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Rhodium(III)-Catalyzed Oxidative Annulation of Ketoximes with Sulfonamide: A Direct Approach to Indazoles

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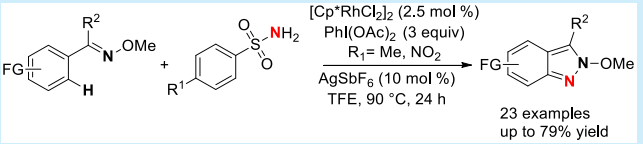
Supporting Information

ABSTRACT: A rhodium(III)-catalyzed intermolecular C–H amination of ketoxime and iodobenzene diacetate-enabled N–N bond formation in the synthesis of indazoles has been developed. A variety of functional groups were well tolerated, providing the corresponding products in moderate to good yields. Moreover, the nitro-substituted ketoximes are well compatible in this reaction, leading to the corresponding products in moderate to good yields.



Transition-metal-catalyzed C–H functionalization reactions have been successfully developed, which greatly enriched the route to construct vital synthetic skeletons in chemistry. In particular, this approach provides a highly efficient approach to directly realize the bioactive compounds in high atom efficiency.[1]

Indazoles are usually the key scaffolds of a range of pharmaceuticals, bioactive compounds, and natural products (Figure 1).[2] Therefore, it is very attractive to obtain the

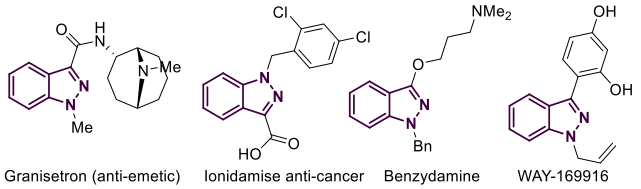
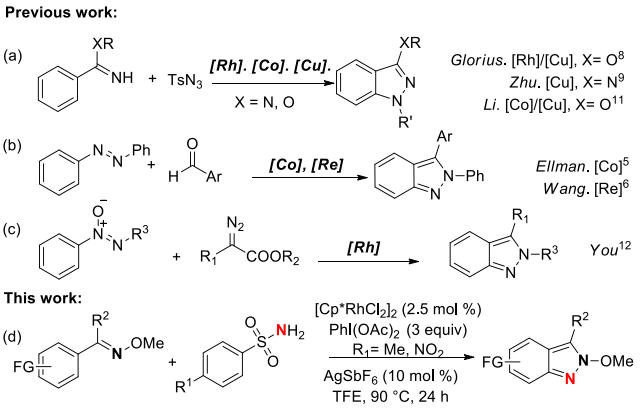


Figure 1. Representative drugs containing the indazole skeleton.

indazoles from ubiquitous compounds. Traditionally, indazoles have been synthesized via the condensation/cyclization of aryl ketones with hydrazines[3] or by cross-coupling/cyclization of *o*-halophenylacetylenes with hydrazines.[4] Recently, the transition-metal-catalyzed C–H functionalization strategy has provided an atom- and step-economy approach to the indazole derivatives. For instance, a redox-neutral coupling of azobenzenes with aryl aldehydes via Rh(III) or Co(III) catalysts for the synthesis of indazoles has been disclosed by the research group of Ellman (Scheme 1b).[5] Simultaneously, Glorius and co-workers reported a Rh(III)[7]-catalyzed oxidative annulation of arylimidates with organo azides to form the 1*H*-indazoles (Scheme 1a).[8] Subsequently, a copper-catalyzed tandem C–N/N–N bond formation in the synthesis of 1*H*-Indazoles was disclosed by the research group of Zhu (Scheme 1a).[9] Later, Li and co-workers developed an efficient Co(III)/Cu(II)[10]-catalyzed oxidative annulation of imidates with

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



anthranils to directly generate the indazoles (Scheme 1a).[11] Several other research groups such as those of You (Scheme 1c),[12] Kim,[13] Iiao,[14] Zhu, and Xi[15] have extensively worked in this field, thus providing different methods for synthesizing indazole derivatives from azoxybenzenes, azobenzenes, arylpyridines, or hydrazones. The group of Lee reported an efficient approach to synthesize the 2-aryl-2*H*-benzotriazoles from azobenzenes via sequential Rh-catalyzed amination and oxidantion in one pot. It was proposed that $PhI(OAc)_2$ was the key factor in realizing the oxidative cyclization reaction.[17] Although these developments have greatly enriched the route to indazole synthesis, it is still uncommon to directly synthesize indazoles by employing simple ketoximes as the substrates. Due to the exceeding importance of indazoles and the limitations of the reported methods, the development of new methods using readily available substrates would be very attractive in synthetic chemistry. Herein, we report the

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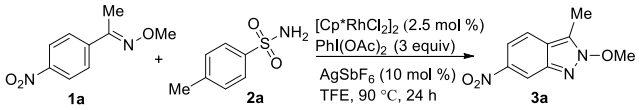
synthesis of indazoles by directly coupling ketoximes with sulfonamides using rhodium(III) as a catalyst and iodobenzene diacetate as an oxidant. Moreover, the nitro-substituted ketoximes are all well compatible, leading to the corresponding products in moderate to good yields.

The nitro group is a versatile functionality which can be easily converted into amino, halogen, and hydroxyl groups.[16] However, only a few reports on the transition-metal-catalyzed C−H functionalization to synthesize indazoles with the nitro functional group have been reported. Hence, we herein tried to address this issue through the further study of C−H functionalization reactions. At the beginning of our study, the 4-nitroacetophenone oxime (**1a**) and 4-toluenesulfonamide (**2a**) were selected as substrates for the optimization studies. Gratifyingly, the substrates **1a** and **2a** could be transformed into the indazole product **3a** in 39% yield through heating in the presence of $[Cp^*RhCl_2]_2$, $AgSbF_6$, and $PhI(OAc)_2$ in ethanol at 90 °C for 24 h (Table 1, entry 2). Next, a variety of

Table 1. Optimization of Reaction Conditions[a]



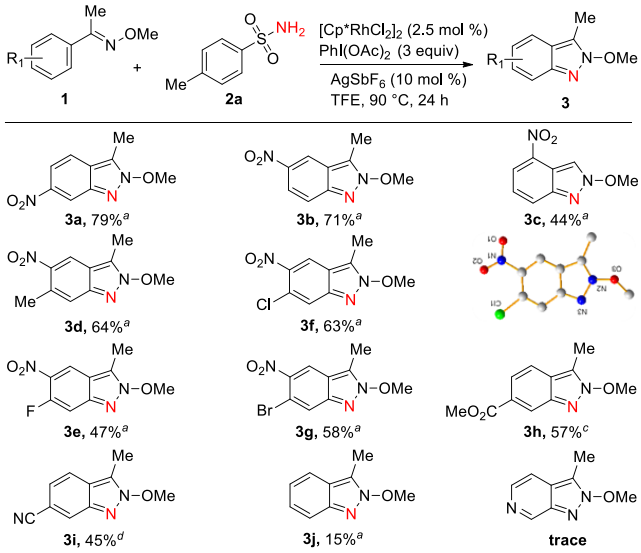
entry	additive	oxidant	solvent	yield[b] (%)
1	$AgSbF_6$	$PhI(OAc)_2$	MeOH	35
2	$AgSbF_6$	$PhI(OAc)_2$	EtOH	39
3	$AgSbF_6$	$PhI(OAc)_2$	*t*-Amyl−OH	31
4	$AgSbF_6$	$PhI(OAc)_2$	HFIP	76
5	$AgSbF_6$	$PhI(OAc)_2$	TFE	79
6	$AgSbF_6$	$K_2S_2O_8$	TFE	NR
7	$AgSbF_6$	$NaIO_4$	TFE	trace
8	$AgSbF_6$	$Cu(OAc)_2$	TFE	trace
9		$PhI(OAc)_2$	TFE	65
10[c]	$AgSbF_6$	$PhI(OAc)_2$	TFE	trace

[a]Reaction conditions, unless otherwise noted: **1a** (0.2 mmol), **2a** (0.6 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $PhI(OAc)_2$ (0.6 mmol), $AgSbF_6$ (10 mol %) in TFE (1.5 mL) at 90 °C for 24 h. [b]Isolated yields are given. [c]Without $[Cp^*RhCl_2]_2$.

solvents was explored; it was observed that the desired product **3a** can be obtained only when alcohol was used as the solvent (Table 1, entries 1−5). On the other hand, solvents such as 1,2-dichloroethane (DCE), toluene, 1,4-dioxane, and DMF did not afford the product **3a**, and the starting material was recovered (see Supporting Information).

Delightfully, a satisfactory yield of **3a** was obtained when trifluoroethanol was used as the solvent (Table 1, entry 5). Subsequently, several other oxidants such as $K_2S_2O_8$, $NaIO_4$, and $Cu(OAc)_2$ were screened, among which none gave the products in good yields (Table 1, entries 6−8). Furthermore, only 65% yield of **3a** was obtained when $AgSbF_6$ was not used in the reaction (Table 1, entry 9). A control reaction revealed that the rhodium(III) catalyst is indispensable for this oxidative annulation reaction (Table 1, entry 10). It is worth noting that the intermolecular amination reaction was not observed under these reaction conditions. With the optimized reaction conditions in hand, we next investigated the functional group tolerance on ketoximes, and the data are presented in Scheme 2. The nitro-substituted acetophenone oxime derivatives all performed well, leading to the corresponding indazoles in moderate to good yields (**3a−g**). The 2-nitrobenzaldehyde

Scheme 2. Substrate Scope of Ketoximes[a]



[a]Reaction conditions: **1** (0.2 mmol), **2b** (0.6 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $PhI(OAc)_2$ (0.6 mmol), $AgSbF_6$ (10 mol %) in TFE(1.5 mL) at 90 °C for 24 h. [b]Isolated yields are given. [c]**1** (0.2 mmol), **2** (0.6 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $PhI(OAc)_2$ (0.6 mmol), $AgSbF_6$ (10 mol %), KOAc (20 mol %) in TFE (1.5 mL) at 90 °C for 24 h. [d]**1** (0.2 mmol), **2c** (0.6 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $PhI(OAc)_2$ (0.6 mmol), $AgSbF_6$ (10 mol %), KOAc (50 mol %) in TFE(1.5 mL) at 90 °C for 24 h. **2c**: 4-methoxybenzenesulfonamide.

oxime only afforded the product **3c** in moderate yield, along with the starting material being recovered. In this case, the lower yield was ascribed to steric effects. The disubstituted acetophenone oxime derivatives were all compatible in this transformation, affording the corresponding products in good yields (**3d−g**). In addition, the crystal structure of **3f** further established the structure of the product. Further study revealed that both *p*-ester- (**2h**) and cyano-substituted (**2i**) acetophenone oximes all reacted smoothly, providing the corresponding products in moderate yields. However, the acetophenone oxime was unreactive, leading to less than 15% yield of **3j**, accompanied by the recovery of the starting material. Although the underlying reason is unclear, we inferred that the 4-toluenesulfonamide was less reactive for this transformation. Therefore, a variety of amides were further screened to address the predicament of the narrow substrate scope (Scheme 3).

The results of this study clearly demonstrated that the phenylsulfonamides substituted with electron-withdrawing functional groups provided better yields of the products. For instance, 4-nitrobenzenesulfonamide provided the indazole product **3j** in 52% yield. Benzamide and trifluoroacetamide afforded the desired products in less than 10% yields, while trifluoromethanesulfonamide generated the product **3j** in 51% yield. We next explored various substituted acetophenone oximes with 4-nitrobenzenesulfonamide under the standard reaction conditions, and the results are presented in Scheme 4. Propiophenone, *n*-butyrophenone, cyclopropyl phenyl ketone, and diphenylketone were all well tolerated, providing the corresponding products in good yields. The lower yield of **3o** and **3w** might be attributed to the de composition of the substrates (**1o** and **1w**) in the reaction. The acetophenone oximes substituted with functional groups such as F, Br, I, and CF_3 all reacted well, leading to the corresponding products in good yields (**3q−v**). It is worth noting that the iodide

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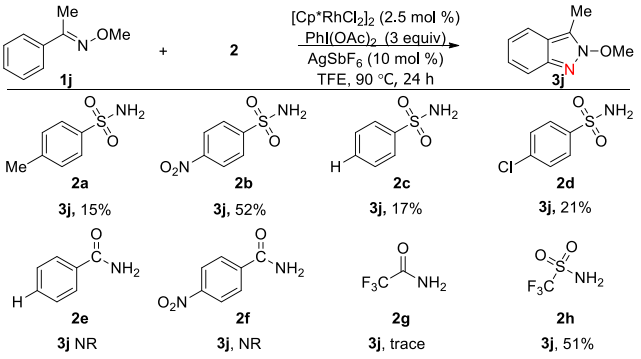
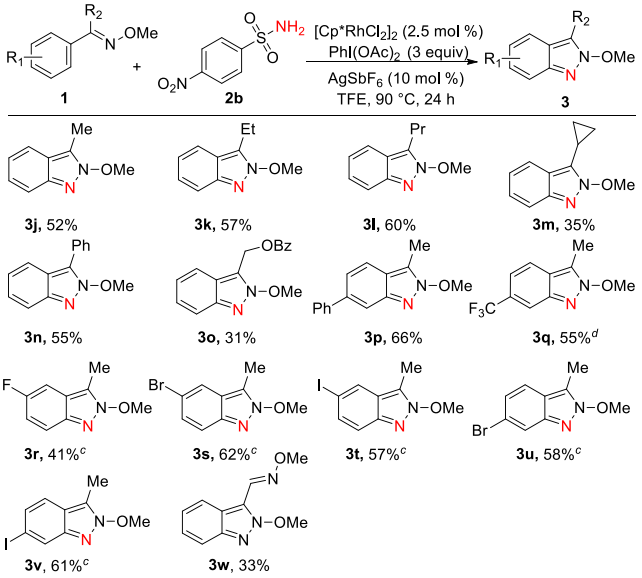
Scheme 3. Amide Effect[a]



[a]Reaction conditions, unless otherwise noted: **1** (0.2 mmol), **2a** (0.6 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $PhI(OAc)_2$ (0.6 mmol), $AgSbF_6$ (10 mol %) in TFE (1.5 mL) at 90 °C for 24 h. [b]Isolated yields are given. [c]**1** (0.2 mmol), **2b** (0.6 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $PhI(OAc)_2$ (0.6 mmol), $AgSbF_6$ (10 mol %) in TFE (1.5 mL) at 90 °C for 24 h. [d]**1** (0.2 mmol), **2a** (0.6 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $PhI(OAc)_2$ (0.6 mmol), $AgSbF_6$ (10 mol %), KOAC (20 mol %) in TFE (1.5 mL) at 90 °C for 24 h.

Scheme 4. Substrate Scope of Ketoximes[a]



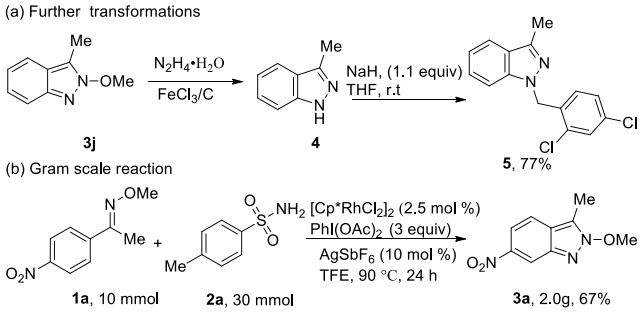
[a]Reaction conditions, unless otherwise noted: **1** (0.2 mmol), **2** (0.6 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $PhI(OAc)_2$ (0.6 mmol), $AgSbF_6$ (10 mol %) in TFE (1.5 mL) at 90 °C for 24 h. [b]Isolated yields are given.

functional group might provide a convenient means to install other functional groups through known protocols.

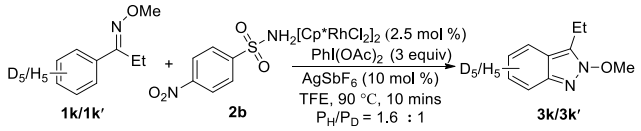
To further demonstrate the synthetic utility of this method, the methoxy group on the indazole was first removed under mild reaction conditions (see the Supporting Information). Furthermore, the product **5** can be easily prepared and may be used as a key precursor to synthesize ionidamise (Scheme 5a). The reaction could also be easily scaled up to grams with slightly reduced yields (Scheme 5b).

To explore the pathway of this rhodium(III)-catalyzed annulation of ketoximes with arylsulfonamide, several parallel reactions were carried out to elucidate the role of each reagent. First, a kinetic isotopic effect (PH/PD = 1.6) was observed from the intermolecular completion experiment (Scheme 6).

Scheme 5. Applications of the Reaction

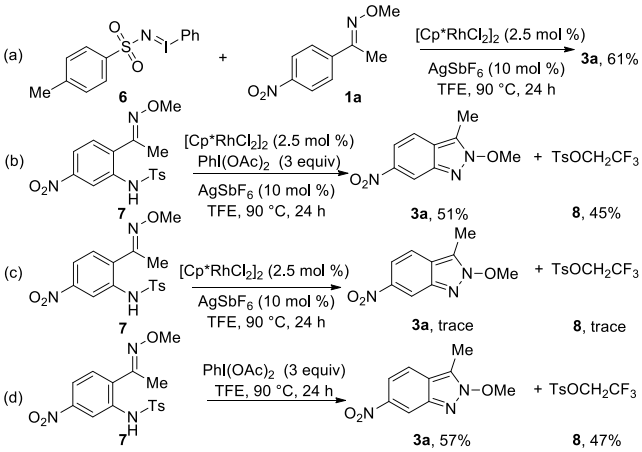


Scheme 6. Kinetic Isotopic Effect



Second, when iodonium (**6**) was used instead of 4-toluenesulfonamide, the corresponding product **3a** was obtained in 61% yield (Scheme 7a). This result indicates

Scheme 7. Preliminary Mechanistic Study



that **6** may be generated in the reaction, followed by its reaction with the rhodium complex. Finally, when the substrate **7** was subjected to the standard reaction conditions, the desired product **3a** was isolated in 51% yield, accompanied by the product **8** in 45% yield (Scheme 7b). Interestingly, when **7** was treated with rhodium(III) catalyst and $AgSbF_6$, without iodobenzene diacetate, the product **3a** was not obtained, while **1a** was completely recovered (Scheme 7c). On the other hand, the product **3a** could be attained in 57% yield, along with the product **8** in 47% yield, when iodobenzene diacetate was used as the oxidant (Scheme 7d).[17] Altogether, these results indicated that the intermolecular amination occurred first followed by N−N bond formation with iodobenzene diacetate as the oxidant. The obtained product **8** may explain the reason why only alcohol as the solvent could provide the C−N/N−H bond formation product.

Based on these results and previous reports, a plausible catalytic cycle was proposed in Scheme 8. The cationic $[Cp^*Rh^{III}]$ complex I would be generated in the presence of $AgSbF_6$ in the reaction, which would coordinate with ketoxime, followed by the C−H activation, leading to the complex II.

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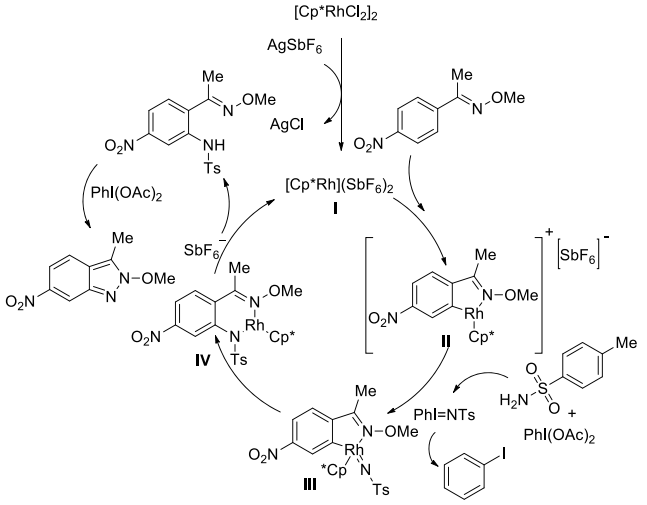
Scheme 8. Proposed Mechanism



The iodonium **6** which was formed in situ in the reaction can oxidize the complex II, providing the complex III, followed by the migratory insertion, generating the complex IV. The intermolecular amination product would be formed and release the active complex I. Subsequently, the product **3a** reacted with iodobenzene diacetate to give the final product.

In conclusion, we have developed a practical approach for the synthesis of indazoles via the rhodium(III)-catalyzed intermolecular C−H amination of ketoxime and iodobenzene diacetate-enabled N−N bond formation. Moreover, the well-known nitro-substituted ketoximes were all well compatible, leading to the corresponding products in good to excellent yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03488.

Experimental procedures, characterization data, and ^{1}H and ^{13} NMR spectra for all compounds (PDF)

Accession Codes

CCDC 1875850 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.

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