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# $Rh^{III}/Cu^{II}$-Cocatalyzed Synthesis of 1*H*-Indazoles through C−H Amidation and N−N Bond Formation

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Supporting Information

**ABSTRACT:** Substituted 1*H*-indazoles can be formed from readily available arylimidates and organo azides by $Rh^{III}$-catalyzed C−H activation/C−N bond formation and Cu-catalyzed N−N bond formation. For the first time the *N*-H-imidates are demonstrated to be good directing groups in C−H activation, also capable of undergoing intramolecular N−N bond formation. The process is scalable and green, with $O_2$ as the terminal oxidant and $N_2$ and $H_2O$ formed as byproducts. Moreover, the products could be transformed to diverse important derivatives.

Due to their diverse pharmacological activities, 1*H*-indazoles are widely used as anti-cancer, anti-inflammatory, anti-HIV, and anti-microbial drugs (Figure 1).[1] The efficient synthesis of 1*H*-indazoles has attracted much attention for a long time.[2] Initially, the methods were mainly limited to transition-metal-free processes, including diazotization or nitrosation of *o*-alkyl-substituted anilines,[3] condensation of *o*-halo- or mesylate-substituted arylaldehydes or ketones with hydrazines,[4] and 1,3-dipolar cycloadditions of diazomethanes with benzynes.[5] These methods suffer from several disadvantages, such as harsh reaction conditions with high temperatures or strong acids, expensive starting materials, or limited substrate scope.

Transition-metal catalysis has become one of the most important methods to generate heterocycles, including 1*H*-indazoles. For example, many groups have developed efficient Pd- or Cu-catalyzed intramolecular amination/amidation of *o*-halo or *o*-alkoxy arylhydrazones to synthesize 1*H*-indazoles.[6] Recently, transition-metal-catalyzed C−H activation has become more and more important and powerful, arising mainly from its high atom- and step-economy.[7] Starting from arylhydrazones, only three examples of Pd-, Fe-, and Cu-catalysis were reported to synthesize 1*H*-indazoles through C−H amidation/amination (Figure 2A).[8] However, carcinogenic organo-hydrazines must be used, and the substrates are limited to diaryl ketone derivatives, which suffer from regioselectivity issues. Here we report an attractive process to synthesize 1*H*-indazoles from easily available arylimidates and organo azides with good functional group tolerance via Rh-catalyzed C−H activation/C−N bond formation and Cu-catalyzed N−N bond formation (Figure 2D).

Previously, our group developed an efficient synthesis of substituted pyrazoles from enaminoesters and nitriles through oxidative C−C/N−N bond formation in the presence of stoichiometric or catalytic $Cu(OAc)_2$ (Figure 2B).[9] Due to the importance of 1*H*-indazoles and the limitations of previous

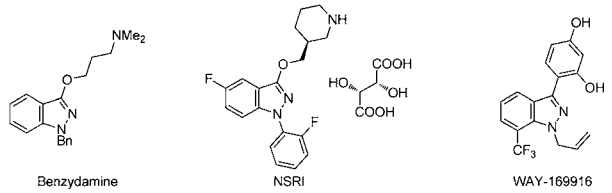


**Figure 1.** Some examples of biologically active 1*H*-indazoles.

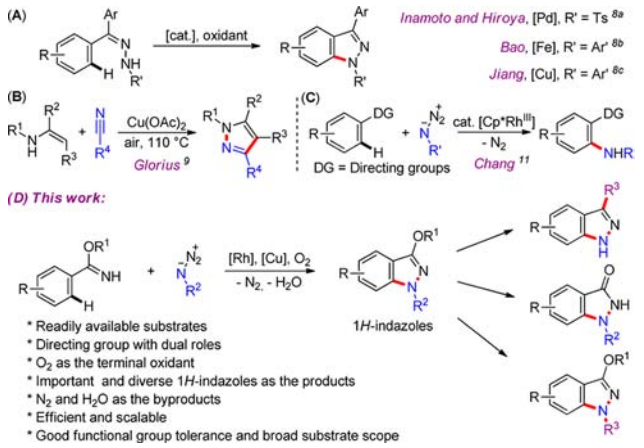


**Figure 2.** Novel syntheses of diverse 1*H*-indazoles.

methods, we wished to apply the oxidative N−N bond formation in the efficient synthesis of such structures without use of toxic organo-hydrazines.[10] Recently, Chang et al. developed an attractive Rh-catalyzed amidation/amination[11,12] of aryl C−H bond with organo azides[13] as the nitrogen source (Figure 2C). Inspired by these works and other Rh(III)-catalyzed C−H activations,[14,15] we report the development of an efficient synthesis of 1*H*-indazoles through Rh-catalyzed directed C−H amidation/amination with organoazides and following oxidative N−N bond formation.

There were mainly two challenges: (1) the compatibility of C−N and N−N bond formation. In Chang's work,[11] the C−N bond was formed under redox- and pH-neutral reaction conditions. The need for oxidant and in situ-generated acid in the N−N bond formation step may inhibit the C−N bond formation. (2) Proper and stable N−H-containing directing groups. Several N-containing groups, such as pyridine, quinoline,

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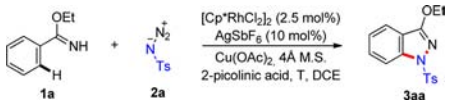
**Table 1. Optimization of Reaction Conditions**[a]



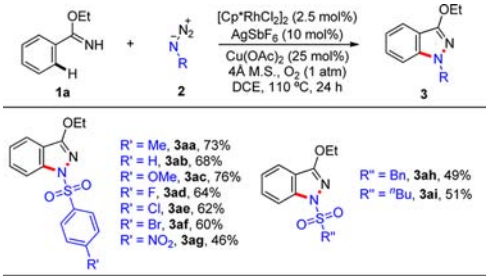

| entry | **2a** (equiv) | $Cu(OAc)_2$ (equiv) | 2-picolinic acid (mol%) | *T* (°C) | atmosphere | yield[b] (%) |
|---|---|---|---|---|---|---|
| 1 | 1.5 | 2.1 | – | 110 | argon | (62) |
| 2 | 2.0 | 2.1 | – | 110 | argon | 67 |
| 3 | 2.0 | 2.1 | – | 90 | argon | 30 |
| 4 | 2.0 | 2.1 | – | 130 | argon | 61 |
| 5[c] | 2.0 | 2.1 | – | 110 | argon | 38 |
| **6** | **2.5** | **2.1** | – | **110** | **argon** | **(73)** |
| 7 | 2.5 | 0.25 | 5.0 | 110 | $O_2$[j] | 67 |
| 8[d] | 2.5 | 0.25 | 5.0 | 110 | $O_2$[j] | 58 |
| 9[e] | 2.5 | 0.25 | 5.0 | 110 | $O_2$[j] | 11 |
| 10[f] | 2.5 | 0.25 | 5.0 | 110 | $O_2$[j] | 25 |
| **11** | **2.5** | **0.25** | – | **110** | **$O_2$[j]** | **(73)** |
| 12[g] | 2.5 | 0.25 | – | 110 | $O_2$[j] | 55 |
| 13[h] | 2.5 | 0.25 | – | 110 | $O_2$[j] | <5 |
| 14 | 2.5 | 0.10 | – | 110 | $O_2$[j] | 56 |
| 15 | 2.5 | – | – | 110 | argon | <5 |
| **16**[i] | **2.5** | **0.25** | – | **110** | **$O_2$[j]** | **(69)** |

[a]**1a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), 4 Å MS (150 mg), DCE (1.0 mL), 24 h. [b]GC yields are given with mesitylene as an internal standard, and isolated yields are given in parentheses. [c]Without 4 Å MS. [d]Pivalic acid (25 mol%) was added. [e]CsOPiv (25 mol%) was added. [f]Without $AgSbF_6$. [g]$[Cp^*RhCl_2]_2$ (1.0 mol%) was used. [h]Without $[Cp^*RhCl_2]_2$. [i]7.0 mmol scale (1.0 g of **1a**), 48 h. [j]1 atm.

pyrazole, oxime, and amides, have been demonstrated to show good ability to direct C−H amination/amidation.[11] However, in these cases it is difficult to successively generate a N−N bond. For example, when various amide directing groups were explored at the initial stage of this project, only amidation but no successive N−N bond formation occurred. We hypothesized that increasing the electron density of the N-atom might enhance the oxidative process. After testing *N*-H-benzophenone imine with only limited success (see Supporting Information (SI)), we tested the ethyl phenylimidate **1a**, easily synthesized from benzonitrile and ethanol,[16] as the starting material in the presence of $Rh^{III}$ complex as the catalyst and stoichiometric $Cu(OAc)_2$ as the oxidant. To our delight, the corresponding 1*H*-indazole **3aa** was obtained in 62% isolated yield (Table 1, entry 1). To our best knowledge, this is the first example of the use of *N*-H-imidates as substrates in transition-metal-catalyzed C−H activation and also in a cascade with N−N bond formation.[17]

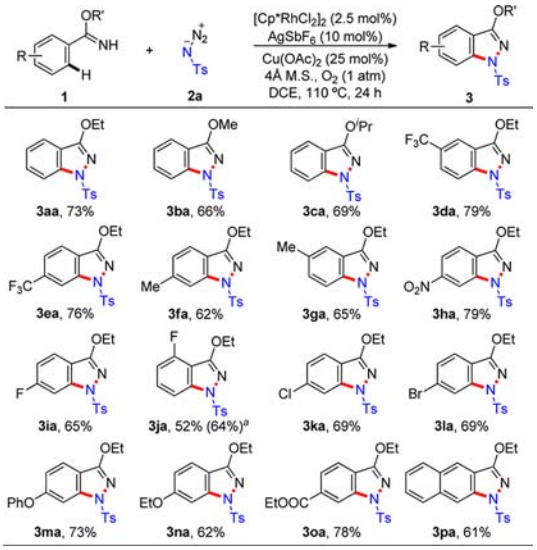
Further optimization study indicated that the use of molecular sieves was important to improve the efficiency (Table 1, entries 2 and 5). Temperature showed a great impact on this reaction. The imidate **1a** showed very low reactivity at 90 °C (entry 3), and higher reaction temperature did not improve the yield (entry 4). Using slightly more of tosyl azide **2a** afforded the product in 73% isolated yield (entry 6). To make the process greener, we further investigated the possibility of using $Cu(OAc)_2$ as the catalyst and $O_2$ as the oxidant.[18] In the presence of 25 mol% of $Cu(OAc)_2$ and 5 mol% of picolinic acid as the additive, similar yield could be achieved under an atmosphere of $O_2$ (entry 7). Under such reaction conditions, adding base or acid induced lower yields (entries 8 and 9). To our surprise, higher yield could be obtained in the absence of picolinic acid (entry 11). Lower loading of Rh (1.0 mol%) or Cu catalyst (10 mol%) still could give synthetically

**Scheme 1. Rh/Cu-Cocatalyzed Synthesis of 1*H*-Indazoles from 1a with 2**[a]




[a]Reaction conditions: **1a** (0.2−0.25 mmol), **2** (2.5 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), $Cu(OAc)_2$ (25 mol %), 4 Å MS (150 mg), $O_2$ (1 atm), DCE (1 mL), 110 °C, 24 h.

**Scheme 2. Rh/Cu-Cocatalyzed Synthesis of 1*H*-Indazoles from 1 with 2a**[a]




[a]For reaction conditions, see Scheme 1. The crude NMR yield is given in parentheses when 2.1 equiv of $Cu(OAc)_2$ was used under argon.

useful yields (entries 12 and 14). It is important to note that only a trace amount of **3aa** was detected in the absence of either Rh or Cu catalyst (entries 13 and 15), indicating the importance of these two catalysts. Moreover, such a reaction could be carried out on a gram scale with similar yields and efficiency (entry 16).

With the optimized reaction conditions in hand, we first investigated the scope of organo azides **2** (Scheme 1). A variety of arylsulfonyl azides with different functional groups were tested. The azides with electron-donating groups showed better reactivity than those with electron-withdrawing groups. Various kinds of functional groups, such as OMe, $NO_2$, C−F, C−Cl, and even C−Br, were well tolerated. Besides arylsulfonyl azides, alkylsulfonyl azides (**2h**, **2i**) also showed reactivity in this transformation with synthetically useful yields. However, aryl azides, which showed good reactivity in previous work,[11b] gave the desired product in very low yields only.

Furthermore, the reactivity of different arylimidates **1** was tested with **2a** as the reaction partner (Scheme 2). First, the impact of the alkyl in the alkoxy group was investigated. We found that the ethylimidate (**1a**) showed better reactivity than methyl (**1b**) and isopropyl (**1c**) derivatives. Furthermore, different ethyl arylimidates were applied in this reaction. It was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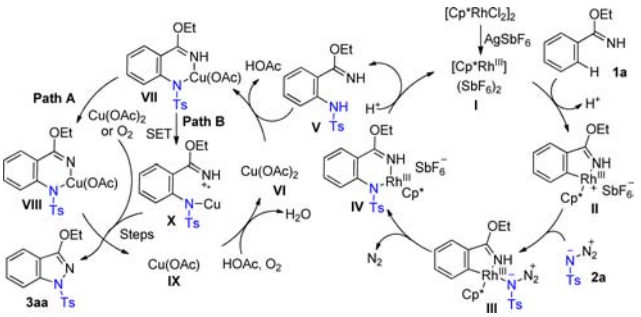
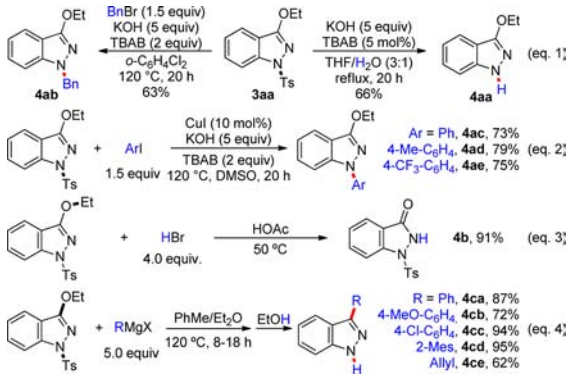
**Scheme 3. Mechanistic Hypothesis**



found that the reaction was sensitive to the steric demand of the arenes. Both 3-$CF_3$ (**1d**) and 3-Me (**1g**) derivatives showed excellent selectivity to the C−H bond with less steric hindrance. The imidate with *o*-F (**1j**) also afforded the desired product in 52% yield. In contrast with electron-rich arylimidates, the electron-poor imidates showed better reactivities. For example, 4-$CF_3$ (**1e**) and 4-PhO (**1m**) derivatives gave the desired product in 76% and 73% yield, respectively, while 4-EtO (**1n**) only afforded the product in 62% yield. These reaction conditions tolerated various kinds of functional groups on arene, including EtO, PhO, ester, $NO_2$, $CF_3$, C−F, C−Cl, and even C−Br bonds, which could be further transformed to other functionalities. Besides the phenyl ring, naphthylimidate also showed good reactivity in this reaction to give the product **3pa** in good yield and excellent regioselectivity.

Based on the experiments and previous mechanistic studies, we propose the following mechanism (Scheme 3). In the presence of $AgSbF_6$, cationic [Cp*$Rh^{III}$] (**I**) is generated in situ as the active catalyst, which coordinates to imidate and further undergoes C−H activation to afford rhodacyclic complex **II**. (The KIE of 2.1 indicated that the C−H activation might be involved in the rate-determining step.) Coordination of azide to rhodium and further migratory insertion generate the $Rh^{III}$ amido species **IV** with release of $N_2$. The complex may undergo protonation to regenerate active [Cp*$Rh^{III}$] catalyst **I** and give the amidated product **V** (see SI), which coordinate to $Cu(OAc)_2$ or be directly transmetalated to generate complex **VII**. Higher valent $Cu^{III}$ complex **VIII** might be generated through oxidation by another $Cu(OAc)_2$ or $O_2$ (path A). Further N−N bond formation through reductive elimination afforded the desired product **3aa** and $Cu^{I}$ complex **IX**, which could be oxidized by $O_2$ in the presence of acid to regenerate $Cu(OAc)_2$ (**VI**). Another pathway (path B) is also possible to form a N−N bond via double single-electron transfer. To test this hypothesis, we tested several radical scavengers (such as BHT, hydroquinone, and TEMPO) and radical clock (diallyl ether) in the reaction with stoichiometric $Cu(OAc)_2$ (see SI). All the reactions were significantly inhibited, which indicated that radicals might be involved in the N−N bond formation.[19]

To demonstrate the utility of the products, we further investigated transformations of **3aa**. First, detosylation of **3aa** occurred smoothly under basic reaction conditions, giving **4a** in 66% yield (eq 1).[20] Moreover, in situ detosylation and further benzylation (eq 1) and arylation (eq 2) could afford the products in good efficiency, which gave an alternative method to construct such structures. Second, selective cleavage of the C−O bond was realized in different reaction conditions in the absence of transition metals. For example, selective cleavage of the $sp^3$ C−O bond gave **4b** in high yield under acidic reaction conditions[21] (eq 3), while arylation and allylation of the $sp^2$ C−O bond with



Grignard reagents generated various 3-aryl-1*H*-indazoles (**4ca**−**4cd**) and **4ce** in moderate to good yields (eq 4). In these cases, in situ detosylation was followed by arylation.[22] Notably, 2-mesitylmagnesium bromide could afford the desired product in good yield. Arylation reagents with both electron-donating groups and electron-withdrawing groups worked well in the *N*-1 or *C*-3 position, and many functional groups, such as OMe, $CF_3$, and C−Cl bond, were well tolerated. The plethora of postsynthetic modifications of the formed 1*H*-indazoles significantly enhances the value of this method.

In conclusion, we have developed a novel synthesis of substituted 1*H*-indazoles from easily available arylimidates and organo azides via $Rh^{III}$-catalyzed C−H activation/C−N bond formation and Cu-catalyzed N−N bond formation. *N*-H-Imidates were applied as versatile directing groups in $Rh^{III}$-catalyzed C−H activation, delivering substrates that undergo intramolecular N−N bond formation. The process is scalable and green, with $O_2$ being used as the terminal oxidant and only $N_2$ and $H_2O$ formed as the byproducts. The corresponding 1*H*-indazoles were obtained in moderate to high yields with good functional group tolerance. Moreover, the products could also be further transformed to diverse important derivatives. Further mechanistic studies, synthesis of drug candidates, and other novel transformations of arylimidates are underway in our laboratory.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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†D.-G.Y. and M.S. contributed equally to this work.


### Notes

The authors declare no competing financial interest.

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