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Copper Nitrate Mediated Regio- and Stereoselective Difunctionalization of Alkynes: A Direct Approach to α-Chloro-β-nitroolefins

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Supporting Information

ABSTRACT: An efficient copper nitrate mediated chloronitration reaction was developed for the direct synthesis of α-chloro-β-nitroolefins with high regio- and stereoselectivity from simple alkynes and low toxic stannous chloride. This protocol provides a direct access to polysubstituted alkenes with operational simplicity, good functional group tolerance, and a wide substrate scope. Various applications of given products allowed the straightforward assembly of molecular complexity and indicated them as promising and valuable building blocks in organic synthesis.

Polysubstituted alkenes represent a class of versatile structural motifs that could easily be found in pharmacologically active compounds,[1a−c] natural products,[1b,d] or functional materials.[1e] Among them, α-chloro-β-nitroolefins occur as one of the most useful building blocks with respect to their exceptionally rich synthetic possibilities and various transformations of the functional groups. Considering their great synthetic value, previous methods for the synthesis of α-chloro-β-nitroolefins were mainly concentrated on the direct nitration of olefinic chloride with nitric acid,[2] elimination of hydrochloride from α-nitro dichlorides under basic conditions,[2c,3] or addition of alkynes using nitryl chloride or nitrosyl chloride as sources of chloro and nitro group.[4] However, these methods suffered from harsh reaction conditions or the use of highly toxic reagents, which is unbeneficial and unfriendly from the viewpoint of green chemistry and sustainable development. Transition-metal-promoted difunctionalization of alkynes has been widely investigated in the past several decades,[5] which could provide various polysubstituted alkenes with two distinct functional groups installed in one pot. Thus, the development of efficient syntheses of α-chloro-β-nitroolefins from readily available starting materials through a direct difunctionalization of alkynes will be an active and rewarding research area.

Copper nitrate has been proven to be an efficient catalyst in C−H activation;[6] in addition, it is also well-known as a common nitration reagent for arenes.[7] Recently, we have disclosed a novel [2+2+1] cyclization of alkynes and alkenes to isoxazolines,[8] where copper nitrate acts as both the activator of simple alkynes and the nitrogen source. Inspired by previous works, we envisioned synthesis of α-chloro-β-nitroolefins selectively from alkynes in the presence of a chloro source under the promotion of copper nitrate. Nevertheless, it will be a challenge to avoid the undesired formation of 1,3-diynes via Glaser−Hay homocoupling reaction[9] and the isoxazole byproducts that could be easily derived from the annulation of copper nitrate and alkynes (Scheme 1).[8] Also, more attention should be paid to the difunctionalization of alkynes in a regio- and stereoselective manner. Herein, we report a novel copper nitrate trihydrate mediated chloronitration reaction from simple alkynes and stannous chloride dihydrate to give polysubstituted (*E*)-α-chloro-β-nitroolefins selectively under mild conditions (Scheme 1). To the best of our knowledge, the given approach represents the first example for the copper-promoted difunctionalization of alkynes to α-chloro-β-nitroolefins with high regio- and stereoselectivities, where copper nitrate was employed to mediate the transformation of alkynes and as the nitro source with easily available low toxic stannous chloride as the crucial chlorine source.

Scheme 1. Copper Nitrate-Mediated Difunctionalization of Alkynes

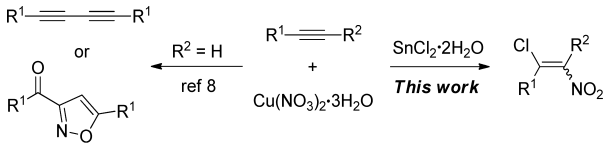

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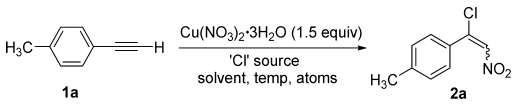
Table 1. Optimization of the Reaction Conditions[a]



1a 2a

entry	Cl source (X equiv)	solvent	temp (°C)	atm	time (h)	yield[b] (%)
1	NaCl (2)	CH_3CN	60	air	21	69 (85:15)
2	LiCl (2)	CH_3CN	60	air	21	50 (86:14)
3	$CuCl_2·2H_2O$ (1)	CH_3CN	60	air	7	66 (79:21)
4	CuCl (2)	CH_3CN	60	air	2	42 (73:27)
5	$FeCl_3$ (0.7)	CH_3CN	60	air	4	80 (85:15)
6	NCS (2)	CH_3CN	60	air	7	30 (31:69)
7	$SnCl_2·2H_2O$ (1)	CH_3CN	60	air	1	83 (84:16)
8	$SnCl_2·2H_2O$ (1)	toluene	60	air	1	trace
9	$SnCl_2·2H_2O$ (1)	DMF	60	air	1	0
10	$SnCl_2·2H_2O$ (1)	DMSO	60	air	1	0
11	$SnCl_2·2H_2O$ (1)	dioxane	60	air	1	52 (90:10)
12	$SnCl_2·2H_2O$ (1)	DCE	60	air	1	trace
13	$SnCl_2·2H_2O$ (1)	CH_3CN	40	air	4	85 (88:12)
14	$SnCl_2·2H_2O$ (1)	CH_3CN	30	air	8	81 (91:9)
15	**$SnCl_2·2H_2O$ (1)**	**CH_3CN**	**40**	**N_2**	**4**	**90 (88:12)**
16	$SnCl_2·2H_2O$ (1)	CH_3CN	40	O_2	4	50 (90:10)
17	$SnCl_2·2H_2O$ (1)	CH_3CN	40	N_2	4	85[c] (88:12)
18	$SnCl_2·2H_2O$ (1)	CH_3CN	40	N_2	4	85[d] (87:13)
19	$SnCl_2·2H_2O$ (1)	CH_3CN	40	N_2	4	43[e] (94:6)
20	$SnCl_2·2H_2O$ (1)	CH_3CN	40	N_2	4	0[f]

[a]Reaction conditions: **1a** (0.3 mmol), $Cu(NO_3)_2·3H_2O$ (0.45 mmol), Cl source (0.3 mmol), solvent (1.5 mL). DCE = 1,2-dichloroethane. NCS = *N*-chlorosuccinimide. [b]Isolated yield as mixture of *E*/*Z* isomers and the *E*/*Z* ratio given in the parenthese was determined by proton NMR. [c]$Cu(NO_3)_2·3H_2O$ (1.0 equiv) was used. [d]$Cu(NO_3)_2·3H_2O$ (2.0 equiv) was used. [e]$Fe(NO_3)_3·9H_2O$ (1.0 equiv) was used. [f]KNO_3 (3.0 equiv) was used.

At the outset of this study, we started our investigation by exploring the reaction of **1a** with copper nitrate trihydrate and sodium chloride in acetonitrile at 60 °C under air. Intriguingly, the desired product **2a** was isolated in 69% yield with *E*/*Z* selectivity as 85/15 after 21 h (entry 1, Table 1). Encouraged by this result, various Cl sources were tested, including LiCl, $CuCl_2·2H_2O$, CuCl, $FeCl_3$, NCS, and $SnCl_2·2H_2O$, and the stannous salt stood out as the superior choice due to its higher yield and selectivity with shorter reaction time (entries 2−7). Screening of solvents such as toluene, DMF, DMSO, dioxane, and DCE indicated acetonitrile to be the suitable choice (entries 8−12). The stereoselectivity was increased at lower temperature, albeit with prolonged reaction time (entries 13 and 14). Fortunately, the reaction conducted under nitrogen atmosphere at 40 °C afforded better results in high yield and good selectivity (entry 15), while low yield was observed under an oxygen atmosphere (entry 16). Reducing or increasing the amount of the copper salts failed to improve the reaction (entries 17 and 18). No reaction or less effective results could be observed when iron nitrate or potassium nitrate was used as the nitration reagent (entries 19 and 20), which indicated that the copper salt was crucial to the success of this reaction.

With the optimized conditions in hand, we next examined the substrate scope of alkynes. As illustrated in Scheme 2, a wide variety of substitution patterns and functional groups were tolerated. Aryl acetylenes bearing either electron-withdrawing or -donating groups in the *para* position of the aryl ring were smoothly converted into the corresponding products in moderate to excellent yields with excellent stereoselectivities (**2a**−**f**). Substrates containing different substitutions, such as alkyl (**2g**), alkoxy (**2k**), halides (**2h** and **2l**), nitrile (**2i**), and sulfamide (**2j**), were compatible with this reaction as well, regardless of their different electronic properties and *meta*- or *ortho*- substitutions. The newly established protocol was not limited to a simple monosubstituted benzene ring. For example, 3,4-dimethoxybenzene-containing trisubstituted alkene (**2m**) was obtained smoothly in the (*Z*)-form as the major product, and substrates bearing a naphthyl (**2n**) or thienyl (**2o**) group could also be transformed into the corresponding products in good yields. Notably, aliphatic alkynes with tertiary alcohol substitutions proceeded gradually to afford the corresponding alkenes with only one isomer isolated at increased reaction temperature (**2p** and **2q**), which may be due to the coordination of the hydroxyl group to the copper salt. Furthermore, success of this conversion could be further extended to triisopropylsilylacetylene, and the product with both chlorine and triisopropylsilyl groups assembled was obtained in moderate yield (**2r**), which implied it was the key intermediate for further transformations. Significantly, various internal alkynes afforded the corresponding tetrasubstituted alkenes in good yields, albeit in moderate stereoselectivities (**2s**−**u**). However, when SnF_2 or $SnBr_2$ was used as the halide source under the standard conditions, the reactions failed to afford the desired product or led to a complicated result. It should be noted that nitroalkene **3** could be synthesized in moderate yield through the given chloronitration reaction and successive Suzuki coupling reaction, which could be further transformed into pharmacologically interesting 3-aryl-substituted indole analogues (Scheme 3).[10]

A gram-scale synthesis of the product **2a** was next carried out under the standard conditions (Scheme 4). Pleasingly, the product could be isolated predominantly in its *E*-isomer in 76% yield, which could be further purified to give **2a** with single configuration through recrystallization. The identity of **2a** was determined by spectral analysis and further confirmed by X-ray crystallographic analysis.[11]

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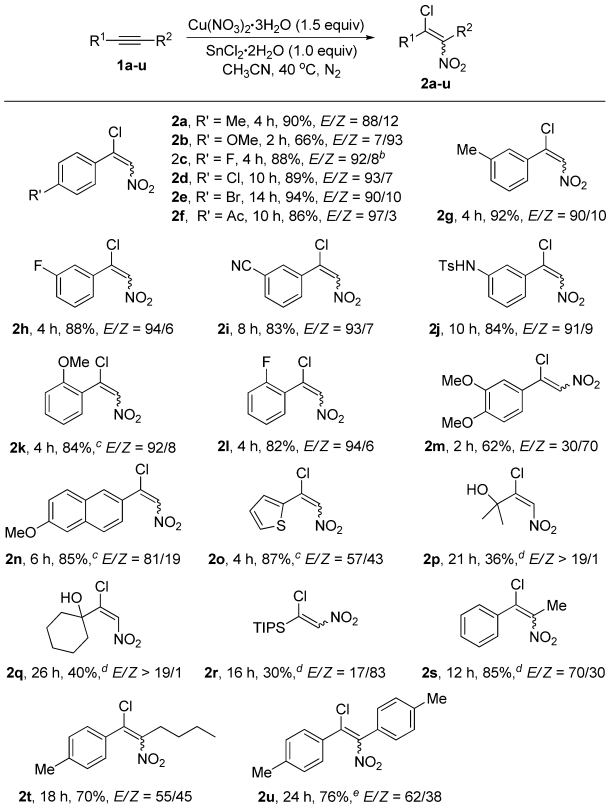
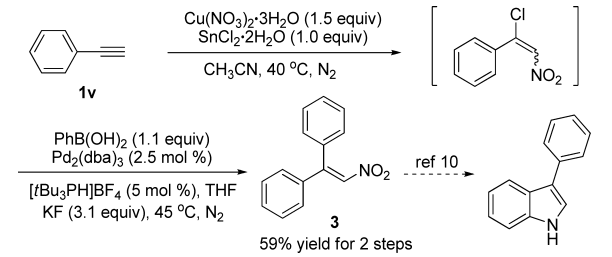
Scheme 2. Substrate Scope of Alkynes[a]

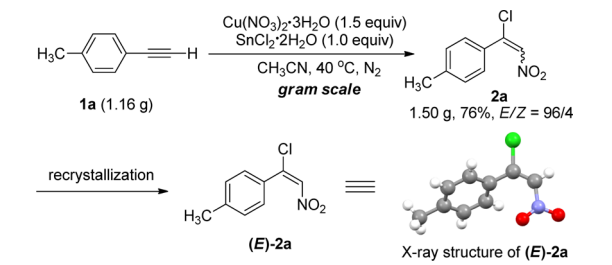


[a]Reaction conditions: **1** (0.3 mmol), $Cu(NO_3)_2{\cdot}3H_2O$ (0.45 mmol), $SnCl_2{\cdot}2H_2O$ (0.3 mmol), CH_3CN (1.5 mL), 40 °C, N_2 atmosphere. Isolated yield as mixture of *E*/*Z* isomers, and the *E*/*Z* ratio was determined by ^1H NMR spectroscopy. [b]The *E*/*Z* ratio was determined by ^{19}F NMR spectroscopy. [c]30 °C. [d]60 °C. [e]80 °C.

Scheme 3. Difunctionalization/Suzuki Stepwise Reaction

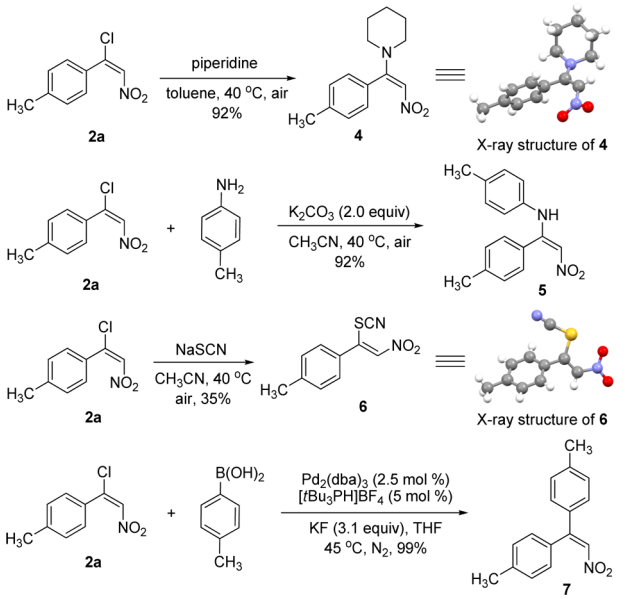


Scheme 4. Gram-Scale Reaction



To illustrate the synthetic utility and demonstrate the broad application prospect of the reaction, further transformations of given product were investigated (Scheme 5). A series of nucleophiles were first introduced. Intriguingly, products were isolated in (*E*)-form from nitrogen nucleophiles, such as aliphatic

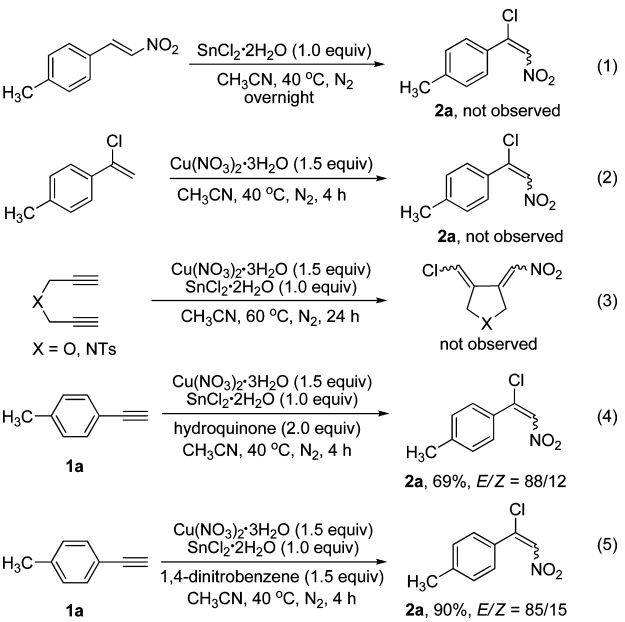
Scheme 5. Application of α-Chloro-β-nitroolefin Product



(**4**) or aryl amines (**5**), and the absolute configuration of **4** was further determined by X-ray crystallography.[11] The reason for the configuration retention may be attributed to an elimination−addition mechanism.[12] However, alkene **6** was obtained in (*Z*)-form when sodium thiocyanate was used as the nucleophile,[11] owing to a fast configuration rotation of the intermediate from the (*E*)- to (*Z*)-form.[13] Furthermore, the well-documented Suzuki reaction proceeded smoothly, with the corresponding product **7** obtained in almost quantitive yield.

To define the possible intermediates and pathway, several control experiments were carried out as shown in Scheme 6. The desired alkene product **2a** was not observed when β-nitro- (eq 1) or α-chloro- (eq 2) substituted alkene was used as starting material in the absence of copper nitrate or stannous chloride, which suggested that the above two proposed intermediates could be

Scheme 6. Mechanistic Studies



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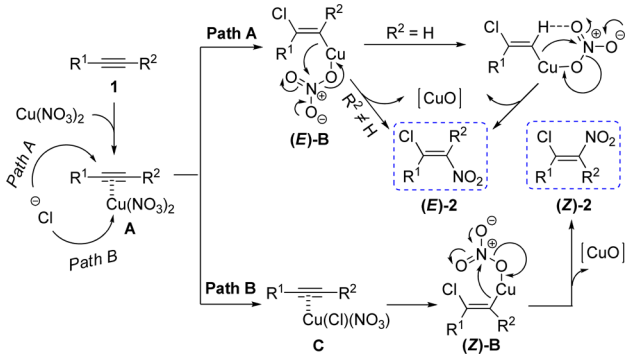
Scheme 7. Plausible Mechanism (Ligands Are Omitted for Clarity)



excluded for this reaction. Considering the fact that no cyclic products could be formed from dipropargyl ether or amine (eq 3),[14] as well as the results that the reaction was not inhibited with the addition of hydroquinone (eq 4) or 1,4-dinitrobenzene (eq 5), we could rule out the possibility of a radical pathway.

Although the detailed reaction pathway remained to be clarified, a plausible mechanism for this reaction was proposed on the basis of above results (Scheme 7). Initially, copper nitrate was coordinated to the C≡C triple bond of alkyne to give complex **A**. In most cases, the activated C≡C triple bond was attacked by the Cl ion generated from $SnCl_2$ and achieve the intermediate (***E***)-**B** (path A), which afforded alkene (***E***)-**2** as the major product through the [1,3]-shift of the nitro group.[8] Notably, intermediate (***E***)-**B** could be stabilized by a six-membered intramolecular hydrogen-bonding interaction (R^2 = H).[15] However, for substrates with strong electron-donating groups (**1b** and **1m** in Scheme 2), a ligand exchange between Cl and nitrate ions occurred predominately to give complex **C** (path B), which led to the formation of complexed adduct (***Z***)-**B** through *cis*-insertion and finally afforded (***Z***)-**2** as the major product.

In summary, we have described a novel and efficient copper nitrate mediated approach for the direct access of synthetic interesting polysubstituted α-chloro-β-nitroolefins from simple alkynes and low toxic stannous chloride. The reaction featured a wide substrate scope with functional groups tolerated. Various applications of given products allowed the straightforward assembly of molecular complexity and indicated them as promising and valuable building blocks in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02464.

Experimental procedures and characterization data for all compounds (PDF)
X-ray data for compound (***E***)-**2a** (CIF)
X-ray data for compound **4** (CIF)
X-ray data for compound **6** (CIF)

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Notes

The authors declare no competing financial interest.

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