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Copper-Catalyzed Vicinal Oxyazidation and Diazidation of Styrenes under Mild Conditions: Access to Alkyl Azides

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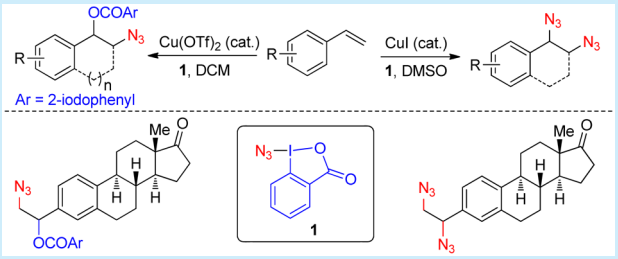
Supporting Information

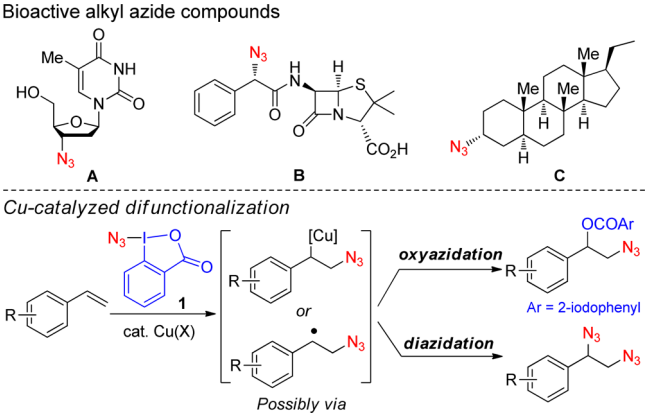
ABSTRACT: A novel and efficient copper-catalyzed oxyazidation and diazidation of styrenes is described. The stable azidoiodine(III) reagent is used as an efficient azide radical source in this reaction. A variety of synthetically useful functional groups are compatible with the mild reaction conditions. This protocol enables the straightforward synthesis of various functionalized azides in good-to-excellent yields.



Organic azides have been recognized as important intermediates and building blocks in organic synthesis due to their synthetic versatility, in particular, as powerful precursors of nitrogen-containing reactive species and nitrogen-rich heterocycles.[1] For instance, organic azides can be easily transformed into amines, isocyanates, and pharmaceutically important heterocycles. Organic azides have shown wide applications in materials science, polymer synthesis, and drug discovery.[2] Within the concept of "Click" chemistry, organic azides have enjoyed a renaissance in recent years because of their ever-increasing applications in copper-catalyzed azide–alkyne cycloaddition (CuAAC) reactions.[3] More importantly, many azido-substituted compounds exhibit valuable biological activities, such as antiviral activity and enzyme inhibition (Scheme 1).[4] Accordingly, the development of efficient and practical methods for the incorporation of an azide group into organic molecules, to construct functionalized azides in a highly chemo- and regioselective manner, has inspired considerable interest in past decades.[5]

With regard to the synthesis of aliphatic azides, conventional methods are mainly based on nucleophilic substitution reactions of electrophilic substrates with inorganic azides.[1a,6] However, these methods often suffer from limited substrate scope because of the need for harsh reaction conditions. The direct azidation of aliphatic C–H bonds using azidoiodine(III) reagent **1**, reported by the groups of Zhdankin, Groves and Hartwig, provides a straightforward approach to the synthesis of alkyl azides.[7] Another efficient method to alkyl azides is to carry out hydroazidation of alkenes since they are readily available chemical feedstocks.[8] Despite the value of these methods, it is highly attractive to take advantage of the more effective synthetic strategy of metal-catalyzed difunctionalization of alkenes that enables direct installation of two functional groups in one step to afford substituted organic azides with a maximal increase in molecular complexity. Elegant work involving aminoazidation,[9] carboazidation,[10] azidocyanation,[11] azidofluorination,[12] and trifluoromethylazidation[13] of alkenes using different azide reagents (NaN_3, TfN_3, or $TMSN_3$) has been realized. Recently, the groups of Shi, Wang, and Xia independently reported the oxyazidation reaction of alkenes.[9c,14] In these reactions, the azide group was incorporated by the addition of oxygen radicals to the C=C bond followed by trapping with a suitable azide reagent. In this context, the strategy of direct generation of a stable azidyl radical followed by an oxygen-trapping pathway is highly appealing yet more challenging. To the best of our knowledge, such reactions have

Scheme 1. Representative Azido-Substituted Bioactive Compounds and Copper-Catalyzed Oxyazidation and Diazidation of Styrenes



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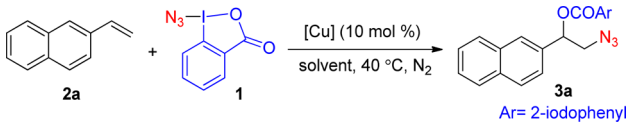
been scarcely investigated.[15] Inspired by recent advances and our continuing interest in difunctionalization of alkenes,[16] we report herein a novel copper-catalyzed oxyazidation and diazidation of styrenes that takes advantage of the stable azidoiodine(III) reagent **1** under mild conditions (Scheme 1). It is worth mentioning that azidoiodine(III) reagent **1** plays a dual role as an azidyl radical source and also as a coupling partner for the oxyazidation of styrenes.

To identify reaction conditions for the oxyazidation of styrenes, we began our studies with 2-vinylnaphthalene (**2a**) as a model substrate with azidoiodine(III) reagent **1**, in the presence of $Cu(MeCN)_4PF_6$ as catalyst, in DCE at 40 °C. We were rather pleased to find that the oxyazidation product **3a** was obtained in 14% yield (Table 1, entry 1). However,

Table 1. Optimization of Reaction Conditions[a]



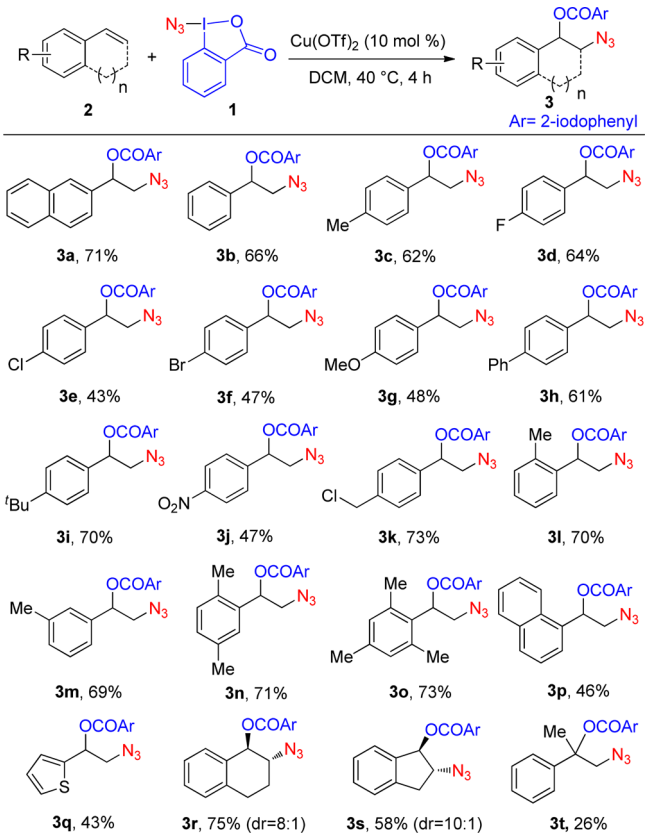
entry	catalyst	solvent	time (h)	yield[b] (%)
1	$Cu(MeCN)_4PF_6$	DCE	2	14
2	CuCl	DCE	2	0
3	CuBr	DCE	2	0
4	CuI	DCE	2	0
5	$Cu(OAc)_2$	DCE	2	0
6	$Cu(OTFA)_2$	DCE	2	11
7	CuOTf·toluene	DCE	2	27
8	$Cu(OTf)_2$	DCE	2	53
9	$Cu(OTf)_2$	THF	2	10
10	$Cu(OTf)_2$	dioxane	2	43
11	$Cu(OTf)_2$	DCM	2	59
12[c]	$Cu(OTf)_2$	DMSO	2	trace
13	$Cu(OTf)_2$	DMF	2	trace
14	$Cu(OTf)_2$	DCM	4	67
15[d]	$Cu(OTf)_2$	DCM	4	64
16[e]	$Cu(OTf)_2$	DCM	4	71
17[f]	$Cu(OTf)_2$	DCM	4	52
18		DCM	4	trace

[a]Reaction conditions: **2a** (0.2 mmol), **1** (0.24 mmol, 1.2 equiv), catalyst (0.02 mmol, 10 mol %), solvent (2 mL), 40 °C, under N_2. [b]Isolated yields. [c]The diazidation product was isolated in 30% yield. [d]At 50 °C. [e]1.5 equiv of **1** was used. [f]5 mol % of $Cu(OTf)_2$ was used.

catalysts such as CuCl, CuBr, CuI, or $Cu(OAc)_2$ turned out to be ineffective for this transformation (Table 1, entries 2−5). $Cu(OTf)_2$ was found to be the optimal catalyst, delivering the desired product in 53% yield (Table 1, entry 8). Dichloromethane (DCM) was the best solvent (Table 1, entry 11). It should be noted that only trace amounts of the oxyazidation product were detected in DMSO, whereas a diazidation product **4a** was isolated as a side product in 30% yield (Table 1, entry 12). The yield of **3a** was further improved to 67% with a prolonged reaction time (Table 1, entry 14). Furthermore, increasing the reaction temperature to 50 °C afforded the desired product in a slightly lower yield (Table 1, entry 15). The best yield of **3a** was obtained when 1.5 equiv of azidoiodine(III) reagent was employed (Table 1, entry 16). It was also observed that a lower catalyst loading failed to improve the efficiency of this transformation (Table 1, entry 17). Finally, reaction of **2a** with **1** in the absence of the copper catalyst delivered the desired product in only a trace amount, and the styrene substrate was recovered (Table 1, entry 18).

With the optimal conditions in hand (Table 1, entry 16), we next investigated the substrate scope of this reaction, and the results are summarized in Scheme 2. A variety of styrenes

Scheme 2. Scope of the Copper-Catalyzed Oxyazidation of Styrenes[a,b]



[a]Reaction conditions: **2** (0.2 mmol), **1** (0.3 mmol), $Cu(OTf)_2$ (10 mol %), DCM (2 mL), stirred at 40 °C for 4 h under N_2. [b]Isolated yields.

bearing both electron-donating and electron-withdrawing substituents on the aromatic ring reacted smoothly to provide the desired products in moderate-to-excellent yields (**3b−m**). It is worth noting that many synthetically relevant functional groups such as fluoro, chloro, and bromo were compatible with the conditions, revealing the possibility of further transformations by the well-established cross-coupling reactions. Styrenes with a di- and trisubstituted phenyl ring proved to be favorable substrates, affording the desired products in good yields (**3n** and **3o**). Reaction of 1-vinylnaphthalene with azidoiodine(III) reagent **1** afforded the product **3p** in 46% yield. The heterocyclic substrate 2-vinylthiophene exhibited slightly lower reactivity, and the product **3q** was isolated in 43% yield. The cyclic substrates gave the products **3r** and **3s** in 75% and 58% yields, respectively. However, 1,1-disubstituted substrate **2t** successfully delivered the corresponding product **3t**, albeit with lower efficiency.

We next focused on the diazidation of styrenes to obtain vicinal diazides which were particularly useful precursors for the synthesis of 1,2-diamines.[17] This important structural motif is found in a wide range of bioactive natural products,

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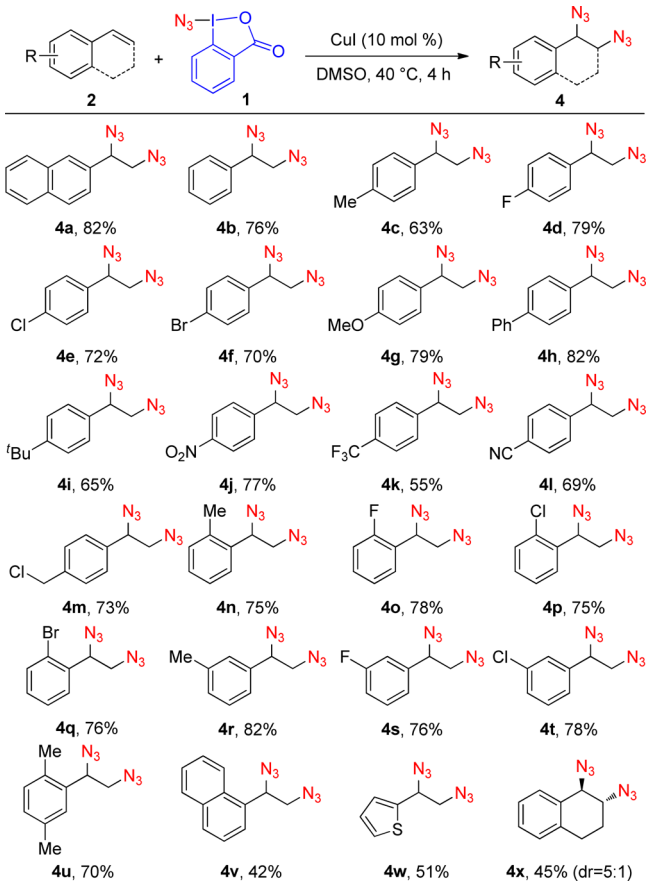
pharmaceutical molecules, as well as ligands or catalysts used in asymmetric catalytic reactions.[18] Therefore, practical and convenient methods for the synthesis of vicinal diazides are highly desirable.[19] As noted above, the diazidation product **4a** was isolated in 30% yield when the reaction was performed in DMSO. Encouraged by this promising result, we attempted to investigate a novel method for direct 1,2-diazidation of styrenes to afford vicinal diazides. Gratifyingly, treating **2a** with **1** in the presence of CuI as catalyst in DMSO gave the diazidation product **4a** in 82% yield (Scheme 3).[20] Various substrates

Scheme 3. Scope of the Copper-Catalyzed Diazidation of Styrenes[a,b]

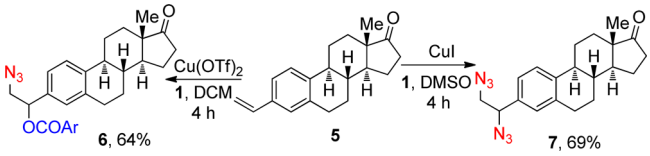


[a]Reaction conditions: **2** (0.2 mmol), **1** (0.5 mmol, 2.5 equiv), CuI (10 mol %), DMSO (2 mL), stirred at 40 °C for 4 h under N_2. [b]Isolated yields.

bearing a wide range of functional groups at the *ortho* position were well compatible with the conditions to furnish the diazidation products in good-to-excellent yields (**4b**–**m**). Importantly, substituents such as CF_3, NO_2, and CN were well tolerated in this reaction without any compromise. Styrenes with substituents at the *ortho* or *meta* position of phenyl ring did not affect the efficiency of this process, and excellent yields were achieved (**4n**–**t**). Moreover, styrene with a disubstituted phenyl ring was also suitable and afforded **4u** in 70% yield. Reactions of 1-vinylnaphthalene and 2-vinylthiophene with azidoiodine(III) reagent **1** gave products **4v** and **4w** in moderate yields. Finally, the cyclic styrene afforded **4x** in 45% yield with moderate diastereoselectivity (5:1).[21]

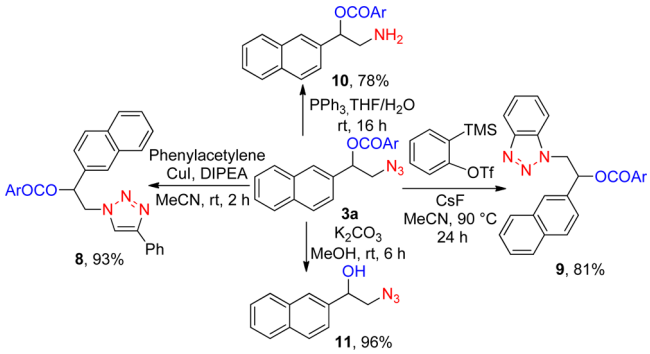
To illustrate the synthetic potential of this reaction, we applied this protocol to the late-stage modification of biologically relevant complex moleclues. When estrone-derived substrate **5** was subjected to the corresponding reaction conditions, the desired products **6** and **7** were obtained in 64% and 69% yields, respectively (Scheme 4).

Scheme 4. Vicinal Oxyazidation and Diazidation of an Estrone Derivative



Considering the synthetic utility of these products, we further investigated the diverse transformations of the oxyazidation product **3a** (Scheme 5). A click reaction of **3a** with

Scheme 5. Transformations of Oxyazidation Product 3a



phenylacetylene readily afforded the corresponding triazole **8** in 93% yield. Reaction of **3a** with benzyne generated in situ proceeded smoothly to provide benzotriazole **9** in 81% yield. Moreover, the amine **10** was obtained in 78% yield by the Staudinger reduction of **3a**. Importantly, the iodobenzoate group can be easily removed by treatment of **3a** with K_2CO_3 in MeOH, providing the valuable 2-azido alcohol product **11** in excellent yield. It is worth noting that 2-azido alcohol product **11** is a highly important intermediate in organic synthesis which could be readily transformed into 1,2-amino alcohols, aziridines, and other azaheterocycles.[22]

To investigate the mechanism of this reaction, a series of trapping reactions were conducted. When we added 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) to the reaction mixture, the oxyazidation product **3a** was isolated only in 8% yield. Addition of 2,6-di-*tert*-butyl-4-methylphenol (BHT) resulted in complete inhibition of the oxyazidation reaction (eq 1, Scheme 6). Moreover, the diazidation reaction was strongly inhibited by addition of TEMPO or BHT (eq 2, Scheme 6). Furthermore, when the radical clock **12** was employed, the cyclization product **13** were obtained in 26% yield (eq 3, Scheme 6). These observations suggest the general features of radical mechanism of this process.

In summary, we have developed a novel copper-catalyzed vicinal oxyazidation and diazidation of styrenes that takes advantage of the azidoiodine(III) reagent **1** as a azide source under mild conditions. This protocol tolerates a wide range of functional groups and enables the convenient synthesis of alkyl azides in good-to-excellent yields. The synthetic potential of

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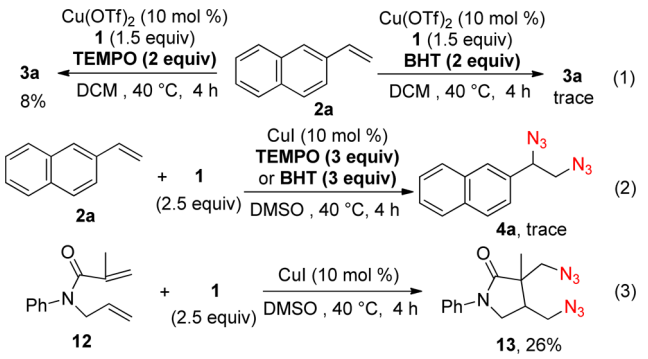
Scheme 6. Mechanistic Studies



this protocol is also demonstrated by a variety of synthetically useful transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03130.

Experimental procedures and spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, HRMS) (PDF)

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Notes

The authors declare no competing financial interest.

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(20) See the Supporting Information for details.

(21) Unfortunately, alkyl olefins were not suitable for this protocol, and only trace amounts of the desired products were detected under the optimal conditions.

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