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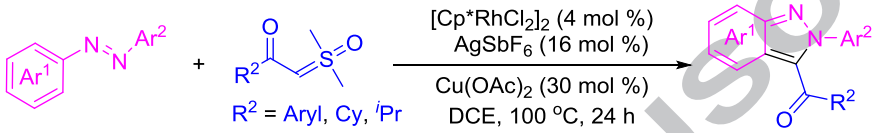

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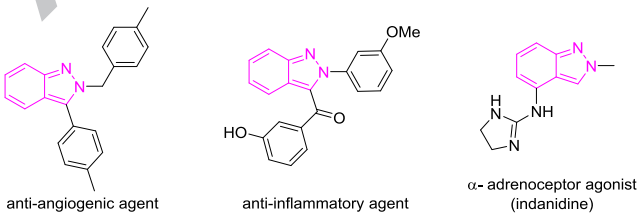
ABSTRACT

A Rh(III)-catalyzed [4 + 1]-annulation of azobenzenes with *α*- carbonyl sulfoxonium ylides was developed to access 2*H*-indazoles in moderate to excellent yields with good functional group compatibilities. It proceeded with the sequential insertion of the Rh(III) carbene to the C−H bond and cyclization steps, where sulfoxonium ylides served as efficient and stable carbene precursor.

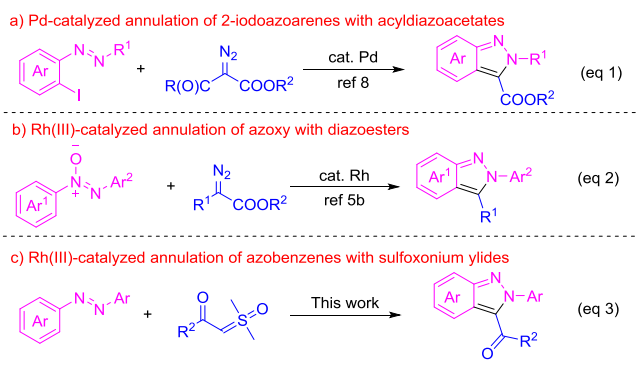
The indazole backbone is ubiquitous in natural products, drugs, agrochemicals, and bioactive compounds.[1] Therefore, numerous efforts have been developed to construct these biologically important skeletal motifs due to their potential pharmaceutical properties (**Figure 1**).[2] However, compared with the well-developed methodologies toward 1*H*-indazoles,[3] only a limited number of approaches were demonstrated to access 2*H*-indazoles,[4,5] especially 3-acyl-2*H*-indazoles.[6] Thus, it is attractive and highly desirable to develop straightforward and atom-economic pathways toward 3-acyl-2*H*-indazoles in organic chemistry.

Figure 1. Selected Bioactive 2*H*-Indazoles.



Transition-metal-catalyzed sequential directing group-assisted C−H bond activation/cyclization represents a powerful approach for the construction of heterocycles.[7] Significant progress have been made by Glorius,[8] Ackermann,[9] Wang,[10] Chang,[11] and others.[12] α-Diazocarbonyl compounds have been extensively considered as metal-carbene precursors to insert into C−H bonds followed annulation toward heterocycles. With this regard, In the case of 2*H*-indazole, Lee developed a palladium-catalyzed [4 + 1]-annulation of 2-iodoazoarenes with acyldiazoacetates to access 2*H*-indazoles (**Scheme 1a**).[13] Afterwards, You reported the Rh(III)-Catalyzed [4 + 1]-annulation of azoxy compounds with diazoesters to access 2*H*-indazoles (**Scheme 1b**).[5b] However, these reactions are mostly limited to functionalized azobenzenes (halogenated or azoxylated) and acceptor diazo compounds; while simple diazoacetates or diazoketones failed to work.

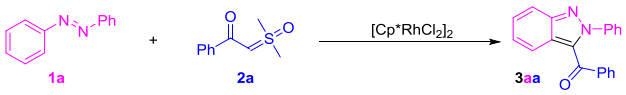
Scheme 1. Transition-Metal-Catalyzed [4+1] Annulation of Carbene Precursors toward 2*H*-Indazoles



Thus, it is urgent to develop efficient and stable surrogate of diazo compounds[14] to overcome these limitations. Sulfur ylides function as surrogates of diazo compounds in metal-catalyzed

reactions due to the relatively higher security and stability. Recently, Aissa and co-workers pioneered a rhodium-catalyzed coupling of aromatic C(sp^2)–H with α-aroyl sulfur ylides.[15a] Afterward, Li applied this strategy in the synthesis of a variety of carbocycles and N-heterocycles.[15b] Herein, we wish to report a Rh(III)-Catalyzed [4 + 1] annulation proceeded with the sequential insertion of the C–H bond to the Rh(III) carbenes derived from sulfoxonium ylides,[15,16] reductive elimination and cyclization steps towards 3-acyl-(2*H*)-indazoles (**Scheme 1c**).

Table 1. Selected Results for Screening the Optimized Reaction Conditions.[a]



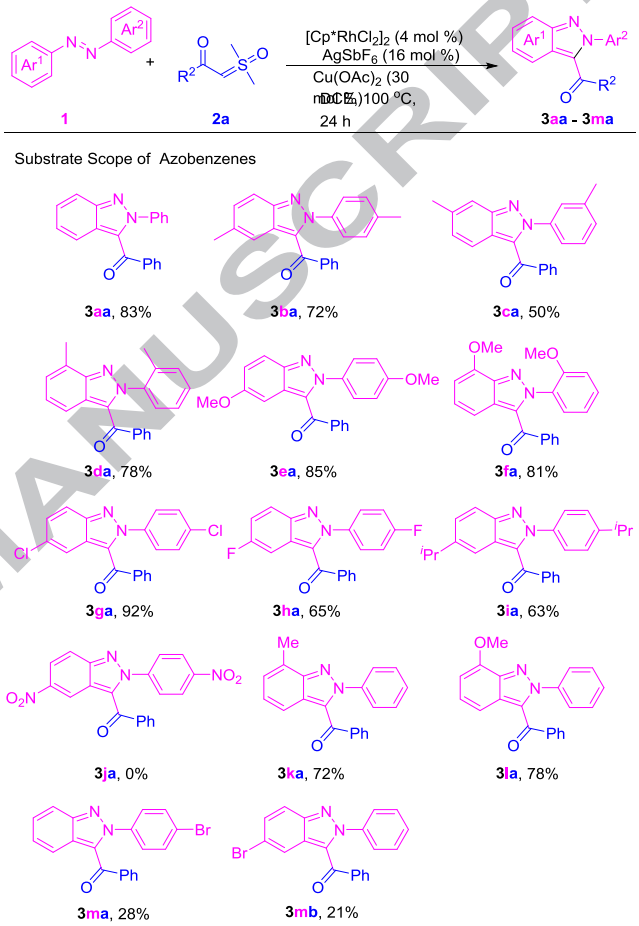
entry	[Ag]	additive	solvent	yield (%)[b]
1	$AgSbF_6$	NaOAc	MeOH	43
2	$AgSbF_6$	NaOAc	THF	< 5
3	$AgSbF_6$	NaOAc	DMSO	15
4	$AgSbF_6$	NaOAc	Dioxane	< 5
5	$AgSbF_6$	NaOAc	MeCN	25
6	$AgSbF_6$	NaOAc	DCE	55
7	$AgSbF_6$	AcOH	DCE	63
8	$AgSbF_6$	$Cu(OAc)_2$	DCE	83[c], 47[d], 65[e],73[f]
9	AgOAc	$Cu(OAc)_2$	DCE	33
10	Ag_2O	$Cu(OAc)_2$	DCE	< 5
11	$AgSbF_6$	--	DCE	20
12	--	$Cu(OAc)_2$	DCE	< 5[g]

[a] Reaction conditions: Azobenzene **1a** (0.2 mmol), sulfoxonium ylide 2a (0.4 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), [Ag] (16 mol %), additive (30 mol %), in DCE (2 mL), under air, 100 °C, 24 h. [b] Isolated yield. [c] Under air. [d] Under N_2. [e] At 80 °C. [f] At 120 °C. [g] without $[Cp^*RhCl_2]_2$ or $AgSbF_6$.

Initially, we tested the reaction of azobenzene **1a** (0.2 mmol), and sulfoxonium ylide **2a** (0.4 mmol) in the presence of $[Cp^*RhCl_2]_2$ (4 mol %), $AgSbF_6$ (16 mol %) and NaOAc (30 mol %) in MeOH (2 mL) under air at 100 °C for 24 h. To our delight, the product 3-acyl-(2*H*)-indazole **3aa** was isolated in 43% yield (Table 1, entry 1). During the screening of solvents, DCE was superior to THF (< 5%), DMSO (15%), 1,4-dioxane (< 5%), and MeCN (25%, entries 1–6). Notably, the yield increased to 63% and 83% by using AcOH and $Cu(OAc)_2$ as the additives, respectively (entries 7 and 8). Besides, varying either the N_2 atmosphere or reaction temperature (80 and 120 °C) all decreased the reaction efficiency (Table 1, entry 8). Other silver additives such as AgOAc (33%) and Ag_2O (< 5%) were inferior to $AgSbF_6$ (entries 9 and 10). The product **3aa** was isolated in 20% yield in the absence $Cu(OAc)_2$ (entry 11). Finally, the blank reaction revealed no reaction took place at all in the absence of either $[Cp^*RhCl_2]_2$ or $AgSbF_6$ (entry 12).

To evaluate the scope and limitation of this process, the reactivity of various azobenzene derivatives was investigated, as shown in **Scheme 2**. As expected, both substituted azobenzenes worked well with good to excellent yields. When methyl and methoxy- substituted azobenzenes were treated with **2a** under the standard conditions, the corresponding products (**3ba-fa**, 50-85%) were isolated in moderate to good yields. Azobenzenes bearing halogen groups on the phenyl ring ran smoothly under the standard procedure with moderate to excellent yields. For example, 4-chloro-substituted azobenzene **1g** provided the 2*H*-indazole **3ga** in 92% yield. The sterically hindered substituents slightly influenced the reaction, as **3ia** was isolated in 63% yields. In the case of the *meta*- substituted substrate, the cyclization selectively took place in the *ortho*- position of phenyl with less hindrance (**3ca**). Unfortunately, the 4-nitro analogue **1j** failed to work (**3ja**, 0%). Notably, the practicability of this transformation was further increased as **3aa** was isolated in an acceptable 78% yield in a 3 mmol scale reaction (for details, see the Supporting Information).

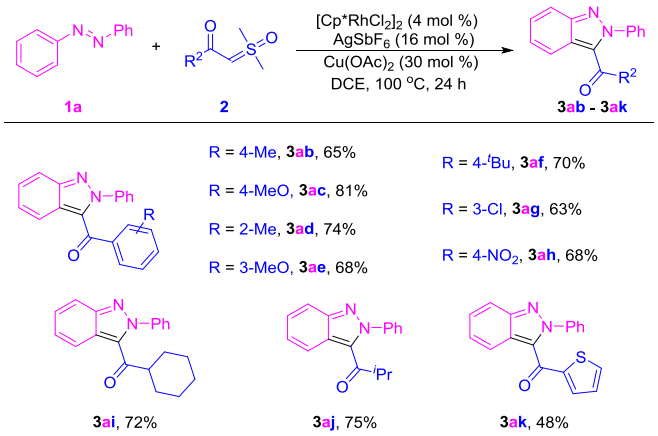
Scheme 2. The Scope of Azobenzenes.[a]



[a] Reaction conditions: Azobenzene **1a** (0.2 mmol), sulfoxonium ylide **2a** (0.4 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), $AgSbF_6$ (16 mol %), $Cu(OAc)_2$ (30.0 mol %), in DCE (2 mL), under air, 100 °C, 24 h.

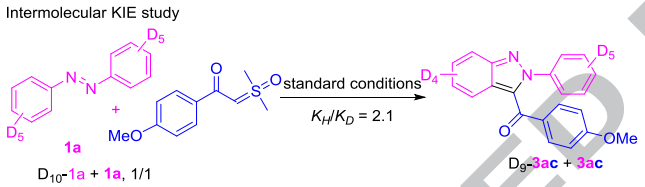
In this case of unsymmetrical azobenzenes, such as (*E*)-1-phenyl-2-(*o*-tolyl)diazene and (*E*)-1-(2-methoxyphenyl)-2-phenyldiazene, it was the electron nature but not the hindrance in the phenyl controlled the selectivity. The reaction selectively took place in the electron-rich aryl ring substituted with electron-donating group, providing **3ka** (72%) and **3la** (78%) in good yields, respectively. Moreover, unsymmetrical azobenzene **1m** was also compatible to afford a mixture of 3- acyl (2*H*)-indazoles **3ma** and **3mb** in 49% combined yield with a 1.3:1 ratio.

Scheme 3. The Scope of α- Carbonyl Sulfoxonium Ylides[a]



[a] Reaction conditions: Substituted azobenzene **1a** (0.2 mmol), sulfoxonium ylide **2** (0.4 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), $AgSbF_6$ (16 mol %), $Cu(OAc)_2$ (30 mol %), in DCE (2 mL), under air, 100 °C, 24 h.

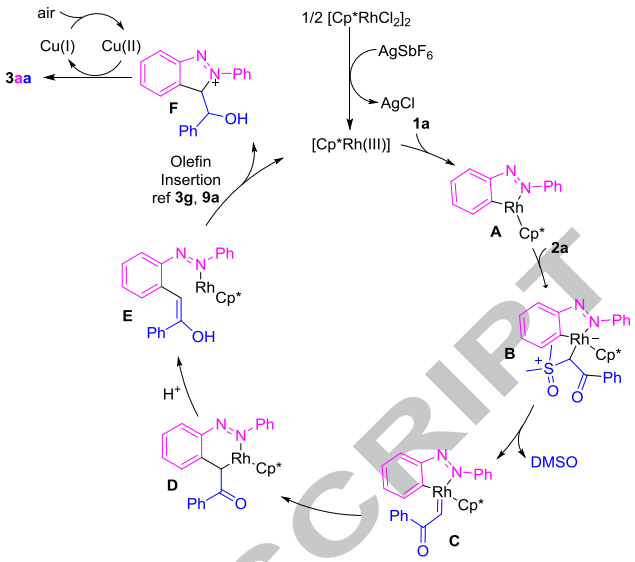
Meanwhile, the scope of α- carbonyl sulfoxonium ylides was studied, as shown in **Scheme 3**. Sulfoxonium ylides bearing both electron-donating groups (**3ab-af**, 65-81%) and electron-withdrawing groups (**3ag**, 63%; **3ah**, 67%) all coupled smoothly with azobenzene in moderate to good yields under the standard conditions. Furthermore, alkyl- and heteroaryl-substituted analogues also worked well under the standard conditions, leading to corresponding 3-acyl-(2*H*)-indazoles derivatives in 72% (**3ai**), 75% (**3aj**) and 48% (**3ak**) yields, respectively.



Scheme 4. KIE Study.

Next, more experiments were conducted to get insight into the reaction mechanism (**Scheme 4**). The inter-molecular kinetical isotope effect (KIE) was found to be 2.1. Thus, the *ortho*- C−H bond cleavage of azobenzene might be involved in the rate-determining step.

Based on these experimental results (**Scheme 4**) and reported literature,[3g, 9a] a proposed mechanism as shown in **Scheme 5**. First, the C−H bond of azobenzene is activated by Rh(III) species to provide a five-membered cyclo-rhodium species **A**. Following the insertion of sulfoxonium ylides to the rhodium-species **A** gives a Rh(III) intermediate **B**. Second, Rh(III) intermediate **B** undergoes α- elimination of DMSO gives a reactive carbene species **C**. Afterward, migratory insertion would deliver a six-membered rhodacycle species **D**. Third, the keto-enol tautomerization generates an olefined azobenzene **E**. Subsequently, it undergoes insertion of C=C bond into Rh−N bond to the intermediate **F**. Finally, the oxidation and aromatization provides indazoles. Copper may also take part in this step.



Scheme 5. A Tentative Mechanism.

In conclusion, we have disclosed Rh(III)-Catalyzed [4 + 1]-annulation of substituted azobenzenes with α- carbonyl sulfoxonium ylides leading to a wide range of of 3-acyl 2*H*-indazoles, which are crucial motifs of biologically active compounds. It represents a novel and efficient method to access such frameworks from simple starting material.

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1. Annulation of azobenzenes with α- carbonyl sulfoxonium ylides

2. Features with excellent yields and good functional group compatibilities.

3. Sulfoxonium ylides served as efficient and stable carbene precursor