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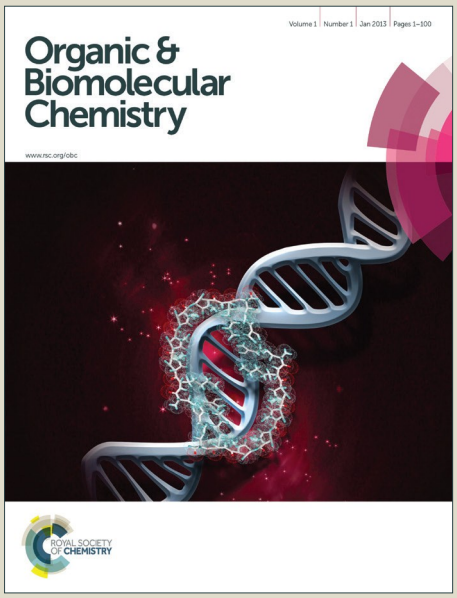

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Copper-catalyzed intermolecular chloroazidation of α,β-unsaturated amides

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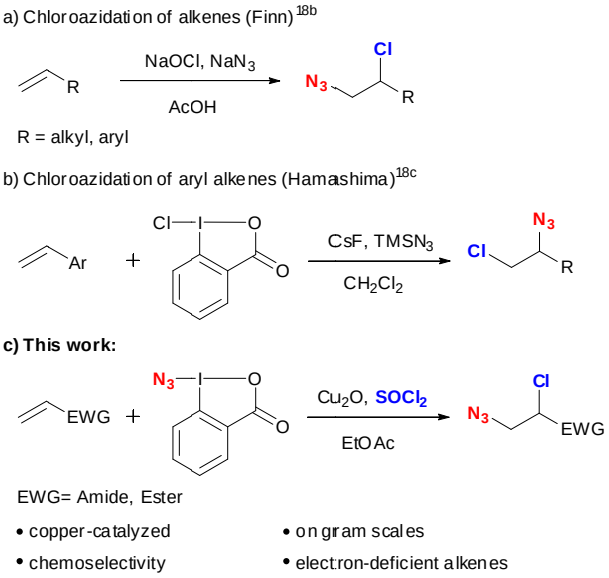
A highly practical copper-catalyzed intermolecular chloroazidation of α,β-unsaturated amides has been described, giving a series of azidochlorides in good-to-excellent yields. The stable azidoiodine-(III) reagent and $SOCl_2$ were used as azide and chlorine sources, respectively. The synthetic applications of this protocol were also explored by a variety of synthetically useful transformations.

Organic azides are one of the most important nitrogen containing compounds and have attracted ever-increasing interest of chemists due to their potential application as versatile intermediates and building blocks in organic synthesis as well as their remarkable bioactivities.[1] For example, Many efficient approaches have been developed for the transformation of organoazides into nitrogen-containing heterocycles which have shown wide applications in material science, chemical biology and drug discovery.[2] Therefore, the development of new methods for highly efficient and reliable incorporation of an azide group into organic molecules with a highly regio- and chemoselectivity has attracted much attention.[1-3] A number of transition-metal-catalyzed methods for the azidation of aromatic halides,[4] boronic acids,[5] C–H positions,[3h,6] arenes,[7] carbonyl compounds[8] and alkenes[9] have been well documented.

In recent years, the azidation of alkenes using electrophilic azidation reagents, such as Zhdankin's reagents,[10] has become a research hotspot and many effective methods have been studied intensively.[9-18] Especially, a variety of alkene difunctionalizations involving azidation, such as oxy-,[11] amino-,[9a,12] hydro-,[13] azido-,[14] cyano-,[15] aryl-,[16] phosphono[17] and halo-containing[18] azidation, have also been developed. Although similar vicinal haloazidations of alkenes have been reported (Scheme 1a and 1b),[18b-c] their applications are limited due to certain disadvantages, including the use of hazardous azide sources, such as NaN_3 or $TMSN_3$, addition of excess base, low reaction temperature, and complex reaction conditions. Therefore, the development of a simple, low cost, effective, mild and economic approache for the preparation of azidochlorides from electron-deficient alkenes is still highly desirable. Furthermore, chloridized compounds also serve as useful building blocks due to they can be readily transformed to amine, hydroxyl, hydrocarbon, and hydrogen. Inspired by recent advances and our continuing interest in copper catalyzed the intermolecular difunctionalization of alkenes,[19] we disclose here a novel Cu(I)-catalyzed chloroazidation of electron-deficient alkenes employed the stable Zhdankin's reagent and thionyl chloride ($SOCl_2$) as the azide and chlorine sources, respectively (Scheme 1c).



Scheme 1 Previous and Present Works

At the outset of our studies, we chose 3-methylene-1-(1-naphthylmethyl)-2-pyrrolidinon **1a** as the model substrate to optimize the reaction conditions (Table 1). Initially, the reaction was carried out with Zhdankin's reagent **2a** (1.5 equiv) and thionyl chloride (1.5 equiv) in the presence of 5 mol %

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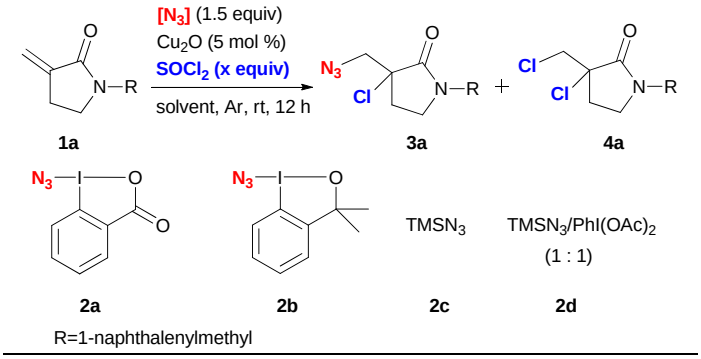
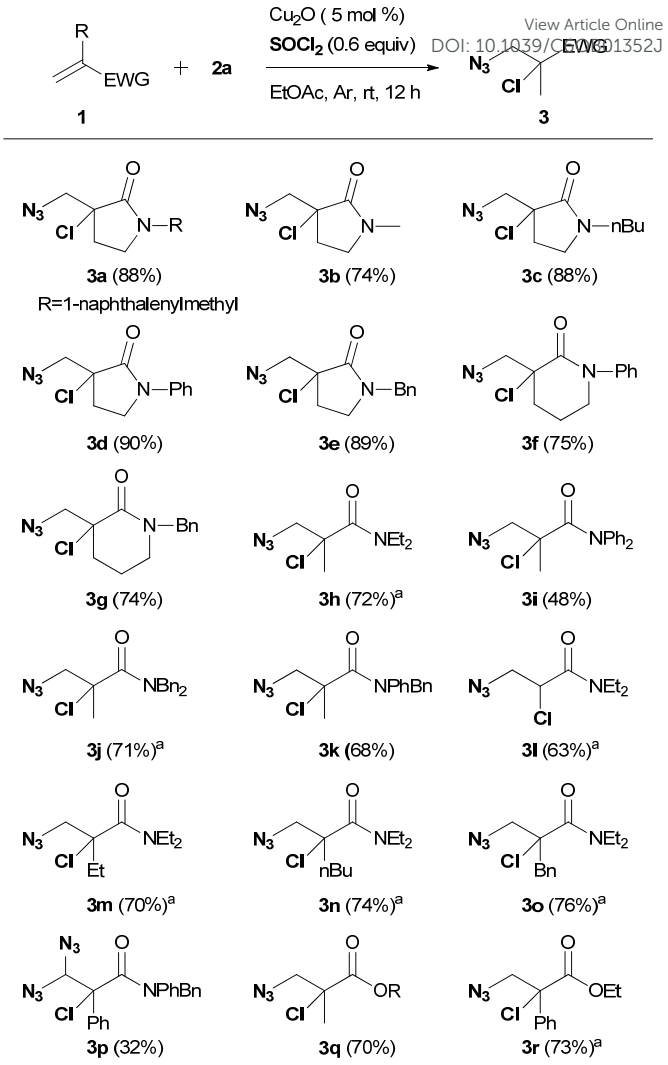
Table 1 Optimization of reaction conditions[a]



Entry	[N_3]	x equiv	Solvent	Yield[b] (%)	**3a/4a**[b]
1	**2a**	1.5	$CHCl_3$	40	1:1
2	**2a**	1.0	$CHCl_3$	35	3:2
3	**2a**	0.75	$CHCl_3$	37	7:2
4	**2a**	0.6	$CHCl_3$	47	>20:1
5	**2a**	0.5	$CHCl_3$	42	>20:1
6	**2a**	0.6	CH_2Cl_2	34	>20:1
7	**2a**	0.6	MeCN	52	>20:1
8	**2a**	0.6	EtOAc	52	>20:1
9	**2a**	0.6	MeOH	40	>20:1
10	**2a**	0.6	THF	45	1:4
11	**2a**	0.6	dioxane	46	1:3
12	**2a**	0.6	DMF	46	1:1
13[c]	**2a**	0.6	EtOAc	73	>20:1
14[c]	**2b**	0.6	EtOAc	48	>20:1
15[c]	**2c**	0.6	EtOAc	N.R.	-
16[c]	**2d**	0.6	EtOAc	62	3:2
17[c,d]	**2a**	0.6	EtOAc	88	>20:1
18[c,d,e]	**2a**	0.6	EtOAc	N.R.	-

[a] Reaction conditions: **1a** (0.2 mmol), azide sources (0.3 mmol, 1.5 equiv), Cu_2O (5 mol %) and $SOCl_2$ in solvent (1.0 mL) at rt for 12 h. [b] The ratio of **3a/4a** and yield were based on ^1H NMR spectra of the crude reaction mixture with 1,3,5-trimethoxybenzene as the internal standard. [c] 0.5 mL solvent was used. [d] 0.5 equiv Et_2NH was added. [e] Without Cu_2O.



Scheme 2 Scope of chloroazidation. Reaction conditions: **1** (0.4 mmol), **2a** (0.6 mmol, 1.5 equiv), Cu_2O (5 mol %) and $SOCl_2$ (0.24mmol, 0.6 equiv), diethylamine (0.2 mmol, 0.5 equiv), in EtOAc (1.0 mL) at rt for 12 h. [a] PCl_3 (0.4 equiv) was used as the chlorine source without diethylamine.

Cu_2O in $CHCl_3$ at room temperature under an argon atmosphere for 12 h. Gratifyingly, the desired chloroazide **3a** was obtained in 40% yield with an unexpected almost equal amount byproduct dichlorine **4a** (Table 1, entry 1). It was further found that the amount of thionyl chloride was an important factor for the chemoselectivity of the reaction (Table 1, entries 2-5). Almost no dichlorine **4a** was observed and the yield was increased slightly when the amount of $SOCl_2$ was decreased from 1.5 equiv to 0.6 equiv. Further optimization of the solvent revealed that EtOAc and MeCN provided the best results, giving the corresponding product **3a** in 52% yield (Table 1, entries 7-8). It is noteworthy that dichlorine **4a** was detected as the major product when THF and dioxane were employed. Other solvents, such as DCM, MeOH, and DMF were investigated, but no superior result was obtained. It should be indicated that, the reaction was very sensitive to water, air, and the purity of chlorine sources. Considering ethyl acetate is much cheaper than acetonitrile, EtOAc was chosen as the best solvent for the following investigation. To our delight, when half amount of solvent (0.5 mL) was used, the product was obtained in good yield (Table 1, entry 13). For comparison, other azide sources were also studied. Using Zhdankin's reagent **2b** led to much lower yield, probably due to its lower reactivity (48% yield, Table 1, entry 14). No reaction occurred with the use of trimethyl-silylazide ($TMSN_3$). A mixture (**3a/4a** = 3/2) in 62% yield was obtained when $PhI(OAc)_2$ was used as an oxidant combined with $TMSN_3$. When 0.5 equiv Et_2NH was used in the end, the reaction yield was increased to 88% (Table 1, entry 17). Changing the catalyst loading from 5% to 1%, 2% and 10% slightly decreased the catalyst performance, providing the azidochloride **3a** in 86%, 86% and 81% yields, respectively (see the ESI, Table S7). Finally, the controlled experiment indicated that the copper catalyst was essential in catalyzing the reaction (Table 1, entry 18).

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Under the optimized conditions (Table 1, entry 17), a study on the substrate scope of this transformation was carried out, and the results are summarized in Scheme 2. First, different alkyl and aryl substituted groups on the nitrogen atom of 2-pyrrolidinon were compatible with the reaction conditions afforded the corresponding products with excellent yields (Scheme 2, **3a-3e**). Meanwhile, a single crystal of **3a** was obtained, and the product structure was further confirmed (Figure 1). Six-membered *α,β*-unsaturated cyclic amides reacted smoothly to provide the desired products (**3f-3g**) in good yields. Second, linear unsaturated amides with different substituted groups on the nitrogen atom or bearing H, Et, nBu, Bn on the α-position were also suitable substrates for the reaction and afforded the corresponding products **3l-o** with good yields (48-76%). It is noteworthy that phenyl substitution on the α-position was also tested under the reaction conditions, an eliminated product (azide substituted alkene) was formed. And it undergoes the second chloroazidation to provide the diazido chloride **3p**. Finally, under the similar reaction conditions, two *α,β*-unsaturated esters were tested, affording the corresponding adducts in satisfactory yields (**3q** and **3r**).

To further probe the potential scalability of this approach, a gram scale synthesis of chloroazide was carried. The reaction proceeded smoothly delivering **3l** in synthetically acceptable yield using only a 1 mol% catalyst loading (Scheme 3). The chloroazide **3l** could be converted into various derivatives. Reacting with phenyl acetylene afforded a 97% yield of the triazole product **5**. A vicinal diazide **6** was obtained with excellent yield by the treatment of **3l** with NaN_3 in DMSO at 75 °C. The azide moiety in **3l** was easily reduced by Pd/C and successfully afforded the valuable 2-chloro amine **7**. The chlorine group can also be readily transformed into the corresponding ester **8** in 86% yield.

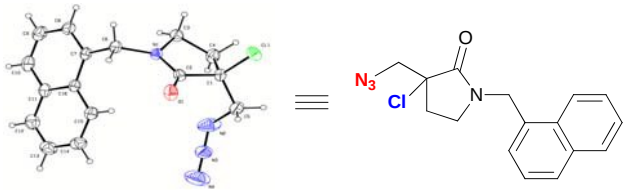
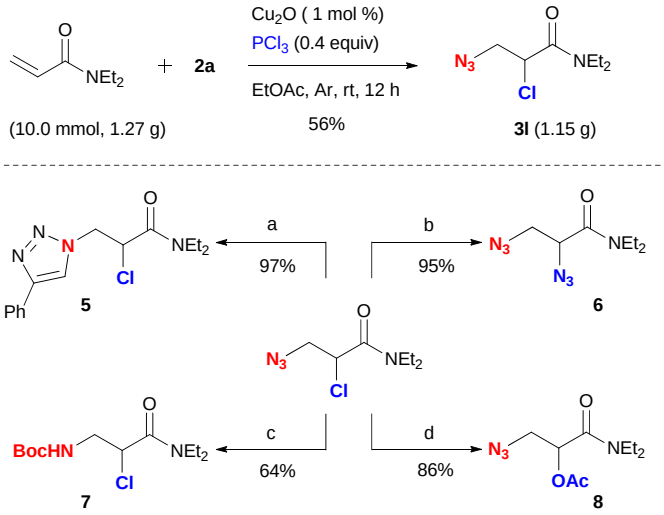
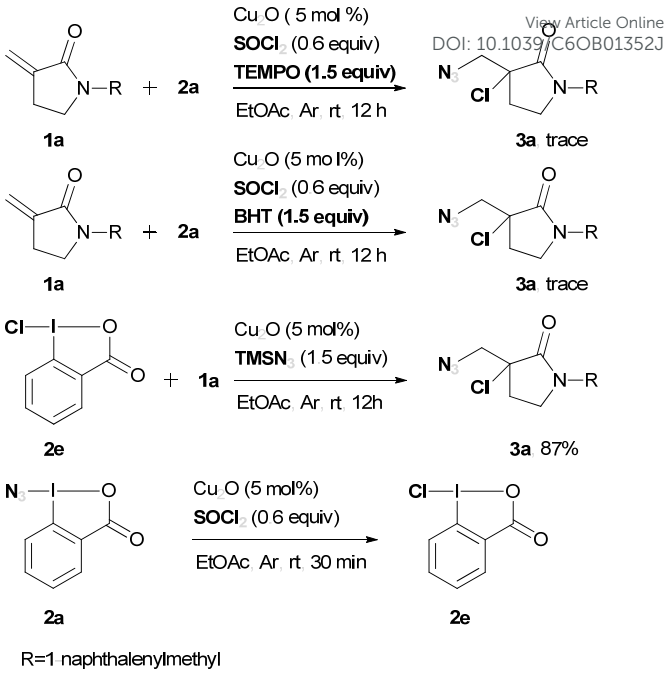


Figure 1 Crystal structure of **3a**.



Scheme 3 Scale-Up of Cu(I)-Catalyed chloroazidation and synthetic transformation. [a] Reaction conditions: (a) Phenyl acetylene (1.1 equiv), $CuSO_4{\cdot}5H_2O$, sodium ascorbate, THF/H_2O, rt, 12 h. (b) NaN_3 (1.5 equiv), DMSO, 75 °C, 4 h. (c) Pd/C, H_2 and $(Boc)_2O$, rt, 36 h. (d) NaOAc (1.5 equiv), DMF, 80 °C, 10 h.



Scheme 4 Mechanistic studies

To further investigate the mechanism of this reaction, several control experiments were conducted under the standard conditions (Scheme 4). When 1.5 equiv of radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) or BHT (2,6-di-tert-butyl-4-methylphenol) were respectively added to the reaction of **1a**, no desired product **3a** could be detected except a messy reaction system. These results may suggest that a radical process was possibly involved during the initial stage of this reaction. Moreover, the combination of chloroiodane(III) reagent **2e**, $TMSN_3$ and Cu_2O provided the same azidochloride product **3a** in 87% yield. Finally, we measured the ^1H NMR spectrum of crude reaction mixture that Zhdankin's reagent **2a** was treated in the absence of alkene **1a** after 30 min, only chloroiodane(III) reagent **2e** was obtained (see the ESI for details). It indicated that the chlorine azide (ClN_3) may be generated in the reaction mixture.[18c]

On the basis of the above results and related publications, a plausible mechanism of this intermolecular transformation is proposed (Scheme 5).[9-18] Initially, a copper catalyst activates Zhdankin's reagent **2a**, reacting with $SOCl_2$ to generate the intermediate **I**. Further decomposition of **I** affords Cu(I) species **II** with simultaneous release of the chlorine azide (ClN_3), which reacts with the alkene **1a** resulting in the radical intermediate **III**. Finally, the radical intermediate **III** was trapped by the

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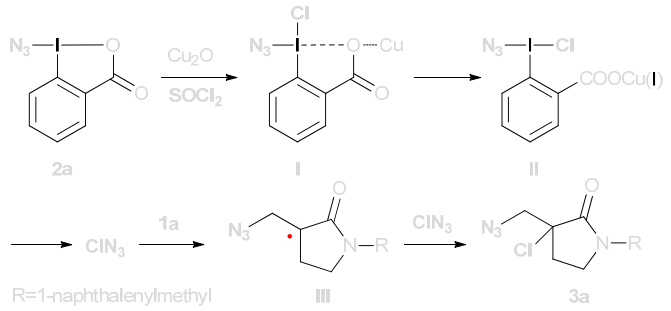

Scheme 5 Proposed reaction mechanism.

chlorine radical from ClN_3 to generate the final chloroazidation product **3a**.

In summary, we have developed an efficient and practical approach to construct chloroazides via copper catalyzed three component reaction of α,β-unsaturated amides under mild reaction conditions. The reaction takes advantage of the Zhdankin's reagent **2a** and $SOCl_2$ as azide and chlorine sources, respectively. The synthetic utility of the current method is also demonstrated by a variety of synthetically useful transformations. Further studies on the asymmetric version of the reaction and applications of this multicomponent reaction in organic synthesis are currently underway in our lab.

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