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Room-temperature Cu(II)-catalyzed aromatic C–H azidation for the synthesis of *ortho*-azido anilines with excellent regioselectivity[†]

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Cu(n)-catalyzed aromatic C–H azidation with azido-benziodoxolone under mild conditions has been described. The primary amine exhibits an excellent *ortho*-directing effect, providing *ortho*-azidated anilines as the sole products.

Besides their important roles in the click chemistry of cycloaddition, aromatic azides are also well known for providing an electron-deficient nitrene species, which is able to insert into a C-H bond. Thus, aryl azides have found numerous biological and industrial applications, such as the construction of N-containing structural motifs in drug discovery,¹ photoaffinity labelling reagents in structural proteomics,² cross-linkers for high-performance polymer materials,³ and photografting on polymer surfaces.⁴

Although numerous approaches for the synthesis of aliphatic azides are available, the preparation methods of aryl azides are still limited. The conventional methods for constructing aryl azides involve classical direct nucleophilic aromatic substitution (S_NAr) of activated aryl halides or sulfonates with NaN₃,⁵ diazotization of aryl amines with NaNO2 at low temperature under strong acidic conditions and subsequent treatment with the azide ion,⁶ or the cross-coupling of aryl boronic acids with azide sources such as TfN₃ and NaN₃.⁷ Although powerful, these transformations suffer from a long reaction time, harsh acidic or basic conditions, and use of oxidative reagents, which are not compatible with many functional groups present in a substrate. What needs to be pointed out is that the direct C-H azidation of aromatic rings to obtain aryl azides under mild conditions has been gradually realized, making it a much more ideal and straightforward azidation process. Recently, K. A. Sasane et al. disclosed a sonication-mediated C-H azidation of aryl derivatives

through a Friedel–Crafts reaction process.⁸ N. Jiao *et al.* developed a Cu(i)-catalyzed regioselective C–H azidation of anilines.⁹ X. Li *et al.* described Rh(m)-catalyzed C–H azidation of arenes, in which pyridine acted as an efficient directing group.¹⁰ However, the hazardous azide sources, such as NaN₃ or TMSN₃, still used in these reactions are deterrents to their practical applications.

Azides of polyvalent iodine, such as $PhI(N_3)OAc$ or $PhI(N_3)_2$, generated *in situ* from the combinations of PhIO or $PhI(OAc)_2$ with $TMSN_3$ or NaN_3 , were found to be reactive intermediates in radical-based aliphatic C-H azidation reaction.¹¹ However, the instability and high reactivity of these azidoiodinanes have restricted their practical applications as efficient reagents for the introduction of the azido function into organic molecules. Fivemembered heterocyclic azidoiodines as novel azidating reagents are found to exhibit high thermal and storage stabilities.¹² So far, however, only a few reports on these azidobenziodoxoles as efficient azidating reagents have been reported.¹³ To the best of our knowledge, there is no report on the aromatic C-H azidation based on the thermally stable azidobenziodoxoles.

Herein, we disclose a mild, simple, highly efficient protocol for the diverse synthesis of aryl azides through C–H azidation of anilines catalyzed by less expensive $Cu(OAc)_2$, in comparison with copper(I) salts, at ambient temperature. The thermally stable azidobenziodoxolone as a reliable azide source was first applied in the metal-catalyzed aromatic azide formation. The amino group is found to exhibit an *ortho*-directing effect in the azidation reactions, regioselectively affording the mono-azidated derivative.

In the initial studies, the azidation of 4-methyl aniline (1a) with azidoiodine reagent 2 as a model reaction was carried out to optimize the reaction conditions (for safety notes for using azidobenziodoxolone see ESI†). As shown in Table 1, Lewis acid as a catalyst was found to be important to initiate the azidation (entry 1). A survey of the catalysts revealed that Cu(I) halide or acetate could give good yields when CH₃CN was used as solvent at room temperature (entries 2–5). Fe(ClO₄)₃ and Zn(ClO₄)₂·6H₂O were ineffective in the azidation (entries 6 and 7), while ZnI₂, ZnCl₂, FeCl₃, CuCl₂ and CuSO₄ afforded the desired products with moderate yields (entries 8–11, see Table S1 for studies using

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Table 1 Optimization of reaction conditions^a

		H ₂ + 2 N ₃ Lewis A Solvent	Acid , rt	NH ₂	
Entry	1a (equiv.)	Lewis acid (mol%)	Solvent	$T(^{\circ}C)$	Yield ^b
1	1.0	None	CH ₃ CN	20	0
2	2	CuI (10)	CH_3CN	20	67
3	2	CuBr (10)	CH_3CN	20	59
4	2	CuCl (10)	CH_3CN	20	57
5	2	CuOAc (10)	CH_3CN	20	52
6	2	$Fe(ClO_4)_3$ (10)	CH_3CN	20	0
7	2	$Zn(ClO_4)_2 \cdot 6H_2O(10)$	CH ₃ CN	20	0
8	2	$ZnI_{2}(10)$	CH ₃ CN	20	63
9	2	$ZnCl_2$ (10)	CH ₃ CN	20	57
10	2	$CuCl_2(10)$	CH ₃ CN	20	45
11	2	$CuSO_4(10)$	CH ₃ CN	20	57
12	2	$Cu(OAc)_2$ (10)	CH ₃ CN	20	72
13	2	$Cu(OAc)_2$ (10)	CH_2Cl_2	20	69
14	2	$Cu(OAc)_2$ (10)	THF	20	79
15	2	$Cu(OAc)_2$ (10)	MeOH	20	0
16	2	$Cu(OAc)_2$ (20)	THF	20	85
17	2	$Cu(OAc)_2$ (20)	THF	30	86
18	1.0	$Cu(OAc)_2$ (20)	THF	20	57

 a Reagent 2 (0.3 mmol), 4-methyl aniline, catalyst, solvent, temperature and indicated solvents under $\rm N_2.$ b Isolated yield.

other Lewis acids in ESI[†]). Cu(OAc)₂ appeared to give better results and acceptable yield (up to 72%) of 3a (entry 12). It was found that reactions carried out in a range of solvents produced the desired products in good yields, while THF provided the best results (entry 14). However, the reaction did not work when the polar protic solvent of MeOH was used (entry 15). Increasing the catalyst loading from 10% to 20% significantly improved the catalyst performance, providing the azidation product in 85% vield (entry 16). Elevated temperature gave only a slightly higher vield without a remarkable decrease of reaction time (entry 17). When the molar ratio of the aniline and azidoiodine(III) 2 was 1:1, the diazidated product of 2,6-diazidoaniline was also obtained in a total yield of 73% with a mono/di ratio of 3.5:1 (entry 18). However, aniline and azidoiodine(III) reagent 2 in a molar ratio of 2:1 produced 2-azidoaniline as the sole product with traces of the diazidated by-product under these conditions. The excess of aniline could be recovered.

With the optimized reaction conditions established (entry 16), the scope and functional group tolerance of this Cu(n)-catalyzed azidation reaction were investigated (Table 2).

Aryl amines with inert alkyl substituents underwent smooth azidation to afford the desired *ortho*-substituted products in moderate to high yields (**3a-3f**). The substitution pattern of the aromatic ring was found to have an apparent influence on the reaction efficiency, with *para*-substituted substrates working more efficiently to provide the desired products in higher yields (**3a**, **3c**, and **3d**). Functionalities such as alkoxy, halide, acetyl, and ester, which serve as useful reaction handles for further investigation, were well-tolerated under the mild reaction conditions (**3g-3o**). Note that the substrate with a Br group, which has been shown to be a prominent leaving group in a variety of transition-metal-catalyzed cross-coupling reactions, also underwent smooth azidation to afford the desired azides in good

Table 2 Screening results of azidation reactions to form *ortho*azido anilines



yields (**3i** and **3j**). Interestingly, high azidation efficiency was also observed for the biaryl and fused aromatic substrates, affording the respective azidation products in good to high yield (**3p**-**3v**). A diamino-containing substrate produced the corresponding mono-azidation product **3u** in moderate yield. The heterocycle-containing anilines **3w** and **3x** were found to be viable substrates albeit giving acceptable yields. It should be emphasized that azidation was found to take place only on the amino-containing aromatic rings. The *para*-azidation reaction was observed when *o*,*o*'-dimethyl aniline **2y** was employed, affording 36% isolated yield (**3y**) with a large amount of starting material remaining.

The synthetic utility was further demonstrated by performing the chemical modification of the *o*-azido anilines. As shown in Scheme 1, azidation reduction was achieved by treatment with Zn–NH₄Cl in reflux EtOH, providing almost stoichiometric 1,2-diamino benzene 4.^{14*a*} By means of the well-known Sandmeyer reaction, diazotization of **3h** with *t*-butyl nitrite, followed by treatment with KI, produced 2-azido-4-chloro-1-iodobenzene **5** in high yield.^{14*b*} As expected, **3b** or **3h** was a suitable substrate for the Cu-catalyzed [3+2] alkyne–azide cycloaddition, giving trizoles **6** and **7** in excellent yields.^{14*c*} N-formylation of the 2-azido aniline **3c**, followed by dehydration, provided 2-azido-1-isocyanobenzene **8**, which is an important precursor in the template-controlled synthesis of NH and NH–NHC complexes.^{14*d*}



In order to gain insight into the role of the amino group, the effect of the substituent on the amino group was investigated. Though a primary amino-directed *ortho* azidation reaction was found to proceed well, a complex mixture was obtained when the secondary amine of *N*-phenyl aniline or *N*-methyl aniline was applied in the azidation reaction. No conversion was observed for *N*-acetyl aniline, *N*,*N*-dimethyl aniline and phenyl-methanamine under the standard conditions. These results demonstrated that a free amino group in anilines is required for this azidation.

Preliminary studies on the mechanism were performed, using 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and hydroquinone (HQ) separately as radical scavengers in the reaction of aniline and azidoiodine(III) reagent 2. The azidation reaction was completely inhibited, indicating that a radical process may be involved in this reaction. Further GC-MS analysis confirmed the formation of TEMPO-N₃ (see the ESI[†]). This result is consistent with the literature data on the radical mechanism for aliphatic C-H azidations by the unstable azidoiodinanes, PhI(N₃)OTMS and $PhI(N_3)_{2}$ ¹⁵ and the report on the stable azidobenziodoxoles. However, in contrast to the previously reported aliphatic C-H azidation with azidobenziodoxolone 2 in the presence of a radical initiator at high reaction temperature,12 the Cu(II)-catalyzed aromatic C-H azidation by reagent 2 in this work proceeded well in the absence of any radical initiator under very mild reaction conditions, providing the ortho-azidated products in good yields.

On the basis of this result in hand, a plausible working hypothesis is proposed for the reaction mechanism (Scheme 2). It is assumed that initial one-electron oxidation of aniline by



Scheme 2 Plausible mechanistic pathways.

oxidative hypervalent iodine(m) reagent 2 results in the formation of the aniline radical cation and radical anion A.¹⁶ Rapid collapse of radical anion A would lead to Lewis acid catalyzed bond cleavage, producing N₃-containing 2-iodo-benzoate **B**. Decomposition of **B** gives copper(n) salt **C**, with simultaneous release of a relatively stable azide radical. The N₃ radical preferentially attacks the aromatic ring *ortho* to the primary amino group of the aniline radical cation, regioselectively generating the cyclohexadienyl cation species **D**. Finally, deprotonation of **E** by 2-iodobenzoate **C** could afford the desired azidation product **3**. The generated 2-iodobenzoic acid **F** in the last step was also detected by ¹H NMR spectroscopy. Further investigation will be required to elucidate the nature of the C–H azidation reaction in this work, though a SET process proposed for the reaction mechanism under the present study is more probable.

In conclusion, we have described a mild procedure of aromatic C-H azidation with azidobenziodoxolone 2 catalyzed by cheap Cu(OAc)₂. With the efficient *ortho*-directing effect of the primary amino group, the reactions exhibit a unique regioselectivity in that *ortho*-azidation is strongly preferred. This azidation procedure provides an easy access for further chemical modifications of the *ortho*-azido anilines.

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