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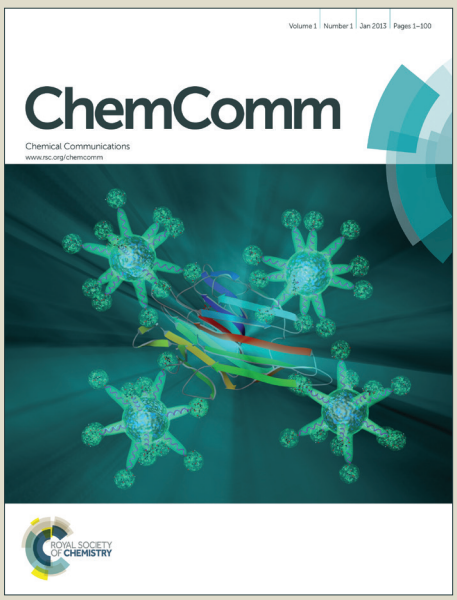

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Rh(III)-Catalyzed 7-Azaindole Synthesis *via* C–H Activation/Annulative Coupling of Aminopyridines with Alkynes

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Yechan Kim,[a,b] and Sungwoo Hong*[,b,a]

An efficient Rh(III)-catalyzed 7-azaindole synthesis was developed *via* C–H activation/annulative coupling of aminopyridines with alkynes. The reaction was highly regioselective and tolerated various functional groups, permitting the construction of various 7-azaindoles.

7-Azaindoles have been widely used as key scaffolds for a variety of drug candidates.[1] 7-Azaindole moiety possesses more favorable bioactive utility than the corresponding indoles because of their desirable physicochemical properties that are caused by additional nitrogen atom.[2] Moreover, the two nitrogen atoms on 7-azaindole scaffolds could serve as efficient hydrogen bond donating and –accepting groups to form bidentate hydrogen bonds in the binding site, which results in enhanced potency (Figure 1). Based on the favorable bioactive features of 7-azaindoles, our group has reported a variety of 7-azaindoles as potent kinase inhibitors.[3]

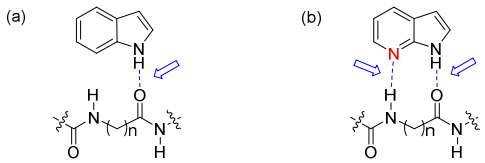
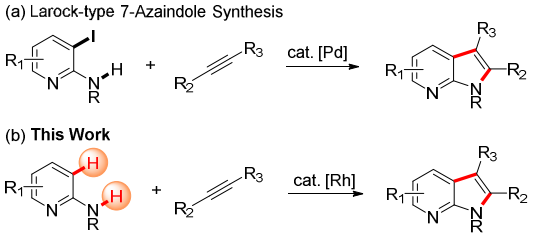


Figure 1 Bidentate H-bonding pattern of 7-azaindole in the binding site.

Accordingly, 7-azaindoles have been extensively investigated, and various synthetic strategies have been developed to construct 7-azaindole scaffolds.[4] Although classical approaches, such as Fisher[5] and Madelung-type[6] indole syntheses, have been applied to synthesize a range of substituted 7-azaindole rings, most of these routes suffer from limited substrate scope, harsh reaction conditions, or low reaction yields, caused by the unfavorable electron-deficient characteristics of the pyridine ring in the starting material. Recently, efficient approaches for synthesizing indole derivatives were achieved via annulative couplings of anilines with alkynes.[7] However, the low reactivity and high Lewis basicity of aminopyridines as starting materials pose challenges to this type of synthetic approach for the construction of 7-azaindoles.[8,9] These difficulties have prompted substrate prefunctionalization, and Larock-type synthetic methods have been developed using *ortho*-halogenated aminopyridines to access differentially substituted 7-azaindoles (Scheme 1a).[10] Although these are promising approaches for preparing aryl-substituted 7-azaindoles, the installation of activating functionality on substrates is often difficult, thus limiting further application. Based on our ongoing efforts to construct 7-azaindole-focused chemical libraries to identify potent kinase inhibitors, we were particularly interested in exploring a catalytic oxidative annulation approach to avoid substrate preactivation.[11] We envisioned that the 7-azaindole architecture could be constructed through a C–H activation/annulation process if the Lewis basicity of the aminopyridine is attenuated via coordination of a Lewis acid to the pyridyl nitrogen atom. Through these efforts, we established an efficient rhodium (III) catalytic protocol, which is broadly applicable to the readily accessible aminopyridine systems for streamlined synthesis of diverse 7-azaindole derivatives (Scheme 1b).

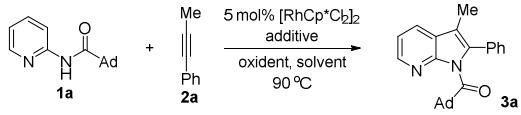
Scheme 1 Strategy for the synthesis of 7-azaindole.



The feasibility of this process was tested through an investigation of the oxidative annulation of 2-amidopyridine **1a** and an alkyne **2a** as model substrates. Our initial attempts were not successful with $[RhCp^*Cl_2]_2/AgSbF_6$ and $Cu(OAc)_2$, which are known to facilitate the indole synthesis. The difficulties of the type of annulation reaction may be associated with the high Lewis basicity of the aminopyridine. Because silver ions are commonly used to coordinate to pyridyl nitrogen atoms,[12] we screened a variety of Ag sources to lower the Lewis basicity of the aminopyridine. To our delight, the use of Ag_2O was found to initiate the reactions to some extent (entry 2, 7%). Among the various Ag reagents screened, Ag_2CO_3 displayed the best catalytic reactivity to afford the desired 7-azaindole product **3a** as a single regioisomer in 56% yield (Table 1, entry 3). Based on these results, a working hypothesis was conceived in which Ag^+ would function as both an oxidant and Lewis acid, whereas CO_3^{2-} removes protons during the reaction. Other catalytic systems, including $[RhCp^*(MeCN)_3][SbF_6]$, $[IrCp^*Cl_2]_2$, and [Ru(*p*-

cymene)$Cl_2]_2$ led to the complete loss of reactivity under the reaction conditions.[13] The additive choice was also critical for the reaction efficiency, and $AgSbF_6$ was found to be the most effective additive to sequester chloride anions (entries 4-6). Further investigations of the reaction conditions revealed that the solvent influenced the efficiency of the reaction, and the best outcome was obtained with the use of a co-solvent system (1,2-DCE/PhMe = 5:1, entry 10). Selection of the directing group had a dramatic impact on the reactivity. Other directing groups, such as acetyl and pyridyl groups, were much less effective.[13] Under the optimized reaction conditions, the C–H activation/annulation process of **1a** (1 equiv) with **2a** (1.5 equiv) in the presence of $[RhCp^*Cl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), and Ag_2CO_3 (1.5 equiv) in 1,2-DCE at 90 °C proceeded to provide the product **3a** in 74% yield. A lower yield of isolated product was obtained at higher temperature, as a result of competitive decomposition of starting substrate or its intermediate. The adamantyl group of **3a** is easily removed under mild conditions (KOH in MeOH/DCM at rt).[13]

Table 1 Optimization of C–H Alkynylation/Annulative Coupling[a]

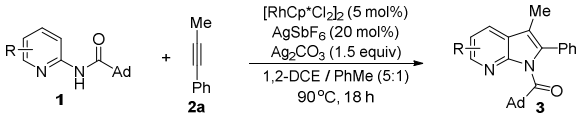


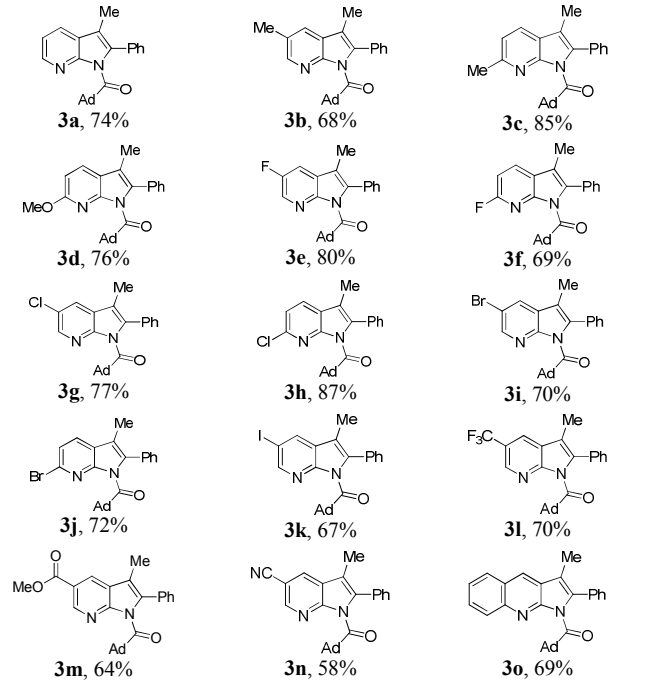
entry	additive (20 mol%)	oxidant (1.5 equiv)	solvent	yield (%)[b]
1	$AgSbF_6$	$Cu(OAc)_2$	1,2-DCE	-
2	$AgSbF_6$	Ag_2O	1,2-DCE	7
3	$AgSbF_6$	Ag_2CO_3	1,2-DCE	56
4	$AgNTf_2$	Ag_2CO_3	1,2-DCE	47
5	$AgPF_6$	Ag_2CO_3	1,2-DCE	24
6	$AgBF_4$	Ag_2CO_3	1,2-DCE	-
7[c]	-	Ag_2CO_3	1,2-DCE	39
8	$AgSbF_6$	Ag_2CO_3	1,2-DCE/MeCN (5:1)	21
9	$AgSbF_6$	Ag_2CO_3	1,2-DCE/PhMe (5:1)	74
10	$AgSbF_6$	Ag_2CO_3	1,2-DCE/*t*-AmOH (5:1)	63

[a]Reactions were conducted with substrate (0.10 mmol), 1-phenyl-1-propyne (0.15 mmol), catalyst, additive, oxidant, and solvent (1.2 mL) at 90 °C for 18 h. [b]Isolated yields. Ad = 1-adamantyl. [c]$[RhCp^*(MeCN)_3][SbF_6]$ was used as the catalyst.

With the optimized reaction conditions in hand, we set up a series of experiments to investigate the substrate scope of various amidopyridine substrates (Scheme 2). The present methodology was amenable to the presence of a variety of functional groups, such as methyl, methoxy, and halogens (F, Cl, Br, and I), and provided the desired products with moderate to good yields (**3a**-**k**). Notably, the synthetically versatile **3i**, **3j**, and **3k** were isolated in good yields with intact bromo or iodo moieties, providing an opportunity for further modification of the 7-azaindole scaffold. Substitution with an electron-donating or electron-withdrawing group on the amidopyridine core minimally affected the reactivity, and amidopyridines bearing trifluoromethyl (**3l**), ester (**3m**), or cyano (**3n**) groups readily reacted with alkyne **2a** to afford the corresponding desired products. Expanding the scope from the amidopyridine to the aminoquinoline system was also possible, leading to the formation of **3o**.

Scheme 2 Substrate scope of amidopyridines[a]

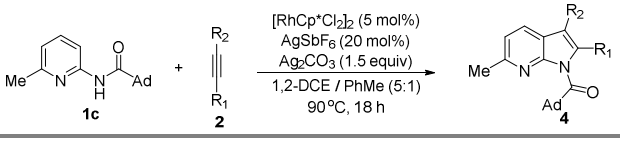


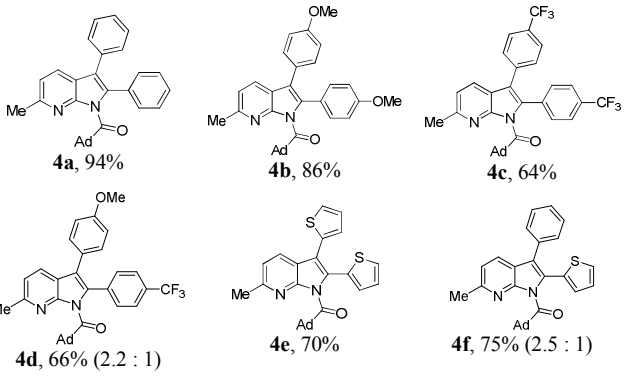


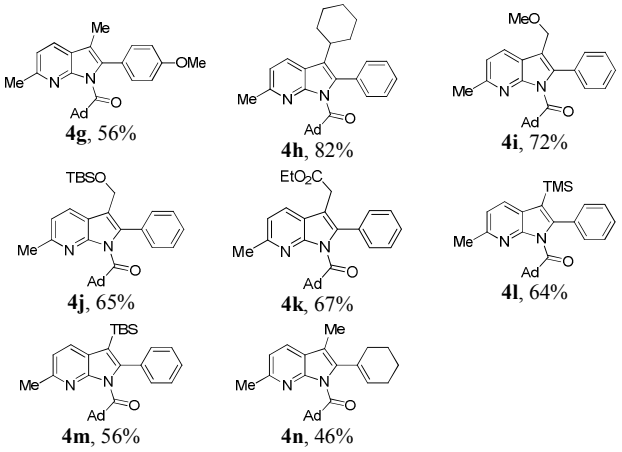
[a]Reactions were conducted with substrate (0.10 mmol), 1-phenyl-1-propyne (1.5 equiv), $[RhCp^*Cl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), and Ag_2CO_3 (1.5 equiv) in 1,2-DCE/PhMe (5:1) at 90 °C for 18 h: isolated yields.

To further test the scope of this methodology, a range of functionally diverse alkyne substrates were investigated as illustrated in Scheme 3. Gratifyingly, we observed that the oxidative annulative couplings of amidopyridine worked well with various types of alkynes. A variety of diaryl-substituted alkynes were tested and provided the desired products with moderate to good reaction yields. The coupling reaction with the cyclohexyl-substituted alkyne was also efficient to afford **4g**. Methyl- or TBS-protected propargyl alcohols were tolerated and gave the 7-azaindole products **4i** and **4j**, respectively. In addition, C3-silylated substrates were successfully synthesized with silyl-substituted phenylacetylene (**4l**, **4m**), and the C2-aryl mono-substituted azaindole can be provided via the desilylation reaction with TBAF.[13] We further investigated additional substrates and were pleased to observe that 1-cyclohexenyl-2-propyne also worked well under the optimized system, leading to the formation of the desired product **4n**.

Scheme 3 Substrate scope of internal alkynes[a]



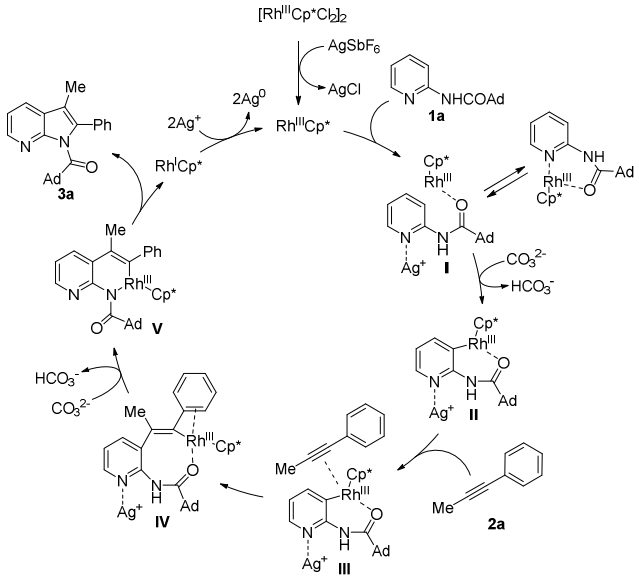




[a]Reactions were conducted with substrate (0.10 mmol), alkyne (1.5 equiv), $[RhCp^*Cl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), Ag_2CO_3 (1.5 equiv) in 1,2-DCE/PhMe (5:1) at 90 °C for 18 h: isolated yields.

A plausible mechanism for the rhodium-catalyzed 7-azaindole synthesis is shown in Scheme 4. The activated Rh(III) species is prepared by the $[RhCp^*Cl_2]_2/AgSbF_6$ catalytic system, followed by C–H bond cleavage directed by the carbonyl group to afford intermediate **I**. Silver ions may coordinate to the pyridyl nitrogen atom and thus facilitate C–H bond cleavage of aminopyridine.[11] Subsequently, coordination and migratory insertion of alkyne lead to the formation of seven-membered rhodacycle intermediate **III**. At this point, additional coordination of the aryl group to Rh might contribute to the stabilization of the intermediate, placing the aryl group proximal to the 7-azaindole nitrogen. The relatively unstable seven-membered rhodacycle intermediate **III** is rearranged to the more stable six-membered intermediate **IV**. The C–N bond of the 7-azaindole product **3a** is produced by reductive elimination and Ag^+ oxidized the Rh(I) species to Rh(III).

Scheme 4 Plausible reaction pathway



In summary, we have developed a method to efficiently construct 7-azaindole *via* Rh(III)-catalyzed C–H activation/annulative coupling of aminopyridines with alkynes. The reaction was highly regioselective and tolerated various functional groups, providing direct access to various 7-azaindoles, which are prominent structural motifs in many biologically active compounds.

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Notes and references

[a]*Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST), Daejeon, 305-701, Korea.*
[b]*Center for Catalytic Hydrocarbon Functionalizations, Institute for Basic Science (IBS), Daejeon 305-701, Korea, Fax: (+82) 42-350-2810; Tel: (+82) 42-350-2811; E-mail: hongorg@kaist.ac.kr*

†Electronic Supplementary Information (ESI) available: See DOI: 10.1039/b000000x/

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