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Rhodium(III)-Catalyzed C(sp^2)−H Chemoselective Annulation to O-Cyclized Isochromen-imines from Benzamides

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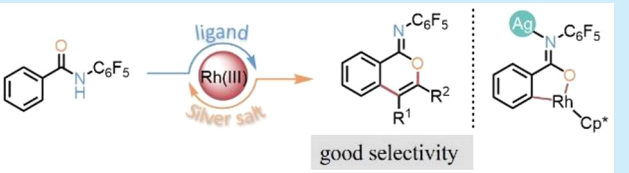
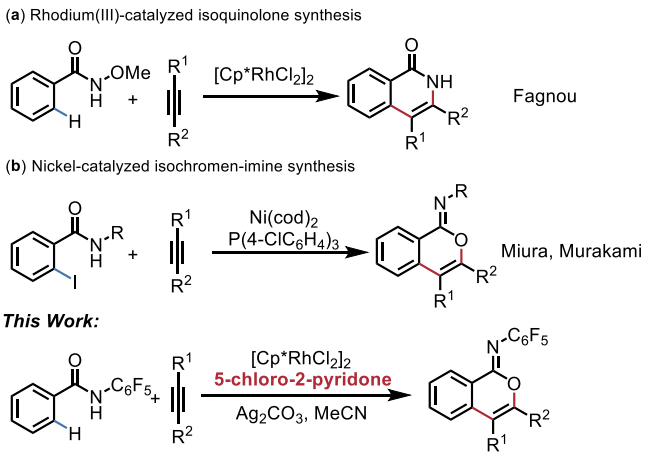
ABSTRACT: Through the development of ligands and reaction conditions, the Rh(III)-catalyzed selective annulation of benzamides with internal alkynes has been achieved to the formation of *O*-cyclized isochromen-imines. Various substituents are well-tolerated under mild reaction conditions. Density functional theory calculations indicate that silver carbonate could act as a Lewis acid to assist the ligand to improve the chemical selectivity of the reaction in a catalytic system.



Heterocycles have received enormous interests due to their invaluable biological activity in the past few decades, and various efficient approaches to construct these heterocycles were developed.[1] In recent years, direct C−H bond activation has emerged as a powerful tool in organic synthesis.[2] However, the chemoselective transformation to different products from the same substrates by tuning the catalysts or the reaction conditions is still a significant challenge.[3] For example, the amide functional group contains two interchangeable nucleophilic sites; therefore, different cyclization products may be obtained depending on either a N or O atom acting as a nucleophile. Isoquinolone scaffolds have been constructed via oxidative [4 + 2] annulation of benzamide derivatives with alkynes catalyzed by different transition metals, such as Rh,[3b,d,e,4] Ru,[5] Co,[6] Ni,[7] and others.[8] Previous works by the research groups of Fagnou,[4b,f] Miura and Satoh,[4a] Rovis,[4c] and Li[4g] have demonstrated the effective dehydrogenative annulation reactions of benzamide derivatives with alkynes by rhodium(III) catalysts to afford the *N*-cyclization isoquinolone motifs (Scheme 1a). Fagnou and co-workers observed a byproduct in the process of condition optimization, which was identified as the *O*-annulation product later by Huang.[4b,8b] At the same time, Miura, Murakami, and co-workers applied 2-iodobenzamides with alkynes in the presence of a nickel(0)/P(4-ClC$_6$H$_4$)$_3$ catalyst to produce *O*-cyclization products (Scheme 1b).[9] In all these reports, the selectivity of the *O*-cyclized versus *N*-cyclized formation was dependent on the structure of the *N*-substituent groups, where NH to OH tautomerization of the amides proceeded.[4c,g,t] Recently, the Li group has reported a Cp*Rh-(OAc)$_2$-catalyzed chemodivergent oxidative [4 + 1] annulation of *N*-methoxy benzamides and 1,3-enynes to give either lactam or iminolactone by the variation of reaction conditions.[10]

Encouraged by these works, we apply the ligands and other additives to a rhodium(III) catalytic system to adjust the coordination ability of metal ions to switch the structure of the products. We report here a ligand-promoted selective annulation of benzamides with internal alkynes to construct *O*-cyclized isochromen-imines in the presence of rhodium(III) catalyst, with the assistance of silver salt.

Scheme 1. Annulation of Benzamides with Alkynes



At the outset of our studies, we initiated our attempts on the oxidative annulation of *N*-pentafluorophenylbenzamide (**1a**) with diphenylacetylene (**2a**) using [Cp*RhCl$_2$]$_2$ as a catalyst

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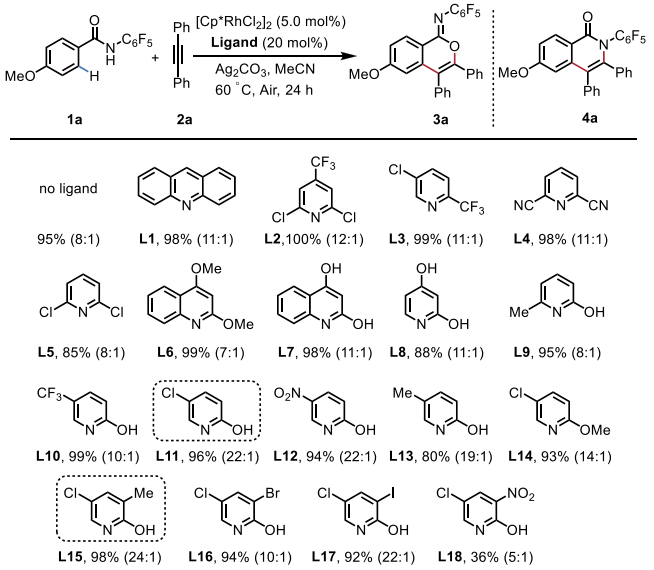
Org. Lett. XXXX, XXX, XXX−XXX

and Ag_2CO_3 as an oxidant at 100 °C. A mixture of (1*H*)-isochromen-1-imine (**3a**) and isoquinolin-1(2*H*)-one (**4a**) was obtained during the screening of solvents. It is worth noting that **3a** was preferred in all the solvents, reaching a ratio of 4/1 (**3a**/**4a**) with the total yield of 96% in CH_3CN (Table S1, entry 1). The structure was unambiguously determined by single-crystal X-ray analysis (see section 2.6 in the Supporting Information). The result was consistent with the previous reports that electron-withdrawing groups on the amides played prominent roles in the formation of isochromen-imine.[4c,g,t] A screening of the catalysts, temperature, and oxidants for the reaction showed that $[Cp^*RhCl_2]_2$, 60 °C, and Ag_2CO_3 were optimal for this transformation (Tables S2−S4). However, the chemoselectivity remained unsatisfactory with the ratio of **3a**/**4a** for 8/1. Recently, our group has realized a series of ligands promoted rhodium(III)-catalyzed C−H functionalization of benzamides,[11] especially the pyridine-based ligands promoted Rh(III)-catalyzed amination reaction of an aryl C−H bond with free amnines.[11c] On the basis of these results, we wondered if we could improve the selectivity by introducing a proper ligand to potentially tune the steric and electronic properties of the catalyst. Therefore, a variety of pyridine-based ligands was examined (Scheme 2). There was no significant

Scheme 2. Ligand Evaluation of the Synthesis of 3a[a,b,c]

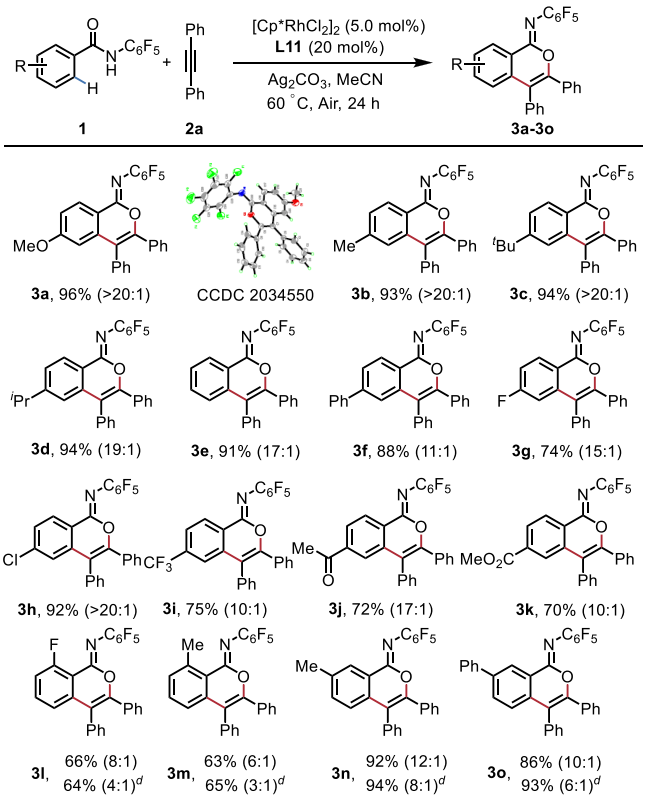


[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), $[Cp^*RhCl_2]_2$ (5.0 mol %), and Ag_2CO_3 (1.0 equiv) in CH_3CN (1.0 mL) at 60 °C oil bath for 24 h under air. [b]The yield was determined by ^1H NMR analysis of crude product using 1,3,5-trimethoxybenzene as an internal standard. [c]The ratio of **3a**/**4a** was based on a ^1H NMR analysis.

improvement in the chemoselectivity of the products upon addition of pyridine analogues **L1**−**L6**. Inspired by previous work that the introduction of a hydroxyl group at the 2-postion may be beneficial for chemical selectivity,[12] some 2-pyridone ligands with various substituents at the 4-, 5-, or 6-positions (**L8**−**L13**) were applied. Fortunately, 5-chloro-2-pyridone **L11** dramatically improved the ratio of **3a**/**4a** to 22:1. **L14** was selected to verify the necessity of the hydroxyl group at the 2-position of the pyridine. Furthermore, ligands with electron-donating and -withdrawing groups at the 3-position had been tested as well. A pyridone ligand with a methyl group at the 3-position (**L15**) can improve the ratio of **3a**/**4a** to 24:1, yet the nitro group at the 3-position made the reaction sluggish and depressed the ratio to 5:1 (**L18**). Considering the cost of the ligands, **L11** was chosen as the optimized ligand for this reaction.

With the optimized catalytic system in hand, we investigated the generality of the reaction by exploiting *ortho*-, *meta*-, and *para*-substituted benzamides, as shown in Scheme 3. Treatment of benzamides (**1**) and diphenylacetylene (**2a**) bearing different substituents in the aromatic ring delivered the desired products (**3a**−**3o**) in moderate to excellent yields. The substrates with electron-rich substituents at the *para* position of the benzamides showed excellent reactivity and high chemoselectivity (**3a**−**3d**). The benzamide **1e** gave rise to the corresponding product **3e** with good selectivity. Electron-deficient functional groups such as phenyl, fluoro, chloro, trifluoromethyl, and acetylandmethoxycarbonyl substituents at the C-4 position were compatible in the present catalytic reaction (**3f**−**3k**). *Ortho*-substituted substrates exhibited less conversion efficiency compared to *para*-substituted ones. *Meta*-substituted arene derivatives **1n** and **1o** occurred at the less-hindered site. Although the *ortho*- and *meta*-substituted benzamides proceeded with a relatively low selectivity, the selectivity is much better than the one without ligands. Furthermore, the product **3e** can be easily transformed into the corresponding (1*H*)-isochromen-1-one **5e** in 89% yield under aqueous acidic conditions (see section 2.4 in the Supporting Information).

Scheme 3. Scope of Benzamides[a,b,c]



[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.15 mmol), $[Cp^*RhCl_2]_2$ (5.0 mol %), **L11** (20 mol %), and Ag_2CO_3 (1.0 equiv) in CH_3CN (1.0 mL) at 60 °C in oil bath for 24 h under air. [b]Isolated yields. [c]The ratio of **3**/**4** was based on a ^1H NMR analysis. [d]The ratio of **3**/**4** is observed without ligand **L11**.

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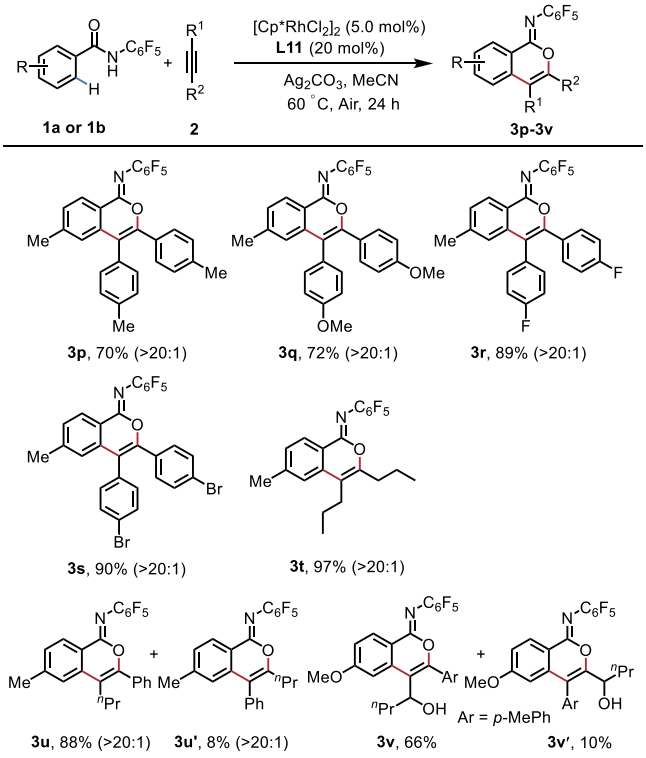
Org. Lett. XXXX, XXX, XXX−XXX

Meanwhile, we also made efforts to verify the feasibility of this transformation with diverse internal alkynes (Scheme 4).

Scheme 4. Scope of Alkynes[a,b,c]



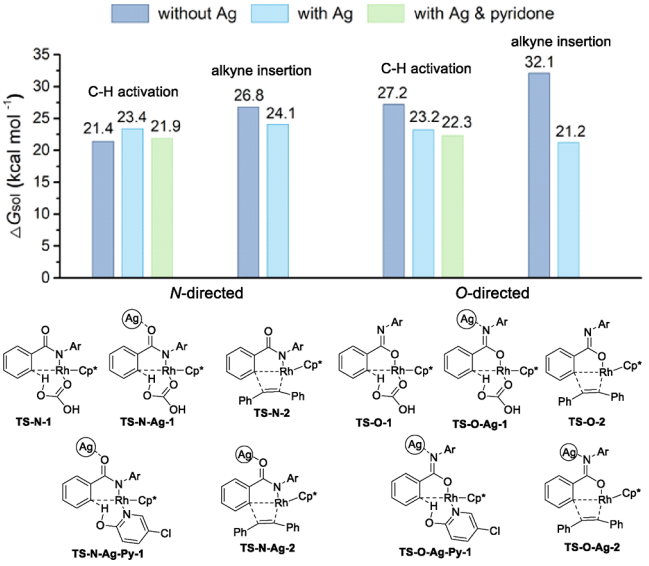
[a]Reaction conditions: **1a** or **1b** (0.1 mmol), **2** (0.15 mmol), $[Cp^*RhCl_2]_2$ (5.0 mol %), **L11** (20 mol %), and Ag_2CO_3 (1.0 equiv) in CH_3CN (1.0 mL) at 60 °C in oil bath for 24 h under air. [b]Isolated yields. [c]The ratio of **3**/**4** was based on a ^1H NMR analysis.

The *O*-cyclization products (**3p**−**3t**) could be obtained with good to excellent yields (70−97%) and high selectivity (>20:1). Notably, the oxidative annulation of unsymmetrical 1-phenyl-1-pentyne with **1b** worked well to obtain the regioisomeric mixture of **3u** and **3u′** in 88% and 8% yield, respectively. Propargyl alcohol **2v** was tested as well and provided a 6:1 mixture of isomers.

To understand the chemoselectivity of this reaction, we performed a series of density functional theory (DFT) calculations using diphenylacetylene (**2a**) and amide **1e** as the substrates in the catalytic system.[13] The calculations have shown that the reaction proceeded through a C−H activation, alkyne insertion, and metallallylcarbenoid annulation. We found that the silver salt can act as a Lewis acid to coordinate with the deprotonated amide moiety in intermediates and transition states. Different from previous reports on silver additives serving as either a halide scavenger or a terminal oxidant for the regeneration of catalytic centers in C−H transformation, silver carbonate also acts as a Brønsted base and a Lewis acid to assist the ligands to control the selectivity of the products in the catalytic system in our work. The silver carbonate dimer was used as a computational model to illustrate this effect (see section 2.7.2 in the Supporting Information).[14]

The free energies of C−H activation and alkyne insertion transition states are illustrated in Scheme 5. In the C−H activation step, coordination of silver carbonate dimer

Scheme 5. Transition States of C−H Activation and Alkyne Insertion



dramatically decreases the energy barrier of the *O*-directed pathway by 4.0 kcal·mol^{-1}. In the alkyne insertion step, the silver carbonate dimer exhibits an analogous role in stabilizing the transition states for the catalytic system. According to the hard−soft acid−base theory, the soft acidic silver ion prefers the soft basic nitrogen atom to the oxygen atom, reducing the energy barrier of the alkyne insertion more remarkably. On the contrary, the *N*-directed pathway proceeds with a less-favorable activation free energy, which is 0.9 kcal·mol^{-1} higher than the corresponding *O*-directed pathway in the presence of silver carbonate dimer (**TS−N-Ag-2**: 24.1 kcal·mol^{-1} vs **TS−O-Ag-1**: 23.2 kcal·mol^{-1}). This indicated that the *O*-cyclization product **3e** would be obtained as the major product, which is consistent with the observed moderate chemoselectivity (8:1).

In addition, when pyridone **L11** was added, the energy barrier of the C−H activation in the *O*-directed pathway was further lowered by 0.9 kcal·mol^{-1}. Accordingly, the overall activation free energy of the *O*-directed pathway is 1.8 kcal·mol^{-1} lower than that of the *N*-directed pathway (**TS−N-Ag-2**: 24.1 kcal·mol^{-1} vs **TS−O-Ag-Py-1**: 22.3 kcal·mol^{-1}), in good agreement with the enhanced chemoselectivity of this reaction (17:1).

The kinetic isotope experiments were conducted with **1e** and **1e**-d_5 under standard reaction conditions. Ambiguous kinetic isotope effect (KIE) values were obtained (parallel experiment: k_H/k_D = 1.26; intermolecular: k_H/k_D = 1.57), indicating that the C−H activation step has a slightly higher barrier than the next steps. According to our calculations, the C−H activation step (via **TS−O-Ag-Py-1**) is only 1.1 kcal mol^{-1} higher than the alkyne insertion (via **TS−O-Ag-2**) in the *O*-directed pathway, which is consistent with isotope experiments.

On the basis of the experimental results and DFT calculations, a proposed catalytic cycle is presented in Scheme 6. The catalytic cycle is initiated by the coordination of amide **1e** to the activated Rh(III) species, which is dissociated from the rhodium dimer precatalyst, leading to Rh-amidate intermediate **A**. Subsequently, the cyclic rhodium complex **Int-O-3** was furnished through the C−H activation transition state **TS−O-Ag-Py-1** in the presence of silver carbonate dimer.

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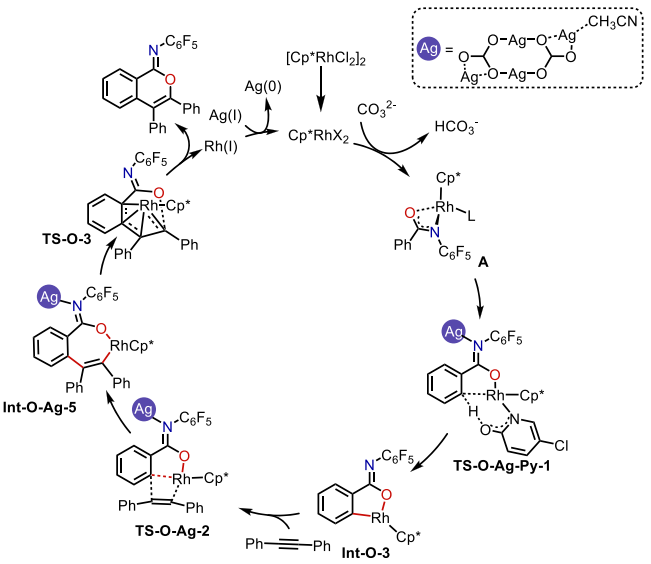
Scheme 6. Proposed Mechanism



Seven-membered cyclic rhodium **Int−O-Ag-5** was generated from complex **Int-O-3** and alkyne **2a** via the alkyne insertion transition state **TS−O-Ag-2**. Finally, through the metallallylcarbenoid annulation,[15] the *O*-cyclized isochromen-imine was obtained together with the Rh(I) species, which is oxidized to the Rh(III) species.

In summary, we have demonstrated that, through the development of the reaction conditions, the transformation of *O*-cyclized isochromen-imines was successfully achieved through the Rh(III)-catalyzed annulation of benzamides with internal alkynes. On the basis of the experimental results and DFT calculations, it is indicated that ligands together with the silver salts are essential in controlling the chemical selectivity of the reaction. This transformation exhibits a broad substrate scope and good functional group tolerance.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03425.

Experimental details and characterization data of all new compounds (PDF)

Accession Codes

CCDC 2034550 contains 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, U.K.; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

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