OL | Organic Letters

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

Letter

pubs.acs.org/OrgLett

Three-Component Synthesis of Isoquinoline Derivatives by a Relay Catalysis with a Single Rhodium(III) Catalyst

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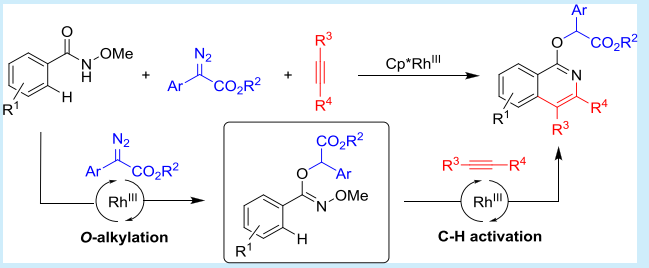
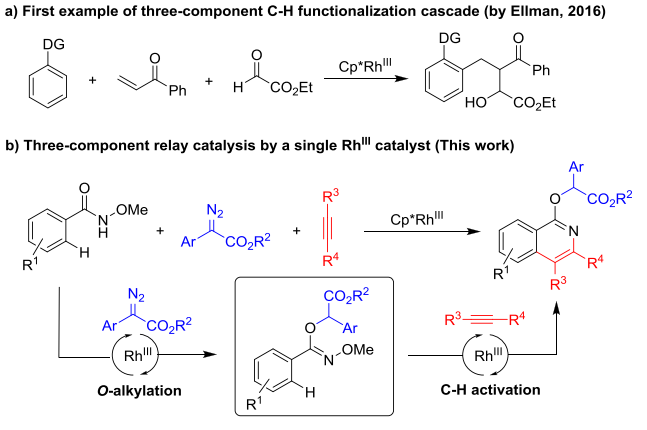
Supporting Information

ABSTRACT: A rhodium(III)-catalyzed one-pot three-component reaction of *N*-methoxybenzamide, α-diazoester, and alkyne was developed, providing an alternative way to synthesize isoquinoline derivatives. Mechanistically, it is a relay catalysis, and the reaction occurred via successive *O*-alkylation and C−H activation processes, both of which were promoted by the same catalyst.



The one-pot multicomponent reaction constitutes a class of very important and highly attracting reactions in organic chemistry owing to its high efficiency and step economy. This field has attracted a great deal of attention from chemists and has achieved tremendous success.[1] Recently, with the boom in the area of inert C−H bond activation,[2] multicomponent reactions involving inert C−H bond activation have been developed,[3] which was pioneered by Ellman in 2016 (Scheme 1a).[3i] Meanwhile, multicatalysis has also been emerging as a powerful strategy to achieve multistep organic transformations in one pot.[4] As one of the types of multicatalysis, relay catalysis contains two or more mechanistically different catalytic cycles, in which the product released from the prior catalytic cycle serves as the starting material for the succeeding catalytic cycle. In recent years, great advances have been achieved in the field of relay catalysis,[4] employing either a single catalyst[3a,5] or a multicatalyst system.[6] However, the relay catalysis involving C−H bond activation is still very rare.[3a,6o] Its multicomponent variant is even rarer, for example, the Cp*Rh^{III}-catalyzed multicomponent synthesis of isoindolinones by Zhu et al.[3a] Herein we report a three-component relay catalysis involving C−H bond activation, which is promoted by a single rhodium(III) catalyst. In this reaction, *N*-methoxybenzamide, α-diazoester,[7] and alkyne are smoothly transformed into various isoquinoline[8] derivatives via successive *O*-alkylation and inert C−H activation processes (Scheme 1b).

Scheme 1. Three-Component Reaction Involving C−H Activation



Our initial studies revealed that in the presence of Cp*Rh^{III} catalyst, *N*-methoxybenzamide **1a**, *tert*-butyl 2-diazo-2-phenylacetate **2a**, and diphenylacetylene **3a** could undergo the three-component reaction at room temperature, affording product **4aaa** in 47% yield (Table 1, entry 1). Solvent screening indicated that dichloromethane (DCM) was the most effective, giving product **4aaa** in 70% yield (entries 2−4). The yield increased to 81% when the reaction time was extended to 20 h, but no additional increment was achieved by further prolonging the reaction time to 30 h (entries 5 and 6). An investigation of the reaction temperature indicated that room temperature was optimal (entries 7 and 8). For the detailed optimization of the reaction conditions, please refer to the Supporting Information (Tables S1−S7).

With the optimized reaction conditions in hand, we set out to explore the substrate scope of this three-component reaction (Figure 1). First, a series of substituted *N*-methoxybenzamides were examined. The desired products **4aaa**−**4iaa** were obtained in good yield (62−81%). The structure of product **4baa** was confirmed by single-crystal X-ray diffraction. Second, an array of substituted α-diazoesters were investigated. The

Received: April 26, 2019

DOI: 10.1021/acs.orglett.9b01456
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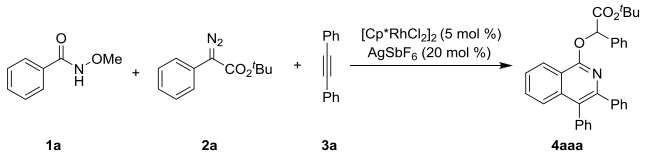
Table 1. Optimization of Reaction Conditions[a]



1a 2a 3a 4aaa

entry	solvent	time (h)	t (°C)	yield (%)[b]
1	DCE	16	rt	47
2	DMF	16	rt	31
3	PhCl	16	rt	21
4	DCM	16	rt	70
5	DCM	20	rt	81
6	DCM	30	rt	78
7	DCM	20	10	48
8	DCM	20	50	60

[a]Reaction conditions: under a nitrogen atmosphere, *N*-methoxybenzamide **1a** (0.1 mmol), diazoester **2a** (0.12 mmol), diphenylacetylene **3a** (0.15 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), and solvent (0.2 mL). [b]Isolated yield.

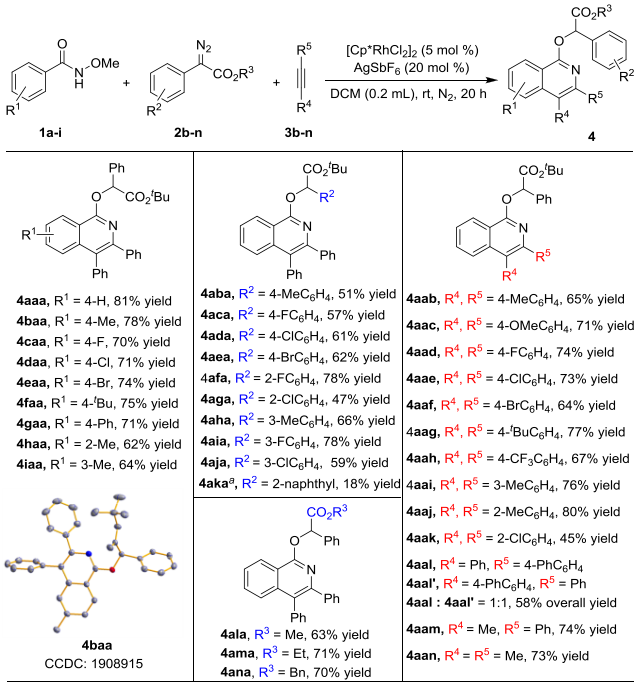
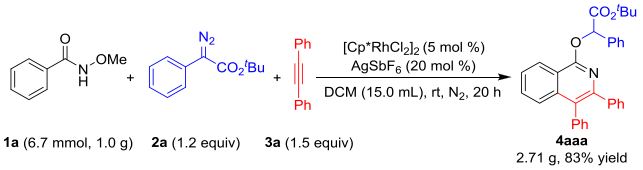


Figure 1. Scope of substrates. All of the reactions were carried out under a nitrogen atmosphere with **1a-i** (0.10 mmol), **2b-n** (0.12 mmol), **3b-n** (0.15 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), and $AgSbF_6$ (20 mol %) in DCM (0.2 mL) at room temperature for 20 h. Isolated yields were reported. [a]Purified by silica gel column chromatography and recrystallization from petroleum ether/dichloromethane (3 mL/0.1 mL).

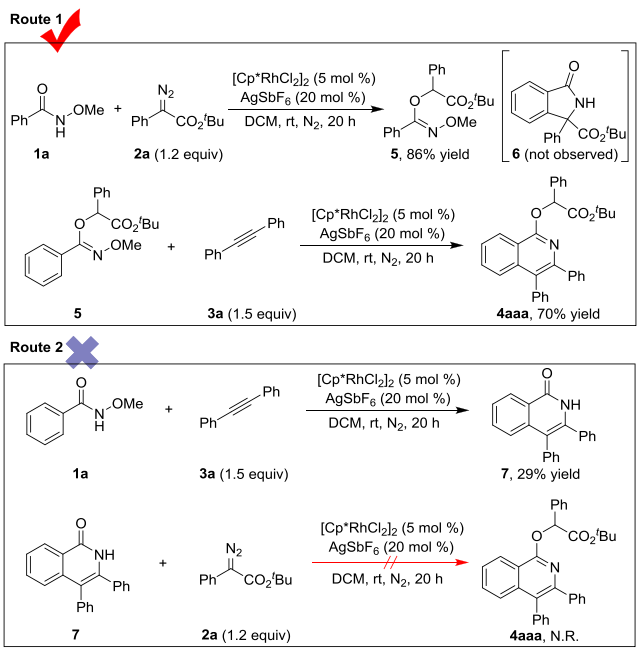
corresponding products **4aba**–**4aka** were obtained in up to 78% yield. In addition, 2-diazo-2-phenylacetates with varied ester groups were also tested, generating the desired products **4ala**, **4ama**, and **4ana** in 63, 71, and 70% yield, respectively. Finally, we investigated a variety of diaryl acetylenes bearing either electron-withdrawing (4-F, 4-Cl, 4-Br, 4-CF_3, and 2-Cl) or electron-donating groups (4-OMe, 4-Me, 2-Me, and 4-^{t}Bu), affording the corresponding products **4aab**–**4aak** in good yield (up to 80%). Besides symmetric diaryl alkynes, some asymmetric alkynes were also investigated. When the asymmetric diaryl alkyne (4-phenylphenyl) phenyl ethyne was subjected to the reaction, two regioisomeric products **4aal** and **4aal′** were obtained in equal amounts. In contrast, when phenyl methyl acetylene was employed, only the single regioisomer **4aam** was obtained in 74% yield. The aliphatic alkyne but-2-yne was also attempted, giving the desired product **4aan** in 73% yield. Notably, the reaction could be easily scaled up. As shown in Scheme 2, when 1.0 g of **1a** was subjected to the reaction, the desired product **4aaa** was obtained in 83% yield (2.71 g).

Scheme 2. Gram-Scale Reaction



Then, preliminary mechanistic studies were carried out by designing some control experiments. As shown in Scheme 3,

Scheme 3. Control Experiments



two possible reaction pathways were proposed for this reaction. The first one involves the initial reaction of *N*-methoxybenzamide **1a** with α-diazoester **2a** to form intermediate **5**, which then reacts with **3a** to form the final product **4aaa** via C–H bond activation (Scheme 3, Route 1). The second one includes the initial reaction of *N*-methoxybenzamide **1a** with diphenylacetylene **3a** to give isoquinolone **7**, which then reacts with α-diazoester **2a** to give the final product **4aaa** (Scheme 3, Route 2). Interestingly, it was observed that under the standard reaction conditions, *N*-methoxybenzamide **1a** indeed reacted well with α-diazoester **2a** to form intermediate **5** in 86% yield. Isoindolone **6** was not detected in this reaction, which was in accord with the observations by Rovis and Yu.[9] Furthermore, imidate **5** was found to be able to smoothly react with **3a** to produce the final

DOI: 10.1021/acs.orglett.9b01456
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product **4aaa** in 70% yield. In contrast, *N*-methoxybenzamide **1a** was found to react rather sluggishly with diphenylacetylene **3a**, giving isoquinolone **7** in a low yield of 29%.[10] Moreover, isoquinolone **7** failed to react with α-diazoester **2a** to give product **4aaa** under the standard reaction conditions. These findings strongly imply that the reaction should proceed via the proposed reaction pathway Route 1.

To further confirm the validity of the proposed reaction Route 1, the reaction was monitored by a nuclear magnetic resonance (NMR) spectrometer in real time. Indeed, imidate **5** could be detected in the reaction mixture, and its trend of change is shown in Figure 2. As shown in Figure 2a, the

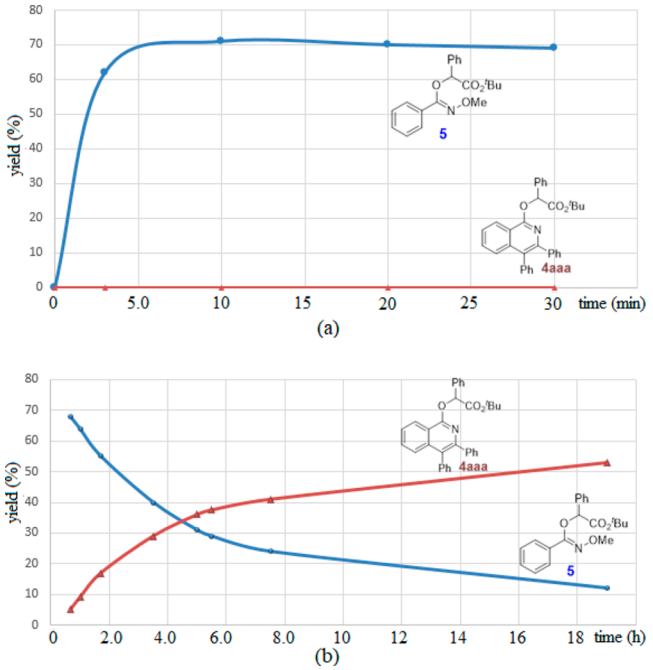
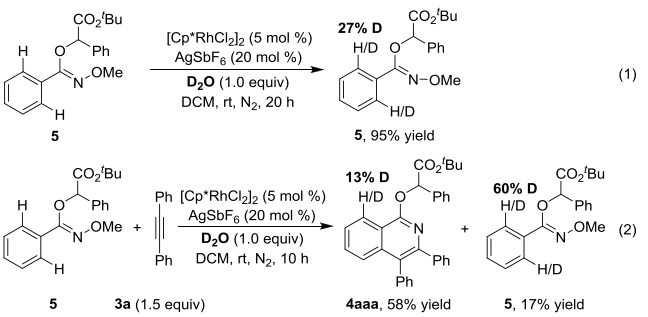


Figure 2. Reaction progress monitored by NMR spectrometer.

formation of imidate **5** was very fast and was completed within 10 min (71% yield). In sharp contrast, no isoquinoline product **4aaa** was detected, even after 30 min, implying that this three-component relay catalysis proceeds in a temporal separation manner. Namely, the reaction of *N*-methoxybenzamide **1a** and α-diazoester **2a** finished before the reaction of imidate **5** with alkyne **3a** began. From about the 40th minute, the amount of imidate **5** started to decline along with the gradual increment of the isoquinoline **4aaa** as well as the side product methanol, further confirming that imidate **5** was the actual reaction intermediate (Figure 2b). Notably, the reaction of imidate **5** and alkyne **3a** was much slower than the reaction of *N*-methoxybenzamide **1a** and α-diazoester **2a**.

Subsequently, the H/D exchange experiments were conducted. When imidate **5** was treated with D_2O under the standard reaction conditions, considerable H/D exchange on the ortho position was observed, indicating that the C−H bond activation process was reversible (Scheme 4, eq 1). Moreover, when imidate **5** was allowed to react with diphenylacetylene **3a**, product **4aaa** was obtained in 58% yield with a contamination of 13% of **4aaa**-d_1, suggesting that the reverse reaction of C−H activation was much slower than the reaction step following the C−H activation (Scheme 4, eq 2). In addition, the incorporation of 60% D on the ortho

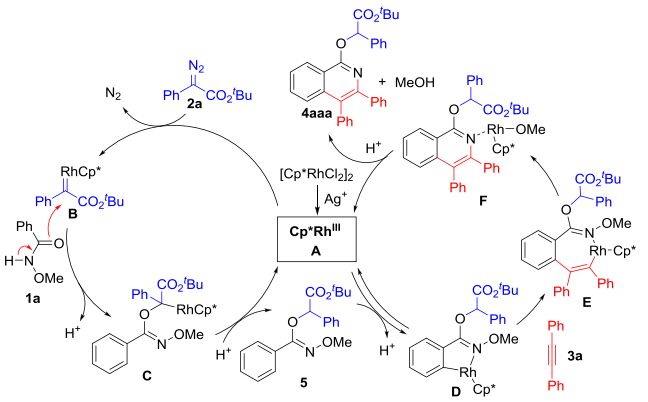
Scheme 4. D/H Exchange Experiment



position of the directing group was also observed for the recovered imidate **5**.

According to the above mechanistic studies, a plausible reaction mechanism is proposed (Scheme 5). First,

Scheme 5. Proposed Reaction Mechanism



$[Cp^*RhCl_2]_2$ reacts with $AgSbF_6$ to produce the catalytically active rhodium species **A**, which can efficiently decompose diazoester **2a** to generate carbenoid **B**. The attack of carbenoid **B** by amide **1a** gives intermediate **C**, which is further transformed to imidate **5** by protonation with the concurrent regeneration of rhodium species **A**. Then, the Cp^*Rh^{III}-catalyzed C−H activation of imidate **5** occurs to generate the five-membered cyclorhodium intermediate **D**. Coordination, followed by the subsequent migratory insertion of diphenylacetylene **3a** into the C−Rh bond of intermediate **D**, affords the seven-membered rhodacycle intermediate **E**. Reductive elimination along with the oxidation of rhodium by the N−O bond gives intermediate **F**. Lastly, the protonation and dissociation of metal delivers the final product **4aaa** together with methanol and the recovered Cp^*Rh^{III} catalyst.

In conclusion, a rhodium-catalyzed one-pot three-component reaction has been developed, providing an alternative way to synthesize isoquinoline derivatives. The reaction proceeds via a relay catalysis mechanism, involving successive *O*-alkylation and C−H activation processes, both of which are promoted by the same Cp^*Rh^{III} catalyst. Preliminary mechanistic studies were carried out, and a plausible reaction mechanism is depicted.

DOI: 10.1021/acs.orglett.9b01456
Org. Lett. XXXX, XXX, XXX−XXX

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01456.

Experimental details, characterization data, and ^{1}H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1908915 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, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (grant 21402244).

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DOI: 10.1021/acs.orglett.9b01456
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