JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

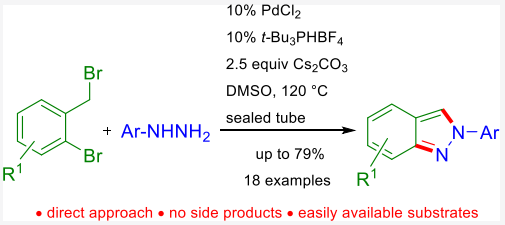
Direct Formation of 2-Substituted 2*H*-Indazoles by a Pd-Catalyzed Reaction between 2-Halobenzyl Halides and Arylhydrazines

Nayyef Aljaar, Mousa Al-Noaimi, Jürgen Conrad, and Uwe Beifuss*

Cite This: https://dx.doi.org/10.1021/acs.joc.0c01923 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A direct and operationally simple method for the regioselective synthesis of 2-aryl-substituted 2*H*-indazoles is reported. The Pd-catalyzed reaction between easily available 2-bromobenzyl bromides and arylhydrazines employing Cs_2CO_3 as the base and *t*-Bu_3PHBF_4 as the ligand in DMSO at 120 °C in a sealed tube delivers the 2-substituted-2*H*-indazoles in a single synthetic step with yields up to 79%. The new method is based on a regioselective intermolecular *N*-benzylation followed by intramolecular *N*-arylation and oxidation.



INTRODUCTION

Heterocycles play a very important role in organic synthesis because they occur in countless natural products and other biologically active compounds. 1*H*- and 2*H*-indazoles are common heterocyclic motifs with interesting biological properties.[1] Typical examples include antiaggregation,[1b] antihypertensive,[2] HIV protease inhibiting,[3] antitumor,[4] antidepressant,[5] anti-inflammatory and analgesic,[6] antimicrobial,[7] and antifungal[8] activities. 2*H*-indazoles are known for their wide range of pharmacological activities. They can act as vascular endothelial growth factor receptor inhibitors (Pazopanib),[9] poly(ADP-ribose)polymerase inhibitors (Niraparib),[10] viral polymerase inhibitors,[11] glucokinase activators,[12] anti-inflammatory drugs,[13] antinociceptives,[14] antimicrobials,[15] estrogen receptor β agonists,[16] and farnesoid X receptor antagonists.[17] Because of the great importance of 1*H*-indazoles, many routes for their preparation have been established. In contrast to the synthesis of the thermodynamically more stable 1*H*-indazoles, only a few methods have been developed for the synthesis of 2*H*-indazoles. The most obvious method, the direct synthesis by arylation/alkylation is not suitable because usually mixtures of substituted 1*H*-indazoles and 2*H*-indazoles are obtained. Among the selective methods for 1*H*-indazoles are the Pd-catalyzed intramolecular amination of 1-*o*-bromobenzyl-1-phenylhydrazines,[18] the reductive cyclization of 2-nitrobenzylamines with $TiCl_4$/Zn,[19] the reductive cyclization of *o*-nitrobenzylidene amines,[20] and the Fe-catalyzed N-N bond formation of 2-azidophenylketoximes (Scheme 1).[21] Other examples include the Pd-catalyzed domino reaction of 2-halophenylacetylenes with hydrazines,[22] the reaction between 2-chloromethylarylzinc reagents and aryldiazonium salts,[23] the [3 + 2] cycloaddition of arynes and sydnones,[24] and the Co(III)-catalyzed C-H addition of azobenzenes to aldehydes[25a] as well as the Rh(III)-catalyzed C-H addition of azobenzenes to ethyl glyoxalate and aryl glyoxals[25b] and the Cu-catalyzed reaction of 2-bromobenzaldehydes with primary amines and sodium azides.[26] A closer inspection reveals that some of these methods suffer from certain drawbacks, such as the use of difficult accessible substrates and catalysts, the need for an excess of reagents, or poor atom economy. A number of methods mentioned have the disadvantage that only one bond is formed during the key step. This is why there is still a great need to develop simple to perform and direct methods for the synthesis of 2*H*-indazoles starting from readily available substrates.

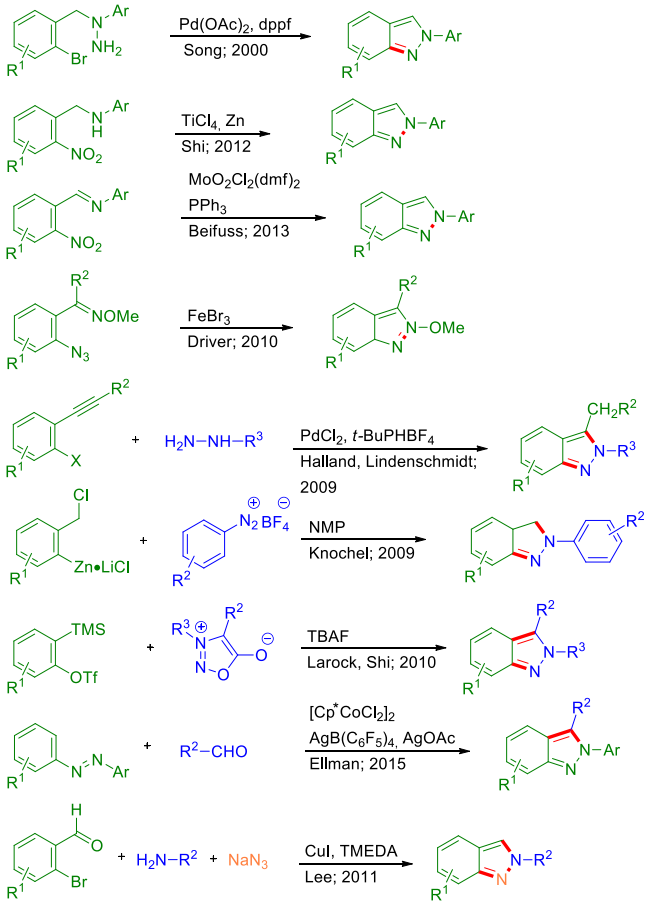
During the last few years, we have contributed to the synthesis of a number of carbo and heterocycles by developing reactions between 2-halobenzyl halides/tosylates and bisnucleophiles.[27] In continuation of our work, we wondered whether it is possible to synthesize 2-aryl-2*H*-indazoles **3** in a regioselective manner in one step by direct reaction of easily available 2-bromobenzyl bromides **1** and arylhydrazines **2** (Scheme 2). It was envisaged that the reaction starts with the selective formation of a 1-*o*-bromobenzyl-1-arylhydrazine **4** by regioselective *N*-benzylation, which in turn undergoes an intramolecular *N*-arylation to **5**. This is followed by oxidation to finally yield the 2-aryl-2*H*-indazole **3**. Of course, the main challenge of this approach is to achieve the completely regioselective formation of the 1-*o*-bromobenzyl-1-arylhydrazines **4** and to exclude the formation of the corresponding 1-*o*-bromobenzyl-2-arylhydrazines **6**, which would result in the formation of the 1-aryl-1*H*-indazoles **7**.

Song and Yee have circumvented this problem by performing the synthesis of the 2-aryl-2*H*-indazoles **3** in two separate

Received: August 9, 2020

https://dx.doi.org/10.1021/acs.joc.0c01923
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 1. Different Approaches for the Synthesis of 2*H*-Indazoles



synthetic steps.[18] In the first step, the 1-*o*-bromobenzyl-1-arylhydrazines **4** were synthesized and isolated in yields between 60 and 70% by reaction of 2-bromobenzyl bromides **1** with the hydrochlorides of the arylhydrazines **2** under strongly basic conditions (NaHMDS) based on the method of Lerch und König.[28] In the second step, the so-formed 1-*o*-bromobenzyl-1-arylhydrazines **4** were cyclized in a Pd-catalyzed reaction to yield the corresponding 2-aryl-2*H*-indazoles **3** in yields between 51 and 60%. Using this approach, a number of 1-*o*-bromobenzyl-1-arylhydrazines **4** have been synthesized and cyclized to the corresponding 2-aryl-2*H*-indazoles **3** by Song and Yee. Without doubt, it would be a considerable improvement if the isolation and chromatographic purification of the 1-*o*-bromobenzyl-1-arylhydrazines **4** could be avoided. Here, we report on a method for the synthesis of 2-aryl-2*H*-indazoles **3** that makes the isolation and purification of the 1-*o*-bromobenzyl-1-arylhydrazines **4** superfluous. This makes the synthesis of the 2-aryl-2*H*-indazoles **3** from 2-bromobenzyl bromides **1** and arylhydrazines **2** more efficient, and we will demonstrate that the yields are much higher than those obtained by a two-step method.

RESULTS AND DISCUSSION

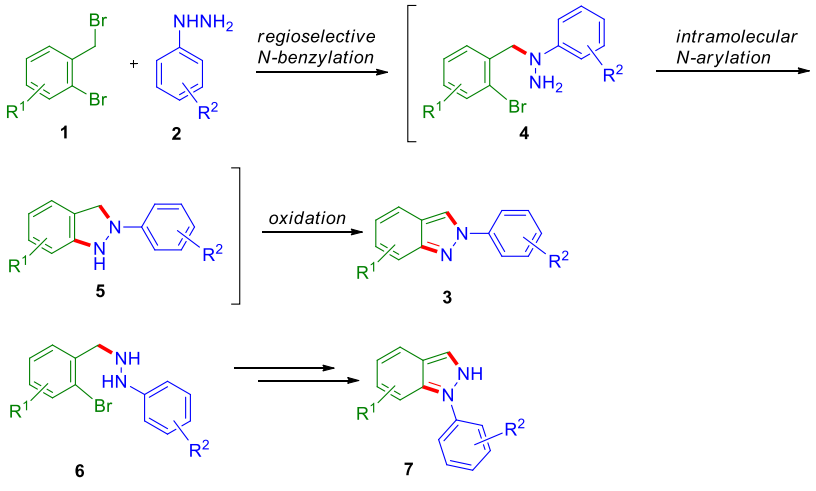
As a model reaction for our study, the reaction between 2-bromobenzyl bromide (**1a**) and phenylhydrazine (**2a**) was chosen. When 1 equiv **1a** and 2.5 equiv **2a** were reacted in the presence of 10 mol % $PdCl_2$, 10 mol % *t*-Bu_3PHBF_4, and 2 equiv Cs_2CO_3 in DMF in a sealed tube at 100 °C for 16 h, 2-phenyl-2*H*-indazole (**3a**) could be isolated in only 12% along with 5% of the undesired isomeric 1-phenyl-1*H*-indazole (**7a**) (Table 1, entry 1). The yield of **3a** could be slightly increased by changing reaction time and temperature (Table 1, entries 2−7). The best result was achieved under the conditions of Table 1, entry 5 with a yield of 31% for **3a** and only traces of **7a**.

To facilitate the reaction between **1a** and **2a**, the transformations were run in a microwave oven at different temperatures (Table 1, entries 8−12). Increasing the temperature from 120 to 150 °C leads to a slight increase of the yield of **3a** from 31 to 35% (Table 1, entries 8−11). However, when the reaction temperature was raised to 160 °C, the yield of **3a** dropped to 29% (Table 1, entry 12).

Then, the influence of solvents on the outcome of the model reaction was examined (Table 1, entries 13−19). The experiments clearly demonstrated that the reaction can not only be performed in polar solvents (Table 1, entries 13, 14, 16, 17, and 19) but also in nonpolar solvents such as dioxane and toluene (Table 1, entries 15 and 18). The best yields of **3a** were obtained with DMSO and H_2O as solvents (Table 1, entries 13 and 17).

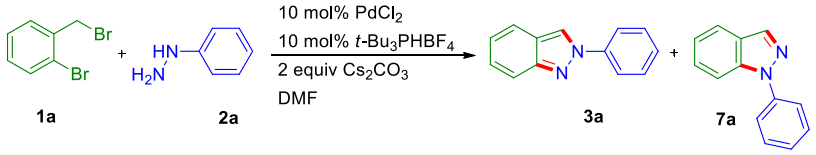
After some experimentation, it was found that the yield of **3a** as well as the **3a**: **7a** ratio could be considerably improved

Scheme 2. Proposed Method for the Direct Synthesis of 2-Substituted-2*H*-Indazoles (3)



https://dx.doi.org/10.1021/acs.joc.0c01923
J. Org. Chem. XXXX, XXX, XXX−XXX

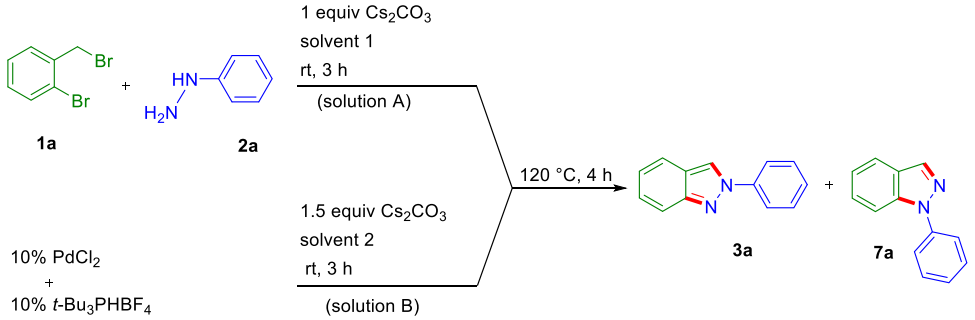
Table 1. Initial Experiments and Optimization of the Reaction Conditions for the Selective Formation of 2-Phenyl-2*H*-Indazole (3a)



entry	T (°C)	t	solvent	yield **3a** (%)	yield **7a** (%)
1[a]	100	16 h	DMF	12	5
2[a]	100	5 h	DMF	18	6
3[a]	110	20 h	DMF	21	trace
4[a]	110	5 h	DMF	28	trace
5[a]	120	4 h	DMF	31	trace
6[a]	130	5 h	DMF	26	trace
7[a]	130	4 h	DMF	15	trace
8[b]	120	10 min	DMF	31	trace
9[b]	140	10 min	DMF	30	trace
10[b]	150	10 min	DMF	34	trace
11[b]	150	15 min	DMF	35	trace
12[b]	160	10	DMF	29	trace
13[a]	120	4 h	DMSO	33	2
14[a]	120	4 h	NMP	31	10
15[a]	120	4 h	dioxane	18	8
16[a]	110	4 h	CH_3CN	21	11
17[a]	110	4 h	H_2O	34	trace
18[a]	120	4 h	toluene	15	trace
19[c]	120	4 h	DMF	23	11

[a]1 Equiv **1a** and 2.5 equiv **2a** were heated in a sealed tube using an oil bath. [b]1 Equiv **1a** and 2.5 equiv **2a** were reacted in a sealed tube under microwave conditions (50 W and 5 bar). [c]1 Equiv **1a** and 2.5 equiv **2a** were heated in a Schlenk tube.

Table 2. Influence of Mixed Solvents on the Outcome of the Model Reaction between 1a and 2a[a]



entry	solvent 1	solvent 2	yield **3a** (%)	yield **7a** (%)
1[b]	DMF	DMF	45	4
2[b]	H_2O	DMF	27	1
3[b]	H_2O	DMSO	52	3
4[b]	H_2O	H_2O	40	2
5[b]	DMSO	DMSO	57	2
6[b]	DMSO/H_2O	DMSO/H_2O	53	11
7[c]	DMSO	DMSO	50	7

[a]In all cases, 1 equiv **1a** was reacted with 2.5 equiv **2a**. A solution of **1a**, **2a**, and Cs_2CO_3 in solvent 1 (solution A) and a solution of $PdCl_2$, *t*-Bu_3PHBF_4, and Cs_2CO_3 in solvent 2 (solution B) were prepared, and after 3 h at room temperature (rt), the two solutions were combined. [b]The reaction mixture was heated for 4 h in a sealed tube at 120 °C using an oil bath. [c]The reaction was performed in a microwave oven (50 W) at 150 °C for 10 min.

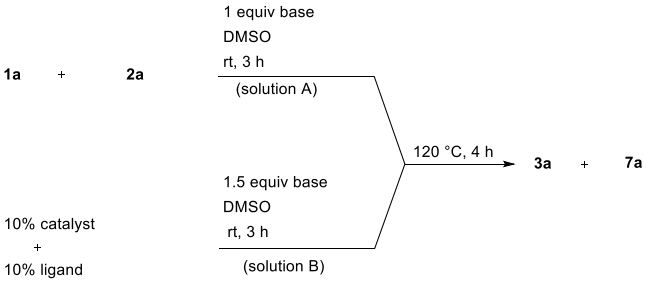
using a different experimental approach (Table 2). We prepared solutions of (a) reactants **1a**, **2a**, and Cs_2CO_3 in solvent 1 (solution A) and (b) catalyst, ligand, and Cs_2CO_3 in solvent 2 (solution B). Then, the two solutions A and B were combined and reacted at 120 °C for 4 h. Using this approach, the yield of **3a** could be improved to 57% (Table 2, entry 5) when DMSO was used as the solvent in both solutions A and B. At least as important was the observation that under these conditions the formation of **7a** could be almost completely suppressed (only 2% of the isomer **7a** was formed).

For further optimization, the reaction between **1a** and **2a** was conducted with different Pd catalysts, ligands, and bases

https://dx.doi.org/10.1021/acs.joc.0c01923
J. Org. Chem. XXXX, XXX, XXX−XXX

(Table 3). It was found that the reaction can be run with 10 mol % of several Pd catalysts (Table 3, entries 1−3). However,

Table 3. Influence of Catalysts, Ligands, and Bases on the Outcome of the Reaction 1a + 2a → 3a[a]



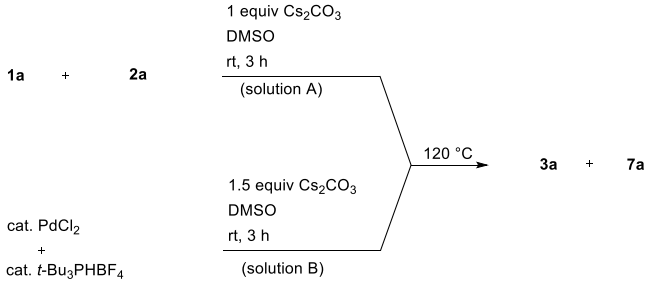
entry	catalyst	ligand	base	yield **3** (%)	yield **7a** (%)
1	$Pd(OAc)_2$	t-Bu_3PHBF_4	Cs_2CO_3	42	3
2	$Pd_2(dba)_3$	t-Bu_3PHBF_4	Cs_2CO_3	51	3
3	$Pd(acac)_2$	t-Bu_3PHBF_4	Cs_2CO_3	46	6
4	$PdCl_2$	PPh_3	Cs_2CO_3	5	trace
5	$PdCl_2$	dppf	Cs_2CO_3	26	5
6	$PdCl_2$	DIPHOS	Cs_2CO_3	4	trace
7	$PdCl_2$	t-Bu_3PHBF_4	K_3PO_4	38	3
8	$PdCl_2$	t-Bu_3PHBF_4	K_2CO_3	27	4
9	$PdCl_2$	t-Bu_3PHBF_4	KO^{t}Bu	10	trace
10		t-Bu_3PHBF_4	Cs_2CO_3		
11	$PdCl_2$		Cs_2CO_3		
12	$PdCl_2$	t-Bu_3PHBF_4			

[a]In all cases, 1 equiv **1a** was reacted with 2.5 equiv **2a**. A solution of **1a**, **2a**, and base in DMSO (solution A) and a solution of the catalyst, ligand, and base in DMSO (solution B) were prepared. After 3 h at rt, the two solutions were combined, and the reaction mixture was heated for 4 h in a sealed tube at 120 °C using an oil bath.

the yields were lower than those with $PdCl_2$. The replacement of t-Bu_3PHBF_4 with other ligands was also not met with success (Table 3, entries 4−6). Furthermore, the replacement of Cs_2CO_3 with other bases did not pay off (Table 3, entries 7−9). At this stage, we also took the opportunity to perform some control experiments. For this purpose, the reaction between **1a** and **2a** was conducted in the absence of a Pd catalyst (Table 3, entry 10), a ligand (Table 3, entry 11), and a base (Table 3, entry 12). In none of these control experiments, the formation of 2-phenyl-2*H*-indazole (**3a**) could be observed.

Finally, the reaction was performed with different molar ratios **1a**: **2a**, different amounts of $PdCl_2$ and t-Bu_3PHBF_4, and different reaction times (Table 4). With a molar ratio **1a**: **2a** = 1:2.5, 10 mol % $PdCl_2$, 10 mol % t-Bu_3PHBF_4, and a reaction time of 13 h, the yield of **3a** could be raised to 60%, and the formation of **7a** could be almost suppressed (Table 4, entry 5). An increase of the reaction time from 13 to 18 h delivered the best result: Under these conditions, **3a** could be isolated in 64%, and the side product formation could be effectively suppressed (Table 4, entry 6). A further increase of the reaction time from 18 to 22 h and 42 h, respectively, did not pay off (Table 4, entries 7 and 8). Finally, the influence of the molar ratio **1a**: **2a** was examined. It was found that the exclusive formation of **3a** could also be achieved when different molar ratios **1a**: **2a**, such as 1:1, 1:2, and 1:3, were used (Table 4, entries 9−11). However, in no case, the yield of **3a** exceeded 64%. In summary, the highest yield of **3a** could be achieved under the conditions presented in Table 4, entry 6.

Table 4. Influence of the Molar Ratio 1a: 2a and the Amounts of Catalyst and Ligands as well as the Reaction Time on the Outcome of the Model Reaction[a]



entry	molar ratio **1a**: **2a**	$PdCl_2$ (mol %)	t-Bu_3PHBF_4 (mol %)	t (h)	yield **3a** (%)	yield **7a** (%)
1	1:2.5	5	10	4	49	2
2	1:2.5	15	10	4	54	5
3	1:2.5	10	5	4	44	3
4	1:2.5	10	15	4	54	8
5	1:2.5	10	10	13	60	< 1%
6	1:2.5	10	10	18	64	
7	1:2.5	10	10	22	61	
8	1:2.5	10	10	42	46	
9	1:1	10	10	18	53	
10	1:2	10	10	18	60	
11	1:3	10	10	18	63	

[a]A solution of **1a**, **2a**, and Cs_2CO_3 in DMSO (solution A) and a solution of $PdCl_2$, t-Bu_3PHBF_4, and Cs_2CO_3 in DMSO (solution B) were prepared. After 3 h at rt, the two solutions were combined, and the reaction mixture was heated in a sealed tube at 120 °C using an oil bath.

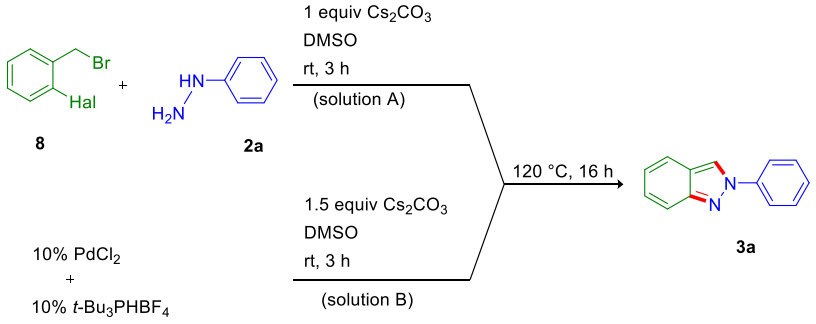
Of course, we have also studied whether 2-bromobenzyl bromide (**1a**) can be replaced with other 2-halobenzyl bromides (Table 5). The experiments revealed that **1a** can easily be replaced by 2-iodobenzyl bromide (**8a**). 2-Chlorobenzyl bromide (**8b**) can also be used as a substrate for the Pd-catalyzed indazole synthesis. However, the yield of **3a** was much lower (Table 5, entry 2). Because the yields with 2-bromobenzyl bromide (**1a**) and 2-iodobenzyl bromide (**8a**) were comparable, all further reactions were conducted with 2-bromobenzyl bromides **1** as substrates.

With optimized reaction conditions in hand, we focused on the scope and limitations of the new method for the synthesis of 2-aryl-2*H*-indazoles **3**. For this purpose, selected 2-bromobenzyl bromides **1** were reacted with several arylhydrazines **2** under the conditions given in Table 4, entry 6. First, the substituted 2-bromobenzyl bromides **1b−e** were reacted with the unsubstituted **2a**. In all cases, the 2-phenyl-2*H*-indazoles **3b−e** were formed exclusively with yields up to 76% (Table 6, entries 2−5). Then, it was clearly demonstrated that not only substituted 2-bromobenzyl bromides **1** but also a considerable number of substituted arylhydrazines **2b−l**, including alkyl-, halogen-, and methoxy-substituted ones can be employed as substrates for the selective preparation of 2-aryl-2*H*-indazoles **3** (Table 6, entries 6−16). The yields were in the range between 50 and 79%. Some preliminary experiments with methylhydrazine and *tert.*-butyl hydrazine as substrates did not yield the corresponding 2-alkyl-2*H*-indazoles.

With respect to the reaction mechanism, it is assumed that the formation of 2-aryl-2*H*-indazole **3** proceeds by a domino intermolecular *N*-benzylation/intramolecular *N*-arylation/oxi-

https://dx.doi.org/10.1021/acs.joc.0c01923
J. Org. Chem. XXXX, XXX, XXX−XXX

Table 5. Reactions of Different 2-Halobenzyl Bromides 8 with Phenylhydrazine (2a)[a]



entry	8	hal	yield 3a (%)
1	a	I	66
2	b	Cl	34

[a]In all cases, 1 equiv **8** was reacted with 2.5 equiv **2a**. A solution of **8**, **2a**, and Cs_2CO_3 in DMSO (solution A) and a solution of $PdCl_2$, t-Bu_3PHBF_4, and Cs_2CO_3 in DMSO (solution B) were prepared. After 3 h at rt, the two solutions were combined, and the reaction mixture was heated for 16 h in a sealed tube at 120 °C using an oil bath.

dation reaction between a 2-bromobenzyl bromide **1** and an arylhydrazine **2** (Scheme 3). The reaction starts with an intermolecular *N*-benzylation of an arylhydrazine **2** with a 2-bromobenzyl bromide **1**, which proceeds completely regioselective and produces exclusively the 1-*o*-bromobenzyl-1-arylhydrazines **4**. In the next step, the so-formed 1-*o*-bromobenzyl-1-arylhydrazine **4** undergoes a Pd-catalyzed intramolecular Buchwald–Hartwig *N*-arylation, which starts with the oxidative addition of the C-Br bond of **4** to the Pd(0) species by which the intermediate **A** is generated. **A** then undergoes intramolecular nucleophilic attack by the terminal amino group of the hydrazine, which is accompanied by elimination of HBr and gives the six-membered palladacycle **B**. Reductive elimination yields the dihydroindazole **5**, which undergoes spontaneous oxidation to the corresponding 2-aryl-2*H*-indazole **3**. It is assumed that the oxidation takes place during product isolation with aerial oxygen as the terminal oxidant.[29] To support this mechanism, the proposed intermediate, that is, 1-*o*-bromobenzyl-1-phenylhydrazine (**4a**)[18] was prepared according to Song and Yee in 53% yield. Subsequently, **4a** was cyclized under our reaction conditions elaborated for the intramolecular *N*-arylation (1.5 equiv Cs_2CO_3, 10 mol % $PdCl_2$, and 10 mol % t-Bu_3PHBF_4 in DMSO at 120 °C for 18 h). Under these conditions, the indazole **3a** was formed with 72% yield. The outcome of this control experiment strongly suggests that **4a** is an intermediate for the formation of indazole **3a**. The outcome of the two experiments also verifies that the total yield of **4a** using a two-step method amounts to only 38% and is therefore significantly lower than the yield obtained employing the procedure presented in this contribution (64%) (Table 6, entry 1).

To exclude a subsequent conversion of a 1-substituted 1*H*-indazole **7** in a 2-substituted 2*H*-indazole **3**, it was decided to address the stability of the 1-aryl-1*H*-indazoles **7** under our standard reaction conditions (Scheme 4). For this purpose, 1-phenyl-1*H*-indazole (**7a**) was prepared in 75% yield by reaction of phenylhydrazine (**2a**) with 2-bromobenzaldehyde (**9**) according to the procedure of Cho and Shim.[30] The 1-phenyl-1*H*-indazole (**7a**) obtained was then mixed with 1.5 equiv Cs_2CO_3, 10 mol % $PdCl_2$, and 10 mol % t-Bu_3PHBF_4 in DMSO. After heating at 120 °C for 16 h in a sealed vial, work up, and purification, the starting material **7a** was recovered in 98% yield. This experiment clearly demonstrates that **7a** is stable under reaction conditions.

Because it is known that many Pd-catalyzed *N*-arylations can also be performed under Cu-catalyzed reaction conditions, we have tried to establish a Cu(I)-catalyzed method for the formation of 2-substituted 2*H*-indazoles **3** using 2-bromobenzyl bromides **1** and arylhydrazines **2** as substrates. However, all experiments between 2-bromobenzyl bromide (**1a**) and phenylhydrazine (**2a**) in the presence of a Cu catalyst revealed that instead of the expected 2-phenyl-2*H*-indazole (**3a**) the noncyclized 1-*o*-bromobenzyl-1-phenylhydrazine (**4a**) was formed as the major product. For example, when **1a** and **2a** were reacted in the presence of 2 equiv Cs_2CO_3 and 10 mol % CuI in water at 110 °C using an oil bath, only 9% of **3a** and 58% of **4a** were isolated (Scheme 5). Unfortunately, it was not possible to increase the yield of **3a** by variation of the Cu catalysts, bases, solvents, and reaction conditions.

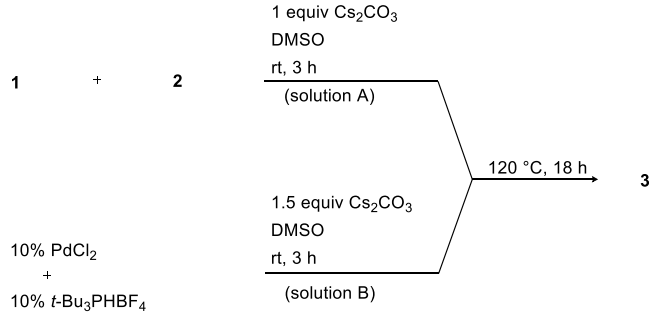
The structures of all compounds were unambiguously elucidated by ^{1}H and ^{13}C NMR spectroscopy as well as mass spectrometry.

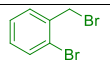
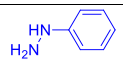
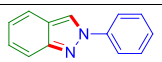
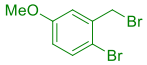
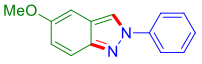
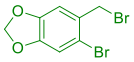
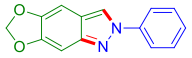
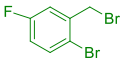
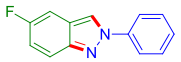
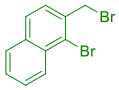
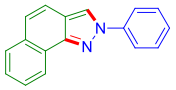
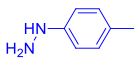
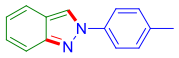
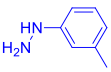
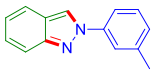
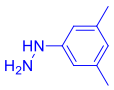
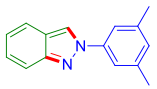
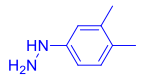
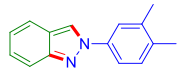
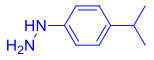
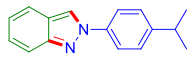
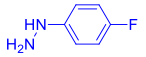
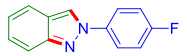
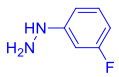
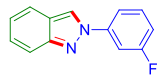
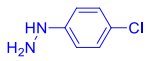
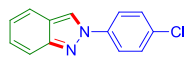
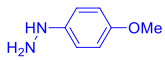
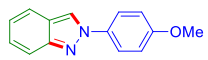
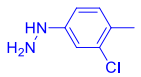
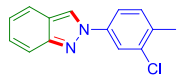
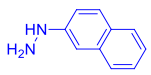
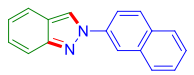
CONCLUSIONS

In conclusion, we have developed an operational simple and efficient method for the regioselective synthesis of 2-substituted-2*H*-indazoles **3** relying on simple starting materials. The 2-substituted-2*H*-indazoles **3** can be prepared in a single preparative step between 2-bromobenzyl bromides **1** and arylhydrazines **2**. No traces of the 1-substituted-1*H*-indazoles **7** are formed. The selective preparation of 2-substituted-2*H*-indazoles **3** is based on a regioselective intermolecular *N*-benzylation followed by a Pd-catalyzed intramolecular *N*-arylation and a final oxidation. Best results were achieved when 1 equiv of a 2-bromobenzyl bromide **1** and 2.5 equiv of an arylhydrazine **2** were reacted with 2.5 equiv Cs_2CO_3, 10 mol % $PdCl_2$, and 10 mol % t-Bu_3PHBF_4 in DMF at 120 °C for 18 h. Using this protocol, a range of substituted 2*H*-indazoles **3** was made available in yields up to 79%. The advantage of our method is that the completely regioselective intermolecular *N*-benzylation of the arylhydrazines **2** with the 2-bromobenzyl bromides **1** to the corresponding 1-*o*-bromobenzyl-1-arylhydrazines **4** can be linked with their Pd(0)-catalyzed intramolecular cyclization and the final oxidation to the 2-aryl-2*H*-indazoles **3**. This is why our method does not require the

https://dx.doi.org/10.1021/acs.joc.0c01923
J. Org. Chem. XXXX, XXX, XXX−XXX

Table 6. Reaction of Different 2-Bromobenzyl Bromides 1 with Different Hydrazines 2[a]



Entry	1	2	3
1	 **1a**	 **2a**	 **3a**, 64%
2	 **1b**	**2a**	 **3b** 76%
3	 **1c**	**2a**	 **3c** 70%
4	 **1d**	**2a**	 **3d** 52%
5	 **1e**	**2a**	 **3e** 61%
6	**1a**	 **2b**	 **3f** 73%
7	**1a**	 **2c**	 **3g** 62%
8	**1a**	 **2d**	 **3h** 77%
9	**1a**	 **2e**	 **3i** 75%
10	**1a**	 **2f**	 **3j** 71%
11	**1a**	 **2g**	 **3k** 68%
12	**1a**	 **2h**	 **3l** 50%
13	**1a**	 **2i**	 **3m** 60%
14	**1a**	 **2g**	 **3n** 79%
15	**1a**	 **2k**	 **3o** 68%
16	**1a**	 **2l**	 **3p** 61%

[a]In all cases, 1 equiv **1** was reacted with 2.5 equiv **2**. A solution of **1**, **2**, and Cs_2CO_3 in DMSO (solution A) and a solution of $PdCl_2$, t-Bu_3PHBF_4, and Cs_2CO_3 in DMSO (solution B) were prepared. After 3 h at rt, the two solutions were combined, and the reaction mixture was heated for 18 h in a sealed tube at 120 °C using an oil bath.

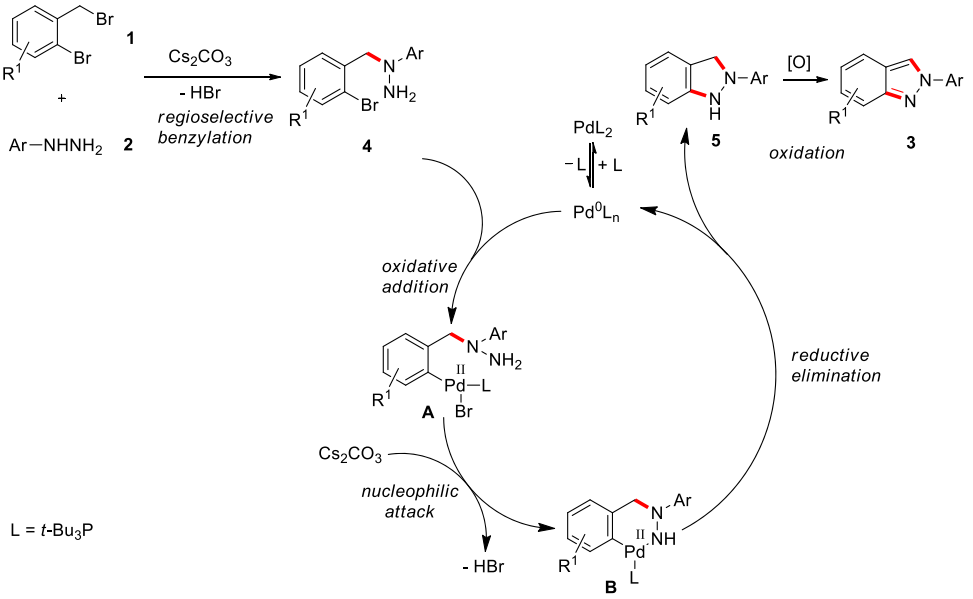
isolation and purification of the 1-*o*-bromobenzyl-1-arylhydrazines **4**. As a result, the yields of the 2-aryl-2*H*-indazoles **3** are much better than those obtained by traditional two-step methods.

EXPERIMENTAL SECTION

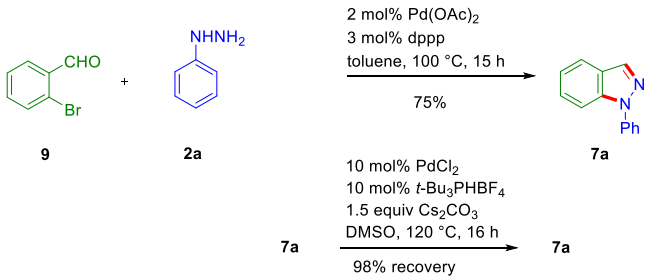
General Remarks. All commercially available reagents were used without further purification. Glassware was dried overnight at 140 °C. Solvents used in reactions were distilled over appropriate drying agents prior to use. Solvents used for extraction and purification were distilled prior to use. Reaction temperatures are reported as bath temperatures. Thin-layer chromatography (TLC) was performed on TLC silica gel 60 F254. Compounds were visualized with UV light (λ = 254 nm) and/or by immersion in an ethanolic vanillin solution or by immersion in $KMnO_4$ solution followed by heating. Products were purified by flash chromatography on silica gel, 0.04−0.063 mm. Melting points were obtained on a melting point apparatus with open capillary tubes and are uncorrected. Infrared spectra were recorded on

https://dx.doi.org/10.1021/acs.joc.0c01923
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 3. Plausible Mechanism for the Formation of 2-Substituted-2*H*-Indazoles



Scheme 4. Synthesis of 1-Phenyl-1*H*-indazole (7a) and Treatment under Standard Reaction Conditions



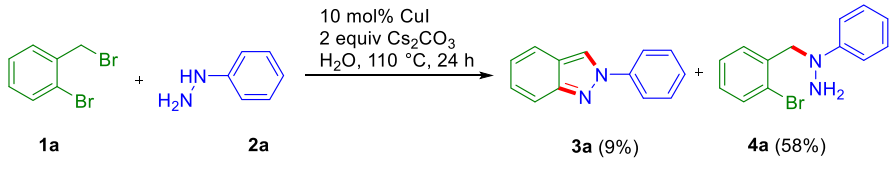
a Fourier transform infrared spectrometer. UV spectra were recorded with a spectrophotometer. ^{1}H (^{13}C) NMR spectra were recorded at 300, (75), 500 (125), and 600 (150) MHz using $CDCl_3$ as the solvent. The ^{1}H and ^{13}C chemical shifts were referenced to residual solvent signals at δ 7.26 H/77.0 C relative to TMS as the internal standard. HSQC-, HMBC-, NOESY-, ROESY-, HSQMBC-, and COSY spectra were recorded on a NMR spectrometer at 500 MHz. Coupling constants J [Hz] were directly taken from the spectra and are not averaged. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), m (multiplet), and br (broad). 1D and 2D homonuclear NMR spectra were measured with standard pulse sequences. Low-resolution electron impact mass spectra (MS) were obtained at 70 eV using a double-focusing sector field mass spectrometer. Intensities are reported as percentages relative to the base peak (I = 100%).

Procedure for the Preparation of Compound 3a. A dry vial was flushed with argon and charged with Cs_2CO_3 (651 mg, 2 mmol), 2-bromobenzyl bromide (**1a**) (250 mg, 1 mmol), phenylhydrazine (**2a**) (270 mg, 2.5 mmol), $PdCl_2$ (18 mg, 0.1 mmol), and *t*-Bu_3PHBF_4 (29 mg, 0.1 mmol). The vial was sealed, the solvent (1.5 mL) was added under argon, and the reaction mixture was heated under the conditions given in Table 1. After cooling to rt, the reaction mixture was partitioned between EtOAc (20 mL) and sat. NH_4Cl (20 mL). The organic layer was isolated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (cyclohexane/EtOAc = 10:1) to yield **3a**.

General Procedure for the Preparation of Compounds 3a–p. A dry vial was charged with Cs_2CO_3 (326 mg, 1 mmol), a 2-bromobenzyl bromide **1** (1 mmol), and an arylhydrazine **2** (2.5 mmol) under argon. The vial was sealed, dry DMSO (1.5 mL) was added under argon, and the mixture was stirred at rt for 3 h (solution A). Another dry vial was charged with Cs_2CO_3 (488 mg, 1.5 mmol), $PdCl_2$ (18 mg, 0.1 mmol), and *t*-Bu_3PHBF_4 (29 mg, 0.1 mmol) under argon. The vial was sealed, dry DMSO (1.5 mL) was added under argon, and the mixture was stirred at rt for 3 h (solution B). Solution A was added to solution B, and the resulting reaction mixture was stirred at 120 °C using an oil bath for 18 h under argon. After cooling to rt, the reaction mixture was partitioned between EtOAc (20 mL) and sat. NH_4Cl (20 mL). The organic layer was isolated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (cyclohexane/EtOAc = 10:1) to yield **3**.

*2-Phenyl-2H-indazole (**3a**).*[18] According to the general procedure, product **3a** was isolated as a white solid in 64% yield (124 mg, 0.64 mmol): mp 81–82 °C (lit.[18] mp 80–81.6 °C); R_f = 0.47 (PE/EtOAc = 4:1; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.41 (s, 1H), 7.91 (dd, 2H, J = 7.5, 1.3 Hz), 7.80 (d, 1H, J = 8.2 Hz), 7.71 (d, 1H, J = 8.5 Hz), 7.48–7.57 (m, 2H), 7.40 (ddd, 1H, J = 7.5, 7.4, 1.1 Hz), 7.33 (ddd, 1H, J = 7.6, 7.6, 1.0 Hz), 7.11 (ddd, 1H, J = 7.7, 7.6, 1.0 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 149.8, 140.5, 129.5, 127.9, 126.8, 122.7, 122.4, 121.0, 120.40, 120.37, 117.9; MS (EI, 70 eV) m/z 194 [M^+], 180, 165, 152, 139.

Scheme 5. Reaction between 1a and 2a under Cu-Catalyzed Conditions



https://dx.doi.org/10.1021/acs.joc.0c01923
J. Org. Chem. XXXX, XXX, XXX–XXX

*5-Methoxy-2-phenyl-2H-indazole (**3b**).*[18] According to the general procedure, product **3b** was isolated as a white solid in 76% yield (170 mg, 0.76 mmol): mp 144−145 °C (lit.[18] mp 143.1−143.9 °C); R_f = 0.41 (cyclohexane/EtOAc = 6:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.28 (d, 1H, J = 2.3 Hz), 7.85−7.89 (m, 2H), 7.69 (t-like, 1H, J = 9.4 Hz), 7.49−7.54 (m, 2H), 7.37 (t-like, 1H, J = 7.4 Hz), 7.03 (dd, 1H, J = 9.2, 2.3 Hz), 6.90 (d, 1H, J = 2.3 Hz), 3.86 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 155.5, 146.8, 140.6, 129.5, 127.5, 122.8, 122.0, 120.6, 119.33, 119.25, 96.2, 55.3; MS (EI, 70 eV) m/z 224 [M$^+$], 209, 181, 147, 121.

*2-Phenyl-2H-[1,3]dioxolo[4,5-f]indazole (**3c**).*[31] According to the general procedure, product **3c** was isolated as a white solid in 70% yield (166 mg, 0.70 mmol): mp 174−175 °C (lit.[31] mp 174−176 °C); R_f = 0.53 (PE/EtOAc = 4:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.19 (s, 1H), 7.82 (t-like, 2H, J = 8.1 Hz), 7.49 (t-like, 2H, J = 7.9 Hz), 7.34 (t-like, 1H, J = 7.5 Hz), 7.04 (s, 1H), 6.90 (s, 1H), 5.98 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 149.8, 147.3, 146.1, 140.4, 129.5, 127.2, 120.1, 119.7, 118.5, 101.0, 94.9, 94.1; MS (EI, 70 eV) m/z 238 [M$^+$], 208, 180, 161, 135.

*5-Fluoro-2-phenyl-2H-indazole (**3d**).*[32] According to the general procedure, product **3d** was isolated as a white solid in 52% yield (110 mg, 0.52 mmol): mp 136−137 °C (lit.[32] mp 135.5−137.5 °C); R_f = 0.50 (PE/EtOAc = 4:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.37 (s, 1H), 7.86−7.90 (m, 2H), 7.77 (dd, 1H, J = 9.9, 1.7 Hz), 7.51−7.56 (m, 2H), 7.41 (t-like, 1H, J = 8.12 Hz), 7.29 (dd, 1H, J = 9.2, 2.7 Hz), 7.13 (ddd, 1H, J = 9.3, 8.9, 2.4 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 158.7 (d, J (^{19}F, ^{13}C) = 158 Hz), 147.2, 140.4, 129.6, 128.1, 122.1, 120.9, 120.5 (d, J (^{19}F, ^{13}C) = 9.9 Hz), 120.1 (d, J (^{19}F, ^{13}C) = 9.9 Hz), 118.6 (d, J (^{19}F, ^{13}C) = 28.6 Hz), 102.7 (d, J (^{19}F, ^{13}C) = 24.6 Hz); MS (EI, 70 eV) m/z 212 [M$^+$], 195, 185, 165.

*2-Phenyl-2H-benzo[g]indazole (**3e**).*[33] According to the general procedure, product **3e** was isolated as yellow oil in 61% yield (149 mg, 0.61 mmol): R_f = 0.42 (cyclohexane/EtOAc = 6:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.71 (t-like, 1H, J = 7.8 Hz), 8.38 (s, 1H), 7.94−7.97 (m, 2H), 7.82 (d, 1H, J = 8.2 Hz), 7.61 (ddd, 1H, J = 8.4, 7.8, 1.2 Hz), 7.52−7.59 (m, 4H), 7.41 (d, 1H, J = 8.2 Hz), 7.38 (t-like, 1H, J = 7.4 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 147.6, 140.6, 132.7, 129.6, 128.4, 127.3, 127.0, 126.7, 125.7, 124.6, 122.6, 121.1, 120.5, 120.0, 118.3; MS (EI, 70 eV) m/z 244 [M$^+$], 216, 167, 141, 114.

*2-(4-Methylphenyl)-2H-indazole (**3f**).*[18] According to the general procedure, product **3f** was isolated as a white solid in 73% yield (152 mg, 0.73 mmol): mp 96−97 °C (lit.[18] mp 96.5−97.6 °C); R_f = 0.39 (cyclohexane/EtOAc = 6:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.38 (s, 1H), 7.76−7.81 (m, 3H), 7.71 (t-like, 1H, J = 8.7 Hz), 7.30−7.35 (m, 3H), 7.11 (ddd, 1H, J = 8.1, 7.1, 1.2 Hz), 2.42 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 149.6, 138.3, 137.9, 130.1, 126.6, 122.7, 122.3, 120.9, 120.30, 120.28, 117.9, 21.0; MS (EI, 70 eV) m/z 208 [M$^+$], 193, 181, 164.

*2-(3-Methylphenyl)-2H-indazole (**3g**).*[34] According to the general procedure, product **3g** was isolated as yellow oil in 62% yield (129 mg, 0.62 mmol): R_f = 0.57 (cyclohexane/EtOAc = 6:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.40 (d, 1H, J = 1.0 Hz), 7.80 (dd, 1H, J = 8.1, 1.1 Hz), 7.77 (s, 1H), 7.71 (t-like, 1H, J = 8.5 Hz), 7.66 (t-like, 1H, J = 8.5 Hz), 7.40 (dd, 1H, J = 7.8, 2.3 Hz), 7.35 (ddd, 1H, J = 7.6, 7.6, 2.1 Hz), 7.21 (t-like, 1H, J = 7.1 Hz), 7.15 (ddd, 1H, J = 7.8, 7.7, 2.0 Hz), 2.47 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 149.5, 140.3, 139.8, 129.3, 128.7, 126.8, 122.7, 122.4, 121.8, 120.6, 120.4, 118.0, 117.8, 21.4; MS (EI, 70 eV) m/z 208 [M$^+$], 193, 181, 164.

*2-(3,5-Dimethylphenyl)-2H-indazole (**3h**).*[34] According to the general procedure, product **3h** was isolated as a white solid in 77% yield (171 mg, 0.77 mmol): mp 98−99 °C; R_f = 0.43 (cyclohexane/EtOAc = 6:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.39 (s, 1H), 7.79 (dd, 1H, J = 7.6, 1.1 Hz), 7.70 (t-like, 1H, J = 8.3 Hz), 7.52 (s, 2H), 7.33 (ddd, 1H, J = 7.6, 7.6, 2.1 Hz), 7.11 (ddd, 1H, J = 9.1, 7.5, 1.6 Hz), 7.04 (s, 1H), 2.42 (s, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 149.5, 140.3, 139.5, 129.6, 126.8, 122.6, 122.3, 120.5, 120.3, 118.8, 117.8, 21.3; MS (EI, 70 eV) m/z 222 [M$^+$], 207, 180.

*2-(3,4-Dimethylphenyl)-2H-indazole (**3i**).*[32] According to the general procedure, product **3i** was isolated as a white solid in 75% yield (166 mg, 0.75 mmol): mp 118−119 °C; (lit.[32] mp 117−119 °C); R_f = 0.47 (cyclohexane/EtOAc = 6:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.38 (s, 1H), 7.79 (dd, 1H, J = 8.6, 1.1 Hz), 7.72 (d, 1H, J = 2.0 Hz), 7.70 (t-like, 1H, J = 8.5 Hz), 7.58 (dd, 1H, J = 8.1, 2.4 Hz), 7.32 (ddd, 1H, J = 7.8, 7.5, 2.1 Hz), 7.27 (d, 1H, J = 8.0 Hz), 7.11 (ddd, 1H, J = 7.7, 7.5, 2.1 Hz), 2.37 (s, 3H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 149.6, 138.5, 138.1, 136.6, 130.5, 126.6, 122.6, 122.23, 122.19, 120.31, 120.29, 118.1, 117.8, 19.9, 19.4; MS (EI, 70 eV) m/z 222 [M$^+$], 207, 180.

*2-(4-Isopropylphenyl)-2H-indazole (**3j**).*[35] According to the general procedure, product **3j** was isolated as a white solid in 71% yield (167 mg, 0.71 mmol): mp 88−89 °C; R_f = 0.43 (cyclohexane/EtOAc = 6:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.39 (d, 1H, J = 1.1 Hz), 7.81−7.84 (m, 3H), 7.71 (d, 1H, J = 8.5 Hz), 7.39 (d, 2H, J = 8.5 Hz), 7.35 (ddd, 1H, J = 7.8, 7.7, 2.1 Hz), 7.11 (ddd, 1H, J = 7.3, 7.2, 1.2 Hz), 2.99 (sept, 1H, J = 6.9 Hz), 1.31 (d, 6H, J = 7.0 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 149.4, 149.0, 138.3, 127.5, 126.9, 122.6, 122.4, 121.0, 120.5, 120.3, 117.7, 33.8, 23.9; MS (EI, 70 eV) m/z 236 [M$^+$], 221, 194.

*2-(4-Fluorophenyl)-2H-indazole (**3k**).*[32] According to the general procedure, product **3k** was isolated as a white solid in 68% yield (144 mg, 0.68 mmol): mp 104−105 °C (lit.[32] mp 103−104 °C), R_f = 0.48 (cyclohexane/EtOAc = 6:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.35 (s, 1H), 7.85−7.89 (m, 2H), 7.78 (dd, 1H, J = 8.7, 1.0 Hz), 7.71 (dd, 1H, J = 8.6, 2.1 Hz), 7.33 (ddd, 1H, J = 7.6, 7.6, 2.0 Hz), 7.19−7.25 (m, 2H), 7.13 (ddd, 1H, J = 7.8, 7.7, 2.2 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 162.1 (d, J (^{19}F, ^{13}C) = 247.5 Hz), 149.7, 136.8 (d, J (^{19}F, ^{13}C) = 3.3 Hz), 127.0, 122,9, 122.8 (d, J (^{19}F, ^{13}C) = 8.3 Hz), 122.6, 120.6, 120.3, 117.8, 116.5 (d, J (^{19}F, ^{13}C) = 23.3 Hz); MS (EI, 70 eV) m/z 212 [M$^+$], 192, 165, 132, 117.

*2-(3-Fluorophenyl)-2H-indazole (**3l**).*[20a] According to the general procedure, product **3l** was isolated as a white solid in 50% yield (106 mg, 0.50 mmol): mp 89−90 °C; R_f = 0.37 (cyclohexane/EtOAc = 6:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.41 (s, 1H), 7.78 (d, 1H, J = 8.7 Hz), 7.68−7.73 (m, 3H), 7.46−7.53 (m, 1H), 7.34 (ddd, 1H, J = 7.8, 7.6, 2.1 Hz), 7.07−7.16 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 163.0 (d, J (^{19}F, ^{13}C) = 248.0 Hz), 149.8, 141.8 (d, J (^{19}F, ^{13}C) = 9.9 Hz), 130.9 (d, J (^{19}F, ^{13}C) = 9.8 Hz), 127.2, 122.86, 122.81, 120.48, 120.41, 118.0, 116.1 (d, J (^{19}F, ^{13}C) = 3.0 Hz), 114.7 (d, J (^{19}F, ^{13}C) = 21.1 Hz), 108.7 (d, J (^{19}F, ^{13}C) = 26.3 Hz); MS (EI, 70 eV) m/z 212 [M$^+$], 192, 165, 117.

*2-(4-Chlorophenyl)-2H-indazole (**3m**).*[32] According to the general procedure, product **3m** was isolated as a white solid in 60% yield (137 mg, 0.71 mmol): mp 138−138 °C (lit.[32] mp 137−139 °C); R_f = 0.54 (cyclohexane/EtOAc = 6:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.39 (s, 1H), 7.86 (d-like, 2H, J = 8.9 Hz), 7.77 (dd, 1H, J = 8.7, 1.7 Hz), 7.71 (dd, 1H, J = 7.3, 1.3 Hz), 7.50 (t-like, 2H, J = 8.8 Hz), 7.33 (ddd, 1H, J = 7.8, 7.6, 2.1 Hz), 7.12 (ddd, 1H, J = 7.3, 7.2, 1.7 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 149.9, 139.0, 133.6, 129.7, 127.1, 122.9, 122.7, 122.0, 120.4, 120.3, 117.9; MS (EI, 70 eV) m/z 228 [M$^+$], 211, 193, 181.

*2-(4-Methoxyphenyl)-2H-indazole (**3n**).*[18] According to the general procedure, product **3n** was isolated as a white solid in 79% yield (177 mg, 0.79 mmol): mp 130−131 °C (lit.[18] mp 130.1−130.6 °C); R_f = 0.40 (cyclohexane/EtOAc = 6:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.32 (d, 1H, J = 1.1 Hz), 7.77−7.83 (m, 3H), 7.71 (d, 1H, J = 8.5 Hz), 7.32 (ddd, 1H, J = 7.7, 7.7, 2.2 Hz), 7.11 (ddd, 1H, J = 7.6, 7.5, 2.1 Hz), 7.04 (t-like, 2H, J = 9.0 Hz), 3.87 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 159.3, 149.6, 134.1, 126.5, 122.7, 122.4, 122.2, 120.3, 120.2, 117.8, 114.6, 55.6; MS (EI, 70 eV) m/z 224 [M$^+$], 209, 181.

*2-(3-Chloro-4-methylphenyl)-2H-indazole (**3o**).*[36] According to the general procedure, product **3o** was isolated as a white solid in 68% yield (165 mg, 0.68 mmol): mp 130−131 °C; R_f = 0.47 (cyclohexane/EtOAc = 6:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.38 (s, 1H), 7.96 (d, 1H, J = 2.3 Hz), 7.78 (t-like, 1H, J = 8.7 Hz), 7.70 (t-like, 2H, J = 8.3 Hz), 7.37 (d, 1H, J = 8.4 Hz), 7.33 (ddd, 1H, J = 7.7, 7.6, 2.0 Hz), 7.12 (ddd, 1H, J = 7.8, 7.8, 2.2 Hz), 2.44 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 149.8, 139.3, 135.8, 135.2,

https://dx.doi.org/10.1021/acs.joc.0c01923
J. Org. Chem. XXXX, XXX, XXX−XXX

131.6, 130.1, 127.0, 122.6, 121.5, 120.8, 120.3, 118.8, 117.9, 19.7; MS (EI, 70 eV) *m/z* 242 [M^+], 230, 208, 193.

*2-(Naphth-2-yl)-2H-indazole (**3p**).*[20b] According to the general procedure, product **3p** was isolated as a white solid in 61% yield (149 mg, 0.61 mmol): mp 132−133 °C (lit.[20b] mp 131−132 °C); R_f = 0.36 (cyclohexane/EtOAc = 3:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.55 (s, 1H), 8.38 (d, 1H, *J* = 2.1 Hz), 8.07 (dd, 1H, *J* = 8.7, 1.9 Hz), 8.00 (d, 1H, *J* = 8.6 Hz), 7.95 (d, 1H, *J* = 8.2 Hz), 7.91 (d, 1H, *J* = 8.0 Hz), 7.84 (dd, 1H, *J* = 8.8, 1.1 Hz), 7.75 (t-like, 1H, *J* = 8.4 Hz), 7.50−7.60 (m, 2H), 7.35 (ddd, 1H, *J* = 8.6, 6.6, 1.1 Hz), 7.14 (ddd, 1H, *J* = 7.7, 7.5, 1.9 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 149.9, 137.9, 133.5, 132.6, 129.7, 128.3, 127.9, 127.2, 127.0, 126.6, 122.9, 122.5, 120.6, 120.4, 119.5, 118.8, 117.9; MS (EI, 70 eV) *m/z* 244 [M^+], 167, 141, 114.

*1-Phenyl-1H-indazole (**7a**).*[37] In one of the optimization experiments, 1-phenyl-1*H*-indazole (**7a**) was isolated as a side product in 6% (12 mg, 0.06 mmol) as a white solid (see Table 1, entry 2): mp 77−78 °C (lit.[37] mp 76−78 °C); R_f = 0.49 (PE/EtOAc = 4:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.21 (d, 1H, *J* = 1.1 Hz), 7.81 (dt, 1H, *J* = 1.1, 7.8 Hz), 7.72−7.77 (m, 3H), 7.51−7.59 (m, 2H), 7.40−7.47 (m, 1H), 7.33−7.39 (m, 1H), 7.21−7.23 (m, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ 140.2, 138.7, 135.4, 129.4, 127.1, 126.6, 125.3, 122.7, 121.5, 121.3, 110.4; MS (EI, 70 eV) *m/z* 194 (100) [M^+].

*1-o-Bromobenzyl-1-phenylhydrazine (**4a**).*[18] Following the procedure of Song and Yee,[18] phenylhydrazine (**2a**) (108 mg, 1 mmol) was added to a stirred solution of NaHMDS (2 mL, 1.0 M THF, 2 mmol) at 0 °C under argon. After 20 min, the cooling bath was removed, and the reaction mixture was stirred at rt for 1 h. The reaction mixture was cooled to 0 °C, and 2-bromobenzyl bromide **1a** (250 mg, 1 mmol) was added. The reaction mixture was stirred at rt for 1 h and quenched with water. The mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (hexane/ether = 20:1) to yield **4a** as a pale yellow oil in 53% yield (147 mg, 0.53 mmol): R_f = 0.44 (PE/EtOAc = 4:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.61 (d, 1H, *J* = 7.4 Hz), 7.23−7.32 (m, 4H), 7.12−7.18 (m, 1H), 7.02 (d, 2H, *J* = 7.9 Hz), 6.82 (ddd, 1H, *J* = 7.3, 7.2, 1.1 Hz), 4.71 (s, 2H), 3.76 (brs, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ 151.3, 136.6, 133.0, 129.1, 128.8, 128.7, 127.6, 123.5, 118.4, 112.8, 60.7; MS (EI, 70 eV) *m/z* (%) 277 (100) [M^+].

*Procedure for the Preparation of 2-Phenyl-2H-indazole (**3a**) by Pd-Catalyzed Intramolecular Cyclization of 1-o-Bromobenzyl-1-phenylhydrazine (**4a**).* A dry vial was charged with Cs_2CO_3 (488 mg, 1.5 mmol), $PdCl_2$ (18 mg, 0.1 mmol), and *t*-Bu_3PHBF_4 (29 mg, 0.1 mmol) under argon. The vial was sealed, dry DMSO (1.5 mL) was added under argon, and the mixture was stirred at rt for 3 h. Then, 1-*o*-bromobenzyl-1-phenylhydrazine (**4a**) (277 mg, 1 mmol) was added, and the resulting reaction mixture was stirred at 120 °C for 18 h under argon. After cooling to rt, the reaction mixture was partitioned between EtOAc (20 mL) and sat. NH_4Cl (20 mL). The organic layer was isolated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (cyclohexane/EtOAc = 10:1) to yield 2-phenyl-2*H*-indazole (**3a**) in 72% (140 mg, 0.72 mmol).

*Preparation of 1-Phenyl-1H-indazole (**7a**) by the Pd-Catalyzed Reaction between 2-Bromobenzaldehyde (**9**) and Phenylhydrazine (**2a**).*[30] Following the procedure of Cho and Shim, a mixture of 2-bromobenzaldehyde (**9**) (185 mg, 1 mmol), phenylhydrazine (**2a**) (108 mg, 1 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), dppp (12.5 mg, 0.03 mmol), and NaO^{t}Bu (192 mg, 2 mmol) in dry toluene (10 mL) was placed in a pressure vessel. The system was flushed with argon and allowed to react at 100 °C for 15 h. After cooling to rt, the reaction mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (hexane/ethyl acetate = 5:1) to yield **7a** as a white solid in 75% (146 mg, 0.75 mmol).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01923.

^{1}H and ^{13}C NMR spectra for all compounds(PDF)

■ AUTHOR INFORMATION

Corresponding Author

Uwe Beifuss − *Bioorganische Chemie, Institut für Chemie, Universität Hohenheim, Stuttgart D-70599, Germany;* orcid.org/0000-0001-7085-6574; Email: ubeifuss@uni-hohenheim.de; Fax: (+49)711-459-22951

Authors

Nayyef Aljaar − *Chemistry Department, Hashemite University, Zarqa 13115, Jordan;* orcid.org/0000-0002-3963-2238

Mousa Al-Noaimi − *Chemistry Department, Hashemite University, Zarqa 13115, Jordan*

Jürgen Conrad − *Bioorganische Chemie, Institut für Chemie, Universität Hohenheim, Stuttgart D-70599, Germany*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c01923

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support by the Deutsche Forschungsgemeinschaft (grant for the initiation of an international collaboration) is gratefully acknowledged. We thank Mr. Mario Wolf (Institut für Chemie, Universität Hohenheim) for recording of NMR spectra, Dr. Christina Braunberger (Institut für Chemie, Universität Hohenheim), and Dipl.-Ing. (FH) J. Trinkner (Institut für Organische Chemie, Universität Stuttgart) for recording of MS.

■ REFERENCES

(1) (a) Cerecetto, H.; Gerpe, A.; González, M.; Arán, V. J.; de Ocáriz, C. O. Pharmacological Properties of Indazole Derivatives: Recent Developments. *Mini-Rev. Med. Chem.* **2005**, *5*, 869. For reviews on the synthesis and biological activity of indazoles, see (b) Thangadurai, A.; Minu, M.; Wakode, S.; Agrawal, S.; Narasimhan, B. Indazole: a medicinally important heterocyclic moiety. *Med. Chem. Res.* **2012**, 1509. (c) Gaikwad, D. D.; Chapolikar, A. D.; Devkate, C. G.; Warad, K. D.; Tayade, A. P.; Pawar, R. P.; Domb, A. J. Synthesis of indazole motifs and their medicinal importance: An overview. *Eur. J. Med. Chem.* **2015**, *90*, 707.

(2) Goodman, K. B.; Cui, H.; Dowdell, S. E.; Gaitanopoulos, D. E.; Ivy, R. L.; Sehon, C. A.; Stavenger, R. A.; Wang, G. Z.; Viet, A. Q.; Xu, W.; Ye, G.; Semus, S. F.; Evans, C.; Fries, H. E.; Jolivette, L. J.; Kirkpatrick, R. B.; Dul, E.; Khandekar, S. S.; Yi, T.; Jung, D. K.; Wright, L. L.; Smith, G. K.; Behm, D. J.; Bentley, R.; Doe, C. P.; Hu, E.; Lee, D. Development of Dihydropyridone Indazole Amides as Selective Rho-Kinase Inhibitors. *J. Med. Chem.* **2007**, *50*, 6.

(3) Han, W.; Pelletier, J. C.; Hodge, C. N. Tricyclic Ureas: A New Class of HIV-1 Protease Inhibitors. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3615.

(4) (a) Baraldi, P. G.; Balboni, G.; Pavani, M. G.; Spalluto, G.; Tabrizi, M. A.; De Clercq, E.; Balzarini, J.; Bando, T.; Sugiyama, H.; Romagnoli, R. Design, Synthesis, DNA Binding, and Biological Evaluation of Water-Soluble Hybrid Molecules Containing Two Pyrazole Analogues of the Alkylating Cyclopropylpyrroloindole (CPI) Subunit of the Antitumor Agent CC-1065 and Polypyrrole Minor Groove Binders. *J. Med. Chem.* **2001**, *44*, 2536. (b) Lee, J.; Choi, H.;

https://dx.doi.org/10.1021/acs.joc.0c01923
J. Org. Chem. XXXX, XXX, XXX−XXX

Kim, K.-H.; Jeong, S.; Park, J.-W.; Baek, C.-S.; Lee, S.-H. Synthesis and biological evaluation of 3,5-diaminoindazoles as cyclin-dependent kinase inhibitors. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2292. (c) Qian, S.; Cao, J.; Yan, Y.; Sun, M.; Zhu, H.; Hu, Y.; He, Q.; Yang, B. SMT-A07, a 3-(Indol-2-yl) indazole derivative, induces apoptosis of leukemia cells in vitro. *Mol. Cell. Biochem.* **2010**, *345*, 13.

(5) Koide, T.; Matsushi, H. Influence of a chronic new potential antidepressant, 1-[3-(dimethylamino)propyl]-5-methyl-3-phenyl-1H-indazole(FS32) and its N-desmethylated compound(FS97): treatment on monoaminergic receptor sensitivity in the rat brain. *Neuropharmacology* **1981**, *20*, 285.

(6) (a) Mosti, L.; Menozzi, G.; Schenone, P.; Molinario, L.; Conte, F.; Montanario, C.; Marmoe, E. Acetic acids bearing the 1-phenyl-1H-indazole nucleus with analgesic and anti-inflammatory activity. *Farmaco Ed. Sci.* **1988**, *43*, 763. (b) Gomtsyan, A.; Bayburt, E. K.; Schmidt, R. G.; Surowy, C. S.; Honore, P.; Marsh, K. C.; Hannick, S. M.; McDonald, H. A.; Wetter, J. M.; Sullivan, J. P.; Jarvis, M. F.; Faltynek, C. R.; Lee, C.-H. Identification of (*R*)-1-(5-*tert*-Butyl-2,3-dihydro-1*H*-inden-1-yl)-3-(1*H*-indazol-4-yl)urea (ABT-102) as a Potent TRPV1 Antagonist for Pain Management. *J. Med. Chem.* **2008**, *51*, 392.

(7) Li, X.; Chu, S.; Feher, V. A.; Khalili, M.; Nie, Z.; Margosiak, S.; Nikulin, V.; Levin, J.; Sparankle, K. G.; Tedder, M. E.; Almassy, R.; Appelt, K.; Yager, K. M. Structure-Based Design, Synthesis, and Antimicrobial Activity of Indazole-Derived SAH/MTA Nucleosidase Inhibitors. *J. Med. Chem.* **2003**, *46*, 5663.

(8) Park, J. S.; Yu, K. A.; Kang, T. H.; Kim, S.; Suh, Y.-G. Discovery of novel indazole-linked triazoles as antifungal agents. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3486.

(9) Harris, P. A.; Boloor, A.; Cheung, M.; Kumar, R.; Crosby, R. M.; Davis-Ward, R. G.; Epperly, A. H.; Hinkle, K. W.; Hunter, R. N., III; Johnson, J. H.; Knick, V. B.; Laudeman, C. P.; Luttrell, D. K.; Mook, R. A.; Nolte, R. T.; Rudolph, S. K.; Szewczyk, J. R.; Truesdale, A. T.; Veal, J. M.; Wang, L.; Stafford, J. A. Discovery of 5-[[4-[(2,3-Dimethyl-2*H*-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide (Pazopanib), a Novel and Potent Vascular Endothelial Growth Factor Receptor Inhibitor. *J. Med. Chem.* **2008**, *51*, 4632.

(10) Jones, P.; Altamura, S.; Boueres, J.; Ferrigno, F.; Fonsi, M.; Giomini, C.; Lamartina, S.; Monteagudo, E.; Ontoria, J. M.; Orsale, M. V.; Palumbi, M. C.; Pesci, S.; Roscilli, G.; Scarpelli, R.; Schultz-Fademrecht, C.; Toniatti, C.; Rowley, M. Discovery of 2-{4-[(3*S*)-Piperidin-3-yl]phenyl}-2*H*-indazole-7-carboxamide (MK-4827): A Novel Oral Poly(ADP-ribose)polymerase (PARP) Inhibitor Efficacious in BRCA-1 and -2 Mutant Tumors. *J. Med. Chem.* **2009**, *52*, 7170.

(11) Halim, R.; Harding, M.; Hufton, R.; Morton, C. J.; Jahangiri, S.; Pool, B. R.; Jeynes, T. P.; Draffan, A. G.; Lilly, M. J.; Frey, B. Viral polymerase inhibitors. WO 2012051659 A1, 26, 2012.

(12) Pfefferkorn, J. A.; Tu, M.; Filipski, K. J.; Guzman-Perez, A.; Bian, J.; Aspnes, G. E.; Sammons, M. F.; Song, W.; Li, J.-C.; Jones, C. S.; Patel, L.; Rasmusson, T.; Zeng, D.; Karki, K.; Hamilton, M.; Hank, R.; Atkinson, K.; Litchfield, J.; Aiello, R.; Baker, L.; Barucci, N.; Bourassa, P.; Bourbounais, F.; D'Aquila, T.; Derksen, D. R.; MacDougall, M.; Robertson, A. The design and synthesis of indazole and pyrazolopyridine based glucokinase activators for the treatment of Type 2 diabetes mellitus. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7100.

(13) Rosati, O.; Curini, M.; Marcotullio, M. C.; Macchiarulo, A.; Perfumi, M.; Mattioli, L.; Rismondo, F.; Cravotto, G. Synthesis, docking studies and anti-inflammatory activity of 4,5,6,7-tetrahydro-2*H*-indazole derivatives. *Bioorg. Med. Chem.* **2007**, *15*, 3463.

(14) Schenone, S.; Bruno, O.; Ranise, A.; Brullo, C.; Bondavalli, F.; Fillippelli, W.; Mazzeo, F.; Capuano, A.; Falcone, G. 2-Aryl-3-phenylamino-4,5-dihydro-2h-benz[g]indazoles with analgesic activity. *Il Farmaco* **2003**, *58*, 845.

(15) Minu, M.; Thangadurai, A.; Wakode, S. R.; Agrawal, S. S.; Narasimhan, B. S. antimicrobial activity and QSAR studies of new 2,3-disubstituted-3,3a,4,5,6,7-hexahydro-2*H*-indazoles. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2960.

(16) De Angelis, M.; Stossi, F.; Carlson, K. A.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. Indazole Estrogens: Highly Selective Ligands for the Estrogen Receptor. *J. Med. Chem.* **2005**, *48*, 1132.

(17) Benson, G. M.; Bleicher, K.; Feng, S.; Grether, U.; Kuhn, B.; Martin, R. E.; Plancher, J.-M.; Richter, H.; Rudolph, M.; Taylor, S. 3-Amino-indazole or 3-amino-4,5,6,7-tetrahydro-indazole derivatives. WO 2010/034657, 2010.

(18) Song, J. J.; Yee, N. K. A Novel Synthesis of 2-Aryl-2*H*-indazoles via a Palladium-Catalyzed Intramolecular Amination Reaction. *Org. Lett.* **2000**, *2*, 519.

(19) Sun, F.; Feng, X.; Zhao, X.; Huang, Z.-B.; Shi, D.-Q. An efficient synthesis of 2*H*-indazoles via reductive cyclization of 2-nitrobenzylamines induced by low-valent titanium reagent. *Tetrahedron* **2012**, *68*, 3851.

(20) (a) Genung, N. E.; Wei, L.; Aspnes, G. E. Regioselective Synthesis of 2*H*-Indazoles Using a Mild, One-Pot Condensation−Cadogan Reductive Cyclization. *Org. Lett.* **2014**, *16*, 3114. (b) Moustafa, A. H.; Malakar, C. C.; Aljaar, N.; Merisor, E.; Conrad, J.; Beifuss, U. Microwave-Assisted Molybdenum-Catalyzed Reductive Cyclization of *o*-Nitrobenzylidene Amines to 2-Aryl-2*H*-indazoles. *Synlett* **2013**, *24*, 1573.

(21) Stokes, B. J.; Vogel, C. V.; Urnezis, L. K.; Pan, M.; Driver, T. G. Intramolecular Fe(II)-Catalyzed N-O or N-N Bond Formation from Aryl Azides. *Org. Lett.* **2010**, *12*, 2884.

(22) Halland, N.; Nazaré, M.; R'kyek, O.; Alonso, J.; Urmann, M.; Lindenschmidt, A. A General and Mild Palladium-Catalyzed Domino Reaction for the Synthesis of 2*H*-Indazoles. *Angew. Chem., Int. Ed.* **2009**, *48*, 6879.

(23) Haag, B.; Peng, Z.; Knochel, P. Preparation of Polyfunctional Indazoles and Heteroarylazo Compounds Using Highly Functionalized Zinc Reagents. *Org. Lett.* **2009**, *11*, 4270.

(24) Wu, C.; Fang, Y.; Larock, R. C.; Shi, F. Synthesis of 2*H*-Indazoles by the [3 + 2] Cycloaddition of Arynes and Sydnones. *Org. Lett.* **2010**, *12*, 2234.

(25) (a) Hummel, J. R.; Ellman, J. A. Cobalt(III)-Catalyzed Synthesis of Indazoles and Furans by C−H Bond Functionalization/Addition/Cyclization Cascades. *J. Am. Chem. Soc.* **2015**, *137*, 490. (b) Jeong, T.; Han, S. H.; Han, S.; Sharma, S.; Park, J.; Lee, J. S.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. Access to 3-Acyl-(2*H*)-indazoles via Rh(III)-Catalyzed C−H Addition and Cyclization of Azobenzenes with α-Keto Aldehydes. *Org. Lett.* **2016**, *18*, 232.

(26) Kumar, M. R.; Park, A.; Park, N.; Lee, S.; Consecutive Condensation, C.-N. N-N Bond Formations: A Copper-Catalyzed One-Pot Three-Component Synthesis of 2*H*-Indazole. *Org. Lett.* **2011**, *13*, 3542.

(27) (a) Omar, M. A.; Conrad, J.; Beifuss, U. Assembly of 4*H*-chromenes, imidazobenzothiazines and quinazolines via copper-catalyzed domino reactions using 2-halobenzyl tosylates as substrates. *Tetrahedron* **2014**, *70*, 5682. (b) Malakar, C. C.; Baskakova, A.; Conrad, J.; Beifuss, U. Copper-Catalyzed Synthesis of Quinazolines in Water Starting from *o*-Bromobenzylbromides and Benzamidines. *Chem. − Eur. J.* **2012**, *18*, 8882. (c) Malakar, C. C.; Schmidt, D.; Conrad, J.; Beifuss, U. Cu(I)-Catalyzed Domino Reactions: Efficient and Selective Synthesis of 4*H*-Chromenes and Naphthalenes. *Org. Lett.* **2011**, *13*, 1972.

(28) Lerch, U.; König, J. Selective Alkylation of Phenylhydrazines: A Facile and Efficient Synthesis of 1-Alkyl-1-phenylhydrazines. *Synthesis* **1983**, 157.

(29) Frontana-Uribe, B. A.; Moinet, C. 2-Substituted Indazoles From Electrogenerated *Ortho*-nitrosobenzylamines. *Tetrahedron* **1998**, *54*, 3197.

(30) Cho, C. S.; Lim, D. K.; Heo, N. H.; Kim, T.-J.; Shim, S. C. Facile palladium-catalysed synthesis of 1-aryl-1*H*-indazoles from 2-bromobenzaldehydes and arylhydrazines. *Chem. Commun.* **2004**, 104.

(31) Ina, S.; Inoue, S.; Noguchi, I. N-heterocyclic compounds. I. Facile synthesis of 5,6-dialkoxy-2-aryl-2*H*-indazoles. *Yakugaku Zasshi* **1975**, *95*, 1245.

https://dx.doi.org/10.1021/acs.joc.0c01923
J. Org. Chem. XXXX, XXX, XXX−XXX

(32) Khatun, N.; Gogoi, A.; Basu, P.; Das, P.; Patel, B. K. CuO nanoparticle catalysed synthesis of 2*H*-indazoles under ligand free conditions. *RSC Adv.* **2014**, *4*, 4080.
(33) Fang, Y.; Wu, C.; Larock, R. C.; Shi, F. Synthesis of 2*H*-Indazoles by the [3 + 2] Dipolar Cycloaddition of Sydnones with Arynes. *J. Org. Chem.* **2011**, *76*, 8840.
(34) Zhang, R.; Liu, Z.; Peng, Q.; Zhou, Y.; Xu, L.; Pan, X. Access to 2-substituted-2*H*-indazoles via a copper-catalyzed regioselective cross-coupling reaction with diaryliodonium salts. *Org. Biomol. Chem.* **2018**, *16*, 1816.
(35) Panchangam, R. L.; Manickam, V.; Chanda, K. Assembly of Fully Substituted 2*H*-Indazoles Catalyzed by Cu_2O Rhombic Dodecahedra and Evaluation of Anticancer Activity. *ChemMedChem* **2019**, *14*, 262.
(36) Shi, D.-Q.; Dou, G.-L.; Ni, S.-N.; Shi, J.-W.; Li, X.-Y.; Wang, X.-S.; Wu, H.; Ji, S.-J. A. Novel and Efficient Synthesis of 2-Aryl-2*H*-indazoles via $SnCl_2$-Mediated Cyclization of 2-Nitrobenzylamines. *Synlett* **2007**, 2509.
(37) Lebedev, A. L.; Khartulyari, A. S.; Voskoboynikov, A. Z. Synthesis of 1-Aryl-1*H*-indazoles via Palladium-Catalyzed Intramolecular Amination of Aryl Halides. *J. Org. Chem.* **2005**, *70*, 596.

https://dx.doi.org/10.1021/acs.joc.0c01923
J. Org. Chem. XXXX, XXX, XXX−XXX