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Cu(I) mediated one-pot synthesis of azobenzenes from bis-Boc aryl hydrazines and aryl halides

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Abstract—*N*,*N*′-bis-Boc aryl hydrazines underwent Cu(I) catalyzed couplings with aryl halides to provide *N*,*N*′-bis-Boc diaryl hydrazines. The resulting *N*,*N*′-bis-Boc diaryl hydrazines are readily oxidized to the azobenzenes in the presence of Cu(I) and a base. A prolonged heating of the initial coupling reactions directly provides the corresponding azobenzenes in one pot.

Azobenzenes have a wide variety of potential applications toward organic non-linear optics, optical storage media, chemosensors, and photochemical switches, because of their characteristic color and photoresponsive properties.[1] Despite the current interests, the structures of the azobenzenes appeared in the literature are rather limited. We are interested in the synthesis of highly functionalized azobenzenes with multiple diazo linkages for the development of novel photochemical sensing devices. With conventional methods,[2] however, they are not trivial tasks.

Recently, we have reported a new synthetic method for azobenzenes starting from *N*-Boc aryl hydrazines via Pd-catalyzed coupling reactions with various aryl halides followed by direct oxidations with NBS/pyridine in CH_2Cl_2 into azobenzenes.[3] The requisite *N*-Boc aryl hydrazines were prepared via Pd[4] or Cu[5] catalyzed couplings of *tert*-butyl carbazate with aryl halides.

While the Buchwald's CuI/phen system is effective for the couplings with both electron rich and deficient aryl halides, the Skerlj's $Pd_2(dba)_3$/dppf system is effective only with the aryl halides bearing electron withdrawing group.[4] When employed for the couplings of *N*-Boc aryl hydrazines (couplings onto $–NH_2$ side), the $Pd_2(dba)_3$/dppf system showed the similar lack of reactivity with electron rich aryl halides. The CuI/phen system turned out to be completely inactive. The catalyst system $Pd(OAc)_2/P(t\text{-}Bu)_3$ was found to be effective for the couplings of *N*-Boc aryl hydrazides with both electron poor and rich aryl halides.

In this account, we wish to present one-pot synthesis of azobenzenes via Cu(I) catalyzed couplings of *N*,*N*′-bis-Boc aryl hydrazines with aryl halides and concomitant in situ oxidations.

Realizing the Buchwald's CuI/phen catalyst system is for a formal carbamation reaction (couplings onto –NHBoc side), we decided to investigate the Cu(I) catalyzed couplings of *N*′-Boc aryl hydrazines in lieu of *N*-Boc aryl hydrazines with various aryl halides. Simple treatment of phenyl hydrazine with Boc_2O provided *N*′-Boc phenyl hydrazine, which readily undergo coupling reactions with various aryl halides to produce the *N*′-Boc diaryl hydrazines in good yields (Table 1).

Although the coupling reactions themselves proceeded reasonably well, the starting *N*′-Boc aryl hydrazines are not readily available. If not commercial, they need to be prepared through the process involving the coupling of Boc–$NHNH_2$ with aryl halides followed by unmasking and remasking steps.

Use of bis-Boc aryl hydrazines could possibly circumvent the above tedious sequential deprotection and reprotection process. Arterburn et al. reported efficient synthesis of bis-Boc pyridyl hydrazines via

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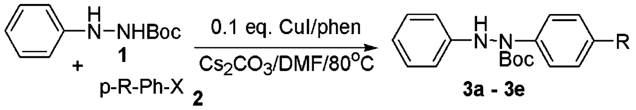
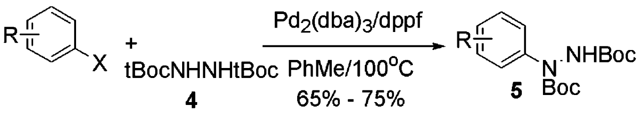
Table 1. Cu-catalyzed *N*-arylation of *N*′-Boc aryl hydrazine



Entry	Halides	Time (h)	Product	Yield (%)
1	R = H, X = I	22	**3a** (R = H)	87
2	R = OMe, X = I	11	**3b** (R = OMe)	81
3	R = NO_2, X = I	5	**3c** (R = NO_2)	51
4	R = CO_2Et, X = Br	48	**3d** (R = CO_2Et)	45
5	R = CN, X = Br	47	**3w** (R = CO_2Me)	56

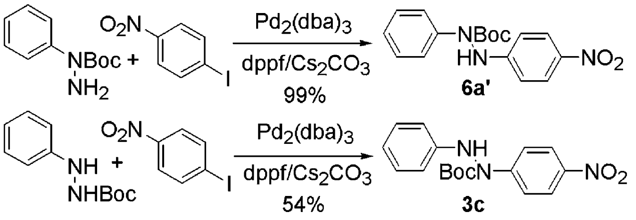


Scheme 1. Syntheses of bis-Boc aryl hydrazines.

Pd-catalyzed couplings of *N*,*N*′-bis-Boc hydrazine with 2-halo-pyridines.[6] Using their conditions, we prepared various *N*,*N*′-bis-Boc aryl hydrazines **5** in good isolation yields (Scheme 1).

The resulting bis-Boc aryl hydrazines **5** underwent coupling reactions with aryl halides under the Buchwald's conditions (CuI/phen), but in only moderate isolated yields. No coupling reactions were observed with Pd catalysts. We later found that the stoichiometric use of CuI dramatically increases the reaction rate and chemical yield. Both electron rich and deficient aryl halides were well coupled, to furnish the corresponding bis-Boc diaryl hydrazines in almost quantitative yields (Table 2).

In entry 1, the isolated product **6a**′ was found to be mono-Boc diaryl hydrazine, resulting from the slow removal of one Boc group during the coupling process. The structure of **6a**′ was assigned by separate syntheses of both regio-isomers as shown below (Scheme 2).

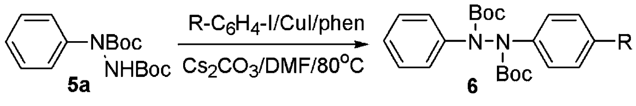


Scheme 2. Separate syntheses of *N*- and *N*′-Boc diaryl hydrazines.

The oxidations of the resulting **6a**–**6j** to the azobenzenes were troublesome as they are not reactive under the conditions that we used previously for the oxidation of mono-Boc diaryl hydrazines to the azobenzenes.[3,8] Removal of one or both Boc groups prior to the oxidations would be the next option, which also turned out to be problematic. Attempted removal of the Boc group(s) under the usual conditions resulted in the cleavage of N–N bond, to give rise to the corresponding aryl amines. We have found, after a number of failures, that bis-Boc diphenyl hydrazines can be directly oxidized into the azobenzenes when heated with NaOH in EtOH, in reasonable yields.[7] The intrinsic incompatibility with the base sensitive group, however, is a serious drawback. Later we have found that bis-Boc diaryl hydrazines are readily oxidized to the azobenzenes under the reaction conditions, identical to those used for the couplings of Boc aryl hydrazines with aryl iodides. Further study using **6a** as a model has revealed that the oxidation reaction is best conducted when heated with stoichiometric amounts of CuI and Cs_2CO_3 at 110 °C in DMF. Under these conditions, we were able to prepare an array of azobenzenes, directly from *N*,*N*′-bis-Boc diaryl hydrazines bearing various otherwise incompatible functional groups, in fair to good isolation yields (Table 3).[8] The hydrazide with free hydroxyl group gave only trace of the product (entry 5).

Although the exact reaction mechanism is unclear at the moment, the oxidation may proceed through the elimination of the Boc group as described in Scheme 3. The

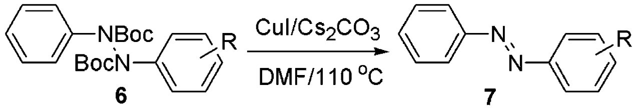
Table 2. Cu-catalyzed arylation of bis-Boc aryl hydrazine



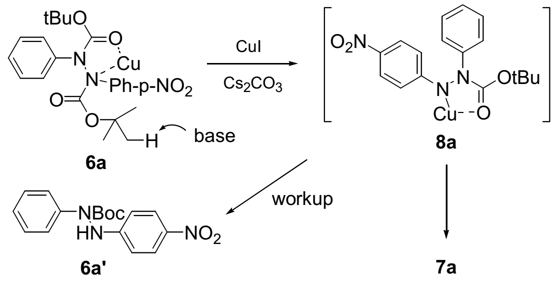
Entry	R–ArI	Time[a] (h)	Product	Yield[a] (%)
1	R = *p*-NO_2	3 (48)	**6a** (**6a**′)	99 (33)
2	R = *p*-CO_2Me	3 (48)	**6b**	99 (43)
3	R = *p*-CN	3 (24)	**6c**	99 (92)
4	R = *p*-OMe	18 (72)	**6d**	86 (25)
5	R = *p*-CH_2OH	4 (48)	**6e**	95 (35)
6	R = H	3 (48)	**6f**	99 (43)
7	R = *p*-Me	3 (48)	**6g**	99 (43)
8	R = *p*-OMe	3 (48)	**6h**	99 (93)
9	R = *p*-Ph	48 (96)	**6i**	90 (71)
10	R = *p*-I	3 (48)	**6j**[b]	99 (43)

[a] The values in ( ) are the results when 0.1 equiv of CuI was used.
[b] bis-Hydrazide.

Table 3. Direct oxidations to azobenzenes with CuI/Cs_2CO_3

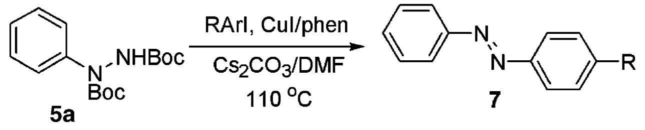


Entry	6	Time (days)	Azo-benzene	Yield (%)
1	**6a** (R = *p*-NO_2)	1	**7a**	54
2	**6b** (R = *m*-CN)	1	**7b**	63
3	**6c** (R = *p*-CO_2Me)	1	**7c**	72
4	**6d** (R = *p*-COMe)	1	**7d**	45
5	**6e** (R = *p*-CH_2OH)	3	**7e**	Trace
6	**6f** (R = H)	3	**7f**	97
7	**6g** (R = *p*-Me)	3	**7g**	64
8	**6h** (R = *p*-OMe)	3	**7h**	47
9	**6i** (R = *p*-Ph)	2	**7i**	83
10	**6j** (R = *p*-N=N–Ph)	3	**7j**	51



Scheme 3. Proposed mechanism for the oxidation of bis-Boc diaryl hydrazine to azobenzene.

Table 4. Cu(I) mediated one-pot synthesis of azobenzenes starting from the couplings with aryl iodides



Entry	R–ArI	Time (days)	7	Yield (%)
1	R = *p*-NO$_2$	2	**7a**	50
2	R = *m*-CN	3	**7b**	60
3	R = *p*-CO$_2$Me	2	**7c**	69
4	R = *p*-COMe	4	**7d**	50
5	R = *p*-CH$_2$OH	7	**7e**	Trace
6	R = H	6.5	**7f**	60
7	R = *p*-Me	6.5	**7g**	46
8	R = *p*-OMe	4	**7h**	43
9	R = *p*-Ph	3	**7i**	67
10	R = *p*-I	3	**7j**	45

TLC monitoring showed that all the starting bis-Boc diaryl hydrazine **6a** is first converted into the low running spot, presumed to be **8a** based on the isolation of mono-Boc diaryl hydrazine **6a**′ upon workup, before subsequent transformation to the high running azobenzene **7a**. A similar elimination of Boc group on **8a** would provide **7a**.

We next studied the one-pot synthesis of azobenzenes from bis-Boc aryl hydrazines and aryl halides. Table 4 summarizes our results under the optimized reaction conditions.[9]

The one-pot syntheses starting with aryl bromides were also feasible, providing the corresponding azobenzenes, somewhat lower yields, compared to aryl iodides.[10]

In summary, we have found that *N*,*N*′-bis-Boc aryl hydrazines undergo Cu(I) mediated coupling reactions with aryl halides bearing either electron withdrawing or donating substituents. The resulting *N*,*N*′-bis-Boc diaryl hydrazines were directly oxidized to the azobenzenes when heated in DMF with CuI/Cs$_2$CO$_3$. The above coupling and oxidation can be performed in one pot to give the corresponding azobenzenes.

Acknowledgements

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7. When R = OMe, H, Me, COPh, COMe, we obtained the corresponding azobenzenes in 30–50% isolated yields.
8. Representative procedure: To a sealed tube were charged with **5a** (54.8 mg, 0.128 mmol), copper(I) iodide (24.3 mg, 1.0 equiv), Cs$_2$CO$_3$ (49.9 mg, 1.2 equiv), and DMF (1.0 mL). After 1 day at 110 °C, the reaction mixture was cooled to rt, filtered through a plug of silica gel and washed with ethyl acetate. The filtrate was concentrated in vacuo and purified by silica-gel chromatography (hexanes/EtOAc = 8:1) to provide 15.6 mg (54% yield) of the product **7a**.
9. Representative procedure: To a sealed tube were charged with *p*-nitro-phenyl iodide (55.1 mg, 0.221 mmol), bis-Boc aryl hydrazine (81.9 mg, 1.2 equiv), copper(I) iodide

(42.1 mg, 0.221 mmol, 1.0 equiv), 1,10-phenanthroline (4.0 mg, 0.1 equiv), Cs_2CO_3 (86.5 mg, 1.2 equiv), and DMF (3.0 mL). Ater 2 days at 110 °C, the reaction mixture was cooled to rt, filtered through a plug of silica gel and washed with ethyl acetate. The filtrate was concentrated in vacuo and purified by silica-gel chromatography (hexanes/EtOAc = 8:1) to provide 25.3 mg (50% yield) of the product **7a**.

10. The reaction of **5a** with *p*-cyano-phenyl bromide and *p*-*tert*-butyl-phenyl bromide provided the corresponding azobenzenes **7k** and **7l** in 53% and 5% isolated yields, respectively.