Heterocycles

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A General and Mild Palladium-Catalyzed Domino Reaction for the Synthesis of 2*H*-Indazoles**

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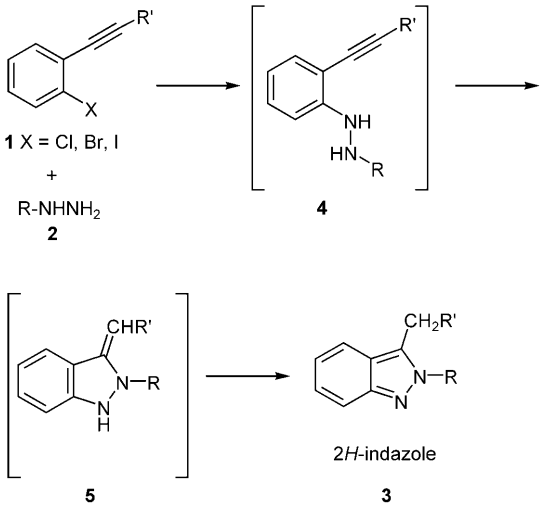
Indazoles play an increasingly important role in drug discovery. They act as an efficient isostere for privileged structures such as indoles and benzimidazoles. Furthermore, this important scaffold is able to interact with a variety of diverse targets, as highlighted by the growing number of reports of biologically active indazole derivatives.[1] However, only a limited number of approaches for the regioselective synthesis of N-substituted indazoles are available today. Most approaches afford the thermodynamically favored 1*H*-indazole or mixtures of 1*H*- and 2*H*-indazoles, whereas the regioselective formation of 2*H*-indazoles remains a very challenging task. The lack of a direct, efficient, and regioselective synthetic procedure for the construction of 2*H*-indazoles prevents their broader application in, for example, medicinal chemistry.[2] Thus, there is an unmet need for the development of a simple and general synthesis of 2*H*-indazoles from readily available precursors. Herein we report a straightforward domino reaction sequence consisting of a regioselective coupling of monosubstituted hydrazines **2** with 2-halophenylacetylenes **1**, followed by an intramolecular hydroamination through a 5-*exo*-dig cyclization and subsequent isomerization of the exocyclic double bond to give the aromatic 2*H*-indazole (Scheme 1).[3]



Scheme 1. Proposed synthesis of 2*H*-indazoles.

The first challenge in this strategy was the development of a regioselective transition-metal-catalyzed coupling of monosubstituted hydrazines **2** with 2-halophenylacetylenes **1** to afford the required *N*,*N*′-disubstituted hydrazines **4**. Although a number of transition-metal-catalyzed coupling reactions of aryl halides with amides, amines, hydrazides, and hydrazones are known, only a few coupling reactions of hydrazines have been reported,[4] and only one of the reported hydrazine couplings, for the formation of *N*,*N*-diaryl hydrazines, is regioselective.[4d] A second challenge in the development of our proposed strategy was the control of the hydroamination/cyclization step to form the 1,2-dihydroindazole **5**, as other possible cyclization pathways lead to other products, such as 1,2-dihydrocinnolines and *N*-azaindoles.[5] The isomerization of the exocyclic double bond in dihydro-2*H*-indazole **5** to give the aromatic 2*H*-indazole **3** was expected to occur spontaneously under the reaction conditions and thus not to pose any problems.

We initiated our investigation by screening for reaction conditions under which the coupling of 1-chloro-2-phenylethynylbenzene (**1a**) and phenylhydrazine (**2a**) would proceed efficiently to give the *N*,*N*′-diaryl hydrazine **4**. Upon optimization of the reaction parameters (the transition metal, metal salt, ligand, base, solvent, and temperature), the desired coupling was found to proceed cleanly within just a few hours and with complete regioselectivity when the catalyst system $[Pd_2(dba)_3]$/P*t*Bu$_3$ (1:2) was used in toluene at 80 °C with NaO*t*Bu as the base (dba = dibenzylideneacetone). This reaction is to our knowledge the first regioselective transition-metal-catalyzed coupling of monosubstituted hydrazines to give *N*,*N*′-disubstituted hydrazine products.[6]

We further optimized the reaction parameters to identify conditions that would promote the complete domino reaction of **1a** with **2a** as a one-pot reaction (Table 1).[7] We found that the use of polar solvents, such as DMF, NMP, or DMA, in combination with Cs_2CO_3 led to the formation of the desired 2*H*-indazole **3a** in good yield (Table 1, entries 2–4), whereas

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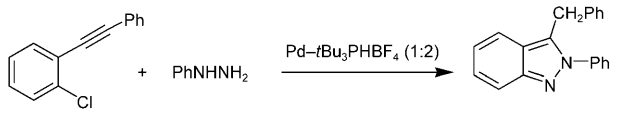
Table 1: Formation of 2-phenyl-3-benzyl-2*H*-indazole (**3a**) under various reaction conditions.[a]



1a **2a** **3a**

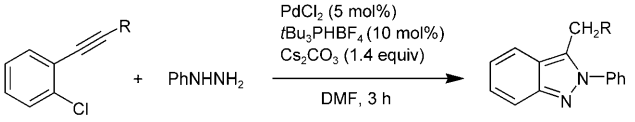
Entry	Pd source (mol% Pd)	Solvent	Base (equiv)	*t* [h]	Yield [%][b]
1	$[Pd_2(dba)_3]$ (10)	toluene	NaO*t*Bu (1.5)	20	<10
2	$[Pd_2(dba)_3]$ (10)	DMF	Cs_2CO_3 (1.5)	20	74
3	$[Pd_2(dba)_3]$ (10)	DMA	Cs_2CO_3 (1.5)	20	72
4	$[Pd_2(dba)_3]$ (10)	NMP	Cs_2CO_3 (1.5)	20	76
5	$PdCl_2$ (5)	toluene	Cs_2CO_3 (1.4)	6	<10
6	$PdCl_2$ (10)	DMF	Cs_2CO_3 (1.5)	20	75
7	$[Pd_2(dba)_3]$ (10)	NMP	Cs_2CO_3 (1.5)	4	77
8	$PdCl_2$ (5)	DMF	Cs_2CO_3 (1.4)	3	81
9[c]	$PdCl_2$ (5)	DMF	Cs_2CO_3 (1.4)	3	79
10	$PdCl_2$ (5)	DMF	Cs_2CO_3 (1.4)	3	71
11	$PdCl_2$ (2)	DMF	Cs_2CO_3 (1.4)	3	74

[a] All reactions were performed with **1a** (0.5 mmol) and **2a** (1.4 equiv) at 110–130°C. [b] Yield of the isolated product after flash chromatography on silica gel. [c] The reaction was performed with 1-bromo-2-phenylethynylbenzene (**1b**) instead of **1a**. DMF = *N*,*N*-dimethylformamide, DMA = *N*,*N*-dimethylacetamide, NMP = 1-methyl-2-pyrrolidone.

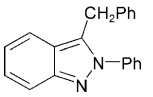
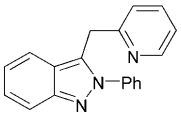
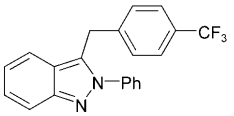
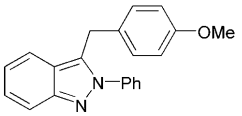
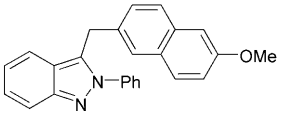
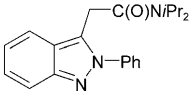
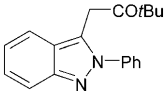
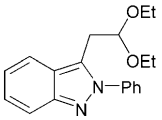
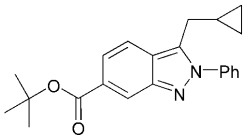
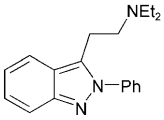
only a trace amount of the 2*H*-indazole was formed in unpolar solvents, such as toluene (Table 1, entry 5).[8] The structure of the 2*H*-indazoles was confirmed by single-crystal X-ray structure analysis of 2*H*-indazole **3r** (Table 3; see the Supporting Information). The palladium source only seemed to have a minor effect on the outcome of the reaction: $[Pd_2(dba)_3]$, $PdCl_2$, $PdBr_2$, and PdI_2 all performed similarly. We therefore chose to use stable and cheap $PdCl_2$ (Table 1, entries 2 and 6). Furthermore, the catalyst loading could be decreased to 2 mol% Pd without any significant drop in the yield of the isolated product (Table 1, entries 6, 8, and 11). As expected, 2-phenyl-3-benzyl-2*H*-indazole (**3a**) was formed in essentially the same yield from 1-bromo-2-phenylethynylbenzene (**1b**) as from the corresponding aryl chloride **1a** (Table 1, entries 8 and 9).

Having optimized the reaction conditions, we prepared a variety of (2-chlorophenyl)acetylenes **1** with different acetylene substituents[9] and explored the scope and generality of this domino reaction sequence. Acetylenes with aromatic substituents containing electron-withdrawing or electron-donating groups, as well as the corresponding 2-pyridyl-substituted acetylene, were transformed into 2-phenyl-2*H*-indazoles in 70–90% yield (Table 2, entries 1–5). The reaction proceeds equally well when the hydrazine salt is used as with the free hydrazine base (Table 2, entry 1). This result is of great practical importance, as most commercially available hydrazines are sold as their more stable hydrochloride salts; thus, the need to liberate and handle the free hydrazine bases is eliminated. (2-Chlorophenyl)acetylenes **1** with electron-withdrawing groups, such as amide, ester, or diacetal substituents, on the acetylene moiety reacted well with phenylhydrazine (**2a**) to provide 2-phenyl-2*H*-indazoles **3f–h** in good to excellent yields (Table 2, entries 6–8). When more-electron-donating substituents, such a cyclopropyl or amino-

Table 2: One-pot domino synthesis of various 2*H*-indazoles.[a]



1 **2a** **3**

Entry	R	Product		Yield [%][b]
1[c]	Ph		**3a**	79
2	2-pyridyl		**3b**	90
3	4-$CF_3C_6H_4$		**3c**	83
4	4-$MeOC_6H_4$		**3d**	86
5	6-MeO-2-naphthyl		**3e**	70
6	C(O)N*i*Pr_2		**3f**	63
7	CO_2tBu		**3g**	93
8	$CH(OEt)_2$		**3h**	55
9[d]	cyclopropyl		**3i**	47
10	CH_2NEt_2		**3j**	30

[a] All reactions were performed with **1** (0.5 mmol), **2a** (1.4 equiv), the Pd catalyst (5 mol%), and Cs_2CO_3 (1.4 equiv) in DMF at 110–130°C for 3 h. [b] Yield of the isolated product after flash chromatography on silica gel. [c] The reaction was performed with $PhNHNH_2HCl$ and Cs_2CO_3 (2.7 equiv). [d] The reaction was performed with 3-chloro-4-cyclopropylethynylbenzoic acid *tert*-butyl ester (**1c**).

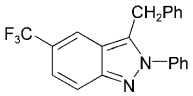
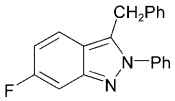
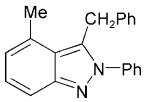
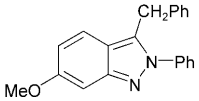
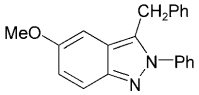
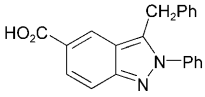
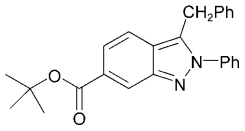
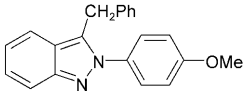
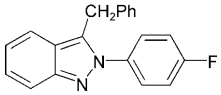
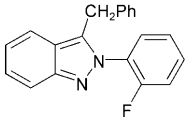
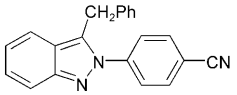
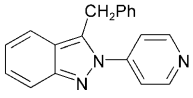
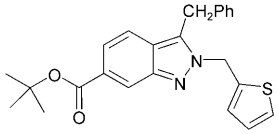
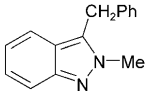
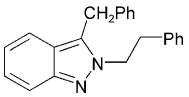
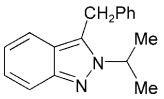
methyl group, were present on the alkyne, the 2-phenyl-2*H*-indazoles were generally formed in only moderate yields (Table 2, entries 9 and 10).

To further expand the scope of the reaction, we treated several (2-chlorophenyl)acetylenes **1** substituted with electron-withdrawing (CF_3, F, CO_2H, or CO_2tBu) or electron-

donating groups (Me or MeO) in various positions with phenylhydrazine (**2a**) under the standard conditions. The corresponding 2-phenyl-2*H*-indazoles **3k–q** were formed in moderate to good yields (Table 3, entries 1–7). We then turned our attention to the hydrazine component. The use of aryl and heteroaryl hydrazines with electron-withdrawing or electron-donating functionalities afforded 2-aryl-3-benzyl-2*H*-indazoles **3r–u** in excellent yields (Table 3, entries 8–11). Thus, the electronic nature of the aryl hydrazine does not significantly influence the outcome of the reaction. The 2*H*-indazole **3v** was formed in almost quantitative yield when 4-pyridylhydrazine was used (Table 3, entry 12), whereas the reaction of (thiophen-2-ylmethyl)hydrazine afforded **3w** in only very moderate yield (Table 3, entry 13). Alkyl hydrazines, such as methylhydrazine, isopropylhydrazine, and phenethylhydrazine, reacted readily with **1a** to provide the desired 2-alkyl 3-benzyl-2*H*-indazoles in reasonable yields and with higher than 10:1 regioselectivity, as determined by ^{1}H NMR spectroscopy of the crude reaction mixture (Table 3, entries 14–16). These results demonstrate the high versatility, mildness, and high functional-group tolerance of this novel domino reaction.

In summary, we have developed a practical and general one-pot procedure for the synthesis of 2*H*-indazoles from readily available 2-halophenylacetylenes and hydrazines. The method involves the first regioselective coupling of aryl halides with monosubstituted hydrazines, which undergo reaction at the unsubstituted N atom, and the incorporation of this reaction into a domino coupling/cyclization/isomerization sequence. This practical and highly versatile one-pot procedure is a completely novel approach to the formation of 2*H*-indazoles and thus closes a gap in current synthetic methodology.

Table 3: One-pot domino synthesis of substituted 2*H*-indazoles.[a]

Entry	Product		Yield [%][b]
1[c]		**3k**	61
2[c]		**3l**	43
3		**3m**	64
4		**3n**	73
5		**3o**	63
6		**3p**	46
7		**3q**	69
8[d,e]		**3r**	81
9[d]		**3s**	85
10[d]		**3t**	81
11[d]		**3u**	93
12[d]		**3v**	94
13[d]		**3w**	36
14		**3x**	63
15		**3y**	50
16[c,d]		**3z**	55

[a] All reactions were performed with **1** (0.5 mmol), hydrazine **3** (1.4 equiv), the Pd catalyst (5 mol%), and Cs_2CO_3 (1.4 equiv) in DMF at 110–130°C for 3–6 h. [b] Yield of the isolated product after flash chromatography on silica gel. [c] Reaction time: 20 h. [d] The reaction was performed with the hydrazine hydrochloride salt and Cs_2CO_3 (2.7 equiv). [e] See the Supporting Information for the X-ray crystal structure of **3r**.

Experimental Section

General procedure: $PdCl_2$ (5 mol%), tBu$_3$PHBF$_4$ (10 mol%), Cs_2CO_3 (1.4 equiv), and anhydrous DMF (2.5 mL) were placed in an oven-dried Schlenk tube with a magnetic stirring bar, and the resulting mixture was stirred under argon at ambient temperature for 30 min. The (2-chlorophenyl)acetylene **1** (0.5 mmol) and the hydrazine (1.4 equiv) were then added, and the mixture was heated at 130°C for 3 h. The reaction mixture was then cooled, diluted with water, and extracted twice with EtOAc. The organic phase was dried over Na_2SO_4 and concentrated, and the crude product was purified by flash

chromatography on silica gel with EtOAc/heptane or EtOAc/CH_2Cl_2 as the eluent.

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[5] According to the Baldwin rules, 6-*endo*-dig and 5-*exo*-dig cyclizations to give 1,2-dihydrocinnolines and *N*-azaindoles, respectively, are also allowed.

[6] No cyclization of the *N*,*N*′-diaryl hydrazine **4** coupling product to give the dihydro-2*H*-indazole **5** or 2*H*-indazole **3** was observed under the reaction conditions. The *N*,*N*′-diaryl hydrazines **4** were found to be somewhat labile compounds that undergo benzidine rearrangement.

[7] Clear advantages of a one-pot domino reaction would be the simplification of the procedure (the laborious workup and purification of sensitive *N*,*N*′-diaryl hydrazines **4** would be avoided) as well as a decrease in both the time required for the synthesis of 2*H*-indazoles **3** and the associated costs.

[8] No detailed mechanistic studies of the reaction were performed, but we expect that both the coupling step and the hydroamination step are catalyzed by palladium, as both steps are well-known to be transition-metal-catalyzed reactions; see, for example: F. Pohlki, S. Doye, *Chem. Soc. Rev.* **2003**, *32*, 104. In our case, full conversion of the 2-halophenylacetylenes **1** into intermediates **4** was usually complete within 1 h. We observed the accumulation of intermediate **4**, which indicates that the hydroamination step is rate-determining (see Figure 2 in the Supporting Information).

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