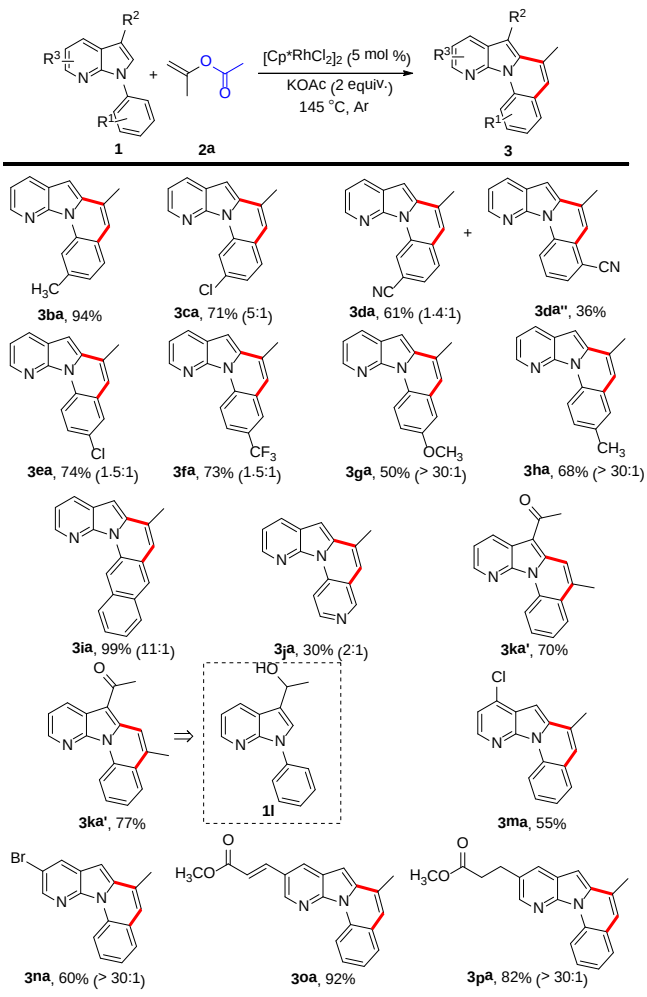


Entry	Catalyst/[equiv.]	Base	Solvent	Yield[b] [%] **3aa**
1	$Cp^*Rh(CH_3CN)_3(SbF_6)_2$/0.1	NaOAc	dioxane	55
2	$[Cp^*RhCl_2]_2$/0.05	NaOAc	dioxane	60
3	$[Cp^*RhCl_2]_2$/0.05	NaOAc	*t*AmOH	52
4	$[Cp^*RhCl_2]_2$/0.05	NaOAc	DMF	54
5	$[Cp^*RhCl_2]_2$/0.05	NaOAc	toluene	44
6	$[Cp^*RhCl_2]_2$/0.05	NaOAc	DCE	40
7	$[Cp^*RhCl_2]_2$/0.05	NaOAc	DME	66
8	$[Cp^*RhCl_2]_2$/0.05	NaOAc	H_2O	30
9[c]	$[Cp^*RhCl_2]_2$/0.05	NaOAc	--	66
10[c,d]	$[Cp^*RhCl_2]_2$/0.05	NaOAc	--	52
11[c]	$[Cp^*RhCl_2]_2$/0.05	KOAc	--	72
12[c]	$[Cp^*RhCl_2]_2$/0.05	CsOAc	--	40
13[c]	$[Cp^*RhCl_2]_2$/0.05	KOH	--	71
14[c,e]	$[Cp^*RhCl_2]_2$/0.05	KOAc	--	80
15[c,f]	$[Cp^*RhCl_2]_2$/0.05	KOAc	--	70
16[c,e]	$[Cp^*RhCl_2]_2$/0.03	KOAc	--	66
17[e,g]	$[Cp^*RhCl_2]_2$/0.05	KOAc	DME	65

[a] Reaction conditions unless otherwise specified: 0.05 mmol of **1a**, 0.2 mL of **2a**, 1 equiv. of base, 0.2 mL of solvent, 145 °C, 80 h, Ar atmosphere. [b] Isolated yield. [c] 0.4 mL of **2a**. [d] 130 °C. [e] 2 equiv. of KOAc. [f] 2.5 equiv. of KOAc. [g] 10 equiv. of **2a**, 0.3 mL of DME.

With the optimal reaction conditions in hand, we next investigated the substrate scope of the substituted 7-azaindoles in this double C–H activation protocol (Table 2). The process showed wide substrate tolerance that the substrates bearing no matter electron-donating or -withdrawing group on 7-azaindole were suitable for this annulation reaction. As we imagined, the C–H cleavage process preferred to occur at less hindered position and gave the corresponding products **3ba** and **3ca** with excellent *ortho*-/*meta*- regioselectivity, while regioselectivity of methyl position (**3ca** and **3ca'**) was not very good. The nitrile group substituted substrate **1d** exhibited high efficiency for coupling with **2a** affording the isomers in 97% total yield, but albeit with dissatisfactory regioselectivity, probably due to less steric hindrance effect of nitrile group. The *para*-substituted substrates **1e-1h** were compatible with the coupling system affording moderate to good yields of corresponding products. From the results that obtained above, we drew the conclusion that the regioselectivity of methyl position between **3** and isomer **3'** is mostly depended on the electrical property of substituents on phenyl ring. It is noteworthy that the *β*-naphthalene-substituted **1i** reacted smoothly with isopropenyl acetate giving the annulated products in excellent yield, in which the C–H bond cleavage occurred at the less sterically hindered site rather than the active α–H of naphthalene. Moreover, 7-azaindole **1j** bearing *N*-heteroaryl group could also be used in this reaction but with low efficiency. To our delight, the substrate **1k** with substituent on pyrrole ring could achieve the double C–H activation process and furnish single configuration product **3ka'** in good yields likely because of the steric effect. To our surprise, when the substrate **1l** was employed, the acetylated coupling product **3ka'** was also obtained in 77% yield, in which hydroxyl group even can be oxidized in the catalytic system.[10] Furthermore, the substituents on pyridine ring of 7-azaindole were also examined to indicate the universality of this approach. Fortunately, the substrates with

Table 2 Reaction scope of 7-azaindole derivatives[a]



[a] General reaction conditions unless otherwise specified: 0.1 mmol of **1**, 0.5 mL of **2a**, 3 mol% of $Cp^*Rh(CH_3CN)_3(SbF_6)_2$, 2 equiv. of KOAc, 1.0 mL of dioxane, 130 °C, 50-100 h, Ar atmosphere. [b] Isolated yield. Ratios of Z/E are given within parentheses and were determined by ^1H NMR analysis.

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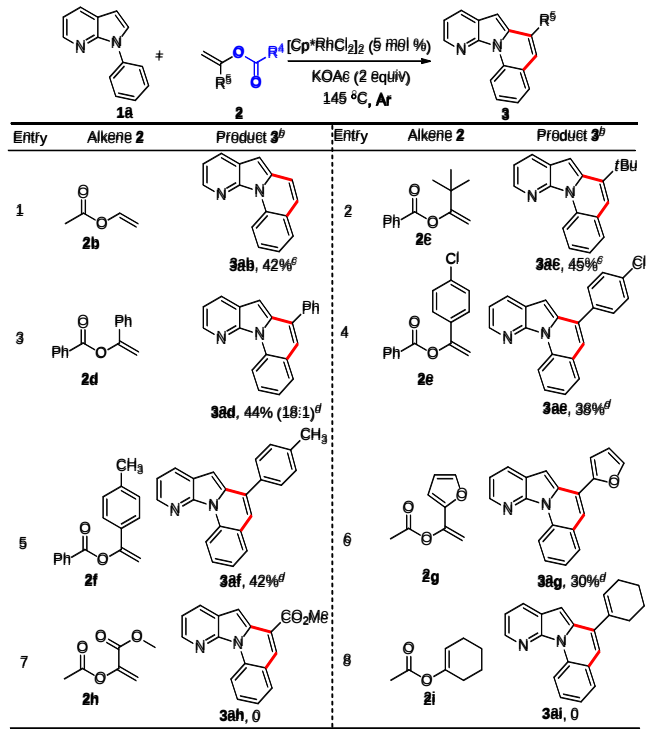
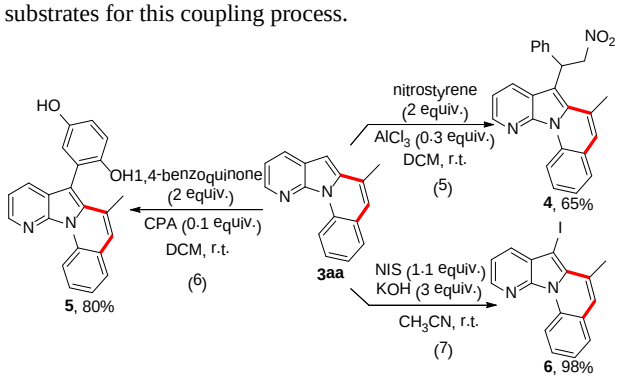
halogen, functionalized alkene group or alkyl group all were suitable for the annulation, preparing the products in moderate to excellent yields.

Table 3 Reaction scope of olefines[a]



[a] General reaction conditions unless otherwise specified: 0.1 mmol of **1a**, 0.8 mL of **2**, 5 mol% of $[Cp^*RhCl_2]_2$, 2 equiv. of KOAc, 145 °C, 50-100 h, Ar atmosphere. [b] Isolated yield. [c] 5 mol% of $Cp^*Rh(CH_3CN)_3(SbF_6)_2$. [d] 0.2 mmol of **2**, 0.8 mL of DME.

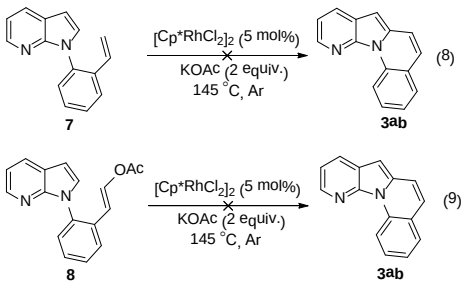
Next, various electron-rich alkenes such as vinyl acetate and substituted vinyl benzoates were tested to demonstrate the applicability of the reaction (Table 3). Luckily, most of electron-rich alkenes can be tolerated in this coupling but giving desired products only in low yields, probably due to lower reactivity than isopropenyl acetate. The cationic $Cp^*Rh(CH_3CN)_3(SbF_6)_2$ was more efficient than $[Cp^*RhCl_2]_2$ when vinyl acetate **2b** was employed in the reaction. Due to the difference of physical properties between acetates and substituted vinyl benzoates, DME was used as solvent to achieve the transformation in the presence of benzoates as substrates. It was worth mentioning that these electron-rich alkenes exhibited excellent regioselectivity of methyl position. In addtion, the allylic esters could also be used in this annulation process.[10] However, **2h** and **2i** were not suitable substrates for this coupling process.



Scheme 2 Synthetic applications of annulation products.

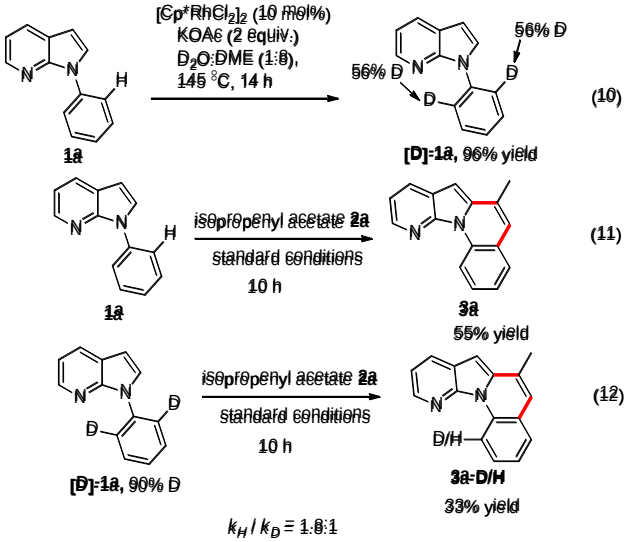
The synthetic utilities of the annulation products were illustrated in Scheme 2, in which the versatile **3aa** could be converted into various useful functionalized compounds.[8a,11] Firstly, direct alkylation of **3aa** with nitrostyrene gave corresponding product **4** in good yield (eq 5). In addition, arylation product **5** could also be achieved (eq 6). Furthermore, iodination of **3aa** generated **6** in excellent yield (eq 7).

In order to gain insight into the mechanism, parallel experiments were examined (Scheme 3). When the olefined product **7** or DHR product **8**, which were obtained from our previous report,[8e] was applied as a substrate under the standard conditions, no reaction occurred (eqs 8 and 9). These results indicate that the products **7** or **8** would not be the intermediates in this catalytic system.



Scheme 3 Parallel experiments.

We further carried out some deuterium experiments to investigate the catalytic mechanism (Scheme 4). Deuterium was observed at both *ortho*-positions when the reaction mixture was performed in the absence of **2a** using D_2O/DME as solvent (eq 10). The result indicated the possibility of the reaction pathway via *ortho* C–H bond activation. The deuterium kinetic isotopic effects were determined to be 1.8, thus indicates that the cleavage of *ortho* C–H bond might be involved in the rate-determining step (eqs 11 and 12).



Scheme 4 Deuterium-labeling experiments

A plausible mechanism was proposed based on these results (Scheme 5). First, the combination of *ortho* C–H activation of 7-

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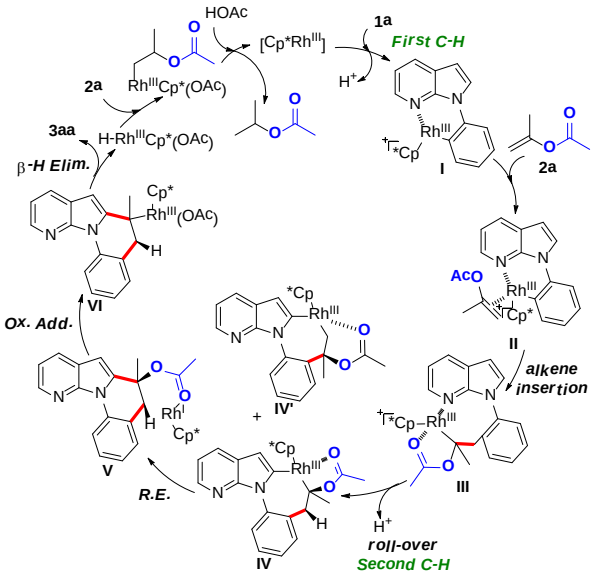
azaindole **1a** and coordination of nitrogen by rhodium forms a rhodacycle **I**. Subsequent isopropenyl acetate **2a** coordinates to rhodacycle **I** to give intermediate **II**. Regioselective insertion of alkene into the Rh-C bond generates a rhodacyclic intermediate **III**, which then undergoes nitrogen decoordination and *roll-over* C–H activation to form the key intermediate **IV** (or isomer **IV'**) followed by reductive elimination and C-O bond oxidative addition yield intermediate **VI**.[9b] Finally, the intermediate **VI** undergoes *β*-Hydride elimination process to release the final product **3aa** and a rhodium hydride species. The resulting H-Rh species reacts with isopropenyl acetate **2a** yielding alkyl rhodium species followed by protonolysis of Rh-C bond with HOAc to regenerate the [Cp*Rh(III)] species and liberate alkyl acetate (which has been detected by LCMS).[10] Base was crucial in the catalytic system not only to prevent undiresd simple alkenylation process but also to accelerate the second C–H activation process.



Scheme 5 Plausible reaction mechanism.

Conclusion

In summary, we have firstly developed the highly efficient rhodium(III)-catalyzed *N*-directed *ortho* C–H activation and subsequent *roll-over* C–H activation using electron-donating olefins as the coupling partners to form a range of π-conjugated 7-azaindole derivatives. The keys of this annulation reaction to success were the application of base. We anticipate that the approach will find broader applications in the formation of fused polycyclic heterocyclic frameworks and useful products.

Acknowledgments

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Graphical Abstract

A Unique Annulation of 7-Azaindoles with Alkenyl Esters to Produce π-Conjugated 7-Azaindole Derivatives

Shuai-Shuai Li, Chen-Fei Liu, Ying-Qi Xia, Wei-Huan Li, Guo-Tai Zhang, Xiao-Mei Zhang, and Lin Dong*