

# Synthesis of 1-Aryl-1*H*-indazoles via Palladium-Catalyzed Intramolecular Amination of Aryl Halides

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Palladium-catalyzed cyclization of arylhydrazones of 2-bromoaldehydes and 2-bromoacetophenones to give 1-aryl-1*H*-indazoles has been studied in detail. The cyclization of arylhydrazone of 2-bromobenzaldehydes can be performed with good to high yields using  $Pd(dba)_2$  and chelating phosphines, of which the most effective are *rac*-BINAP, DPEphos, and dppf, in the presence of  $Cs_2CO_3$  or  $K_3PO_4$  as a base. Electron-rich, bulky ligands commonly employed for intermolecular amination such as  $P'Bu_3$  and *o*-PhC<sub>6</sub>H<sub>4</sub>P'Bu<sub>2</sub> were shown to be ineffective for cyclization and to lead instead to extensive oligomerization and tarring. The method developed is applicable for preparation of a wide scope of indazoles bearing electron-donating or electron-withdrawing substituents, among them, unprotected carboxyl, as well as various indazole heteroanalogues. The cyclization of arylhydrazones of less reactive halides such as 2-chlorobenzaldehyde, as well as 2-bromoacetophenone and bromotetralone, has been achieved. The purity of the starting hydrazone has been shown to be a critical parameter, as various impurities inhibit the cyclization.

## Introduction

The 1-aryl-1*H*-indazole fragment can be recognized in a number of biologically active molecules,<sup>1</sup> as well as known pharmaceuticals, among them antidepressants<sup>2</sup> and contraceptives.<sup>3</sup> Nevertheless, the published methods of synthesis of this system are either limited in scope<sup>4</sup> or poorly elaborated;<sup>5</sup> therefore, an effective approach to obtaining compounds of this class is still desirable. One of the most attractive ways to such products is the catalytic cyclization of hydrazones of 2-haloaldehydes or 2-haloacetophenones. The cyclization of more nucleophilic alkylhydrazones or activated arylhydrazones takes place readily in the absence of a catalyst.<sup>6</sup> However, common unactivated arylhydrazones are not nucleophilic enough to undergo noncatalytic cyclization. Meanwhile, the palladium-catalyzed intermolecular arylation of hydrazones has recently been described.<sup>7</sup> Thus, it seemed reasonable to try the intramolecular catalyzed version.

It should be noted that examples of intramolecular Pdcatalyzed C–N bond formation leading to heteroaromatic fragments are still quite rare in the literature. For example, the synthesis of carbazole from 2-iodo-2'-aminobiphenyl has been described.<sup>8</sup> Other examples are Pd-catalyzed cyclization of *N*-aryl-*N*-(2-bromobenzyl)-

<sup>(1)</sup> Bistochi, G. A.; De Meo, G.; Pedini, M.; Ricci, A.; Brouilhet, H.; Bucherie, S.; Rabaud, M.; Jacquignon P. *Farmaco Ed. Sci.* **1981**, *36*, 315.

<sup>(2)</sup> Gschwend, H. W. (Ciba-Geigy). U.S. Patent 3,681,382, 1972.

 <sup>(3)</sup> Corsi, G.; Palazzo, G.; Germani, C.; Barcellona, P. S.; Silvestrini
 B. J. Med. Chem. 1976, 19, 778.

<sup>(4)</sup> Ruggli, P.; Straub, O. Helv. Chim. Acta 1938, 16, 1084. Theilacker, W.; Raabe, C. Tetrahedron Lett. 1966, 1, 91. Kuehne, M.; Weaver, S. J.; Franz, P. J. Org. Chem. 1963, 29, 1582. Chinn, L. J. J. Org. Chem. 1971, 36, 12. Tsuge, O.; Samura, H. J. Het. Chem. 1971, 8, 707. Croce, P. D.; La Rosa, C. Synthesis 1984, 982. Mercedes, M.-S.; Jose Alvarez de, L. M.; Sequlveda-Arques, J. J. Chem. Soc., Perkin Trans. 1990, 10, 2749. Lyubchanskaya, V. M.; Alekseeva, L. M.; Granik, V. G. Tetrahedron 1997, 53, 15005. Olivera, R.; SanMartin, R.; Domingues, E. J. Org. Chem. 2000, 65, 7010.

<sup>(5)</sup> Frasca, A. R. Tetrahedron Lett. 1962, 24, 1115. Dennler, E. B.;
Frasca, A. R. Tetrahedron, 1966, 22, 3131. Gladstone, W. A. F.;
Norman, R. O. C. J. Chem. Soc. C 1966, 1527. Fedorov, A. Y.; Finet,
J.-P. Tetrahedron Lett. 1999, 40, 2747. Lam, P. Y. S.; Clark, C. G.;
Saubern, S.; Adams, J.; Averill, K. A.; Chan, D. M. T.; Combs, A. Synlett
2000, 674. Collot, V.; Bovy, P. R.; Rault, S. Tetrahedron Lett. 2000,
41, 9053. Krapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. J.
Am. Chem. Soc. 2001, 123, 7727. Chan, D. M. T.; Monaco, K. L.; Li,
R.; Bonne, D.; Crark, C. G.; Lam, P. Y. S. Tetrahedron Lett. 2003, 44,
3863. Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. J.
Org. Chem. 2004, 69, 5578-5587.

<sup>(6)</sup> Borsche, W.; Diacont, K. Ann. Chem. 1934, 510, 287. Borsche,
W.; Buetschli, L. Ann. Chem. 1936, 522, 285. Borsche, W.; Scriba, W.
Ann. Chem. 1939, 541, 283. Showalter, H. D.; Hollis, J. L.; Hoftiezer,
J. M. J. Heterocycl. Chem 1986, 23, 1491. Capps, D. B.; Dunbar, J.;
Kesten, S. R.; Shillis, J.; Werbel, L. M. J. Med. Chem. 1992, 35, 4770.
(7) Wagaw, S.; Yang, B. H.; Buchwald, S. L. J. Am. Chem. Soc. 1998,
120 (26), 6621. Jiang, L.; Job, G. E.; Klapars, A.; Buchwald S. L. Org.
Lett. 2003, 5 (20), 3667.

hydrazines<sup>9a</sup> and N-aryl-N'-(2-bromobenzyl)hydrazines<sup>9b</sup> followed by spontaneous aromatization of aryl-substituted 2.3-dihydro-1H-indazoles formed. Wider application of this promising synthetic strategy is handicapped by the poor availability of cyclizable substrates and side reactions that complicate the intramolecular crosscoupling. The interaction of cyclizable substrates with catalysts often leads to the formation of stable metallacycles, thus leading to catalyst inactivation. Therefore, those palladium<sup>10</sup> and copper<sup>11</sup> catalysts that have proven to be highly useful in intermolecular C-N cross-coupling reactions may fail in cyclizations. Thus, the complexes of Pd with highly basic bulky phosphines, which are among the best catalysts for Pd-catalyzed intermolecular amination, behave poorly in cyclization reactions due to a high preference for intermolecular coupling, leading to oligomerization and tarring. The same is true for effective copper catalysts of intermolecular amination. On the other hand, palladium complexes with chelating diphosphines, which are known to be less effective catalysts for intermolecular amination,<sup>10a</sup> are preferable for cyclization reactions, possibly because the chelating ligand does not allow inactive palladacycle to be formed.12 As soon as catalyst deactivation is suppressed, the use of a less active catalyst is justified; otherwise, the intramolecular process is more favorable than the intermolecular one.

This work is devoted to the development of effective intramolecular amination in palladium-catalyzed cyclization of arylhydrazones of 2-bromoaldehydes or 2-bromoacetophenones (eq 1).



Recently, Cho et al.<sup>13</sup> have shown that various 1-aryl-1*H*-indazoles can be obtained in modest to good yields through the Pd-catalyzed reaction of 2-bromobenzaldehydes and arylhydrazines. However, the reported method suffers from essential limitations of scope. Simultaneously with these researchers, we accomplished a similar study on the Pd-catalyzed synthesis of arylindazoles; we found that the use of preformed hydrazones is

(11) Antilla, J. C.; Klapars, A.; Buchwald, S. L. J. Am. Chem. Soc. 2002, 124, 11684. Kwong, F. Y.; Buchwald, S. L. Org. Lett. 2003, 5, 793. Klapars, A.; Parris, S.; Anderson, K. W.; Buchwald, S. L. J. Am. Chem. Soc. 2004, 126, 3529. the key to better yields, milder reaction conditions, and extension of scope to heterocyclic substrates and 2-chlorobenzaldehyde. Moreover, we succeeded in achieving the cyclization of arylhydrazones of 2-bromoacetophenone and 8-bromo- $\alpha$ -tetralone. Though the yields of the respective indazoles in the latter case are only moderate, the synthesis of these molecules under the conditions reported by Cho et al.<sup>13</sup> is impossible, as shown below.

### **Results and Discussion**

In initial experiments, we have shown that the reaction of 2-bromobenzaldehyde with phenylhydrazine can be performed in toluene in the presence of palladium catalyst and anhydrous  $K_3PO_4$  and yields 65% 1-phenyl-1*H*-indazole (**1b**) after 12 h at 110 °C (eq 2). We believe that the reaction involves intermolecular catalytic arylation of NH fragment of arylhydrazine.



To test this hypothesis, we studied the Pd-catalyzed cyclization of 2-bromobenzaldehyde phenylhydrazone (1a), which was prepared in an analytically pure form by condensation of 2-bromobenzaldehyde with phenylhydrazine. Catalytic cyclization of this compound turned out to give 83% yield of indazole 1b after 12 h at 110 °C with quantitative conversion of starting materials (eq 3), which is a much better result than that achieved in the published method using in situ-generated hydrazone.<sup>13</sup>



In the absence of Pd catalyst, no cyclization occurred. The significant improvement of yield in the reaction with pure hydrazone as compared to the in situ reaction is likely to be associated with the inhibition of catalyst by condensation step byproducts or possibly by starting materials themselves. The negative influence of water liberated during hydrazone formation should also be considered. To estimate the influence of water, we performed a separate test. After a toluene solution of 2-bromobenzaldehyde and phenylhydrazine was stirred for 30 min, water was removed by 4 Å molecular sieves. The solution was charged by a Pd catalyst, and after 12 h at 110 °C the yield was only 65%. Thus, we can conclude that the influence of water is negligible compared to inhibition by byproducts or starting materials. To check the latter hypothesis, we studied the cyclization of 1a in the presence of a 10% additive of either phenylhydrazine or 2-bromobenzaldehyde. The reaction with phenylhydrazine gave essentially the same results as a stoichiometric reaction. On the contrary, the addition of 2-bromobenzaldehyde led to dramatic inhibition of cyclization. The yield of indazole 1b decreased to 40% versus 83% for the reaction with no additive under otherwise identical conditions (12 h at 110 °C), though

<sup>(8)</sup> Driver, M. S.; Hartwig, J. F. J. Am. Chem. Soc. 1995, 117, 4708.
Wood, J.-L.; Stoltz, B. M.; Dietrich, H.-J.; Pflum, D. A.; Petsch, D. T. J. Am. Chem. Soc. 1997, 119, 9641.
(9) (a) Song, J. J.; Yee, N. K. Org. Lett. 2000, 2, 519. (b) Song, J. J.;

<sup>(9) (</sup>a) Song, J. J.; Yee, N. K. Org. Lett. 2000, 2, 519. (b) Song, J. J.;
Yee, N. K. Tetrahedron Lett. 2001, 42, 2937.
(10) (a) Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. Acc. Chem. Res.

<sup>(10) (</sup>a) Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. Acc. Chem. Res.
1998, 31, 805. Hartwig, J. F. Angew. Chem., Int. Ed. 1998, 37, 2046.
Wolfe, J. P.; Yang, B. H.; Buchwald, S. L. J. Organomet. Chem. 1999, 576, 125. (b) Alcazar-Roman, L. M.; Hartwig, J. F.; Rheingold, A. L.;
Liable-Sandc, L. M.; Guzei, I. A. J. Am. Chem. Soc. 2000, 122, 4618.
Alcazar-Roman, L. M.; Hartwig, J. F. J. Am. Chem. Soc. 2001, 123, 1295. Viciu, M. S.; Germaneau, R. F.; Nolan, S. P. Org. Lett. 2002, 4, 4053. Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. J. Am. Chem. Soc. 2003, 125, 13978. Zim, D.; Buchwald, S. L. Org. Lett. 2003, 5, 2413.

<sup>(12)</sup> Paul, F.; Patt, J.; Hartwig, J. F. Organometallics 1995, 14, 3030.
Wagaw, S.; Buchwald, S. L. J. Org. Chem. 1996, 61, 7240.
(13) Cho, C. S.; Lim, D. K.; Heo, N. H.; Kim, T.-J.; Shim, S. C. Chem.

<sup>(13)</sup> Cho, C. S.; Lim, D. K.; Heo, N. H.; Kim, T.-J.; Shim, S. C. Chem. Commun. 2004, 104.

 TABLE 1. Cyclization of 1a to 1b Catalyzed by

 Pd(dba)<sub>2</sub>/Phosphine<sup>a</sup>

entry	$phosphine^b$	time, h	yield (%) of <b>1b</b>	conversion (%) of <b>1a</b>
1	DPEphos	0.5	43	44
2	DPEphos	1	58	60
3	DPEphos	2	94	97
4	DPEphos	12	83	>99
5	rac-BINAP	1	85	85
6	dppf	1	57	65
7	Xantphos	1	12	30
8	Xantphos	12	69	>99
9	dppp	1	1	9
10	dppp	15	10	35
11	$P^{t}Bu_{3}^{c}$	12	< 0.1	40
12	2	12	< 0.1	40
13	3	12	11	12

 $^a$  Conditions: 1a (1.0 mmol), Pd(dba)\_2 (0.02 mmol), phosphine (0.02 mmol), K\_3PO\_4 (2.5 mmol), toluene (6 mL), 110 °C.  $^b$  Phosphines used were bis[2-(diphenylphosphino)phenyl] ether (DPEphos), 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (Xantphos), 1,3-bis(diphenylphosphino)propane (dppp), rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (rac-BINAP), 1,1'-bis-(diphenylphosphino)-1,1'-biphenyl (2), and dicyclohexyl[2-(9-phenanthryl)phenyl]phosphine (3).  $^c$  Pd/P = 1/1 was used; Pd(P'Bu\_3)\_2 was found to have the same activity.

the conversion in both cases was nearly quantitative. This effect can be explained by the initiation of a side reaction, intermolecular C-N coupling, in the presence of 2-bromobenzaldehyde (eq 4). Therefore, all further experiments on the catalytic formation of indazoles were carried out with preformed and carefully purified hydrazones.

$$() \xrightarrow{CHO} \xrightarrow{Pd^0} (Pd^{\underline{I}} Br) \xrightarrow{Ia} (CHO) \xrightarrow{CHO} (I)$$

Next, we investigated the influence of phosphine ligand and base on the cyclization of **1a**. These data are shown in Table 1. It should be noted that indazole **1b** undergoes a slow spontaneous decomposition when heated in toluene solution for a long time. Indeed, while the yields of **1b** were nearly quantitative after 2 h (Table 1, entries 1-3), further refluxing resulted in a decrease of the yield by ca. 12% (entry 4) due to formation of unidentified products. Other indazoles show similar behavior, which should be taken into consideration to avoid losses of product.

A comparison of ligands can best be drawn from the results of incomplete conversion reactions quenched after 1 h (entries 2, 5–7, 9, 13). We tested a wide selection of ligands typically employed in Pd-catalyzed cross-coupling reactions,<sup>14</sup> particularly, the arylation of amines. The best results were obtained with *rac*-BINAP, which afforded an 85% yield after 1 h at reflux. Moreover, in this case, all reacted hydrazone transformed into the product without losses. All other ligands invariably gave yields lower than conversion. The catalysts containing DPEphos and dppf showed similar activities marginally inferior to

 TABLE 2.
 Cyclization of 1a to 1b Catalyzed by

 Pd(dba)<sub>2</sub>/DPEphos in the Presence of Various Bases<sup>a</sup>

entry	base	yield (%) of <b>1b</b>	conversion (%) of <b>1a</b>				
1	$Cs_2CO_3$	68	78				
2	$K_3PO_4$	58	60				
3	$Na_3PO_4$	4	16				
4	$K_2CO_3$	28	37				
5	<sup>t</sup> BuOLi	31	39				
6	<sup>t</sup> BuONa	9	24				
7	<sup>t</sup> BuOK	0	28				
<sup>a</sup> Conditions: <b>1a</b> (1.0 mmol), Pd(dba) <sub>2</sub> (0.02 mmol), DPEphos							

(0.02 mmol), base (2.5 mmol), toluene (6 mL), 1 h, 110 °C.

that of the BINAP complex. As DPEphos is much cheaper and more readily available than BINAP, it should be preferred for practical reasons as the catalyst for the preparative synthesis of 1-aryl-1*H*-indazoles.

The xantphos ligand gave a catalyst with a much lower activity (12% yield/30% conversion after 1 h). After prolonged heating for 12 h, the yield increases to 69% with quantitative conversion of hydrazone. Such ligands as P'Bu<sub>3</sub> or **3** altogether failed to give the desired product, though the conversion was high. Thus, the complexes of palladium with highly basic bulky phosphine ligands, which are among the best catalysts for intermolecular amination,<sup>15</sup> behave poorly in the cyclization reaction due to a preference for intermolecular coupling, leading to oligomerization and tarring.

Further studies on the effect of the base, solvent, and substituents in the substrate were carried out with the DPEphos system, having an optimal combination of activity, selectivity, price, and availability. First, fast cyclization of 1a was shown to occur in dioxane to give 1b in 67% yield over 2 h at 90 °C. Under similar conditions in DMF or toluene solution, the desired product was formed in 7 or 23% yield, respectively. However, in further studies, we used toluene as a solvent, which allowed the reaction to be carried out faster at higher temperatures. For instance, indazole 1b is formed in as high as 94% yield in toluene over 2 h at reflux. The variation of the base gave the results shown in Table 2.  $Cs_2CO_3$  is the best base under the conditions studied. However, K<sub>3</sub>PO<sub>4</sub> was only marginally inferior, and, given the immensely lower price of the latter base, the choice is obvious. Potassium carbonate and lithium tert-butoxide both gave much poorer yields furnishing only a modest yield after 1 h. Sodium phosphate and sodium and potassium *tert*-butoxides are even less useful, causing the decomposition of hydrazone. Thus, in further studies, we used potassium phosphate as an optimal base.

The study of substituent effects on Pd-catalyzed cyclization was performed with arylhydrazones prepared from the respective 2-bromobenzaldehydes and arylhydrazines in an analytically pure state. The results obtained for the cyclization of these hydrazones in the presence of Pd(dba)<sub>2</sub>/DPEphos/K<sub>3</sub>PO<sub>4</sub> are given in Table 3. With all hydrazones, the cyclization occurred only at elevated temperatures. Substituents in arylhydrazine had no significant influence on yields. Similar results were obtained for hydrazones bearing electron-withdrawing (indazoles **5b**, **8b**, **11b**) and electron-donating (inda-

<sup>(14) (</sup>a) Tsuji, J. Palladium Reagents and Catalysts, Innovations in Organic Synthesis; Wiley-VCH: New York, 1995. (b) Metal-Catalyzed Cross-Coupling Reactions; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1997; p 2.

 <sup>(15)</sup> Old, D. V.; Wolfe, J. P.; Buchwald S. L. J. Am. Chem. Soc. 1998, 120, 9722. Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaudhnessy, K. H.; Alcazar-Roman, L. M. J. Org. Chem. 1999, 64, 5575.

TABLE 3. Cyclization of Hydrazones of 2-Bromobenzaldehydes Catalyzed by Pd(dba)<sub>2</sub>/DPEphos<sup>a</sup>

entry	arylhydrazone	product	yield, %	entr y	arylhydrazone	product	yield, %
1	Br H la	Ib	83	13	H Br Me	N Me 15b	70
2	H Me Br Me 4a	Me 4b	85	14	Me Br N <sup>-N</sup> 16a	Me I6b	85
3	Br NO2 5a	5b	96	15	Me Br H OMe	Me I7b	89
4	Br 6a	GUN 60	92	16	Me Br F 18a	Me I8b	35
5	Br NoMe	7b OMe	95	17	Br, N, N, N, N, 19a	Br Me N 19b	32 <sup>d</sup>
6	Br H CF3	Sb CF3	97	18	Br Nr NH HN' N Br 20a	N 20b	92
7	Br H Br 9a	Solution of the second	40 <sup>*</sup>	19	Br 21a	STN 21b	53
8	H Br CN 10a	N 10b	86	20	S H CF3 22a	S N CF <sub>3</sub> 22b	79
9	Br CO <sub>2H</sub>		56°	21	S <sup>Br</sup> H 23a	S N S N N S S S N S S S S S S S S S S S	60
10	$\bigcup_{O_2N} \bigcup_{Br}^{H} \bigcup_{D_2N} 12a$	O2N N 12b	85	22	Br OMe S H 24a	S N OMe 24b	20
11	O <sub>2</sub> N Br H OMe	O <sub>2</sub> N N 13b	75	23	O H D Z5a	0 	91 <sup>¢</sup>
12	O <sub>2</sub> N Br CF <sub>3</sub>	O <sub>2</sub> N N V F <sub>1</sub> (F <sub>1</sub> )	78	24	N Br 26a	N 26b	98

<sup>*a*</sup> Conditions: aldehyde hydrazone (1.0 mmol), Pd(dba)<sub>2</sub> (0.02 mmol), DPEphos (0.02 mmol), base (2.5 mmol), toluene (6 mL), 12 h,110 °C. <sup>*b*</sup> At 43% conversion of the starting arylhydrazone. <sup>*c*</sup> Performed with 3.0 mmol of *t*BuOLi as a base. <sup>*d*</sup> Byproduct observed is indazole **16b** (12%) <sup>*e*</sup> Time = 120 h.

zole **7b**) substituents in the benzene ring of arylhydrazine. Ortho substituents in arylhydrazine were also well tolerated (indazoles **4b**, **6b**). In all cases, the respective indazoles were formed in high yield with quantitative conversion of the starting hydrazones.

Lithium *tert*-butoxide was used as the base for the synthesis of 4-(1*H*-indazol-1-yl)benzoic acid (11b). In this case,  $K_3PO_4$  could not be used, as potassium salt of the respective hydrazone is insoluble in toluene. With lithium *tert*-butoxide, indazole is formed in 56% yield and can be readily isolated upon acidification of the reaction mixture.

The cyclization of 4-bromophenylhydrazone of 2-bromobenzaldehyde was much slower than the reactions of all other hydrazones. Indazole **9b** is formed in only 40% vield (with 43% conversion) after 12 h reflux. Longer heating (130 h) gives 26% yield and quantitative conversion. Apparently, this indazole is unstable toward heating in the presence of Pd catalyst, as the extra Br atom can be involved in followup reactions leading to formation of unidentified oligomeric products. Similarly, the reaction of phenylhydrazone of 2,5-dibromo-4-methylbenzaldehyde gives only 32% yield of target indazole 19b, though in this case we could isolate 12% yield of byproduct indazole 16b (eq 5). Debromination is a well-known side reaction in the Pd-catalyzed amination of aryl bromides.<sup>16</sup> Here again the conversion was quantitative, revealing that the substrate is consumed mostly due to intermolecular reaction.



Further, we investigated the cyclization of arylhydrazones of heterocyclic analogues of 2-bromobenzaldehyde. Pd-catalyzed cyclization of arylhydrazones of 3-bromo-2-thiophencarbaldehyde 21a-23a afforded new 1-arylthieno[3,2]pyrazoles **21b-23b**. These products were, however, obtained in lower yields than in the case of the analogous indazoles, though the conversion was always quantitative. An attempt to carry out the reaction at lower temperatures (80 °C) was unsuccessful, as no product was observed in the reaction mixture. A shorter reaction time (5 h at 110 °C) could not solve the problem: 43% yield of 19b with 65% conversion was formed. Therefore, as prolonged heating at 110 °C is likely to result in considerable destruction of the product, careful optimization is required if higher yields are to be obtained.

The behavior of hydrazones containing a pyridine ring depends strongly on their structure. Hydrazones **27a** and **28a** showed no traces of cyclization in the presence of Pd(dba)<sub>2</sub>/DPEphos/K<sub>3</sub>PO<sub>4</sub> after 120 h at 110 °C (starting materials were not consumed). For hydrazine **27a**, this can be easily explained by inhibition due to chelating of Pd by hydrazone. For hydrazone **28a**, the cause of the inhibition is not obvious, though possible formation of a stable dimer **A** involving a six-membered palladacycle<sup>17</sup>

after the oxidative addition stage may explain the observed low reactivity of  $\alpha$ -bromopyridine hydrazone **28a**. Interestingly, the closest relative of this compound, phenylhydrazone of 3-bromoisonicotinic aldehyde (**26a**), is smoothly transformed into the corresponding 5-azaindazole **26b** in a near-quantitative yield after 12 h at 110 °C.



Next, we attempted to extend the method to chloro derivatives. Phenylhydrazone of 2-chlorobenzaldehyde gave no cyclization product in the system Pd(dba)<sub>2</sub>/ DPEphos (2 mol %), K<sub>3</sub>PO<sub>4</sub> after 120 h at 110 °C. With  $P^tBu_3$ , DPEphos, or P–N ligand, the conversion did not exceed 1%. However, activated substrates such as arylhydrazones of 5-nitro-2-chlorobenzaldehyde 29a-31a were found to give readily the respective indazoles 29b-31b (eq 6). It should be noted that, while 29a (R = H), involving unsubstituted phenyl, gave **29b** in as high as 70% yield, the analogous substituted substrates 30a (R = OMe) and **31a**  $(R = CF_3)$  gave the respective cyclization products in lower yields, i.e., 25 and 43%, respectively. These reactions take place only in the presence of a Pd catalyst. We ascertained in a blank run without Pd catalyst that uncatalyzed nucleophilic substitution<sup>18</sup> does not take place.



Next, we turned our attention to the synthesis of 2-substituted 1-aryl-1H-indazoles from the respective 2-bromoacetophenones. The main difficulty here is to employ a mild and effective method for the preparation of hydrazones. The formation of hydrazones from alkylaromatic ketones is much slower than from benzaldehydes.<sup>19</sup> Moreover, there is a risk of initiating the Fischer indole synthesis<sup>20</sup> if the reaction conditions are not mild enough. After optimization studies, we found that the best and safest method is to perform hydrazone formation by prolonged (50–170 h) reflux of an equimolar mixture of a ketone (2-bromoacetophenone or 8-bromo-α-tetralone) and arylhydrazine (eqs 7, 8) in low-boiling diethyl ether. It should be noted that attempts to increase the reaction rate by increasing the temperature led to the formation of a complex mixture of products. At this point,

<sup>(16)</sup> Hartwig, J. F.; Richards, S.; Baran, D.; Paul, F. J. Am. Chem. Soc. **1996**, *118*, 3626.

<sup>(17)</sup> Benetollo, F.; Bombieri, G.; DiBianca, F.; Crociani, B. Inorg. Chim. Acta **1991**, 188, 51.

<sup>(18)</sup> Beller, M.; Briendl, C.; Riermeier, T. H.; Tillack, A. J. Org. Chem. 2001, 66, 1403.

<sup>(19)</sup> Smith, M. B.; March, J. Advanced Organic Chemistry, 5th ed.; Wiley-VCH: New York, 2001; p 1186.

<sup>(20)</sup> Sundberg, R. J. Indoles; Academic Press: New York, 1996.

## SCHEME 1. Catalytic Cycle for Cyclization of Arylhydrazones of 2-Bromobenzaldehydes



the inapplicability of the previously reported technique<sup>13</sup> became obvious, as it requires prolonged heating.



8-Bromo- $\alpha$ -tetralone for this synthesis was obtained by oxidation of 8-bromo- $\alpha$ -tetralole, which itself was synthesized via ortho lithiation of  $\alpha$ -tetralole followed by treatment with 1,2-dibromoethane (eq 9).

$$\underbrace{\overset{OH}{\overbrace{2.(CH_2Br)_2.-78^\circ C}}}_{37} \underbrace{\overset{Br}{\overbrace{AcOH-H_2O}}} \overset{OH}{\overbrace{AcOH-H_2O}} \underbrace{\overset{Br}{\overbrace{AcOH-H_2O}}}_{34} (9)$$

Hydrazones **32a** and **33a** were found to undergo cyclization in the presence of 7 mol % Pd(dba)<sub>2</sub>/DPEphos and  $K_3PO_4$  to form indazoles **32b** and **33b** in 47% and 48% yields, respectively, after 160 h at 120° (eq 10).



 $\alpha$ -Tetralone hydrazones **35a** and **36a** in this system were reluctant to react. The screening of various ligands has shown that the best, though still rather low, yields are formed with Buchwald's phenanthrene-based phosphine **3**, which is known to form a chelate complex with palladium involving Pd–P and Pd–arene interactions.<sup>21</sup> Thus, indazole **35b** was formed in 45% yield after 24 h at 120 °C with 20 mol % Pd catalyst, and indazole **36b** was formed in 40% yield in the presence of 10 mol % catalyst (eq 11). Lower loadings of catalyst gave unsatisfactory results due to unfavorable competition of slower cyclization and decomposition of indazole product.



The tentative mechanism of the described cyclization reaction should take into consideration the published data on palladacycles formed from phenylhydrazones of aromatic aldehydes and ketones.<sup>22,23</sup>

The oxidative addition of Pd(0) to the carbon-halogen bond of hydrazone I should give the five-membered palladacycle III, possibly in equilibrium with open structure II (Scheme 1). The cyclization should involve a different six-membered palladacycle, which can be formed from II by deprotonation of NH by base and the subsequent metallotropic shift of Pd to form palladacycle IV. The shift should first involve the dissociation of the Pd-N bond; otherwise, cis/trans isomerization of the hydrazone fragment cannot take place. The actual order of these

<sup>(21)</sup> Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. J. Am. Chem. Soc. 2002, 124, 1162.

<sup>(22)</sup> Espinet, P.; Garcia-Herbosa, G.; Herrero, F. J.; Jeannin, Y.;
Philoche-Levisalles, M. *Inorg. Chem.* **1989**, *28*, 4207.
(23) Espinet, P.; Alonso, M. Y.; Garcia-Herbosa, G.; Ramos, J. M.;

<sup>(23)</sup> Espinet, P.; Alonso, M. Y.; Garcia-Herbosa, G.; Ramos, J. M.; Jeannin, Y.; Philoche-Levisalles, M. *Inorg. Chem.* **1992**, *31*, 2501.

events (Pd–N dissociation, deprotonation of NH, isomerization, and reclosure of the palladacycle) cannot be unambiguously established. The transformation of the five-membered palladacycle into indazole by a strong base was described earlier in a study devoted to the chemistry of the palladacyclic carbonyl complex (eq 12), which is transformed into 1-phenyl-3-methylindazole.<sup>24</sup>



One of the key roles of the chelating phosphine ligand in the proposed mechanism should be to promote rupture of the Pd–N bond in palladacycle **III**, which otherwise would be stable enough to terminate the catalytic cycle. In the absence of a good chelating phosphine ligand, these five-membered palladacycles can even be further transformed by deprotonation into very stable dimeric complexes, as has been shown by Espinet et al.,<sup>22</sup> thus resulting in the further deactivation of catalyst (eq 13).



#### Conclusion

In conclusion, we have shown that the cyclization of arylhydrazone of 2-bromobenzaldehydes can be performed in good to high yields using  $Pd(dba)_2$  and chelating phosphines, of which the most effective are *rac*-BINAP, DPEphos, and dppf, in the presence of  $Cs_2CO_3$  or  $K_3PO_4$  as a base. Electron-rich, bulky ligands commonly employed for intermolecular amination such as  $P^tBu_3$  and **2** were shown to be ineffective for cyclization and to lead instead to extensive oligomerization and tarring. We believe that the most important role of chelating ligands in the intramolecular reaction is to

suppress the formation of stable inactive palladacycles such as **III** or similar dimers as shown in eq 13. The method developed is applicable for preparation of a wide variety of indazoles bearing electron-donating or electronwithdrawing substituents, among them, unprotected carboxyl, as well as various heteroanalogues of indazoles. The cyclization of arylhydrazones of less reactive halides such as 2-chlorobenzaldehyde, as well as 2-bromoacetophenone and bromotetralone, has been achieved. The purity of the starting hydrazone has been shown to be a critical parameter, as various impurities inhibit the cyclization.

#### **Experimental Section**

Reaction of arylhydrazines with aldehydes (general procedure A). Hot solutions of 3 mmol of arylhydrazine in a minimal volume of methanol and of 3 mmol of arylaldehyde in 5 mL of methanol were mixed and stirred with refluxing for 30 min. After that, the reaction mixture was cooled to -30 °C and kept at this temperature for 12 h. The precipitates were collected by filtration, washed twice with a small portion of cold methanol, and dried in a vacuum.

Reaction of arylhydrazines with acetophenones (general procedure B). A 24 mL vial was charged with 5 mmol of the corresponding phenylhydrazine, 5 mmol of 2-bromoacetophenone, and 20 mL of dry ether. The vial was flushed with argon, sealed, and thermostated for 140 h at 40 °C. The product was isolated by evaporation of ether, washing of the residue with two 10 mL portions of hot hexanes, and drying in a vacuum.

Synthesis of 1-aryl-1*H*-indazoles (general procedure C). An 8 mL vial was charged with 1 mmol of arylhydrazone, 530 mg (2.5 mmol) of K<sub>3</sub>PO<sub>4</sub>, 10.8 mg (0.02 mmol) of phosphine ligand, 11.5 mg (0.02 mmol) of Pd(dba)<sub>2</sub>, and 6 mL of toluene. This mixture was stirred for 8 h (if not otherwise specified; see Table 3) at 110 °C. Next, the resulting mixture was cooled to room temperature and passed through a short column with Silica Gel 60 (40–63  $\mu$ m, d = 50 mm, l = 30 mm). The column was additionally washed with 50 mL of THF. The eluate was evaporated to dryness, and the product was purified using semipreparative HPLC.

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**Supporting Information Available:** Experimental procedures, characterization of new compounds, and references to known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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<sup>(24)</sup> Carbayo, A.; Cuevas, J. V.; Garcia-Herbosa, G. J. Organomet. Chem. **2002**, 658, 15.