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Copper-Mediated Reductive Amination of Aryl Halides with Trimethylsilyl Azide

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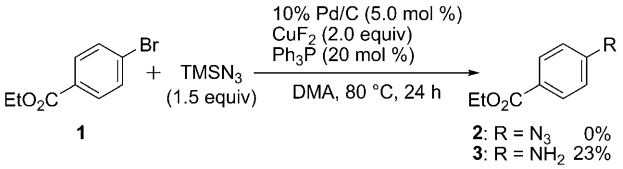
Primary arylamines have found many applications in organic synthesis as synthons for biologically active and other functional compounds.[1] Although the discovery of palladium-catalyzed cross-coupling methods, independently by Buchwald and Hartwig, for the reaction of aryl halides with a variety of amines made it easy to access secondary and tertiary arylamines,[2] the direct synthesis of primary arylamines from aryl halides was not reported until lithium bis(trimethylsilyl)amide was employed as the ammonia equivalent.[3,4] Subsequently, ammonia and ammonium chloride were effectively applied to the palladium-[5] or copper-catalyzed[6] synthesis of primary arylamine derivatives.

Recently, we demonstrated that palladium on carbon (Pd/C) is a versatile catalyst for cross-coupling reactions that create carbon–carbon[7] and carbon–nitrogen bonds.[8] During the course of our study into the Pd/C-catalyzed azidation of aryl halides,[9–11] we found, to our surprise, that the cross-coupling reaction between ethyl 4-bromobenzoate (**1**) and trimethylsilyl azide ($TMSN_3$),[12] in the presence of CuF_2 and triphenylphosphine, gave ethyl 4-aminobenzoate (**3**) as the sole product (23%) instead of the expected ethyl 4-azidobenzoate (**2**; Scheme 1).[11,13]



Scheme 1. The unanticipated formation of ethyl 4-aminobenzoate (**3**) under the Pd/C-catalyzed aromatic-azidation conditions. Ethyl 4-bromobenzoate (81.6 μL, 500 μmol) and DMA (1 mL) were used.

Initial optimization of the reaction conditions for this unexpected, but remarkable, transformation revealed the following: 1) Pd/C was not required,[14] 2) CuF_2 was essential, and 3) the reaction efficiency was significantly improved at elevated temperature and by using triethylamine instead of triphenylphosphine.

The reductive coupling reaction of $TMSN_3$ with **1** also proceeded with a variety of other copper salts, regardless of the oxidation state of copper (Table 1, entries 2–9), and even zero-valence copper metal was an efficient activating agent (Table 1, entry 10). On the other hand, no reaction took place if other metal species, such as $FeCl_3$, $Fe(OAc)_2$, $NiCl_2$, $ZnCl_2$, $TiCl_2$, and $CoBr_2$, were used.

We then investigated the effect of solvents on the reaction using CuF_2, since it gave the highest yield of **3** (Table 1, entry 2, 84%). Polar aprotic solvents, such as dimethylacetamide (DMA), DMF, DMSO, and *N*-methylpyrrolidone (NMP), were found to be effective for the reaction (Table 1, entries 2 and 11–13), while other organic solvents, as well as water, tended to reduce the yield (Table 1, entries 14–19).

In addition, the progress of the reaction was suppressed by the absence of triethylamine or by the use of other tertiary or secondary amines (Table 2, entry 2 vs. entries 1 and 3–7), and the reaction was not initiated at all by tetrabutylammonium bromide (Table 2, entry 8). Diamines and aminoalcohols were also examined with the expectation that they would have a bidentate ligand-like effect (Table 2, entries 9–14). Accordingly, 2-aminoethanol, in particular, was found to be a highly efficient additive for the reaction (Table 2, entry 11),[15] although neither *N*,*N*,*N*′,*N*′-tetramethylethylenediamine nor ethylene glycol exhibited this effect (Table 2, entries 10 and 15). Furthermore, the reaction utiliz-

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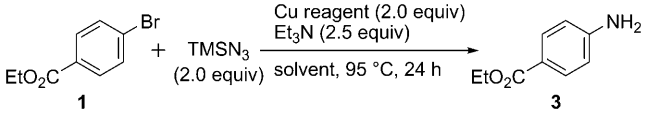
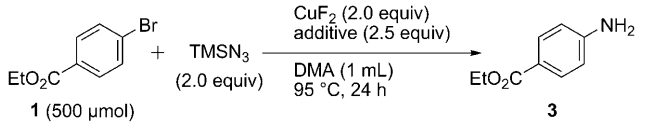
Table 1. Evaluation of copper reagents and solvents in the copper-mediated reductive amination of ethyl 4-bromobenzoate (**1**) with $TMSN_3$.



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_2O	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 $TMSN_3$.



Entry	Additive	Yield [%][a]
1	–	27
2	Et_3N	84
3	$(n\text{Pr})_3N$	55
4	$(n\text{Bu})_3N$	26
5	Bn_3N	53
6	Ph_3N	26
7	Et_2NH	68
8	$(n\text{Bu})_4NBr$	0
9	$H_2N(CH_2)_2NH_2$	69
10	$Me_2N(CH_2)_2NMe_2$	31
11	$H_2N(CH_2)_2OH$	99
12	$H_2N(CH_2)_3OH$	89
13	$H_2N(CH_2)_4OH$	93
14	$H_2N(CH_2)_5OH$	92
15	$HO(CH_2)_2OH$	44
16[b]	$H_2N(CH_2)_2OH$	95
17[c]	$H_2N(CH_2)_2OH$	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.

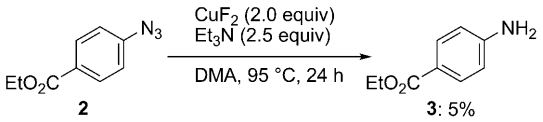
Next, we explored the scope of this reductive amination based upon the cross-coupling of aryl halides with $TMSN_3$ as the amino source under the optimal conditions [CuF_2 (2.0 equiv), amine (2.5 equiv), $TMSN_3$ (2.0 equiv), DMA, 95 °C] (Table 3). Bromobenzenes containing an electron-withdrawing group effectively reacted with $TMSN_3$, 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.

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

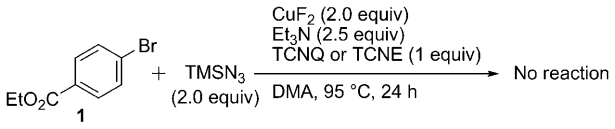
Entry	Ar	X	Amine	Yield [%][a]
1	$4\text{-}NO_2C_6H_4$	Br	$H_2N(CH_2)_2OH$	95
2	$4\text{-}EtO_2CC_6H_4$	Br	$H_2N(CH_2)_2OH$	99
3	$3\text{-}EtO_2CC_6H_4$	Br	$H_2N(CH_2)_2OH$	80
4	$2\text{-}EtO_2CC_6H_4$	Br	$H_2N(CH_2)_2OH$	76
5	$3\text{-}MeO_2CC_6H_4$	Br	$H_2N(CH_2)_2OH$	77
6	$4\text{-}ClC_6H_4$	Br	$H_2N(CH_2)_2OH$	76
7	$2\text{-}Me\text{-}5\text{-}NO_2C_6H_3$	Br	$H_2N(CH_2)_2OH$	75
8[b]	$4\text{-}PhC_6H_4$	Br	$H_2N(CH_2)_2OH$	95
9[b]	$4\text{-}MeOC_6H_4$	Br	$H_2N(CH_2)_2OH$	48
10[b]	$3\text{-}MeOC_6H_4$	Br	$H_2N(CH_2)_2OH$	81
11	$4\text{-}CF_3C_6H_4$	Br	Et_3N	67
12[c]	$4\text{-}AcC_6H_4$	Br	Et_3N	77
13	$4\text{-}MeO_2CC_6H_4$	I	Et_3N	66
14	$4\text{-}AcC_6H_4$	I	Et_3N	59
15	$4\text{-}CF_3C_6H_4$	I	Et_3N	60
16	$4\text{-}NO_2C_6H_4$	Cl	$H_2N(CH_2)_2OH$	32

[a] Isolated yield. [b] Cu^0 powder was used in place of CuF_2. [c] NaN_3 was used in place of TMS-N_3 and the reaction was carried out at 120 °C.

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 $TMSN_3$ 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 μL) 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 μL, 500 μmol) 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 μmol), 2-aminoethanol (74.9 μL, 1.25 mmol), and $TMSN_3$ (132 μL, 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 × 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 → 4:1).

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

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[15] When 2-aminoethanol was added to a mixture of ethyl 4-bromobenzoate and CuF_2 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.

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