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Rh(III)-Catalyzed Synthesis of 3-Amino-4-arylisoquinolinones from 4-Diazoisochroman-3-imines and *N*-Methoxybenzamides

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Supporting Information

ABSTRACT: A Rh(III)-catalyzed reaction of *N*-methoxybenzamides and 4-diazoisochroman-3-imines is described. This method offers a rapid entry to 3-amino-4-arylisoquinolinone architectures from readily available starting materials under mild reaction conditions. A one-pot cascade C−H bond activation/formal [4 + 2] cycloaddition mechanism is proposed. The synthesized 3-amino-4-arylisoquinolinones can be conveniently converted into dibenzo[*c*,*f*][1,8]naphthyridines.

3-Amino-4-arylisoquinolinones are privileged structures in medicinal science (Figure 1).[1] For instance, compound **I** is

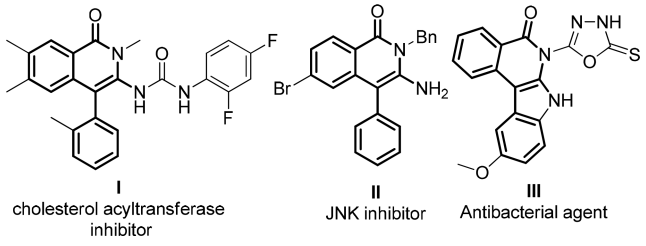
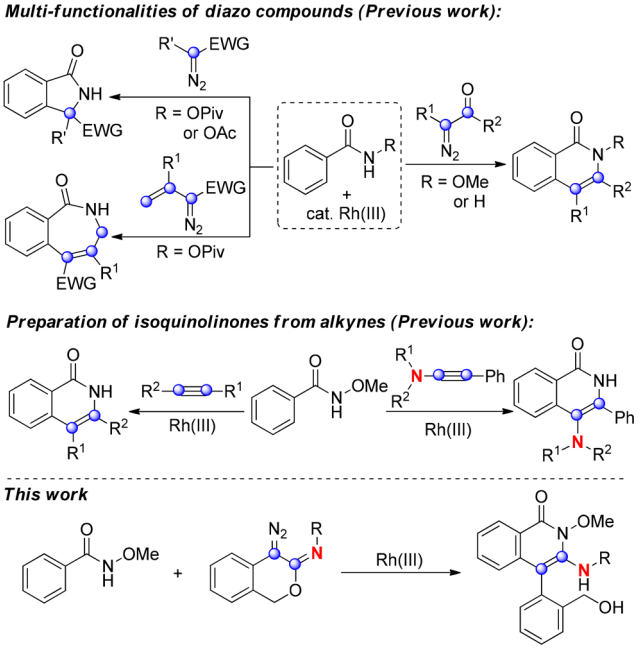


Figure 1. Bioactive molecules containing a 3-amino-4-arylisoquinolinone core.

one of the cholesterol acyltransferase inhibitors that present excellent activity inhibiting cholesterol acyltransferase, controlling absorption of cholesterol from the intestinal tract, and suppressing precipitation of cholesterol at the arterial wall. Therefore, it is useful for the protection of cardiovascular system. For more practical examples, compound **II** is a JNK inhibitor, while compound **III** is an antibacterial agent. Consequently, much attention has been made for construction of this important class of heterocyclic compounds.[2]

Diazo compounds have been reported to be a class of special components for the investigation of the transition-metal-catalyzed *ortho* C−H bond activation/functionalization.[3,4] On the basis of the strategy of the metal−carbene migratory insertion, reactions between benzamides and diazo compounds could form isoindolinones,[5] isoquinolinones,[6] isoquinolinediones,[7,6c] benzo[*c*]azepinones[8] via C−C/C−N bond formation, and isochromenones[9] via C−C/C−O bond formation. In these cases, diazo components exhibited unique advantages and could serve as one-, two-, and three-carbon partners in the construction of five-, six-, and seven-membered heterocycles, respectively (Scheme 1). Among these heterocycles, isoquinolinones are extremely important in pharmaceutics and were alternatively prepared through Rh(III)-catalyzed C−H activation/functionalization of *N*-methoxybenzamides with alkyne

Scheme 1. Rh(III)-Catalyzed Preparation of Isoquinolinones



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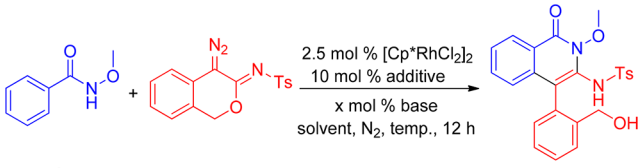
using N−O bond as an internal oxidant in 2010.[10] Following this step, 4-amino-3-arylisoquinolinones could be regioselectively obtained.[11]

On the other hand, we recently reported a new family of diazo compounds, 4-diazoisochroman-3-imines, which could be easily prepared by a copper-catalyzed alkyne−azide cycloaddition.[12] These diazo compounds had been demonstrated to be effective to form rhodium carbenes in the presence of Rh(II) and brought out a series of Rh(II)-catalyzed reactions, such as cyclopropanation as well as formal [3 + 2] and [3 + 4] cycloadditions.[12b] Herein, we examine a new reaction type of these diazo compounds using Rh(III) catalyst.

Initially, we tested the reaction between *N*-methoxybenzamide (**1a**) and 4-diazoisochroman-3-imine **2a** using $[Cp^*RhCl_2]_2$ as catalyst. The reaction was carried out in the presence of $AgSbF_6$ and KOAc in tetrahydrofuran (THF) at 40 °C for 12 h under N_2 atmosphere, and 3-amino-4-arylisoquinolinone **3a** was isolated in 68% yield (Table 1, entry 1). Based on this finding, we screened the reaction conditions. Several other solvents were screened first, and a lower or comparable yield was obtained when toluene, ethyl acetate (EA), dichloroethane (DCE), dichloromethane (DCM), 1,4-dioxane, or acetone was used as solvent (Table 1, entries 2−7). Relatively higher yield was observed when acetonitrile was used as the solvent (Table 1, entry 8). Thus, the optimal solvent was determined to be acetonitrile. The reaction did not occur in the absence of the rhodium catalyst (Table 1, entry 9) or in the absence of potassium acetate (Table 1, entry 10). Without $AgSbF_6$, the reaction still occurred to give **3a** in 72% yield (Table 1, entry 11). Altering KOAc to sodium or cesium acetates led to a lower yield of **3a** (Table 1, entries 12 and 13). When potassium carbonate was used, **3a** was isolated in 23% yield (Table 1, entry 14). No reaction occurred when potassium formate was applied (Table 1, entry 15). Steadily raising the reaction temperature led to a decrease in the yield (Table 1, entries 16 and 17), whereas a slightly higher yield (73%) was obtained when the reaction was conducted at room temperature (Table 1, entry 18). Increasing the amount of base did not improve the reaction, whereas decreasing the amount of base led to a decrease in the yield (Table 1, entries 19−22). When the reaction was carried out in air, a significantly decreased yield (44%) was observed (Table 1, entry 23). Cobalt catalysts such as $[Cp^*Co(CO)I_2]$ were also examined, but no reaction occurred (Table 1, entries 24 and 25).

With the optimized reaction conditions in hand (Table 1, entry 18), we next tested the substrate scope (Scheme 2). First, the tolerance of the substituents on 4-diazoisochroman-3-

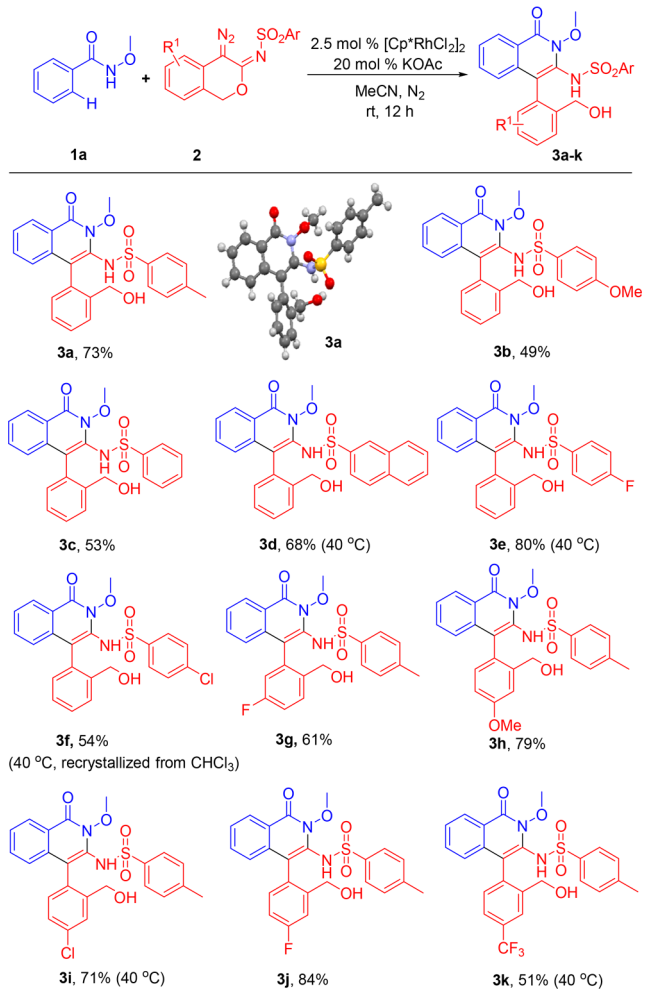
Table 1. Optimization of the Reaction Conditions[a]



entry	additive	base (mol %)	solvent	temp (°C)	yield[b] (%)
1	$AgSbF_6$	KOAc (20)	THF	40	68
2	$AgSbF_6$	KOAc (20)	toluene	40	46
3	$AgSbF_6$	KOAc (20)	EA	40	51
4	$AgSbF_6$	KOAc (20)	DCE	40	52
5	$AgSbF_6$	KOAc (20)	DCM	40	66
6	$AgSbF_6$	KOAc (20)	1,4-dioxane	40	67
7	$AgSbF_6$	KOAc (20)	acetone	40	67
8	$AgSbF_6$	KOAc (20)	MeCN	40	71
9[c]	$AgSbF_6$	KOAc (20)	MeCN	40	NR
10	$AgSbF_6$		MeCN	40	NR
11		KOAc (20)	MeCN	40	72
12		NaOAc (20)	MeCN	40	58
13		CsOAc (20)	MeCN	40	62
14		K_2CO_3 (20)	MeCN	40	23
15		HCO_2K (20)	MeCN	40	trace
16		KOAc (20)	MeCN	60	68
17		KOAc (20)	MeCN	80	51
18		KOAc (20)	MeCN	rt	73
19		KOAc (50)	MeCN	rt	71
20		KOAc (30)	MeCN	rt	73
21		KOAc (10)	MeCN	rt	18
22		KOAc (5)	MeCN	rt	9
23[d]		KOAc (20)	MeCN	rt	44
24[e]	$AgSbF_6$	KOAc (20)	MeCN	rt	NR
25[e]		KOAc (20)	MeCN	rt	NR

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), additive (10 mol %), base (*x* mol %), solvent (2 mL), N_2, 12 h. [b]Isolated yield. [c]Without $[Cp^*RhCl_2]_2$. [d]Under air atmosphere. [e]$[Cp^*Co(CO)I_2]$ (5 mol %).

Scheme 2. Scope of 4-Diazoisochroman-3-imines 2



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imines **2** which were prepared from sulfonyl azides and (2-ethynylphenyl)methanols were examined. The sulfonyl groups could be toluenesulfonyl, *p*-methoxybenzenesulfonyl, benzenesulfonyl, 2-naphthalenesulfonyl, *p*-fluorobenzenesulfonyl, and *p*-chlorobenzenesulfonyl. Thus, products **3a**–**f** were obtained in moderate to good yields. Among these sulfonyls, *p*-fluorobenzenesulfonyl provided the highest yield when the reaction was carried out at 40 °C (**3e**, 80%). The substituent on (2-ethynylphenyl)methanols could be either electron-donating group (MeO) or electron-withdrawing groups (F, Cl, CF_3). Thus, products **3g**–**k** were obtained in 51–84% yields.

Various substituents on *N*-methoxybenzamides tolerated the reaction conditions and provided the corresponding products **3l**–**w** in moderate to good yields (Scheme 3). Thus, the substituent at the 4-position of *N*-methoxybenzamides could be either an electron-donating group (Me, Ph, MeO) or an electron-withdrawing group (Cl, CF_3). The highest yield (**3l**, 75%) was observed in the case where *N*-methoxy-4-methylbenzamide reacted with **2a**. The methyl group or chloro could be altered from the 4-position (**3l** or **3o**) of *N*-methoxybenzamide to the 3-position (**3q** or **3r**) and 2-position (**3s** or **3t**) as well. *N*-Methoxy-1-naphthamide and *N*-ethoxybenzamide were also examined for their reaction with **2a**. In these cases, the desired products **3v** and **3w** were isolated in 51% and 67% yields, respectively. Benzamide, *N*-methylbenzamide, and *N*-hydroxybenzamide did not work for this reaction with the recovery of both starting materials. Single-crystal analysis of **3u** further confirmed the structure of 3-amino-4-arylisoquinolinone.

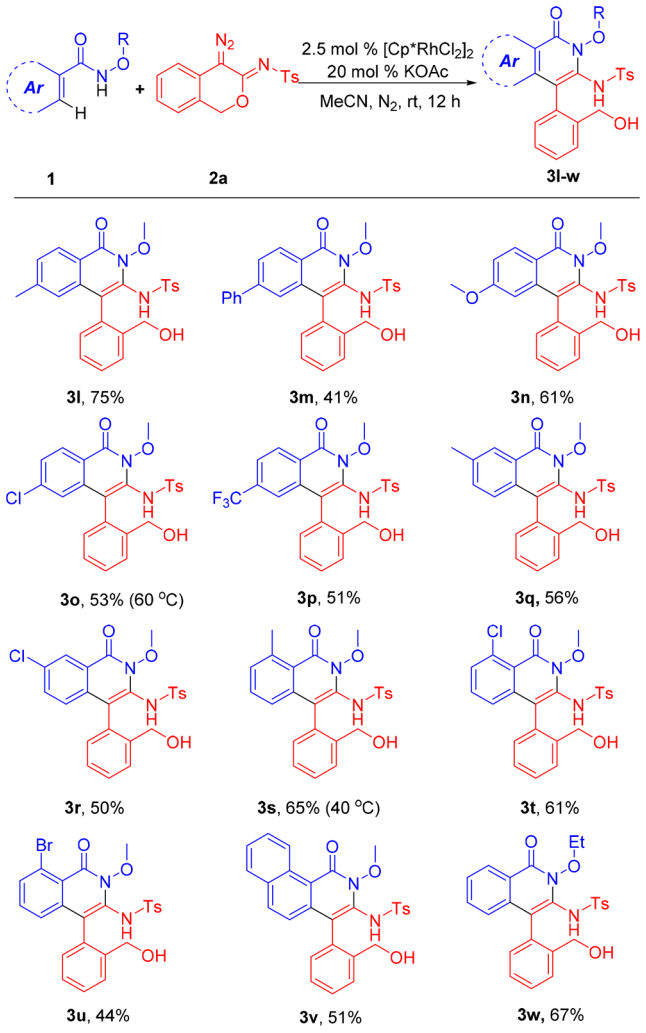
It is noteworthy that this reaction could be run on a gram scale. When **1a** (0.605 g, 4 mmol) and **2a** (1.308 g, 4 mmol) were mixed and reacted under the optimized reaction conditions, 1.368 g (76% yield) of **3a** was obtained by the recrystallization from the mixed solvents of DCM/EA/*n*-hexane.

The prepared 3-amino-4-arylisoquinolinones **3** could be used to construct the skeleton of dibenzo[*c*,*f*][1,8]-naphthyridines (Scheme 4). For instance, **3a** reacted with thionyl chloride to provide dichlorinated compound **4a** in 70% yield. Further treatment of **4a** with triethylamine derived the dechlorinated product **5a** in 95% yield, which owned the skeleton of dibenzo[*c*,*f*][1,8]naphthyridine with four continuously fused ring. The structures of **4a** and **5a** were confirmed by single-crystal analysis. Similar treatment of **3l** and **3i** provided **4b** (69% yield) and **4c** (65% yield) and subsequently furnished **5b** and **5c** in yields of 85% and 92%, respectively.

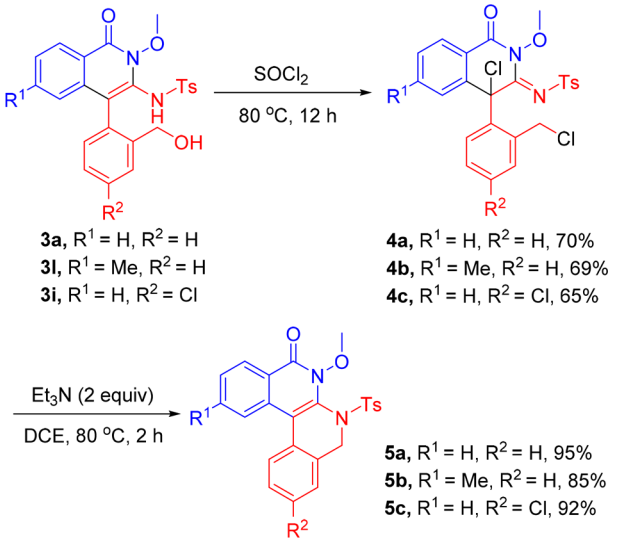
To probe the reaction mechanism for the formation of **3**, deuterium-labeling experiments were performed. When the reaction of **1a** was conducted with the addition of 1 equiv of D_2O under the standard conditions in the absence of diazo compound, a deuterium-incorporated product was obtained. This result indicates that the C–H activation is irreversible (Scheme 5, eq 1). Kinetic isotope effect (KIE) was carried out in parallel experiments (Scheme 5, eq 2). By treatment of **1a** or **1a**-d_5 under standard reaction conditions for 20 min, KIE of the reaction was determined to be 2.0. This value indicated that the C–H activation might be the rate-determining step.

On the basis of these results and the previously reported references,[5a,6a,8,13] a possible mechanism is proposed in Scheme 6. In the presence KOAc, rhodium catalyst is initially activated via ligand exchange to form the rhodium species **A**. Assisted by the *N*-methoxyamido group, the *ortho* C–H bond of *N*-methoxybenzamide **1a** is activated to generate Rh(III) complex intermediate **B**. **B** is active toward diazo partner **2a**,

Scheme 3. Scope of *N*-Methoxybenzamides 1



Scheme 4. Preparation of 4 and 5



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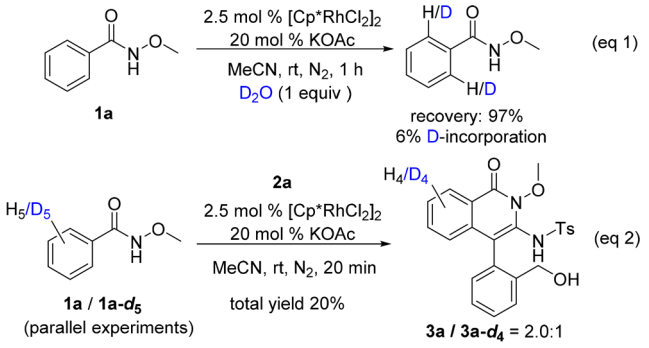
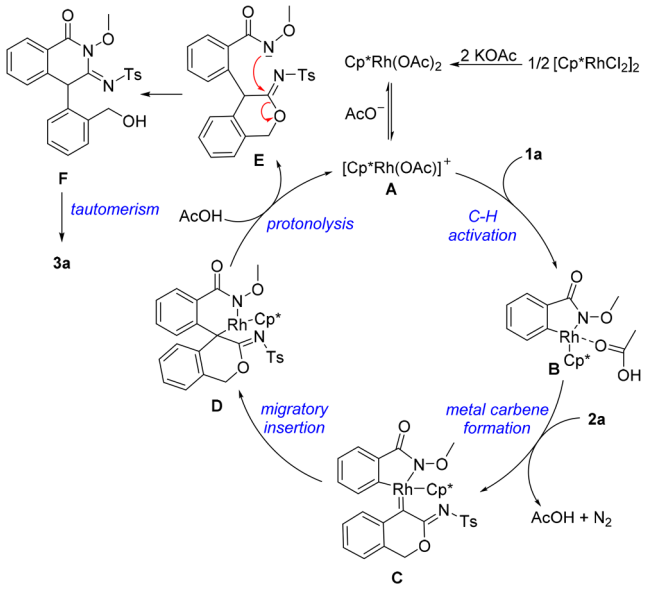
Scheme 5. Mechanistic Experiments



Scheme 6. Possible Mechanism for the Formation of 3a



and thus, rhodium carbene **C** is formed through the sequence of coordination and denitrogenation. Subsequently, **C** undergoes a migratory insertion (**D**), followed by proto-demetalation, to form intermediate **E** as well as the rhodium species **A** for cyclic catalysis. Finally, **3a** is obtained via a cascade intramolecular nucleophilic substitution/tautomerism process.

In conclusion, we have demonstrated a novel method for the preparation of 3-amino-4-arylisoquinolinones from readily available *N*-methoxybenzamides and 4-diazoisochroman-3-imines in the presence of Rh(III) catalyst. The reactions were carried out under mild reaction conditions and provided a wide range of 3-amino-4-arylisoquinolinones in moderate to good yields. It is noteworthy that this strategy is of practical use and could be easily scaled up. Moreover, the obtained 3-amino-4-arylisoquinolinones could be further converted into dibenzo[*c*,*f*][1,8]naphthyridines with four continuously fused rings in high yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00290.

Experimental procedures and characterization data for all new compounds (PDF)

Accession Codes

CCDC 1881378−1881379 and 1881381−1881382 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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