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Novel Route to Azobenzenes via Pd-Catalyzed Coupling Reactions of Aryl Hydrazides with Aryl Halides, Followed by Direct Oxidations[†]

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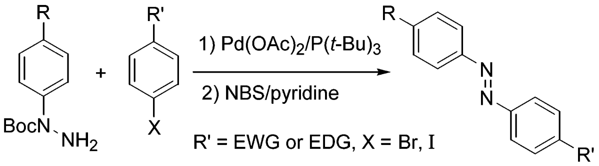
ABSTRACT



N-Boc aryl hydrazines undergo Pd-catalyzed coupling reactions with aryl halides to provide N-Boc diaryl hydrazines in excellent yields. The resulting N-Boc diaryl hydrazines were directly oxidized with NBS/pyridine in CH_2Cl_2 at room temperature to the azobenzenes.

Due to their characteristic color and photoresponsive properties, azobenzenes have gained much interest over the past years. Various types of azobenzenes were prepared and studied for their possible applications in the area of nonlinear optics, optical storage media, chemosensors, and photochemical switches.[1] Diazo bonds in azobenzenes undergo reversible cis−trans isomerizations, causing changes of molecular geometry when subjected to visible light. Also investigated was their potential use as a diagnostic probe for the visualization of amyloid plaques in the brains of mentally deteriorating patients for a definite diagnosis of Alzheimer's disease.[2]

Azobenzenes are commonly prepared from aromatic amines via formation of diazonium ion, followed by diazo coupling with arylamine or alcohol.[3] Less commonly used, but often more effective, is the coupling of nitroso arene with arylamine.[4] Symmetrical azobenzenes can be prepared from either direct reduction of nitroarene or oxidation of aromatic amine.[5] In general, the starting arylamines or alcohols need to be readily available and also sufficiently soluble in acidic media.

Adopting well-developed transition metal-catalyzed amination reactions, we hypothesized a new approach for those compounds starting from a hydrazine and more readily available aryl halides. In principle, consecutive couplings of a hydrazine[6] with two molecules of aryl halides, followed

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[†] Dedicated to Professor Gary H. Posner on the occasion of his 60th birthday.

(1) (a) Willner, I.; Willner, B. In *Bioorganic Photochemistry: Biological Applications of Photochemical Switches*; Morrison, H., Ed.; Wiley: New York, 1993; Vol. 2, pp 1−110. (b) Ghosh, S.; Banthia, A. K.; Maiya, B. G. *Org. Lett.* **2002**, *4*, 3603. (c) Wang, S.; Advincula, R. C. *Org. Lett.* **2001**, *3*, 3831. (d) DiCesare, N.; Lakowicz, J. R. *Org. Lett.* **2001**, *3*, 3891. (e) Harvey, A. J.; Abell, A. D. *Tetrahedron* **2000**, *56*, 9763. (f) Burland, D. M.; Miller, R. D. Walsh, C. A. *Chem. Rev.* **1994**, *94*, 31. (g) Kanis, D. R.; Ratner, M. A.; Marks, T. J. *Chem. Rev.* **1994**, *94*, 195. (h) Ichimura, K. *Photochromism: Molecules and Systems*; Durr, H., Bouas-Laurent, H., Eds.; Elsevier: Amsterdam, 1990; p 903. (i) Kumar, G. S.; Neckers, D. C. *Chem. Rev.* **1989**, *89*, 1915.

(2) (a) Zhen, W.; Han, H.; Anguiano, M.; Lemere, C.; Cho, C.-G.; Lansbury, P. T. Jr. *J. Med. Chem.* **1999**, *42*, 2805−2815. (b) Han, H.; Cho, C.-G.; Lansbury, P. T. Jr. *J. Am. Chem. Soc.* **1995**, *118*, 4506.

(3) For review of azo dyes, see: (a) Zollinger, H. *Diazo Chemistry I. Aromatic and Heteroaromatic Compounds*; VCH: New York, 1994. (b) Hegarty, A. F. In *The Chemistry of Diazonium and Diazo Groups*; Patai, S., Ed.; Wiley: New York, 1978; Part 2, pp 545−551. (c) *The Chemistry of Synthetic Dyes*; Venkataraman, K., Ed.; Academic Press: New York, 1970; Vols. 1−7.

(4) (a) Davey, M. H.; Lee, V. Y.; Miller, R. D.; Marks, T. J. *J. Org. Chem.* **1999**, *64*, 4976. (b) Szele, I.; Zollinger, H. *Top. Curr. Chem.* **1983**, *112*, 1.

(5) (a) Wada, S.; Urano, M.; Suzuki, H. *J. Org. Chem.* **2002**, *67*, 8254. (b) Leyva, E.; Platz, M. S.; Persy, G.; Wirz, J. *J. Am. Chem. Soc.* **1986**, *108*, 3783.

(6) Song, J. J.; Yee, N. K. *Org. Lett.* **2000**, *2*, 519.

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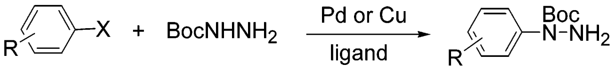
by oxidations, would give azobenzenes. However, we were not able to couple phenyl hydrazine with aryl halides under various catalytic amination conditions, employed successfully in the literature.

A related literature survey showed that *t*-butyl carbazate (Boc-$NHNH_2$) was readily coupled (BocNH− side) with aryl halides to furnish aryl hydrazides in the presence of Pd or Cu catalyst (Scheme 1).[7,8a]

Scheme 1. Literature Methods for the Arylation of $BocNHNH_2$[a]



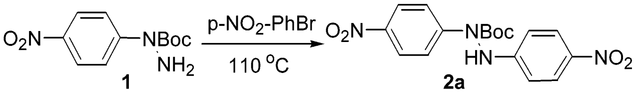
[a] R = EDG or EWG; X = Br,I, OTf.

Provided that the diaryl hydrazides are readily oxidized to the azobenzenes, all that remained to do was to connect the two strings, by elaborating a proper protocol for the couplings of aryl hydrazides with aryl halides.

Despite the numerous examples in the literature for the couplings of simple amines, amides, carbamates, and hydrazones,[8] no precedents were found for the couplings of aryl hydrazides with aryl halides, except for two cases: the intramolecular coupling of aryl hydrazine[6] and its formation as a byproduct.[7]

Lack of a proper method prompted us to study the couplings of aryl hydrazides with aryl halides in depth. Herein, we report Pd-catalyzed couplings of N-Boc aryl hydrazines with various aryl halides for the synthesis of N-Boc diaryl hydrazines as well as their direct oxidations to the corresponding azobenzenes. Table 1 summarizes the couplings of N-Boc aryl hydrazine **1** with 4-nitro-phenyl bromide as a model system under various catalytic conditions, reported to be effective for aminations, amidations, and carbamations.[9]

Table 1. Pd-Catalyzed Coupling Reactions of Aryl Hydrazide[a]

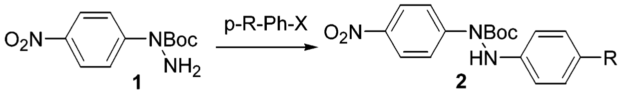


entry	catalyst	ligand	base	solvent	yield
1	$Pd_2(dba)_3$	P(*o*-tol)$_3$	NaOtBu	toluene	trace
2	$Pd_2(dba)_3$	P(*o*-tol)$_3$	Cs_2CO_3	toluene	12%
3	$Pd_2(dba)_3$	BINAP	Cs_2CO_3	toluene	40%
4	$Pd_2(dba)_3$	BINAP	Cs_2CO_3	toluene	72%
5	$Pd_2(dba)_3$	dppf	Cs_2CO_3	toluene	83%
6	$Pd_2(dba)_3$	dppf	Cs_2CO_3	dioxane	80%
7	$Pd_2(dba)_3$	dppf	Cs_2CO_3	toluene	87%
8	$Pd_2(dba)_3$	dppf	NaOtBu	toluene	14%

[a] Catalyst: 1 mol %. Ligand: 3 mol %.

The conditions in entry 7 were better than any other conditions we tested. Skerlj et al. in fact reported that under those conditions, diaryl hydrazide was formed in ∼10% yield as a byproduct during the couplings of Boc-$NHNH_2$ with aryl halides (vide supra).[7] Attempted coupling reactions with various other aryl halides revealed, however, that the current conditions were effective only with the aryl halides bearing electron-withdrawing groups (Table 2).

Table 2. N-Arylation of N-Boc Aryl Hydrazine[a]



entry	aryl halide	time	product	yield
1	R = NO_2, X = Br	30 h	**2a** (R = NO_2)	87%
2	R = NO_2, X = I	27 h	**2a** (R = NO_2)	95%
3	R = NO_2, X = OTf	2 h	**2a** (R = NO_2)	97%
4	R = MeCO, X = Br	48 h	**2a** (R = COMe)	50%
5	R = CN, X = Br	24 h	**2a** (R = CN)	72%
6	R = PhCO, X = Br	48 h	**2d** (R = PhCO)	62%
7	R = CO_2Me, X = I	72 h	**2e** (R = CO_2Me)	trace
8	R = H, X = I	72 h	**2f** (R = H)	trace
9	R = Me, X = Br	72 h	**2g** (R = Me)	trace
10	R = OMe, X = Br	72 h	**2h** (R = OMe)	trace

[a] Reaction conditions: $Pd_2(dba)_3$/dppf/Cs_2CO_3/toluene/110 °C.

Such a lack of reactivity with unactivated aryl halides (entries 7−10) was in fact the problem in the Pd-catalyzed arylations of Boc-$NHNH_2$.[7]

Various types of Pd catalysts and ligands were screened for the couplings of the hydrazide **1** with iodobenzene, a model unactivated aryl halide (Table 3).

The catalytic system, $Pd(OAc)_2$/xantphos (entry 4) was found to be effective, furnishing **2f** in 83% yield. No desired product was observed with Buchwald's CuI/phen system, previously shown to be effective for the couplings of Boc-$NHNH_2$ with unactivated aryl halides.[8a] However, the conditions in entry 4 (Table 3) do not mediate the couplings with more deactivated aryl halides, for example, *p*-iodo-anisole. Attempted coupling gave only a trace of the desired product.

Further screening of Pd catalysts and ligands showed that $Pd(OAc)_2$/P(*t*-Bu)$_3$ is a much better catalytic system in such cases.[10] The best result was obtained when the coupling was

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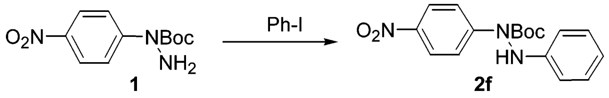
(7) Wang, Z.; Skerlj, R. T.; Bridger, G. J. *Tetrahedron Lett.* **1999**, *40*, 3543.

(8) (a) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581. (b) Alcazar-Roman, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 12905. (c) Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803. (d) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Zappia, G. *Org. Lett.* **2001**, *3*, 2539. (e) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101. (f) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251. (g) Arterburn, J. B.; Rao, K. V.; Ramdas, R.; Dible, B. R. *Org. Lett.* **2001**, *4*, 1351.

(9) In ref 8a, Buchwald et al. reported that Boc-$NHNH_2$ underwent Cu-catalyzed coupling reactions at $-NH_2$ when reacted with aryl halides bearing substituents at the *ortho*-position.

(10) Ogawa, K.; Radke, K. R.; Rothstein, S. D.; Rasmussen, S. C. *J. Org. Chem.* **2001**, *66*, 9067.

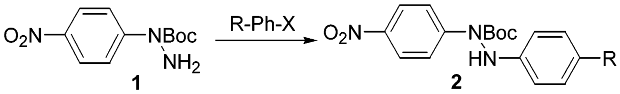
Table 3. Couplings with Iodobenzene under Various Conditions



entry	catalyst	ligand	base	solvent	temp/time	yield
1	$Pd_2(dba)_3$	xantphos	Cs_2CO_3	toluene	110 °C/15 h	30%
2	$Pd_2(dba)_3$	xantphos	NaO*t*Bu	toluene	110 °C/12 h	trace
3	$Pd(OAc)_2$	xantphos	Cs_2CO_3	DMF	80 °C/5 h	trace
4	$Pd_2(dba)_3$	xantphos	Cs_2CO_3	DMF	80 °C/5 h	trace
5	$Pd(OAc)_2$	xantphos	Cs_2CO_3	DMF	110 °C/5 h	83%
6	$Pd(OAc)_2$	BINAP	Cs_2CO_3	toluene	110 °C/5 h	trace
7	CuI	phen	Cs_2CO_3	DMF	80 °C/8 h	trace

conducted with Cs_2CO_3 in toluene at 110 °C. With these reaction conditions, we were able to execute the couplings with various other deactivated aryl halides to provide the corresponding diaryl hydrazides in 78−91% isolated yields (Table 4).[11]

Table 4. Couplings with Deactivated Aryl Halides with $Pd(OAc)_2/P(t\text{-}Bu)_3$[a]



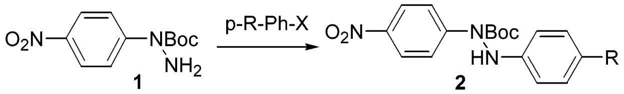
entry	aryl halides	time	product	yield
1	R = H, X = 1	2 h	**2f** (R = H)	84%
2	R = *p*-Me, X = 1	2 h	**2g** (R = Me)	85%
3	R = *p*-OMe, X = 1	2 h	**2h** (R = *p*-OMe)	91%
4	R = *p*-Ph, X = I	1 h	**2i** (R = *p*-Ph)	86%
5	R = *o*-OMe, X = I	1 h	**2j** (R = *o*-OMe)	78%

[a] Reaction conditions: Cs_2CO_3/toluene/110 °C.

A slight excess (1.2 equiv) of aryl hydrazides was used to suppress diarylation (vide infra), as this was found to be an important competing reaction in some cases. The yields reported here are based on equivalents of aryl halides. Notable is that the reaction mixture must be stirred at room temperature for a while, before heating to 110 °C.[12] A substantial drop of the product yield was observed when the reaction mixture was heated directly without such incubation.

The catalytic system, $Pd(OAc)_2/P(t\text{-}Bu)_3$, is also effective for the couplings with aryl halides bearing electron-withdrawing groups, especially with respect to the reaction rates, but not much with respect to the product yields (Table 5).

Table 5. Couplings with Activated Aryl Halides with $Pd(OAc)_2/P(t\text{-}Bu)_3$[a]



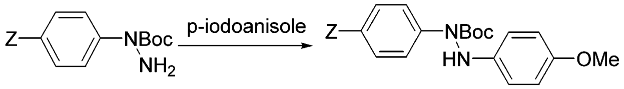
entry	aryl halides	time	product	yield
1	R = NO_2, X = Br	1 h	**2a** (R = NO_2)	83%
2	R - NO_2, X = I	1 h	**2a** (R = NO_2)	91%
3	R = NO_2, X = OTf	12 h	**2a** (R = NO_2)	31%
4	R = MeCO, X = Br	3 h	**2b** (R = COMe)	63%
5	R = CN, X = Br	21 h	**2c** (R = CN)	50%
6	R = PhCO, X = Br	16 h	**2d** (R = PhCO)	63%
7	R = CO_2Me, X = I	5 h	**2e** (R = CO_2Me)	77%

[a] Reaction conditions: Cs_2CO_3/toluene/110 °C.

Prolonged heating of the reaction mixture did not help much, as the starting N-Boc aryl hydrazines underwent deamination reactions to produce the N-Boc arylamines under the reaction conditions.[13]

Other aryl hydrazides were also readily coupled under the current reaction conditions (Table 6).

Table 6. Couplings of Other N-Boc Aryl Halides[a]



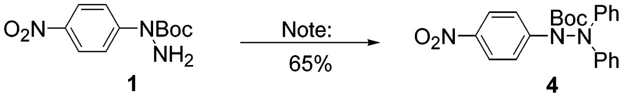
entry	aryl hydrazide	time	product	yield
1	**3a** (Z = H)	0.5 h	**2k** (Z = H)	94%
2	**3b** (Z = CO_2Me)	1 h	**2l** (R = CO_2Me)	51%
3	**3c** (Z = OMe)	1 h	**2m** (R = OMe)	84%

[a] Reaction conditions: $Pd(OAc)_2/P(t\text{-}Bu)_3/Cs_2CO_3$/toluene/110 °C.

The coupling reactions with excess aryl halides result in the formation of diarylated hydrazides (vide supra), along with the monoarylated product in 26% yields (Scheme 2).

A few methods have been reported in the literature for the oxidation of hydrazines to azobenzenes,[14] but with no

Scheme 2. Diarylation of Aryl Hydrazide[a]



[a] Reaction conditions: PhI (3 equiv)/$Pd(OAc)_2/P(tBu)_3$/PhMe/110 °C/10 h.

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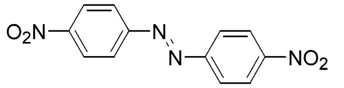
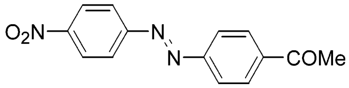
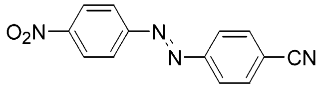
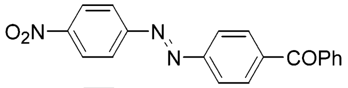
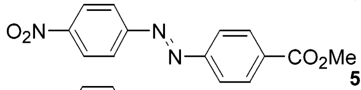
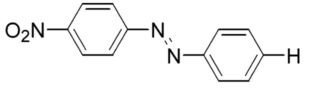
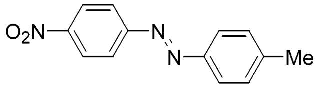
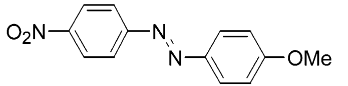
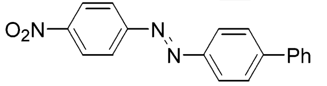
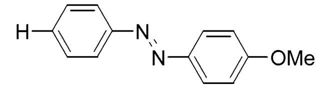
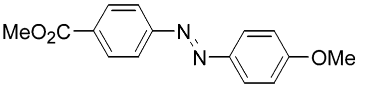
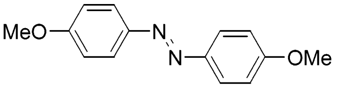
[11] **Representative Procedure.** Into a sealed tube were charged 30 mg (0.13 mmol) of 4-iodo-anisole, 39 mg (0.15 mmol) of **1**, $Pd(OAc)_2$ (5 mol %), $P(t\text{-}Bu)_3$ (5 mol %) dissolved in hexane, 64 mg (0.20 mmol) of Cs_2CO_3, and 1.5 mL of anhydrous toluene at room temperature. The resulting solution was stirred for 30 min at room temperature before being heated at 110 °C. After 1 h, the reaction mixture was cooled, concentrated in vacuo, and chromatographed (hexanes/EtOAc = 9/1) to afford 41 mg of **3h** in 91% yield.

[12] Guari, Y.; van Es, D. S.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Tetrahedron Lett.* **1999**, *40*, 3789.

Table 7. Direct Oxidations of Hydrazides to Azobenzenes.

entry	**2**	time	azobenzene	yield
1	**2a**	2 h	 **5a**	72%
2	**2b**	24 h	 **5b**	84%
3	**2c**	3 h	 **5c**	79%
4	**2d**	2 h	 **5d**	81%
5	**2e**	1 h	 **5e**	65%
6	**2f**	2 h	 **5f**	61%
7	**2g**	2 h	 **5g**	65%
8	**2h**	2 h	 **5h**	35%
9	**2i**	2 h	 **5i**	57%
10	**2k**	2 h	 **5j**	57%
11	**2l**	2 h	 **5k**	62%
12	**2m**	2 h	 **5l**	55%

precedents for the oxidation of hydrazides. Although the Boc group could be removed prior to the oxidations, we studied their direct oxidations to the azobenzenes for obvious reasons. Upon screening various oxidation methods, we found that the N-Boc diaryl hydrazines **2a−l** were readily oxidized with NBS/pyridine in CH_2Cl_2 at room temperature[15] into the corresponding azobenzenes **5a−l** in fair to good isolated yields (Table 7).[16] It is, however, not compatible with the diaryl hydrazide containing a methoxy group (entry 8). Due to its strong electron-donating nature, bromination on the aromatic ring becomes a serious side-reaction, thus interfering with the oxidation reaction.[17] Diaryl hydrazides with electron-withdrawing groups undergo faster oxidation reactions than those without. The oxidation reactions gave virtually a single spot on TLC. Simple filtration through a plug of silica gel furnished the product azobenzenes in excellent purity.

In summary, we have found that $Pd(OAc)_2/P(t\text{-}Bu)_3$ effectively catalyzes the coupling of N-Boc aryl hydrazines with aryl halides bearing either electron-withdrawing or electron-donating groups to afford the diaryl hydrazides. Direct oxidations with NBS/pyridine generate the azobenzenes, which completes a new protocol to the azobenzenes. This new method may be especially powerful for the synthesis of molecules with multiple diazo linkages that are not readily available by conventional approaches.

Acknowledgment. This work was supported by a grant of the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (01-PJ1-PG1-01CHO03-0003).

Supporting Information Available: Characterizations for all unknown diaryl hydrazides and azobenzenes. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Lee, K.-S.; Lim, Y.-K.; Cho, C.-G. *Tetrahedron Lett.* **2002**, *43*, 7463.

(14) Leyva, E.; Monreal, E.; Medina, C.; Leyva, S. *Tetrahedron Lett.* **1997**, *38*, 7847 and references cited therein.

(15) Wang, C.; Wang, X.; Wang, Y. *Indian J. Chem.* **1999**, *38B*, 964.

(16) **Representative Procedure.** To a solution of **2b** (29 mg; 0.078 mmol) dissolved in anhydrous CH_2Cl_2 (3 mL) were added pyridine (0.8 mL; 0.094 mmol; 1.2 equiv) and NBS (17 mg; 0.094 mmol; 1.2 equiv) at room temperature. The reaction mixture was stirred for 2 h at room temperature, concentrated in vacuo, and purified by column chromatography (hexanes/EtOAc = 10/1) to afford 18 mg of the azobenzene **5b** in 84% yield.

(17) We isolated brominated N-Boc diaryl hydrazine (Br *ortho* to the OMe group) as a byproduct in 20% yield.