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Synthesis of *N*-Aryl Hydrazides by Copper-Catalyzed Coupling of Hydrazides with Aryl Iodides

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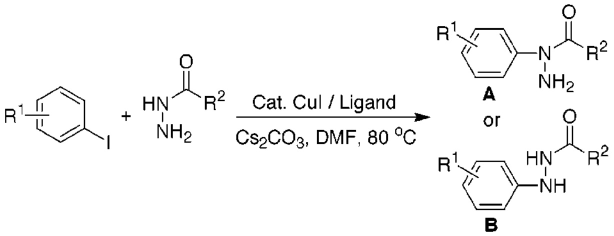
ABSTRACT



A convenient method for intermolecular N-arylation of hydrazides with substituted aryl iodides in the presence of a copper catalyst and Cs_2CO_3 is reported. The C–N coupling of *N*-Boc hydrazine with *para*- and *meta*-substituted aryl iodides afforded the N-arylated products A, regioselectively. A reversal in regioselectivity is observed for the arylation of benzoic hydrazide with *ortho*-substituted aryl iodides, providing the N′-arylated products B.

N-Aryl hydrazides form an important class of organic compounds with many applications in organic synthesis and in industry.[1] They are useful starting materials for the synthesis of biologically active heterocycles, such as indoles, carbazoles, pyrazoles, triazines, indazolones, and indazoles.[2]

N-Aryl hydrazides have traditionally been prepared by reduction of *N*-nitrosoarylamines,[3] formed by nitrosation of anilines, or by electrophilic aminations of aryl Grignard reagents,[4b] aryllithium reagents,[4b,4c] aryl zinc halides,[4a] and electron-rich arenes[5] with azodicarboxylates. These methods often employ expensive reagents or substrates requiring multistep syntheses and/or require harsh conditions, which limit the functional group tolerability.

Recently, a Pd/BINAP-catalyzed coupling of *N*-Boc hydrazine with aryl bromides has been reported.[6] However, high yields were obtained only with substrates having electron-withdrawing substituents in the *para* position. A copper-mediated N′-arylation of benzoic hydrazide, affording low yields of N′,N′-diarylated products,[7] and the arylation of

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[1] (a) Enders, E. In *Methoden der Organischen Chemie*; Stroh, R., Ed.; Georg Thieme Verlag: Stuttgart, 1967; Vol. 10/2, p 546. (b) Dekeyser, M.; McDonald, P. T.; Angle, G. W., Jr. *J. Agric. Food Chem.* **1994**, *42*, 1358−1360. (c) Chee, G.-L.; Park, S. B.; Dekeyser, M. A. U.S. Patent 6,093,843, 2000. (d) Dekeyser, M. A.; McDonald, P. T. U.S. Patent 5,367,093, 1994. (e) Reich, M. F.; Fabio, P. F.; Lee, V. J.; Kuck, N. A.; Testa, R. T. *J. Med. Chem.* **1989**, *32*, 2474−2485.

[2] (a) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045−1075. (b) King, F. D. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3381−3385. (c) Carlin, R. B.; Moores, M. S. *J. Am. Chem. Soc.* **1962**, *84*, 4107−4112. (d) Barnish, I. T., Gibson, M. S. *J. Chem. Soc. C* **1970**, 854−859. (e) Kulagowski, J. J.; Moody, C. J.; Rees, M. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2725−2732. (f) Oliva, A.; Ellis, M.; Fiocchi, L.; Menta, E.; Krapcho, A. P. *J. Heterocycl. Chem.* **2000**, *37*, 47−55. (g) Tamura, Y.; Tsugoshi, T.; Mohri, S.-I.; Kita, Y. *J. Org. Chem.* **1985**, *50*, 1542−1544. (h) Hughes, D. L. *Org. Prep. Proced. Int.* **1993**, *25*, 607.

[3] (a) Enders, E. In *Methoden der Organischen Chemie*; Stroh, R., Ed.; Georg Thieme Verlag: Stuttgart, 1967; Vol. 10/2, pp 224−231. (b) Tschirret-Guth, R. A.; Ortiz de Montellano, P. R. *J. Org. Chem.* **1998**, *63*, 9711−9715.

[4] (a) Velarde-Ortiz, R.; Guijarro, A.; Rieke, R. D. *Tetrahedron Lett.* **1998**, *39*, 9157−9160. (b) Demers, J. P.; Klaubert, D. H. *Tetrahedron Lett.* **1987**, *28*, 4933−4934. (c) Katritzky, A. R.; Wu, J.; Verin, S. V. *Synthesis* **1995**, 651−653.

[5] (a) Zaltsgendler, I.; Leblanc, Y.; Bernstein, M. A. *Tetrahedron Lett.* **1993**, *34*, 2441−2444. (b) Carlin, R. B.; Moores, M. S. *J. Am. Chem. Soc.* **1962**, *84*, 4107−4112.

[6] Wang, Z.; Skerlj, R. T.; Bridger, G. J. *Tetrahedron Lett.* **1999**, *40*, 3543−3546.

[7] Suzuki, H.; Yamamoto, A. *J. Chem. Res., Synop.* **1992**, 280−281.

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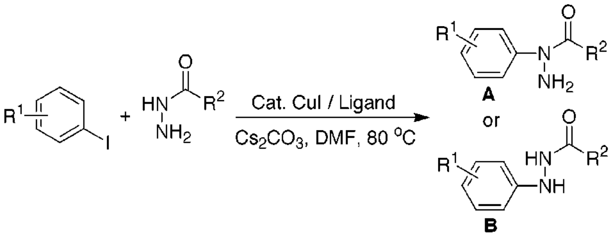
trisubstituted hydrazines with triarylbismuthanes in the presence of stoichiometric amounts of $Cu(OAc)_2$ has also been described.[8]

Recently, we have described the copper-catalyzed amidation of aryl halides.[9] We reported an example of the N-arylation of *N*-Boc hydrazine (Scheme 1, product A in moderate yield) and benzoic hydrazide (Scheme 1, product B in moderate yield) at high temperature. We therefore set out to look for an improved catalyst system for this transformation and to demonstrate the generality with which it can be employed.

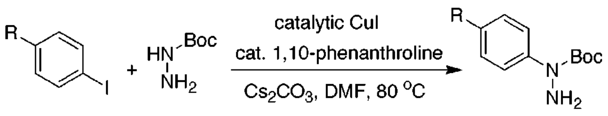
Scheme 1

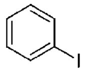
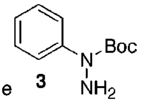
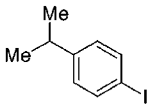
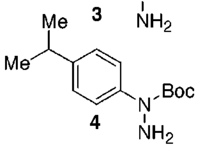
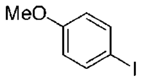
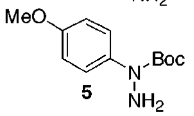
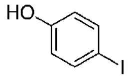
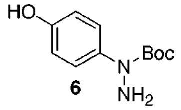
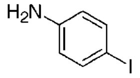
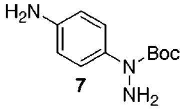
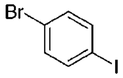
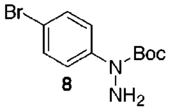
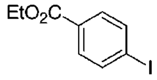
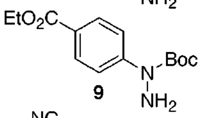
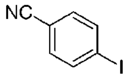
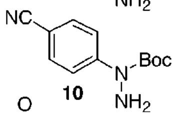
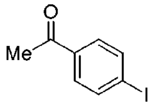
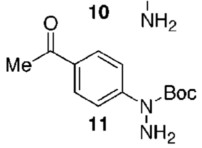


Herein we describe our results in developing an improved protocol. When DMF is used as a solvent, catalytic amounts of CuI and 1,10-phenanthroline (**1**) in the presence of Cs_2CO_3 provide higher yields of N-arylated *N*-Boc hydrazine at 80 °C,[10] as opposed to 110 °C in dioxane as reported in our original investigations. We also show that reasonable yields can be achieved using a ligandless catalyst system.

A series of *para*-substituted aryl iodides, shown in Table 1, were subjected to the reaction conditions described above. Generally, 1−5 mol % of CuI and 10−20 mol % of 1,10-phenanthroline (**1**) were sufficient to obtain the N-arylated products (A in Scheme 1) in good to excellent yields. No N′-arylated product (B in Scheme 1) could be detected by GC. We were pleased to find that electron-withdrawing as well as electron-donating substituents are tolerated under these conditions. Moreover, substrates containing functional groups that have been problematic in palladium-catalyzed methology,[11] such as a phenolic OH (entry 4) and an aromatic NH_2 (entry 5), were successfully transformed. The use of 5 mol % CuI (entries 6−9) as well as shorter reaction times (entries 8 and 9) improved the isolated yield of the N-arylated products **8**−**11**. For example, the isolated yield of compound **10**, which seemed to be more sensitive under the coupling conditions, could be improved from 61% to 78%, using a reaction time of 4 h instead of 21 h.

Table 1. Copper-Catalyzed Coupling of *para*-Substituted Aryl Iodides with *N*-Boc Hydrazine[a]



entry	aryl iodide	mol % CuI	mol % ligand	product	% yield[b]
1		1	10	 **3**	97
2		1	10	 **4**	87
3		1 1	10 none	 **5**	85 76
4		1	10	 **6**	67
5		1	10	 **7**	78
6		5	20	 **8**	71
7		5 5	20 none	 **9**	88 64
8		5	20	 **10**	78[c]
9		5	20	 **11**	43[d]

[a] Reaction conditions: 1 equiv of aryl iodide, 1.2 equiv of hydrazide, 1.4 equiv of Cs_2CO_3, DMF (1 M in aryl iodide), under argon, for 21 h. The reaction time is not optimized for each substrate. [b] Isolated yields are the average of two runs and are estimated to be >95% pure by ^1H NMR and GC analysis. All previously unknown compounds gave satisfactory ^1H NMR, ^{13}C NMR, IR, and combustion analysis data. [c] Yield for a reaction time of 4 h. For 21 h: 61% yield of **10**. [d] Yield for a reaction time of 4 h. For 21 h: 34% yield of **11**.

The reaction was also carried out with a series of *meta*-substituted aryl iodides. As shown in Table 2, the N-arylated products **12**−**16** were obtained regioselectively and in good yields. Again, both electron-donating (entries 1−3) and electron-withdrawing (entries 4 and 5) substituents, as well as a free OH group (entry 3), were tolerated.

The transformation was also carried out in absence of 1,10-phenanthroline (**1**) for some aryl iodides (Table 1, entries 3

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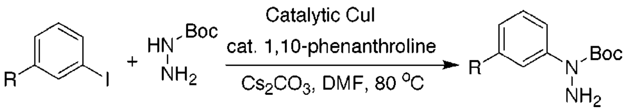
(8) Loog, O.; Mäeorg, U.; Ragnarsson, U. *Synthesis* **2000**, *11*, 1591−1597.

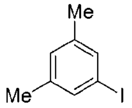
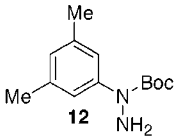
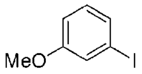
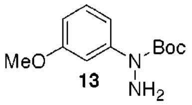
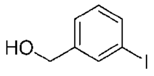
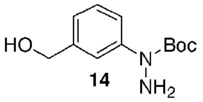
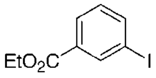
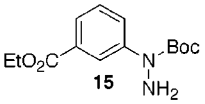
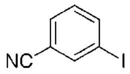
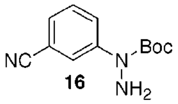
(9) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727−7729.

(10) **Typical Experimental Procedure.** An oven-dried resealable Schlenk tube was charged with CuI (1−5 mol %), ligand (10−20 mol %), and Cs_2CO_3 (1.4 mmol), evacuated, and backfilled with argon. Hydrazide (1.2 mmol), aryl iodide (1.0 mmol), and DMF (1.0 mL) were added under argon. The Schlenk tube was sealed, and the reaction mixture was stirred magnetically at 80 °C for 21 h. The resulting suspension was cooled to room temperature and filtered through a 0.5 × 1 cm^2 pad of silica gel eluting with ethyl acetate. The filtrate was concentrated. Purification of the residue by flash chromatography on silica gel gave the desired product (see Supporting Information).

(11) Deng, B.-L.; Lepoivre, J. A.; Lemière, G. *Eur. J. Org. Chem.* **1999**, 2683−2688.

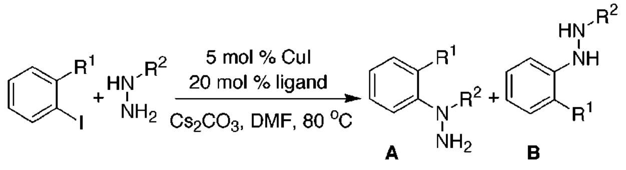
Table 2. Copper-Catalyzed Coupling of *meta*-Substituted Aryl Iodides with *N*-Boc Hydrazine[a]



entry	aryl iodide	mol % CuI	mol % ligand	product	% yield[b]
1		1	10	 **12**	90
2		1 5	10 none	 **13**	80 67[d]
3		1	10	 **14**	89
4		5 5	20 none	 **15**	78 72[e]
5		5	20	 **16**	77[c]

[a] See Table 1. [b] See Table 1. [c] Yield for a reaction time of 4 h. For 21 h: 65% yield of **16**. [d] 7% of the N′-arylated product **24** was also isolated. [e] 5% of the N′-arylated product **25** was also isolated.

Table 3. Copper-Catalyzed Coupling of *ortho*-Substituted Aryl Iodides with *N*-Boc Hydrazine and Benzoic Hydrazide[a,d]



entry	R^1	R^2	ligand[c]	% yield (**A**)[b]	% yield (**B**)[b]
1	CH_3	Boc	**1**	35 (**17**)	4 (**18**)
2	CH_3	Boc	none	13 (**17**)	11 (**18**)
3	CH_3	COPh	**1**		57 (**19**)
4	CH_3	COPh	none		69 (**19**)
5	OCH_3	Boc	**1**	23 (**20**)	8 (GC)
6	OCH_3	COPh	**2**		32 (**21**)
7	OCH_3	COPh	none		34 (**21**)
8	CO_2Et	Boc	**2**		46 (**22**)
9	CO_2Et	COPh	**2**		56 (**23**)
10	CO_2Et	COPh	none		63 (**23**)

[a] See Table 1. [b] See Table 1. [c] **1**: 1,10-phenanthroline, **2**: picolinic acid. [d] Reduction of aryl iodides to substituted arenes was detected by GC in amounts of ~30%.

and 7; Table 2, entries 2 and 4). While the reaction still proceeds fairly well, the yields of the N-arylated products are 10−20% lower for both *meta*- and *para*-substituted aryl iodides. Moreover, for the *meta*-substituted examples, 5−7% of N′-arylated products (**B**) were isolated, along with the N-arylated products **13** and **15**.

The arylation of *N*-Boc hydrazine with *ortho*-substituted aryl iodides is detailed in Table 3. As can be seen in entries 1 and 5, modest yields of the *N*-Boc N-aryl hydrazines **17** and **20** were obtained, and we observed a drop in regioselectivity with N′-arylation products (**B**) now being formed in 4−8% yield. In the absence of **1** (entry 2), a complete loss of regioselectivity is observed. Using a substrate with an electron-withdrawing substituent (entry 8), the N′-arylated product **22** was formed exclusively. For this substrate picolinic acid (**2**) was found to be a better ligand than **1**.

Switching to benzoic hydrazide further improved the yield of the coupling, and we observed a reversal in the regioselectivity with all *ortho*-substituted substrates. In these cases the N′-arylated products **19**, **21**, and **23** were produced in moderate yields (entries 3, 6, 9). An increase in isolated yields was seen in some instances under ligandless conditions (entries 4 and 10).

In summary, we have developed a general and efficient catalyst system for the N-arylation of *N*-Boc hydrazine. We have shown that aryl iodides with electron-withdrawing as well as with electron-donating substituents in *meta* or *para* position undergo the coupling reaction in good to excellent yield. We have also demonstrated a reversal of the regioselectivity for the C−N coupling of certain *ortho*-substituted aryl iodides when benzoic hydrazide is used in place of *N*-Boc hydrazine, providing the corresponding N′-arylated products in moderate yield. The advantages of this method include good substrate generality, the use of the air-stable, inexpensive CuI under mild conditions, and experimental ease.

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Supporting Information Available: Experimental procedures and characterization data for all unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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