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Rhodium-catalyzed Synthesis of 1-Arylisoquinoline Derivatives through Annulative Coupling of 3-Aryl-1,2-benzisoxazoles and Alkynes

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Rhodium-catalyzed Synthesis of 1-Arylisoquinoline Derivatives through Annulative Coupling of 3-Aryl-1,2-benzisoxazoles and Alkynes

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Direct annulative coupling of 3-aryl-1,2-benzisoxazoles and alkynes efficiently proceeds in the presence of a Cp*Rh(III) catalyst to produce 2-(1-isoquinolinyl)phenols of interest in medicinal chemistry as well as materials chemistry. The products may also be useful precursors of quinoline-based bidentate ligands.

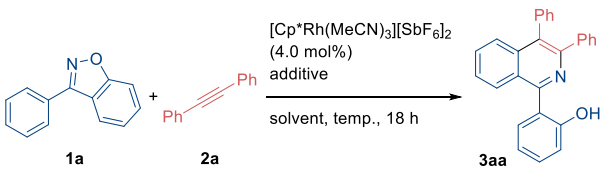
Keywords: C-H activation, Rhodium, Isoquinoline

Isoquinolines are an important class of aromatic molecules of which skeletons are found in many biologically active compounds as well as of vital use to various manufactured products.[1] Transition-metal-catalyzed aromatic C–H bond activation using imines[2] or oxime derivatives[3] as directing groups has emerged as a powerful synthetic tool for the facile construction of isoquinoline skeletons. Especially, there has been considerable attention to the latter reaction systems since the N–O bond of oxime directing groups can act as an internal oxidant, which regenerates the catalytically active high-valent species.[4] Similar phenomena have merged in the Rh-catalyzed reactions using hydrazone or azide directing groups, where the N–N bond behaves as the oxidant.[5]

Recently, we[6] and Zhu *et al.*[7] independently reported the Rh- and Co-catalyzed 1-aminoisoquinoline syntheses,[8] respectively, using 1,2,4-oxadiazoles bearing a labile N–O linkage within the ring system. As part of our successive work, we herein report a Rh-catalyzed annulative coupling of 3-aryl-1,2-benzisoxazoles and alkynes to give 2-(1-isoquinolinyl)phenols. This type of compounds has been an important structural motif for ion channel and receptor modulators[9] as well as components of organic electroluminescent devises.[10] Additionally, they have been employed as precursors in synthesizing various isoquinoline-based ligands including axially chiral scaffolds[11] as exemplified in recent Pd-catalyzed asymmetric transformations such as arylation,[12] phosphination,[13] and amination.[14]

At the outset, optimization study was carried out for the reaction of 3-phenyl-1,2-benzisoxazole (**1a**) with diphenylacetylene (**2a**) in the presence of a Rh catalyst (Table 1). The desired coupling product **3aa** was first obtained in 20% yield using 4 mol% of $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (Cp^* = pentamethylcyclopentadienyl) in 1,4-dioxane at 110 °C (entry 1). The product structure was confirmed by X-ray crystallography.[15] Solvent screening was then conducted and a significant increase of the yield was observed when the reaction was performed in PhCl (entry 6). A further investigation revealed that $PhCF_3$ was more sufficient affording an almost quantitative conversion even at a lower reaction temperature of 80 °C (entry 8). Addition of any bases considerably retarded the reaction (entries 9 and 10). Negligible yield was obtained when $[Cp^*RhCl_2]_2$ was used as the catalyst (entry 11).

Table 1. Optimization study [a]



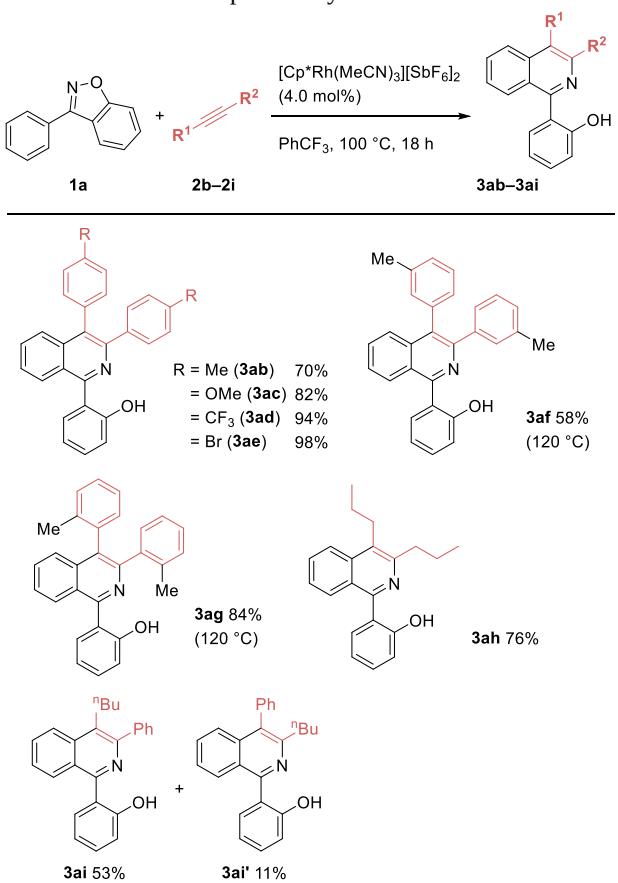
Entry	Additive	Solvent	Temp.	Yield [b]
1	--	1,4-dioxane	110 °C	20%
2	--	toluene	110 °C	trace
3	--	DMF	110 °C	trace
4	--	*t*-AmOH	110 °C	5%
5	--	DCE[c]	110 °C	33%
6	--	PhCl	110 °C	>98%
7	--	PhCl	80 °C	79%
8	--	$PhCF_3$	80 °C	>98% (92%[d])
9	NaOAc (30 mol%)	$PhCF_3$	80 °C	50%
10	CsOAc (30 mol%)	$PhCF_3$	80 °C	63%
11[e]	--	$PhCF_3$	100 °C	n.d.[f]

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.11 mmol), catalyst (4.0 mol%), and $PhCF_3$ (0.5 mL). [b] Determined by GC analysis. [c] DCE = 1,2-dichloroethane [d] Isolated yield (1.0 mmol scale). [e] $[Cp^*RhCl_2]_2$ (4.0 mol%) was used instead of $[Cp^*Rh(MeCN)_3][SbF_6]_2$. [f] Not detected.

We then examined the reaction of **1a** with various alkynes under the optimal conditions (Table 2). 4,4'-Disubstituted diphenylacetylenes bearing electron-donating and -withdrawing groups **2b**-**2d** were compatible to the present protocol, giving the corresponding isoquinolines **3ab**-**3ad** in high yields. The bromo function of **2e** remained intact during the reaction to afford **3ae** in an almost quantitative yield. The *ortho*- and *meta*-substituents on **2f** and **2g** somewhat encumbered the reaction, and a higher reaction temperature was required to reach the adequate yield of **3af** and **3ag**. An aliphatic alkyne **2h** could be adopted successfully to give **3ah**. An unsymmetrically substituted alkyne **2i** furnished a mixture of regioisomers, while the phenyl group was preferentially installed to the nitrogen side to give **3ai** as the major product.[15] Terminal

alkynes were not suitable for the present reaction (not shown).

Table 2. Substrate scope for alkynes [a]



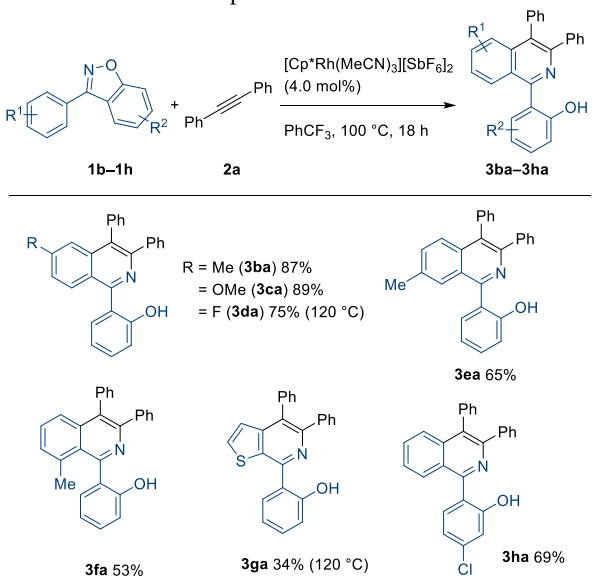
[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.22 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (4.0 mol%), PivOH (20 mol%), and $PhCF_3$ (2.0 mL). Isolated yields are shown.

We also evaluated the substrate scope for isoxazoles (Table 3). 3-(4-Substituted phenyl)-1,2-benzisoxazoles **1b-1d** reacted with **2a** smoothly to afford the corresponding annulated products **3ba-3da** in high yields. For a *meta*-substituted isoxazole **1e**, the cyclization proceeded predominantly at the uncongested position to give **3ea** as the single product. This protocol was suitable for the synthesis of a 1,8-substituted isoquinoline such as **3fa** which would be a useful scaffold for some axially chiral pyridine compounds. Thieno-fused pyridine **3ga** was also accessible, albeit the yield was moderate. Quinolinylphenol **3ha** bearing a chloro function at the phenol ring was obtained in a good yield.

A proposed mechanism for the present catalytic system is illustrated in Scheme 1. The reaction is initiated by the isoxazole-directed *ortho* C–H bond cleavage where another isoxazole **1** may participate as an external base (product **3** can replace from the second cycle), giving the corresponding five-membered intermediate. After insertion of alkyne **2** into the Rh–C bond, C–N bond formation and N–O bond cleavage take place in a stepwise[4g] or concerted[16] manner. The resulted Rh(III) phenoxide complex may be protonated to regenerate the catalytically active $Cp^*Rh(SbF_6)_2$ and liberate an annulated product **3**. Alternatively, the alkoxide complex may directly mediate the C–H bond activation of **1** to close the catalytic cycle.

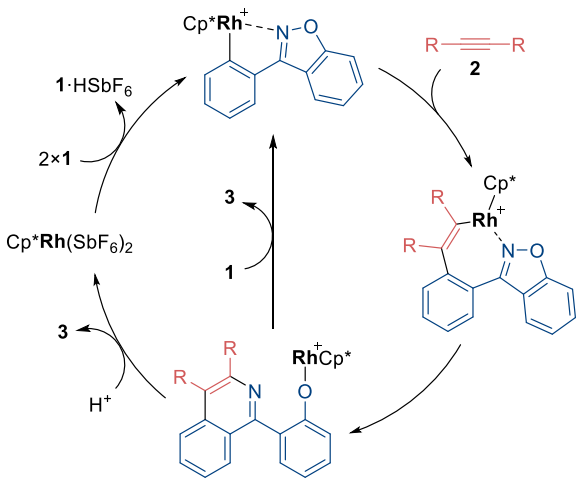
The annulated product **3fa**, whose protrusive methyl substituent would prevent the free rotation along the isoquinoline-phenol bond,[17] was further transformed into a P–N bidentate compound **6** as a representative derivatization (Scheme 2). Phosphine oxide **5** was prepared in two steps from **3fa** though triflation and Ni-catalyzed phosphination, and subsequent deoxygenation by trichlorosilane gave the desired phosphine **6**.

Table 3. Substrate scope for oxadiazoles [a]



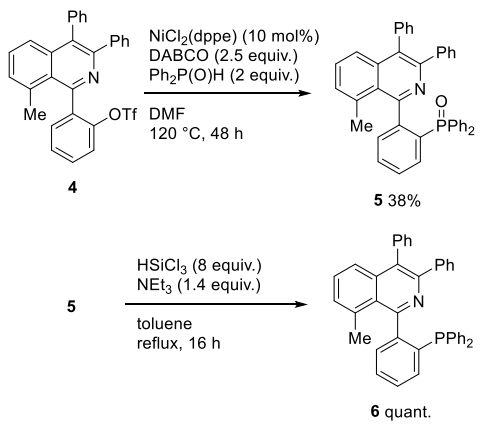
[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.22 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (4.0 mol%), PivOH (20 mol%), and $PhCF_3$ (2.0 mL). Isolated yields are shown.

Scheme 1. Proposed reaction mechanism for the coupling reaction of oxadiazole **1** with alkyne **2**



In summary, the annulative coupling reaction of 3-aryl-1,2-benzisoxazoles and alkynes in the presence of a Rh(III) catalyst to furnish 2-(1-isoquinolinyl)phenols has been developed, in which the N–O bond of isoxazole moiety plays a crucial role for the catalytic turnover. The products are of interest in medicinal chemistry as well as materials chemistry and also as potential precursors for synthesizing a series of isoquinoline-based bidentate ligands.

Scheme 2. Preparation of an N–P bidentate ligand



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Supporting Information is available on http://dx.doi.org/10.1246/cl.******.

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17 HPLC analysis confirmed that **5** retained its chirality at ambient temperature; however, separation condition could not be determined for the phosphine **6**. For detail, see the Supporting Information.