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A Novel Synthesis of 2-Aryl-2*H*-indazoles via a Palladium-Catalyzed Intramolecular Amination Reaction†

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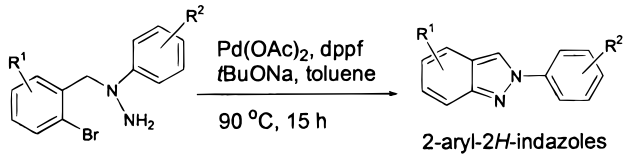
ABSTRACT



A variety of 2-aryl-2*H*-indazoles were synthesized by the palladium-catalyzed intramolecular amination of the corresponding *N*-aryl-*N*-(*o*-bromobenzyl)hydrazines. Of several sets of reaction conditions surveyed, the combination of $Pd(OAc)_2$/dppf/*t*BuONa gave the best results. This method applies to a wide scope of substrates containing electron-donating and electron-withdrawing substituents.

The indazole nucleus is a pharmaceutically important structure[1] and constitutes the key subunit in many drug substances with a broad range of pharmacological activities including antiinflammatory,[2] antitumor,[3] anti-HIV,[4] antidepressant,[5] and contraceptive activities.[6] However, there is still a lack of general and efficient methodologies for the synthesis of *N*-substituted indazoles (Figure 1).[1]

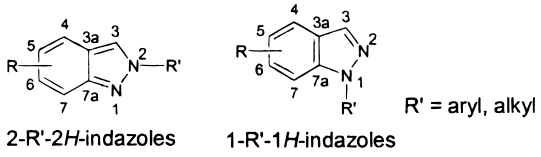


Figure 1.

Attempts to synthesize *N*-substituted indazoles by direct *N*-arylation[7] or *N*-alkylation[8] inevitably yielded a mixture of N(1) and N(2) regioisomers with poor selectivities. The most widely employed method for the construction of *N*-substituted indazoles involves the creation of N(1)−N(2) bond by treating *o*-nitrobenzylamines with Sn, Zn, or Fe in acidic medium[9] or by treating (*o*-nitrobenzylidene)amines with $P(OEt)_3$[10] or $PdCl_2(PPh_3)_2/SnCl_2/CO(g)$.[11] In a recent

† Dedicated to Professor Dietmar Seyferth on the occasion of his 71st birthday for his more than four-decade excellence in chemical research.

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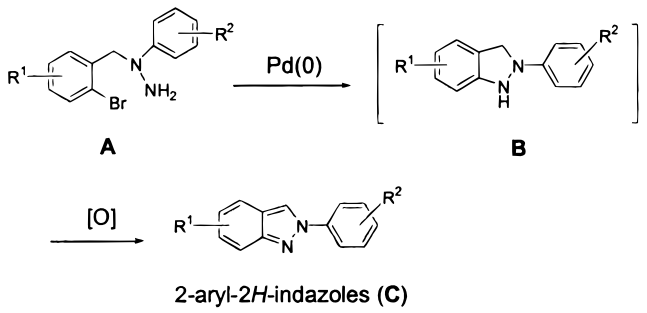
report,[12] reduction of *o*-nitrobenzylamines and subsequent cyclization to 2-substituted indazoles were achieved by an electrochemical method. Certain *N*-substituted indazoles have been prepared via intramolecular N(2)−C(3) bond formation[13] and also by thermal or photolytic decomposition of an appropriate precursor.[14] All of these existing methods require the use of either forcing reaction conditions or special equipment, which has severely limited their applications. In this Letter, we wish to describe a novel synthesis of 2-aryl-2*H*-indazoles through the creation of the N(1)−C(7a) bond via a palladium-catalyzed intramolecular amination reaction.

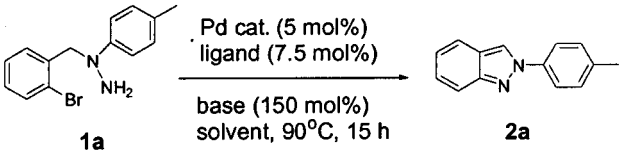
Palladium-catalyzed sp^2-carbon−nitrogen bond-forming reactions have proven to be a valuable synthetic method and found wide applications in organic synthesis.[15] Intramolecular variant of this reaction has been utilized to construct indoline[16] and oxindole derivatives.[17] During the course of our research on the synthesis of *N*-substituted indazoles, we proposed that the cyclization of *N*-aryl-*N*-(*o*-bromobenzyl)-hydrazines such as **A** (Scheme 1) should give the intermediate dihydroindazoles (**B**) which, upon oxidation, would furnish the desired 2-aryl-2*H*-indazole derivatives (**C**).

Scheme 1



In a preliminary study, *N*-(*o*-bromobenzyl)-*N*-(*p*-tolyl)-hydrazine (**1a**, Table 1), which was readily prepared by a modified literature procedure,[18] was used to define the reaction conditions for the amination/oxidation sequence. When compound **1a** was subjected to the conditions of $Pd(OAc)_2$/(*R*)-BINAP/*t*-BuONa at 90 °C for 15 h in toluene, the desired 2-(*p*-tolyl)-2*H*-indazole **2a** was directly obtained in ∼22% yield. Interestingly, the anticipated intermediate (**B**) was not observed under these reaction conditions. Apparently, the intermediate **B** was dehydrogenated either in situ or during the isolation. As a matter of fact, it has been recorded in the literature that dihydroindazoles, which were produced by electrochemical methods, are prone to air oxidation to generate indazoles.[12] However, the nature of the oxidation in the present case is still not clearly understood and is a subject of further investigation.[19]

Table 1. Optimization of Solvent, Ligand, and Base in Palladium-Catalyzed Intramolecular Amination



solvent	Pd source	ligand	base	yield(%)[a]
toluene	$Pd(OAc)_2$	(*R*)-BINAP	*t*BuONa	22
toluene	$Pd(OAc)_2$	dppf	*t*BuONa	65
toluene	$Pd_2(dba)_3$[20]	dppf	*t*BuONa	64
dioxane	$Pd(OAc)_2$	dppf	*t*BuONa	58
toluene	$Pd(OAc)_2$	dppf	Cs_2CO_3	27
toluene	$Pd(OAc)_2$	dppp	*t*BuONa	20
toluene	$PdCl_2$	Ph_3P[b]	*t*BuONa	20
toluene	no metal	no ligand	*t*BuONa	0
toluene	$Pd(OAc)_2$	no ligand	*t*BuONa	1

[a] Yields were determined by ^{1}H NMR of the crude products using 2-methoxynaphthalene as an internal standard.
[b] Ligand used in 20 mol%

Further optimization of the reaction conditions revealed that the use of dppf [20] as the ligand gave superior results than those with BINAP. Both toluene and dioxane were suitable for this reaction, but the former seemed to give slightly better yields. It was found that sodium *tert*-butoxide was a more effective base than cesium carbonate for the amination. Attempts to use the less expensive dppp[20] as the ligand led to a decrease in the yield. It was also noted that the use of $PdCl_2$/PPh_3 for the cyclization afforded the product

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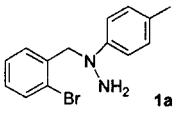
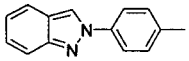
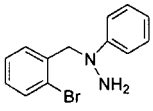
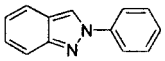
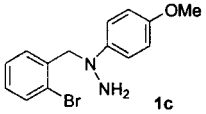
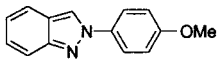
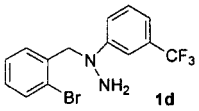
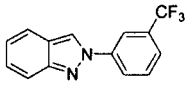
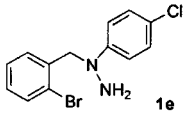
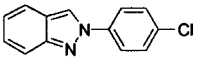
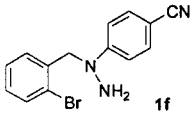
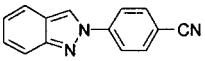
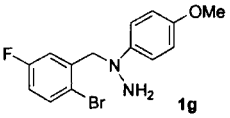
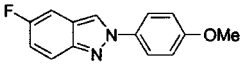
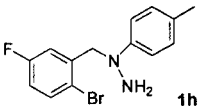
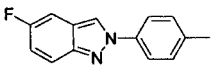
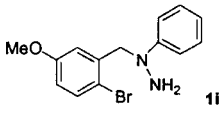
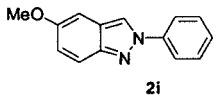
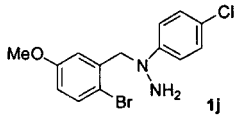
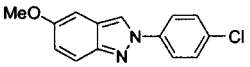
(18) (a) Lerch, U.; Konig, J. *Synthesis* **1983**, 157. (b) See Supporting Information for the modified experimental procedures.

(19) More experiments need to be conducted to determine whether the oxidation occurred with the exposure to the air or through disproportionation.

(20) Ligand abbreviations: dppf = 1,1′-bis(diphenylphosphino)ferrocene; dppp = 1,3-bis(diphenylphosphino)propane; dba = dibenzylideneacetone.

Table 2. Indazole Synthesis via a Palladium-Catalyzed Intramolecular Amination Reaction

substrate[a]	product[b]	yield[c]
 **1a**	 **2a**	55[7a]
 **1b**	 **2b**	58[12]
 **1c**	 **2c**	54[12]
 **1d**	 **2d**	52
 **1e**	 **2e**	55[10b]
 **1f**	 **2f**	52[12]
 **1g**	 **2g**	51
 **1h**	 **2h**	53
 **1i**	 **2i**	60[14b]
 **1j**	 **2j**	52

[a]All substrates were prepared according to the modified literature procedure (see Supporting Information). [b]All new compounds are characterized by ^{1}H/^{13}C NMR spectroscopy and elemental analysis/HRMS. [c]Isolated yields by chromatography.

in ~20% yield. Finally, the control experiments clearly indicated that the cyclization did not proceed without Pd(0) catalysis.

To explore the scope of this transformation, a series of cyclization precursors (**1a**−**1j**, Table 2) were prepared by the selective benzylation of various arylhydrazines.[18] The cyclizations were carried out using the reaction conditions of [Pd(OAc)$_2$/dppf/*t*-BuONa/toluene/90 °C].[21] In all cases examined, starting materials were completely consumed and the desired 2-aryl-2*H*-indazoles (**2a**−**2j**) were readily obtained in moderate to good yields. The major byproduct in this reaction was identified to be the debromonated starting material (10−20%). As can be seen from the table, the catalytic system is equally effective for electron-rich and electron-deficient substrates. The cyclized products are diversely functionalized and amenable to further structural modifications. While a great deal of mechanistic work awaits to be conducted on this reaction sequence, we believe that the reaction proceeds through the initial Pd(0) catalyzed sp^2-C−N bond formation followed by the spontaneous dehydrogenation to yield the 2-aryl-2*H*-indazoles.

In summary, we have demonstrated that the selective alkylation of aryl hydrazines followed by the palladium-catalyzed intramolecular amination and spontaneous aromatization is an efficient strategy for the facile synthesis of a variety of 2-aryl-2*H*-indazoles. It represents the first general method by which the 2-aryl-2*H*-indazoles are constructed through the creation of the N(1)−C(7a) bond. This method applies to a wide scope of substrates and is tolerant of a range of functional groups. Extensions of this methodology to the synthesis of other related compounds are under investigation and will be reported in due course.

Supporting Information Available: Representative experimental procedures for the synthesis of **1a**−**1j**, ^{1}H and ^{13}C NMR data for **1a**−**1j**, **2e**, and **2i**, and characterization data including the reproduction of the ^{1}H NMR spectra for compounds **2d**, **2g**, **2h**, and **2j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) **Representative procedure for the synthesis of 2-aryl-2*H*-indazoles: 5-fluoro-2-(4-methoxyphenyl)-2*H*-indazole (2g)**: To a solution of the *N*-(2-bromo-5-fluorobenzyl)-*N*-(4-methoxyphenyl)hydrazine (325.2 mg, 1.0 mmol) in anhydrous toluene (3.5 mL) in a pressure tube were added Pd(OAc)$_2$ (11.2 mg, 0.05 mmol), dppf (41.6 mg, 0.075 mmol), and *t*-BuONa (144.2 mg, 1.5 mmol). Then the pressure tube was filled with Ar and closed. The reaction was heated at 90 °C for 15 h and filtered through a pad of silica gel (50% ether/hexanes). After the removal of the volatiles, the residue was purified by flash chromatography on silica (5−10% ether/hexanes) to provide the desired product **2g** as white crystals (137.0 mg, 52%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.79−7.73 (m, 3H), 7.27 (dd, J = 2.36, 11.5 Hz, 1H), 7.11 (ddd, J = 2.52, 9.40, 9.40 Hz, 1H), 7.03 (m, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6 (d, J_{C-F} = 238.6 Hz), 159.4, 147.0, 134.0, 122.3, 121.9 (d, J_{C-F} = 11.7 Hz), 120.3 (d, J_{C-F} = 8.4 Hz), 119.8 (d, J_{C-F} = 9.7 Hz), 118.0 (d, J_{C-F} = 28.8 Hz), 114.7, 102.6 (d, J_{C-F} = 24.2 Hz), 55.6; mp 137.6−138.5 °C. Anal. Calcd for $C_{14}H_{11}FN_2O$: C, 69.41; H, 4.58; N, 11.56. Found: C, 69.21; H, 4.46; N, 11.59.