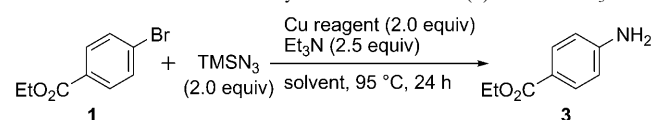


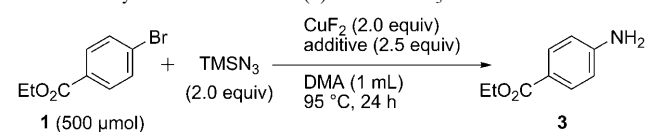
Table 1. Evaluation of copper reagents and solvents in the copper-mediated reductive amination of ethyl 4-bromobenzoate (**1**) with TMSN₃.



Entry	Cu reagent	Solvent	Yield [%] ^[a]
1	–	DMA	0
2	CuF ₂	DMA	84
3	CuBr ₂	DMA	7
4	CuO	DMA	73
5	Cu(OTf) ₂	DMA	32
6	CuOAc	DMA	82
7	CuI	DMA	63
8	CuBr	DMA	73
9	CuCl	DMA	75
10	Cu ^[b]	DMA	82
11	CuF ₂	DMF	69
12	CuF ₂	DMSO	70
13	CuF ₂	NMP	73
14	CuF ₂	1,4-dioxane	35
15	CuF ₂	MeOH	55
16	CuF ₂	acetone	61
17	CuF ₂	EtOAc	27
18	CuF ₂	toluene	15
19	CuF ₂	H ₂ O	0

[a] Isolated yield. [b] Copper powder was used.

Table 2. Evaluation of additives for the copper-mediated reductive amination of ethyl 4-bromobenzoate (**1**) with TMSN₃.



Entry	Additive	Yield [%] ^[a]
1	–	27
2	Et ₃ N	84
3	(<i>n</i> Pr) ₃ N	55
4	(<i>n</i> Bu) ₃ N	26
5	Bn ₃ N	53
6	Ph ₃ N	26
7	Et ₃ NH	68
8	(<i>n</i> Bu) ₄ NBr	0
9	H ₂ N(CH ₂) ₂ NH ₂	69
10	Me ₂ N(CH ₂) ₂ NMe ₂	31
11	H ₂ N(CH ₂) ₂ OH	99
12	H ₂ N(CH ₂) ₃ OH	89
13	H ₂ N(CH ₂) ₄ OH	93
14	H ₂ N(CH ₂) ₅ OH	92
15	HO(CH ₂) ₂ OH	44
16 ^[b]	H ₂ N(CH ₂) ₂ OH	95
17 ^[c]	H ₂ N(CH ₂) ₂ OH	97

[a] Isolated yield. [b] 0.1 mL of DMA was used. [c] 2 mL of DMA was used.

ing 2-aminoethanol proceeded efficiently in either 0.1 or 2 times the volume of DMA used in the test reactions (Table 2, entries 16 and 17), suggesting that the concentration of the reaction mixture does not affect the reaction progress.

Next, we explored the scope of this reductive amination based upon the cross-coupling of aryl halides with TMSN₃ as the amino source under the optimal conditions [CuF₂ (2.0 equiv), amine (2.5 equiv), TMSN₃ (2.0 equiv), DMA, 95 °C] (Table 3). Bromobenzenes containing an electron-

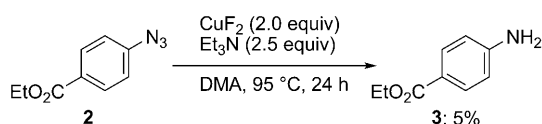
Table 3. Azide and copper-mediated reductive amination of a variety of aryl halides.

Entry	Ar	X	Amine	Yield [%] ^[a]
1	4-NO ₂ C ₆ H ₄	Br	H ₂ N(CH ₂) ₂ OH	95
2	4-EtO ₂ CC ₆ H ₄	Br	H ₂ N(CH ₂) ₂ OH	99
3	3-EtO ₂ CC ₆ H ₄	Br	H ₂ N(CH ₂) ₂ OH	80
4	2-EtO ₂ CC ₆ H ₄	Br	H ₂ N(CH ₂) ₂ OH	76
5	3-MeO ₂ CC ₆ H ₄	Br	H ₂ N(CH ₂) ₂ OH	77
6	4-ClC ₆ H ₄	Br	H ₂ N(CH ₂) ₂ OH	76
7	2-Me-5-NO ₂ C ₆ H ₃	Br	H ₂ N(CH ₂) ₂ OH	75
8 ^[b]	4-PhC ₆ H ₄	Br	H ₂ N(CH ₂) ₂ OH	95
9 ^[b]	4-MeOC ₆ H ₄	Br	H ₂ N(CH ₂) ₂ OH	48
10 ^[b]	3-MeOC ₆ H ₄	Br	H ₂ N(CH ₂) ₂ OH	81
11	4-CF ₃ C ₆ H ₄	Br	Et ₃ N	67
12 ^[c]	4-AcC ₆ H ₄	Br	Et ₃ N	77
13	4-MeO ₂ CC ₆ H ₄	I	Et ₃ N	66
14	4-AcC ₆ H ₄	I	Et ₃ N	59
15	4-CF ₃ C ₆ H ₄	I	Et ₃ N	60
16	4-NO ₂ C ₆ H ₄	Cl	H ₂ N(CH ₂) ₂ OH	32

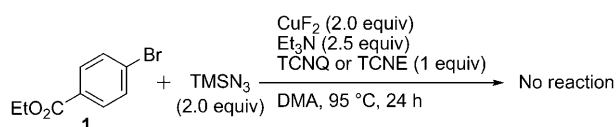
[a] Isolated yield. [b] Cu⁰ powder was used in place of CuF₂. [c] NaN₃ was used in place of TMS-N₃ and the reaction was carried out at 120 °C.

withdrawing group effectively reacted with TMSN₃, regardless of the position of the substituent on the aromatic ring, in the presence of 2-aminoethanol or triethylamine to give the corresponding aniline derivatives in good to excellent yields (Table 3, entries 1–7 and 11). In the cases of 4-bromobiphenyl and the electron-donating methoxy-substituted aryl bromides, copper powder was quite effective as the activator (Table 3, entries 8–10).^[16] Sodium azide, which is a cheaper, widely used azido salt, was also suitable for the reductive coupling (Table 3, entry 12). This protocol was also effectively applied to the amination of iodoarenes (Table 3, entries 13–15). Furthermore, the aniline derivative was also obtained from 4-chloronitrobenzene.

The formation of these aniline derivatives might proceed stepwise through an intermediary aryl azide, which would be generated by the copper-mediated cross-coupling reaction of TMSN₃ with the aryl halides. However, exposure of the corresponding ethyl 4-azidobenzoate (**2**) to the amination conditions scarcely promoted the reduction of the azide functionality and the corresponding aniline derivative (**3**) was only obtained in 5 % yield (Scheme 2). This result suggests that the azide/copper-mediated reductive amination of haloarenes does not chiefly proceed through an aryl azide intermediate. Furthermore, no reaction took place if a single-electron acceptor, such as 7,7,8,8-tetracyanoquinodimethane (TCNQ) or tetracyanoethene (TCNE), was added (Scheme 3), suggesting the participation of a single-electron



Scheme 2. Exposure of an aryl azide to the amination conditions. Ethyl 4-azidobenzoate (95.6 mg, 500 μ L) and DMA (1 mL) were used.



Scheme 3. Addition of a single electron acceptor to the reductive amination of ethyl 4-bromobenzoate (**1**). Ethyl 4-bromobenzoate (81.6 μ L, 500 μ mol) and DMA (1 mL) were used.

transfer in the reaction mechanism, although the actual reductive species and hydrogen source are not yet clear.^[14,17]

In conclusion, we have demonstrated that a variety of aryl halides react with TMSN_3 in the presence of copper species and an amine, in heated DMA, to give aniline derivatives as the sole products, without the formation of the corresponding aryl azides. The copper-mediated aromatic amination formally proceeds through both a cross-coupling between TMSN_3 and an aryl halide and a reduction of an azide functionality to the corresponding amine in a one-pot manner, although the detailed reaction mechanism is currently unclear. Further studies to expand the scope of the substrates, as well as to clarify the reaction mechanism, based on seeking the actual reductive species, are now ongoing in our laboratory.

Experimental Section

General procedure for the copper-mediated reductive amination of aryl halides with TMSN_3 (Table 3): A mixture of CuF_2 (102 mg, 1.00 mmol), the aryl halide (500 μ mol), 2-aminoethanol (74.9 μ L, 1.25 mmol), and TMSN_3 (132 μ L, 1.00 mmol), in DMA (1.00 mL), in a test tube (15 mL), under Ar, was stirred at 95 °C for 24 h by using a Chemist Plaza personal organic synthesizer (Shibata Science Technology Ltd.) and then filtered through a Celite pad. The pad was then washed with EtOAc (30 mL) and the combined filtrates were successively washed with H_2O (20 mL $\times$ 3) and brine (30 mL), dried (MgSO_4), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/ EtOAc , 5:1 $\rightarrow$ 4:1).

Keywords: amination • azides • copper • cross-coupling • reduction

palladium Chemistry for Organic Synthesis Vol. 1 (Ed.: E. I. Negishi), Wiley-Interscience, New York, **2002**, pp. 1051–1097; c) A. R. Muci, S. L. Buchwald, *Top. Curr. Chem.* **2002**, 219, 131–209; d) K. Kunz, U. Scholz, D. Ganzer, *Synlett* **2003**, 2428–2439; e) L. Jiang, S. L. Buchwald in *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed. (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**, pp. 699–760; f) J. F. Hartwig, *Synlett* **2006**, 1283–1294; g) D. S. Surry, S. L. Buchwald, *Angew. Chem.* **2008**, 120, 6438–6461; *Angew. Chem. Int. Ed.* **2008**, 47, 6338–6361.

- [3] S. Lee, M. Jørgensen, J. F. Hartwig, *Org. Lett.* **2001**, 3, 2729–2732.
- [4] LiHMDS and $\text{Zn}(\text{HMDS})_2$ (HMDS = hexamethyldisilazide) were also used as ammonia equivalents, see: a) X. Huang, S. L. Buchwald, *Org. Lett.* **2001**, 3, 3417–3419; b) D.-Y. Lee, J. F. Hartwig, *Org. Lett.* **2005**, 7, 1169–1172.
- [5] a) Q. Shen, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, 128, 10028–10029; b) D. S. Surry, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, 129, 10354–10355; c) G. D. Vo, J. F. Hartwig, *J. Am. Chem. Soc.* **2009**, 131, 11049–11061; d) T. Schulz, C. Torborg, S. Enthaler, B. Schaffer, A. Dumrath, A. Spannenberg, H. Neumann, A. Börner, M. Beller, *Chem. Eur. J.* **2009**, 15, 4528–4533.
- [6] a) J. Kim, S. Chang, *Chem. Commun.* **2008**, 3052–3054; b) N. Xia, M. Taillefer, *Angew. Chem.* **2009**, 121, 343–345; *Angew. Chem. Int. Ed.* **2009**, 48, 337–339; c) L. Jiang, X. Lu, H. Zhang, Y. Jiang, D. Ma, *J. Org. Chem.* **2009**, 74, 4542–4546; d) H. Xu, C. Wolf, *Chem. Commun.* **2009**, 3035–3037.
- [7] a) H. Sajiki, T. Kurita, A. Kozaki, G. Zhang, Y. Kitamura, T. Maegawa, K. Hirota, *J. Chem. Res.* **2004**, 593–595 [Erratum: H. Sajiki, T. Kurita, A. Kozaki, G. Zhang, Y. Kitamura, T. Maegawa, K. Hirota, *J. Chem. Res.* **2005**, 344]; b) H. Sajiki, T. Kurita, A. Kozaki, G. Zhang, Y. Kitamura, T. Maegawa, K. Hirota, *Synthesis* **2005**, 537–542 [Erratum: H. Sajiki, T. Kurita, A. Kozaki, G. Zhang, Y. Kitamura, T. Maegawa, K. Hirota, *Synthesis* **2005**, 852]; c) H. Sajiki, G. Zhang, Y. Kitamura, T. Maegawa, K. Hirota, *Synlett* **2005**, 619–622 [Erratum: H. Sajiki, G. Zhang, Y. Kitamura, T. Maegawa, K. Hirota, *Synlett* **2005**, 1046]; d) T. Maegawa, Y. Kitamura, S. Sako, T. Udzu, A. Sakurai, A. Tanaka, Y. Kobayashi, K. Endo, U. Bora, T. Kurita, A. Kozaki, Y. Monguchi, H. Sajiki, *Chem. Eur. J.* **2007**, 13, 5937–5943; e) Y. Kitamura, A. Sakurai, T. Udzu, T. Maegawa, Y. Monguchi, H. Sajiki, *Tetrahedron* **2007**, 63, 10596–10602; f) Y. Kitamura, S. Sako, T. Udzu, A. Tsutui, T. Maegawa, Y. Monguchi, H. Sajiki, *Chem. Commun.* **2007**, 5069–5071; g) S. Mori, T. Yanase, S. Aoyagi, Y. Monguchi, T. Maegawa, H. Sajiki, *Chem. Eur. J.* **2008**, 14, 6994–6999.
- [8] Y. Monguchi, K. Kitamoto, T. Ikawa, T. Maegawa, H. Sajiki, *Adv. Synth. Catal.* **2008**, 350, 2767–2777.
- [9] Organic azides are recognized as valuable intermediates for the synthesis of nitrogen-containing compounds; for reviews, see: a) E. F. V. Scriven, K. Turnbull, *Chem. Rev.* **1988**, 88, 297–368; b) S. Bräse, K. Gil, K. Knepper, V. Zimmermann, *Angew. Chem.* **2005**, 117, 5320–5374; *Angew. Chem. Int. Ed.* **2005**, 44, 5188–5240; c) M. Minozzi, D. Nanni, P. Spagnolo, *Chem. Eur. J.* **2009**, 15, 7830–7840.
- [10] Palladium species have never been used as a catalyst for aryl azide syntheses based on a cross-coupling reaction between aryl halides and azide sources, although copper-catalyzed aromatic azidations were recently reported, see: a) W. Zhu, D. Ma, *Chem. Commun.* **2004**, 888–889; b) J. Andersen, U. Madsen, F. Björkling, X. Liang, *Synlett* **2005**, 2209–2213.
- [11] During the preparation of this manuscript, an interesting aryl azide synthesis, which uses a copper-catalyzed cross-coupling reaction between potassium haloaryltrifluoroborates and sodium azide, was reported as a communication, including the substrate dependent formation of aniline derivatives in a minority of cases (four examples), see: Y. A. Cho, D.-S. Kim, H. R. Ahn, B. Canturk, G. A. Molander, J. Ham, *Org. Lett.* **2009**, 11, 4330–4333.
- [12] a) L. Birkofer, P. Wegner, *Organic Synthesis, Collective Vol. 6*, Wiley, New York, **1988**, pp. 1030–1032; b) M. Jafarzadeh, *Synlett* **2007**, 2144–2145.
- [13] Olah and Ernst used TMSN_3 for the introduction of an amino group into aromatic rings through an electrophilic aromatic substitution

- process, in the presence of triflic acid, see: G. A. Olah, T. D. Ernst, *J. Org. Chem.* **1989**, *54*, 1203–1204.
- [14] The reaction of aryl halides with secondary amines under transition-metal-free conditions was reported, see: W. Kleist, S. S. Pröckl, M. Drees, K. Köhler, L. Djakovitch, *J. Mol. Catal. A* **2009**, *303*, 15–22; see also reference [8] and [17].
- [15] When 2-aminoethanol was added to a mixture of ethyl 4-bromobenzoate and CuF₂ in DMA, the mixture turned pale blue. The color change was, presumably, due to the enhanced solubility of copper species caused by the formation of a complex with 2-aminoethanol. The dissolved copper species aids the increase in the reaction efficiency.
- [16] Use of copper plate for the reaction of 4-bromobiphenyl was not effective (36%). Therefore, the morphological properties of the copper metal appear to be important for a smooth reaction.
- [17] No formation of the regioisomers of aminobenzenes was observed, suggesting that the reaction does not proceed via hydroamination of a benzyne intermediate, which might be generated by the removal of hydrogen halide with base in heated polar aprotic solvents.

Received: December 22, 2009
Published online: May 18, 2010