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Copper-Catalyzed C−H Azidation of Anilines under Mild Conditions

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Supporting Information

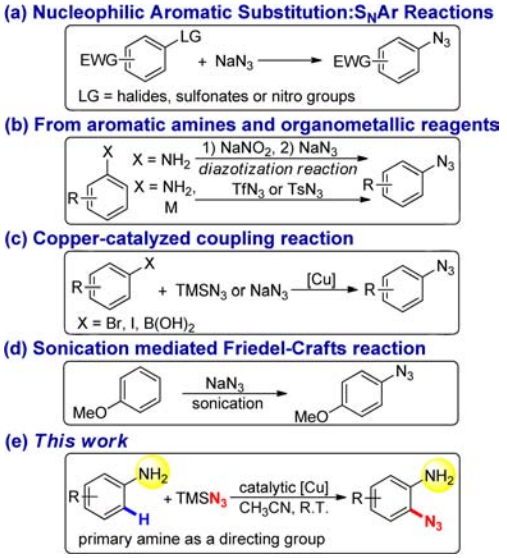
ABSTRACT: A novel and efficient copper-catalyzed azidation reaction of anilines via C−H activation has been developed. This method, in which the primary amine acts as a directing group by coordinating to the metal center, provides ortho azidation products regioselectively under mild conditions. This effective route for the synthesis of aryl azides is of great significance in view of the versatile reactivity of the azide products.

The first organic azide, phenyl azide, was discovered by Griess in 1864.[1] Since then, numerous syntheses of these energy-rich molecules have been developed. In most recent times, organic azides have become widely used in organic synthesis as valuable intermediates and building blocks because of their versatile reactivities,[2] and elegant perspectives have been developed for the application of organic azides, particularly in the synthesis of nitrogen-containing heterocycles, peptide chemistry, materials science, polymer chemistry, and drug discovery.[3] Moreover, aryl azides have found biological and industrial use as photoaffinity labeling agents.[4] Thus, organic azides have assumed an important position at the interface of chemistry, biology, medicine, and materials science.

Conventional methods of incorporating the azide group into aromatic rings[5] include the following: (1) classical nucleophilic aromatic substitution (S_NAr) reaction, which requires activated aromatic systems bearing an electron-withdrawing group (Scheme 1a);[6] (2) diazotization of aromatic amines under strongly acidic conditions and subsequent treatment with sodium azide or diazo transfer reactions involving treatment of aromatic amines with triflyl azide (Scheme 1b);[7] (3) reactions of tosyl azide with organometallic reagents (Scheme 1b);[8] and (4) copper-catalyzed coupling of aryl halides or arylboronic acids (Scheme 1c).[9] More recently, a sonication-mediated C−H azidation of anisole through a Friedel−Crafts reaction process with the azide at the para position has been reported (Scheme 1d).[10] However, these methods suffer from narrow functional group compatibility, poor atom economy, and the need for harsh conditions that may induce decomposition of the azide. Hence, developing new ways to obtain aryl azides involving direct C−H functionalization[11,12] under mild conditions would be very fascinating while challenging at the same time.

On the other hand, directed ortho functionalization of arenes through C−H activation has emerged as an effective tool for constructing substituted arenes.[11,13,14] Although various nitrogen-containing groups have been employed as directing groups,

Scheme 1. Azide Group Incorporation into Aromatic Rings



ortho C−H functionalization of arenes directed by primary amines is still limited. Vinyl C−H bond activation and alkenylation assisted by the amine group of aniline substrates were individually disclosed by the groups of You[15] and Zhang.[16]

Herein we report a novel and efficient Cu-catalyzed C−H azidation of aniline derivatives directed by the amino group under mild conditions (Scheme 1e). The significance of the present chemistry is threefold: (1) To the best of our knowledge, this is a novel amino-group-directed ortho C−H functionalization of simple and readily available anilines. Moreover, the amino group can be converted into a Cl, Br, I, CN, OH, or H substituent by Sandmeyer reaction. (2) Although various C−C and C−heteroatom bond formations via C−H activation have been successfully achieved, the directed ortho C−H azidation of arenes has not been realized until this work. (3) In contrast to methods using expensive transition-metal catalysts, this process is simple, proceeds under mild conditions, uses inexpensive copper catalysts, and forms valuable products that would be difficult to synthesize by other methods.

We commenced our study by investigating the C−H azidation of 2,4-dimethylaniline (**1a**). When the reaction was

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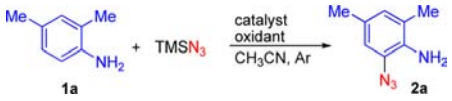
performed in the presence of azidotrimethylsilane ($TMSN_3$) and *tert*-butyl hydroperoxide (TBHP) using CuBr as the catalyst at 60 °C in CH_3CN, 2-azido-4,6-dimethylaniline (**2a**) was obtained in 28% yield (Table 1, entry 1). In view of the fact that high temperature may lead to decomposition of the product, the reaction temperature was decreased from 60 to 30 °C, and a slightly lower yield was obtained (entry 2). To our delight, when the reaction time was decreased from 12 to 1 h, the yield improved to 56% (entry 3). The highest yield (68%) appeared when the reaction time was 2 h (entry 4). In further exploration steps, we tried to decrease the amounts of oxidant and catalyst. However, both resulted in lower efficiencies (entries 5 and 6). When the catalyst was replaced by CuCl or $CuBr_2$, the desired product **2a** was obtained only in 48 or 34% yield, respectively (entries 7 and 8). Notably, this reaction did not work when CuBr was removed or replaced by $FeCl_2$ (entries 9 and 10).

Table 1. Cu-Catalyzed Azidation of 2,4-Dimethylaniline (1a)[a]



1a 2a

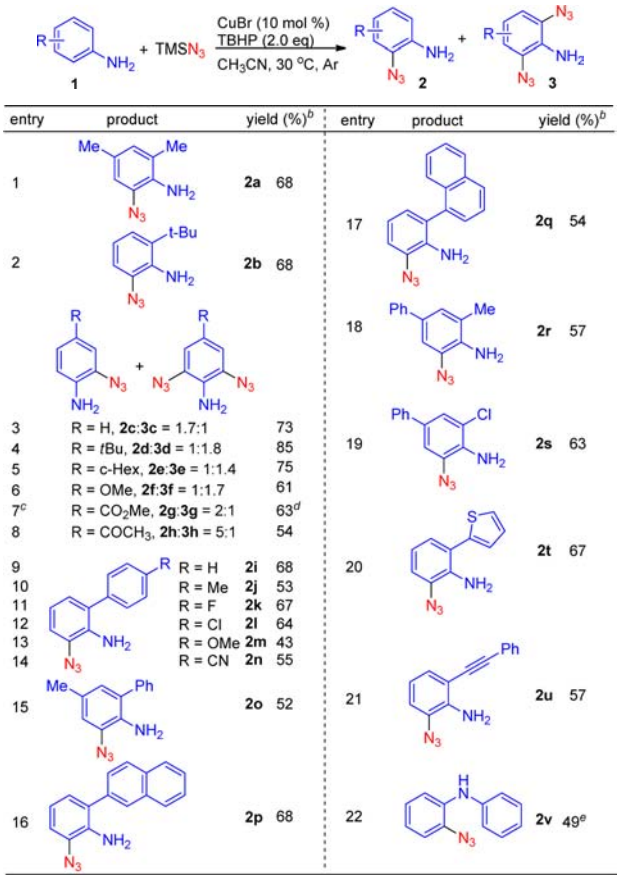
entry	catalyst (mol %)	oxidant (equiv)	T (°C)	time (h)	yield (%)[b]
1	CuBr (10)	TBHP (2.0)	60	12	28
2	CuBr (10)	TBHP (2.0)	30	12	27
3	CuBr (10)	TBHP (2.0)	30	1	56
4	**CuBr (10)**	**TBHP (2.0)**	**30**	**2**	**68**
5	CuBr (10)	TBHP (1.2)	30	2	54
6	CuBr (5)	TBHP (2.0)	30	2	40
7	CuCl (10)	TBHP (2.0)	30	2	48
8	$CuBr_2$ (10)	TBHP (2.0)	30	2	34
9	–	TBHP (2.0)	30	2	0
10	$FeCl_2$ (10)	TBHP (2.0)	30	2	0

[a]Reaction conditions: **1a** (0.5 mmol), $TMSN_3$ (2.0 equiv), catalyst, oxidant, CH_3CN (2 mL), stirred at 30 °C under Ar. TMS = trimethylsilyl. [b]Isolated yields.

Under the optimized reaction conditions, the scope of this copper-catalyzed C–H azidation reaction was demonstrated with a series of aniline derivatives (Table 2). 2-*tert*-Butylaniline (**1b**) also performed well, giving the desired product **2b** in 68% yield (entry 2). Notably, non-ortho-substituted electron-deficient and -rich aniline substrates afforded both mono- and diazidated products, which could be easily separated by column chromatography (entries 3–8). One of the most readily available starting materials, aniline (**1c**), reacted smoothly in a total yield of 73% with a mono/di ratio of 1.7:1. In the presence of an *o*-phenyl substituent, a series of substrates containing electron-donating and -withdrawing groups on the 2-phenyl ring of the aniline were tolerated in this transformation with moderate efficiencies (entries 9–14). In addition, *o*-2-naphthyl (**1p**) and *o*-1-naphthyl (**1q**)-substituted anilines performed well in this transformation (entries 16 and 17). 2-Chloro-substituted aniline **1s** afforded the corresponding chloro-substituted product **2s** in 63% yield (entry 19). The heterocycle-containing substrate 2-(thiophen-2-yl)aniline (**1t**) produced the desired **2t** in 67% yield (entry 20). Moreover, 2-(phenylethynyl)aniline (**1u**) containing an alkynyl group also reacted smoothly in moderate yield (entry 21).

It is noteworthy that when a secondary amine, diphenylamine (**1v**), was employed, this amino-group-directed ortho azidation reaction also proceeded well. However, the biggest obstacle with the secondary amine was that a large amount of starting material remained, thus leading to a relatively low yield. Increasing the reaction time or elevating the reaction temperature did not significantly promote the conversion of the starting material. Under the standard conditions, **1v** yielded the desired product **2v** in 49% isolated yield with recovery of 36% of **1v** (entry 22). The reaction of arylamines with a tertiary amino group did not work under the standard conditions (see eqs S1 and S2 in the Supporting Information), indicating that a free N–H bond is required for this transformation.

Table 2. Cu-Catalyzed Azidation of Anilines (1)[a]



[a]Reaction conditions: **1** (0.5 mmol), $TMSN_3$ (1.0 mmol, 2.0 equiv), CuBr (0.05 mmol, 10 mol %), TBHP (1.0 mmol, 2.0 equiv), CH_3CN (2 mL), stirred at 30 °C under Ar. [b]Isolated yields. [c]Reaction was carried out at 50 °C. [d]25% of **1g** was recovered. [e]36% of **1v** was recovered.

As mentioned above, aryl azides are versatile intermediates and building blocks in organic synthesis.[17,18] After this amino-group-directed ortho azidation protocol was established, we looked forward to applying the aryl azide products in other transformations (Scheme 2). For the classical click reaction, 2-azido-4,6-dimethylaniline (**2a**) was treated with phenylacetylene in the presence of a catalytic amount of $CuSO_4$, thus affording the corresponding triazole **4** in 85% yield. When 2-azidoaniline (**2c**) was treated with benzaldehyde, benzimidazole **5** was produced in 70% yield.[18a] One of the advantages of using a primary amino group as the directing group is the possibility that it can be removed or used in other transformations. By means of the well-known Sandmeyer reaction, diazotization of **2c** with $NaNO_2$ followed by treatment with KI produced 1-azido-2-iodobenzene (**6**) in 73% yield.[18b] The azide group was

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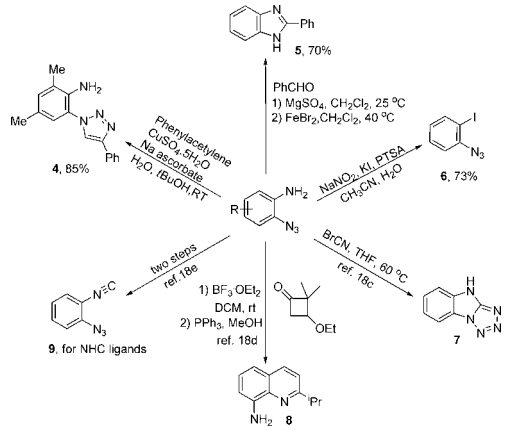
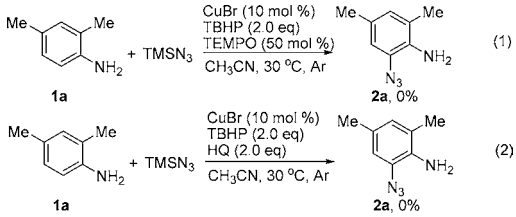
Scheme 2. Transformations of 2-Azidoanilines



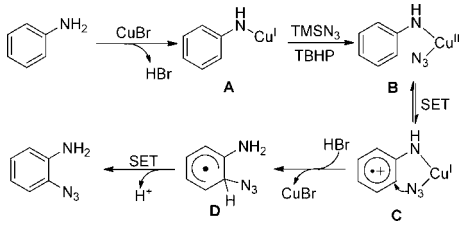
well-tolerated in this reaction, and the resulting product could be used in subsequent conversions. Moreover, 2-azidoanilines could also undergo some other transformations according to the literature. 9*H*-Benzo[4,5]imidazo[1,2-*d*]tetrazole (**7**) was easily prepared by the reaction of **2c** with BrCN via *N*-arylcyanamide as the intermediate.[18c] The biologically important 8-aminoquinoline compound **8** was constructed using **2c** as the starting material.[18d] In addition, 1-azido-2-isocyanobenzene (**9**), which is a precursor of N-heterocyclic carbene ligands, was synthesized from **2c**.[18e]

To understand the mechanism further, the reactions of **1a** in the presence of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) or hydroquinone (HQ) as a radical scavenger were tested. The formation of **2a** was completely inhibited in these reactions (eqs 1 and 2), demonstrating that a radical process may be involved in this reaction.



Although the mechanism of this transformation is not completely clear yet,[19] on the basis of the above results, a possible mechanism is proposed in Scheme 3. Intermediate **A** is

Scheme 3. Proposed Mechanism



initially generated by the coordination of copper to the substrate.[20] Subsequently, **A** combines with an azide radical generated in situ from $TMSN_3$ and TBHP to form intermediate **B**. A single electron transfer (SET) from the aryl ring to the metal center (**B** → **C**) is possibly involved in this process.[21] Next, azido group transfer into the aryl ring with release of CuBr forms intermediate **D**, which undergoes deprotonation via a SET process to give the product.

In conclusion, a novel and practical Cu-catalyzed ortho C−H azidation of anilines has been developed. This azidation reaction is regiospecific at the position ortho to the amino group and has broad substrate scope. This chemistry not only expands the scope of directing groups but also provides a novel C−H azidation approach leading to aryl azides, which are of high synthetic value. Further studies to provide a clearer understanding of the reaction mechanism and synthetic applications are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and analytical data and NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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