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Facile palladium-catalysed synthesis of 1-aryl-1*H*-indazoles from 2-bromobenzaldehydes and arylhydrazines

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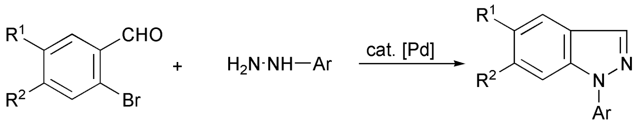
Received (in Cambridge, UK) 30th September 2003, Accepted 4th November 2003
First published as an Advance Article on the web 18th November 2003

2-Bromobenzaldehydes react with arylhydrazines in toluene at 100 °C in the presence of a catalytic amount of a palladium catalyst and phosphorus chelating ligands such as 1,1′-bis(diphenylphosphino)ferrocene and 1,3-bis(diphenylphosphino)propane along with NaO-*t*-Bu to afford 1-aryl-1*H*-indazoles in good yields.

Palladium-catalysed aromatic carbon–nitrogen bond forming reaction by the cross-coupling of aryl halides (or triflates) and amines has recently had an upsurge as a useful synthetic tool.[1] Various primary, secondary and tertiary amines can be prepared by this protocol and its intramolecular version has been introduced to the synthesis of nitrogen heterocycles as an elegant synthetic alternative.[1] In connection with this report, Song *et al.* have reported a palladium-catalysed intramolecular amination of *N*-aryl-*N*′-(*o*-bromobenzyl)hydrazines leading to 1-aryl-1*H*-indazoles.[2–4] However, the uneasy accessibility of the starting substrates in this method, which are prepared *via* several steps from commercial products,[5] precludes a straightforward approach. This led us to develop an efficient palladium-catalysed synthetic method for 1-aryl-1*H*-indazoles. Herein we report a successful palladium-catalysed synthesis of 1-aryl-1*H*-indazoles from readily available commercial substrates, 2-bromobenzaldehydes and arylhydrazines, *via* an intrinsic intramolecular amination.[6]

The results of several attempted cyclisations of 2-bromobenzaldehyde (**1a**) with phenylhydrazine (**2a**) are listed in Table 1 (Scheme 1). Treatment of equimolar amounts of **1a** and **2a** in toluene in the presence of a catalytic amount of $Pd(OAc)_2$ (2 mol%) and 1,3-bis(diphenylphosphino)propane (dppp) (3 mol%) along with NaO-*t*-Bu at 100 °C for 15 h afforded 1-phenyl-1*H*-indazole (**3a**) in 84% yield with concomitant formation of hydrazone (< 5%) by condensation between the starting substrates (run 1). The catalytic systems using $Pd(OAc)_2$ combined with 1,1′-bis(diphenylphosphino)ferrocene (dppf) and $PdCl_2$ combined with dppp were revealed to be as effective as that using $Pd(OAc)_2$ combined with dppp (runs 2, 3). With other phosphorus chelating ligands such as 1,1′-bis(di-*i*-propylphosphino)ferrocene (dipf) and (*S*)-(−)-BINAP, the yield of **3a** was lower than that when dppp and dppf were employed (runs 4, 5), all combined with $Pd(OAc)_2$. However, catalytic systems such as $Pd(OAc)_2$–PPh_3, $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$ were not effective at all for the present reaction; hydrazone was mainly produced as an identifiable product (runs 6–8). As a result, among the various palladium precursors examined the systems shown in runs 1, 2 and 3 are the choices of preference for the effective formation of **3a**.

Given these results, the reactions of various 2-bromobenzaldehydes **1** and arylhydrazines **2** were screened using three sets of reaction conditions, $Pd(OAc)_2$–dppp (condition A), $Pd(OAc)_2$–dppf (condition B) and $PdCl_2$–dppp (condition C), and several representative results are summarised in Table 2.† The reaction of **1b–1d** with **2a** under conditions A–C gave the corresponding 1-phenyl-1*H*-indazoles (**3b–3d**) in 47–79% yield with minimal formation of hydrazones as identifiable side products (runs 1–5). The product yield was not significantly affected by the electronic



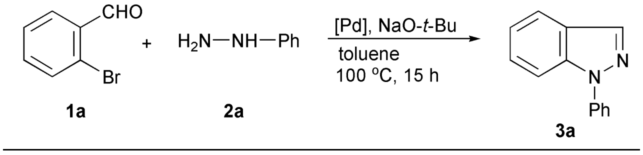
1a R^1 = H; R^2 = H
1b R^1 = OMe; R^2 = H
1c R^1 = OMe; R^2 = OMe
1d R^1 = F; R^2 = H

2a Ar = Ph
2b Ar = 3-MeC_6H_4
2c Ar = 4-MeC_6H_4
2d Ar = 4-$MeOC_6H_4$
2e Ar = 2-ClC_6H_4
2f Ar = 4-FC_6H_4
2g Ar = 2,4-$Cl_2C_6H_3$
2h Ar = 3-Cl-4-MeC_6H_3

3

Scheme 1

Table 1 Palladium-catalysed reaction of **1a** with **2a** under several catalytic systems[a]



Run	Palladium catalysts	Ligands (mol%)	Isolated yield (%)
1	$Pd(OAc)_2$	dppp (3)	84
2	$Pd(OAc)_2$	dppf (3)	84
3	$PdCl_2$	dppp (3)	83
4	$Pd(OAc)_2$	dipf (3)	65
5	$Pd(OAc)_2$	(*S*)-(−)-BINAP (3)	69
6	$Pd(OAc)_2$	PPh_3 (6)	trace
7	$PdCl_2(PPh_3)_2$	—	trace
8	$Pd(PPh_3)_4$	—	trace

[a] Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), palladium catalyst (2 mol%), NaO-*t*-Bu (2 mmol), toluene (10 ml), 100 °C, for 15 h, under argon.

Table 2 Palladium-catalysed synthesis of **3** from **1** and **2**[a]

Run	1	2	Conditions[b]	Products	Yield (%)
1	**1b**	**2a**	B	**3b**	79
2	**1b**	**2a**	C	**3b**	47
3	**1c**	**2a**	A	**3c**	65
4	**1d**	**2a**	B	**3d**	77
5	**1d**	**2a**	C	**3d**	51
6	**1a**	**2b**	B	**3e**	79
7	**1a**	**2c**	B	**3f**	55
8	**1a**	**2d**	B	**3g**	61
9	**1a**	**2e**	A	**3h**	78
10	**1a**	**2f**	A	**3i**	73
11	**1a**	**2g**	B	**3j**	86
12	**1a**	**2g**	C	**3j**	60
13	**1a**	**2h**	A	**3k**	86

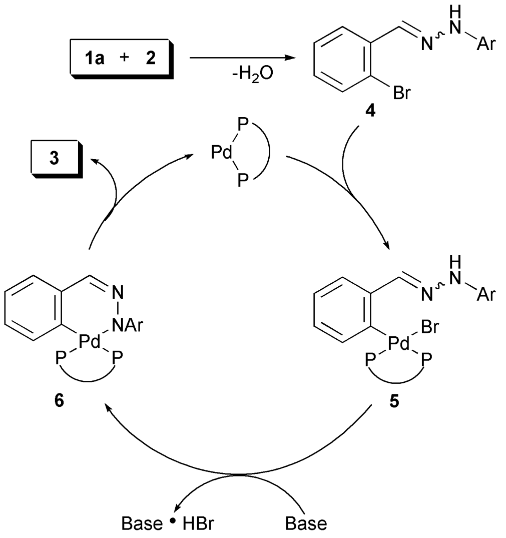
[a] Reaction conditions: **1** (1 mmol), **2** (1 mmol), palladium catalyst (2 mol%), chelating ligand (3 mol%), NaO-*t*-Bu (2 mmol), toluene (10 ml), 100 °C, for 15 h, under argon. [b] A: $Pd(OAc)_2$–dppp; B: $Pd(OAc)_2$–dppf; C: $PdCl_2$–dppp.

DOI: 10.1039/b312154m

nature of the substituent on **1**. In contrast to the reaction between **1a** and **2a**, the product yield varied according to the employed reaction conditions (runs 1,2 and 4,5). From the reactions between **1a** and various arylhydrazines (**2b–2h**), the corresponding 1-aryl-1*H*-indazoles (**3e–3k**) were also produced in good yields irrespective of the examined functional groups on the aromatic ring of **2** (runs 6–13). Comparing the result of runs 11 and 12 with that of two sets of reactions shown in runs (1 and 2) and (4 and 5), condition B was generally superior to condition C for the formation of 1-aryl-1*H*-indazoles.

A plausible reaction pathway is depicted in Scheme 2. Oxidative addition of the carbon–bromide bond of hydrazone **4**, initially formed *in situ* between **1a** and **2**, to Pd(0) produces an arylpalladium(II) complex **5**. This is followed by intramolecular closure to give a palladacycle **6** which can reductively eliminate to afford 1-aryl-1*H*-indazole **3**.[7,8]

In summary, we have demonstrated that 2-bromobenzaldehydes are cyclised with various arylhydrazines in the presence of a catalytic amount of a palladium catalyst and a phosphorus chelating ligand along with NaO-*t*-Bu to give 1-aryl-1*H*-indazoles in good yields. The present reaction is a straightforward methodology for the synthesis of 1-aryl-1*H*-indazoles from readily available 2-bromobenzaldehydes and arylhydrazines. Similar reaction of alkyl 2-bromoaryl ketones with arylhydrazines leading to 1,3-disubstituted indazoles is currently under investigation.



Scheme 2

This work was supported by the Brain Korea 21 Project in 2003 and a Korea Research Foundation Grant (KRF-2002-070-C00055). C.S.C. gratefully acknowledges an MOE-KRF Research Professor Program (2001-050-D00015).

Notes and references

† *Typical experimental procedure*: a mixture of **1a** (1 mmol), **2a** (1 mmol), Pd(OAc)$_2$ (0.02 mmol), dppp (0.03 mmol) and NaO-*t*-Bu (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. The reaction mixture was filtered through a short silica gel column (ethyl acetate) to eliminate inorganic salts. Removal of the solvent left a crude mixture, which was separated by column chromatography (silica gel, ethyl acetate–hexane = 1 : 5) to give **3a** (84%).

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