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Synthesis of 1*H*-Indazoles from Imidates and Nitrosobenzenes via Synergistic Rhodium/Copper Catalysis

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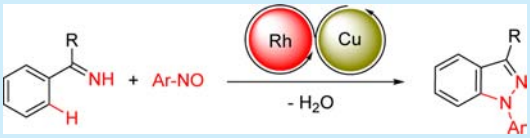
Supporting Information

ABSTRACT: Nitrosobenzenes have been used as a convenient aminating reagent for the efficient synthesis of 1*H*-indazoles via rhodium and copper catalyzed C−H activation and C−N/N−N coupling. The reaction occurred under redox-neutral conditions with high efficiency and functional group tolerance. Moreover, a rhodacyclic imidate complex has been identified as a key intermediate.



1*H*-Indazoles represent an important class of nitrogen-containing heterocycles that are widely found in pharmaceuticals and natural products.[1] Pharmaceuticals incorporating this privileged motif display a wide range of biological functions, such as anti-inflammatory (**A**),[2a] antiviral (**B**),[2b] antimicrobial (**C**),[2c] and anticancer (**D**)[2d] activities (Figure 1). Thus, the

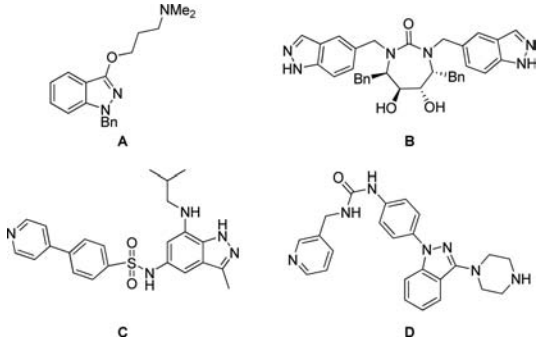
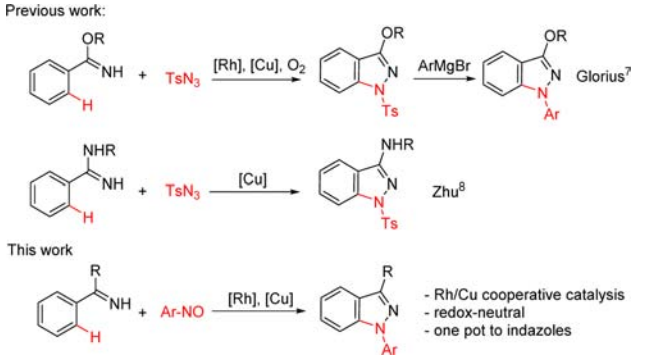


Figure 1. Representative biologically active 1*H*-indazoles.

significance of this heterocyclic moiety has prompted the development of efficient and practical synthetic routes.[3] Traditional transition metal-free synthetic processes often suffered from low regioselectivity, harsh reaction conditions, limited substrate scope, and/or expensive starting materials.[4] Therefore, the development of efficient methods to access 1*H*-indazoles with respect to green chemistry, regioselectivity, and availability of starting materials is highly desirable.

Transition metal-catalyzed direct C−H bond functionalization has allowed for the development of a plethora of methodologies. Such methods provided significant advantages toward the synthesis of a variety of heterocycles and other useful scaffolds.[5] Direct catalytic amination of carbon−hydrogen bonds to construct 1*H*-indazoles has drawn significant attention as in recent notable advances in C−H activation chemistry.[6] Inamoto and Hiroya reported the Pd-catalyzed C−H functionalization of tosylhydrazones followed by intramolecular oxidative amination to afford 3-substituted indazoles.[6a] Bao[6b] and Jiang[6c] independently realized Fe- and Cu-catalyzed aerobic oxidative C−N bond formation of hydrazones for indazole synthesis. In 2013, Glorius reported the oxidative synthesis of *N*-tosylindazoles via Rh(III)-catalyzed C−H activation of arylimidates and subsequent coupling with a sulfonylazide.[7] Zhu developed a copper-catalyzed tandem C−N/N−N bond formation between *N*-(*tert*-butyl)-benzimidamide and a sulfonylazide (Scheme 1).[8] Although these

Scheme 1. Intermolecular Synthesis of 1*H*-Indazoles



approaches are highly promising, either carcinogenic organic hydrazines or explosive azides are used. Given the significance of 1*H*-indazoles and the limitation of previous methods, further development of catalytic synthesis of 1*H*-indazoles from readily available starting materials would be of prime synthetic value.

Nitrosobenzenes have been used as a convenient nitrogen source for the amination of arenes via a rhodium-catalyzed C−H activation pathway.[9] The C−N bond formation occurred via migratory insertion of a M−C bond into the nitroso group, as in the seminal work by Li and Zhou.[9a−c] The *N*-arylhydroxylamine product contains an oxidizing N−O bond and can be readily transformed to an arylamine. Inspired by these work and by Glorius's report,[7] we reasoned that the hydroxylamine

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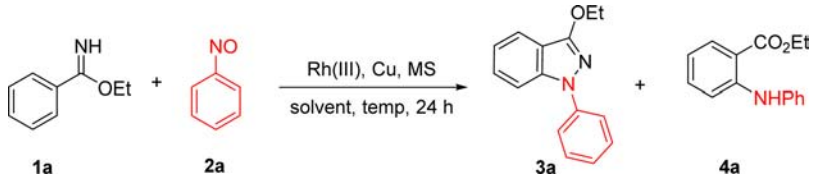
Table 1. Optimization of the Reaction Conditions[a,b]



entry	rhodium cat. (mol %)	Cu (equiv)	additive (mol %)	solvent	temp (°C)	yield of 3a[b]	3a/4a[c]
1	$[Cp^*RhCl_2]_2$ (4)	$Cu(OAc)_2$ (2)	$AgSbF_6$ (16)	DCE	100	30	2:1
2	$[Cp^*RhCl_2]_2$ (4)	$Cu(OAc)_2$ (0.3)	$AgSbF_6$ (16)	DCE	100	35	3:1
3	$[Cp^*RhCl_2]_2$ (4)	$Cu(OAc)_2$ (0.3)	$AgSbF_6$ (16)	DCE	120	23	1:1
4	$[Cp^*RhCl_2]_2$ (4)	$Cu(OAc)_2$ (0.3)	$AgNTf_2$ (16)	DCE	100	37	3:1
5	$[Cp^*RhCl_2]_2$ (4)	$Cu(OAc)_2$ (0.3)	$AgSbF_6$ (16)	PhMe	100	51	8:1
6	$[Cp^*RhCl_2]_2$ (4)	$Cu(OAc)_2$ (0.3)	$AgSbF_6$ (16)	$PhCF_3$	100	62	10:1
7	$[Cp^*RhCl_2]_2$ (4)	$Cu(OAc)_2$ (0.3)	$AgSbF_6$ (16)	$PhCF_3$	80	65	13:1
8	$[Cp^*RhCl_2]_2$ (4)	$CuSO_4$ (0.3)	$AgSbF_6$ (16)	$PhCF_3$	80	<5	
9	$[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5)	$Cu(OAc)_2$ (0.3)		$PhCF_3$	80	70	12:1
10	$[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5)		$FeCl_3$ or $Zn(OTf)_2$	$PhCF_3$	80	ND	
11	**$[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5)**	**$CuCl_2$ (0.3)**		**$PhCF_3$**	**80**	**89**	**18:1**
12	$[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5)	CuCl (0.3)		$PhCF_3$	80	61	16:1
13	$[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5)			$PhCF_3$	80	N.D.	
14		$CuCl_2$ (0.3)		$PhCF_3$	80	N.D.	
15[d]	$[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5)	$CuCl_2$ (0.3)		$PhCF_3$	80	<10	
16[e]	$[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5)	$CuCl_2$ (0.3)		$PhCF_3$	80	77	17:1

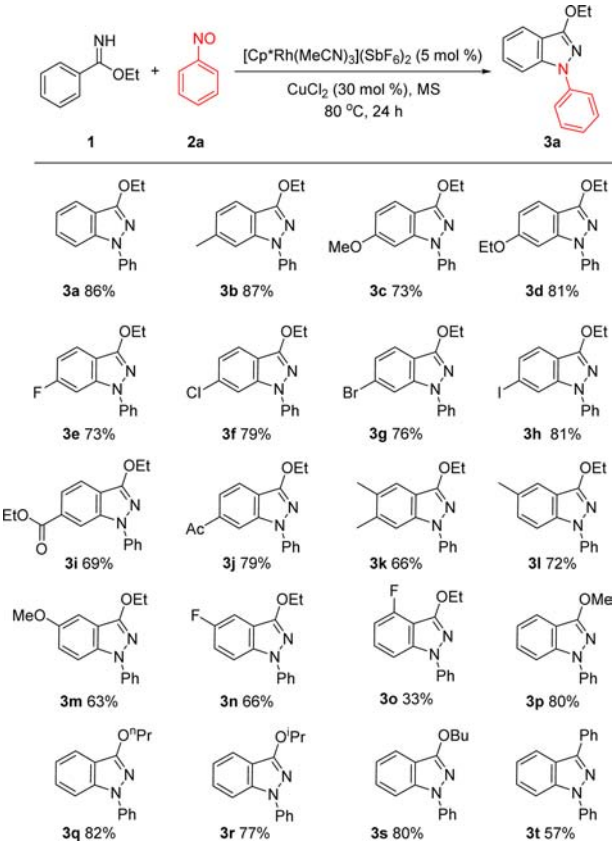
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), Rh(III) catalyst, additive, and 4 Å molecular sieves (200 mg) in a solvent (5 mL). [b]GC yield with 1,3,5-trimethoxybenzene as an internal standard. [c]Ratio determined by GC. [d]Without molecular sieves. [e]Nitrosobenzene (1.2 equiv) was used.

functionality may be employed for subsequent cyclization reactions under redox-neutral conditions. We now report redox-neutral synthesis of indazoles via coupling of imidate esters or NH imines with nitrosobenzenes under cooperative rhodium and copper catalysis.

Ethyl benzimidate (**1a**) and nitrosobenzene (**2a**) were chosen as substrates for optimization studies (Table 1). To our delight, **1a** and **2a** could be converted to the desired indazole **3a** in 30% yield together with diaryl amine **4a** in the presence of $[Cp^*RhCl_2]_2$, $Cu(OAc)_2$, $AgSbF_6$, and 4 Å MS (entry 1). When the loading of $Cu(OAc)_2$ was decreased from 2.0 to 0.3 equiv, the yield of **3a** was slightly improved and the ratio of **3a** and **4a** was promoted to 3:1 (entry 2). Further investigation showed that trifluorotoluene was the best solvent (entry 6). Screening of various copper species revealed that $CuCl_2$ was superior to other Cu catalysts, delivering **3a** in 89% yield (entry 11). Interestingly, CuCl was also an effective additive (entry 12). However, there seemed to be no correlation between the Lewis acidity of the additive and the catalytic efficiency (entries 8, 10). Control experiments confirmed that no desired product was detected when the Rh(III) or copper salt was omitted (entries 13, 14). Further screening indicated that molecular sieve was necessary to ensure high efficiency (entry 15). Thus, the following reaction conditions have been identified: $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5 mol %), $CuCl_2$ (30 mol %), and 4 Å MS (200 mg) in trifluorotoluene at 80 °C under N_2 atmosphere.

With optimized reaction conditions in hand, the scope and generality with respect to imidate esters were next explored (Scheme 2). Benzimidates bearing both electron-donating and -withdrawing para substituents all coupled smoothly to afford the products in good to excellent yields (**3a**–**j**), and no significant effect of the substituent on the reaction efficiency was observed. Of note, halogen substituents such as F, Cl, Br, and I were well tolerated (**3e**–**h**), which provided handles for postcoupling transformations. In addition, imidates with different meta-

Scheme 2. Substrate Scope of Imidates[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5 mol %), $CuCl_2$ (30 mol %), 4 Å MS (200 mg), trifluorotoluene (5 mL), 80 °C under N_2 for 24 h. [b]Yield of the isolated product.

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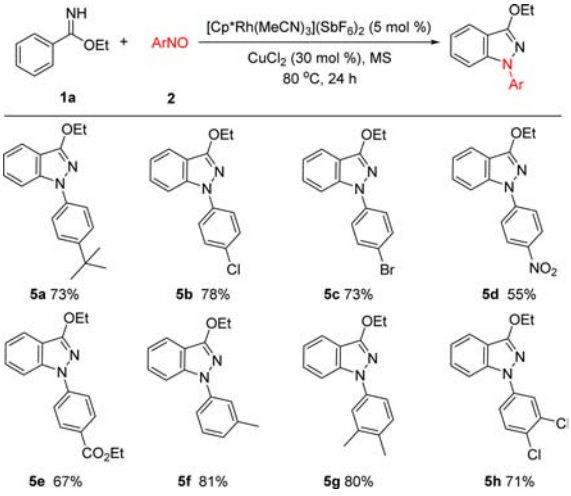
substituents also delivered the desired products (**3k**−**n**) in moderate to good yields with excellent regioselectivity. The imidate bearing an *ortho*-fluoro group was also viable for this transformation, affording the corresponding indazole in 35% yield (**3o**). The imidate substrate is not limited to an ethyl ester, and other alkyl esters (**3p**−**s**) and even a protic benzophenone imine (**3t**) all reacted with comparably high efficiency, leading to diversified products.

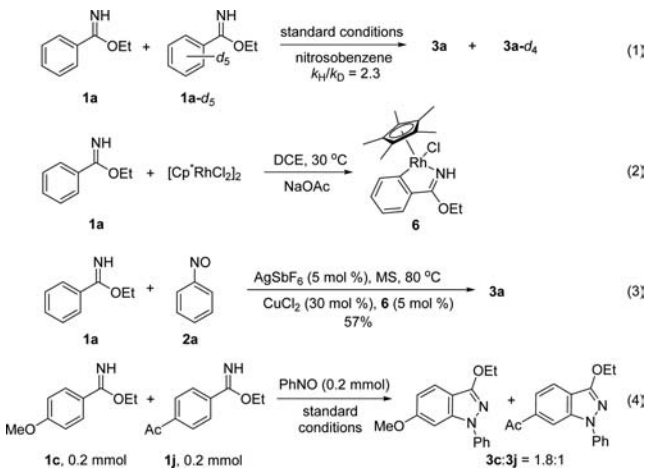
We subsequently examined the scope of the nitrosobenzene substrate. As given in Scheme 3, a wide variety of nitrosobenzenes with electron-donating and -withdrawing group at different positions of the aryl ring were tolerated. Notably, moderate yield was obtained for a nitro-substituted nitrosobenzene (**5d**), suggesting the broad applicability of nitrosobenzenes as an aminating reagent in the current 1*H*-indazoles synthesis.

Scheme 3. Scope of Nitrosobenzenes in Indazole Synthesis[a,b]

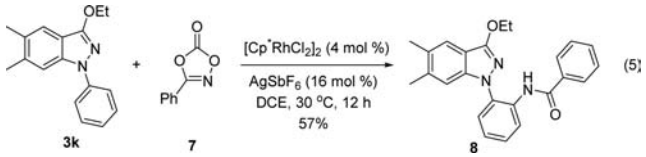


[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), [Cp*Rh(MeCN)$_3$](SbF$_6$)$_2$ (5 mol %), CuCl$_2$ (30 mol %), 4 Å molecular sieves (200 mg), trifluorotoluene (5 mL), 80 °C under N$_2$ for 24 h. [b]Yield of the isolated product.

To obtain insights into this reaction, preliminary mechanistic studies have been performed. First, a moderate kinetic isotopic effect (k_H/k_D = 2.3) was obtained from an intermolecular competition experiment (eq 1), indicating that the C−H bond cleavage might be involved in the turnover-limiting step. Furthermore, we isolated a rhodacyclic imidate complex (**6**) from the stoichiometric C−H activation of **1a** (eq 2). The molecular structure of **6** has been unambiguously confirmed by X-ray crystallography (CCDC 1457730). Complex **6** proved to be an active catalyst for the coupling of **1a** and **2a** (eq 3). In addition, a competition experiment has been performed using an equimolar mixture of **1c** and **1j** under the standard conditions, from which **3c** and **3j** were obtained in 1.8:1 ratio on the basis of ^{1}H NMR analysis (eq 4), indicating that an EDG tends to kinetically favor the reaction.

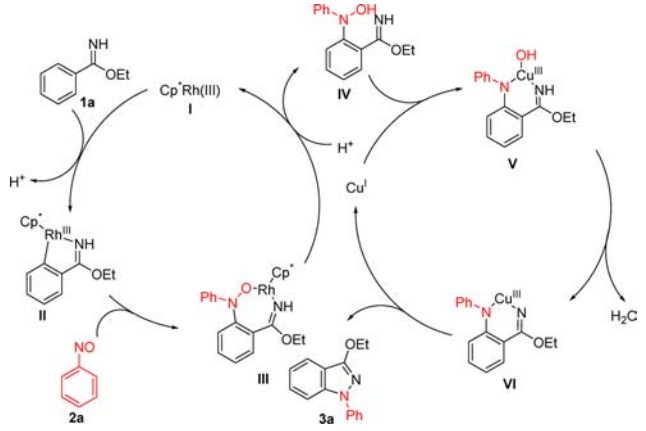


A synthetic application of a coupled product has been briefly explored. With 1,4,2-dioxazol-5-one (**7**) being an amidating reagent, product **3k** was readily amidated at the ortho-position of the *N*-phenyl ring via a Rh(III)-catalyzed C−H activation pathway, affording **8** in good yield (eq 5).[10]



On the basis of our mechanistic studies and literature reports,[11] a proposed mechanism for this coupling is depicted in Scheme 4. Coordination of an imidate to an active [Cp*Rh^{III}] catalyst (**I**) is followed by C−H activation to afford a rhodacycle **II**. Subsequently, the Rh−C bond undergoes migratory insertion into the N═O group to afford a six-membered rhodacycle **III**, protonolysis of which gives a hydroxylamine **IV**, and regenerate the Rh(III) species. In a sequential copper cycle, the Cu(I) species in the catalyst system may undergo N−O oxidative addition to deliver an organocupracycle **V**. The N−N bond was eventually formed via dehydration of **V** and N−N reductive elimination of **VI**. This proposal seems consistent with absence of correlation between the Lewis acidity of the additive and the reaction efficiency (poor efficiency for CuSO$_4$, FeCl$_3$, and Zn(OTf)$_2$). However, we cannot rule out the possible role of CuCl$_2$ as a unique Lewis acid that activates the OH leaving group in **IV** toward the attack of the protic imine group.

Scheme 4. Proposed Mechanism for the Formation of 1*H*-Indazoles



In conclusion, we have developed a cooperative rhodium- and copper-catalyzed C−N and N−N coupling between imidates and nitrosobenzenes, leading to redox-neutral synthesis of 1*H*-

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indazoles from readily available substrates. This method is highly efficient and exhibits good functional group tolerance. The reaction is step- and atom-economic and can be carried out under mild conditions, with H_2O as the sole byproduct. Further studies on the reaction mechanism are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00727.

Crystallographic data for **6** (CIF)

Experimental procedures, characterization data, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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