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Au-Catalyzed Stereoselective Ritter Reaction of Haloalkynes with Nitriles for (*Z*)-β-Halogenated Enamides

Congrong Liu*[a] and Fulai Yang*[b]

Abstract: An efficient and stereoselective protocol has been developed for the synthesis of (*Z*)-β-halogenated enamide through gold catalyzed Ritter reaction. In the presence of 2 mol% BrettPhosAuCl and 2 mol% $AgNTf_2$, a broad range of nitriles smoothly underwent Ritter reaction with aromatic, vinylic or aliphatic haloalkynes to give structurally diverse (*Z*)-β-halogenated enamides in excellent to good yields.

Introduction

Enamides, endowed with a fine reactivity and balance of stability, have emerged frequently as nucleophiles in a manifold of organic reactions.[1] In this respect, β-halogenated enamides are valuable building blocks in organic synthesis.[2,3] They not only constitute versatile intermediates in the construction of biologically active natural products but also serve as key precursors in the synthesis of a variety of pharmaceuticals. For example, they readily undergo addition reactions and cross-coupling reactions and are useful precursors of heterocycles. So developing efficient synthetic approaches to construct differently substituted β-halogenated enamides is one of the most exciting topics in organic synthesis.[4,5] Recently, Jiang and co-workers reported palladium-catalyzed dehydrogenative aminohalogenation of alkenes with molecular oxygen as the sole oxidant.[5d] In 2014, Zhang et al. described an alkyne aminohalogenation enabled by DBU-activated *N*-haloimides.[4i] In spite of the versatility and efficiency of this transformation in this area, significant limitations still exist. For instance, the nitrogen sources have been limited to aromatic amines,[5e,6] carbamates,[7] sulfonamides[8] and amides[9] so far. Simple nitriles have not yet been successfully used as the nitrogen source in the synthesis of β-halogenated enamides.

The Ritter reaction, in which nitriles function as a nitrogen source, is a simple and one-pot synthetic method for preparing *N*-acyl-protected amines.[10] The classical Ritter reaction employs alcohols and alkenes as starting materials.[11] Recent years, carboxylic acids were also applied in the Ritter reaction, which was first described by Minakata et al.[12] Although Ritter reaction has versatile applications in organic chemistry, there are no examples describing the reaction of nitriles with haloalkynes. Herein, we report an efficient and facile method for the synthesis of β-halogenated enamides via Au-catalyzed stereoselective Ritter reaction of nitriles with haloalkynes.

Results and Discussion

We commenced our study by investigating the Au-catalyzed Ritter reaction of phenylethynyl chloride (**1a**) and acetonitrile (**2a**) at 50°C (Table 1). Initially, we treated phenylethynyl chloride with acetonitrile and 2 mol% $IPrAuNTf_2$ without adding water, no desired product (*Z*)-**3aa** was found. We adjusted the amount of water and the yield reached 79 % when 1.0 eq water was added (Table 1, entry 4). The use of $Ph_3PAuOTf$, $Et_3PAuNTf_2$, L_1AuNTf_2 and $Ph_3PAuNTf_2$ as the catalyst led to decreased efficiency (Table 1, entries 6–9). Because LAuCl is rock stable and inactive in Au^I, the labile counterion must be added. The combination of BrettPhosAuCl and $AgNTf_2$ resulted in 85 % yield (Table 1, entry 13). However, replacing NTf_2^- with other counter anions led to decreased yields (Table 1, entries 15–17). Increasing the reaction temperature the yield was decreased slightly (Table 1, entry 18). In addition, a gram-scale synthesis of (*Z*)-**3aa** (1.68 g, 86 % yield) was successfully performed according to this protocol.

After establishing the optimized conditions (Table 1, entry 9), we evaluated the substrate scope of this transformation. The optimized reaction conditions were found to be suitable to a broad range of haloalkynes (Table 2). A number of arylethynyl chloride bearing either electron-donating groups or electron-withdrawing groups on the *ortho*-, *meta*- or *para*-positions of the aromatic rings were transformed into their corresponding (*Z*)-β-halogenated enamides at 50 °C in excellent to good yields (Table 2, entries 1–10). Subsequently, 2-(2-chloroethynyl)-naphthalene reacted efficiently to afford (*Z*)-β-chlorogenated enamides **3ka** in an excellent 95 % yield (Table entry 11). In addition, vinylic or aliphatic chloroalkynes also participated well in this reaction to afford the corresponding products **3la**, **3ma** and **3na** in 80 %, 82 % and 79 % yields, respectively (Table 2, entries 12–14). Notably, bromoalkyne can also undergo the

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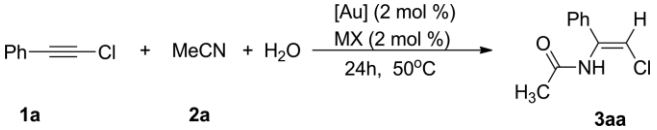
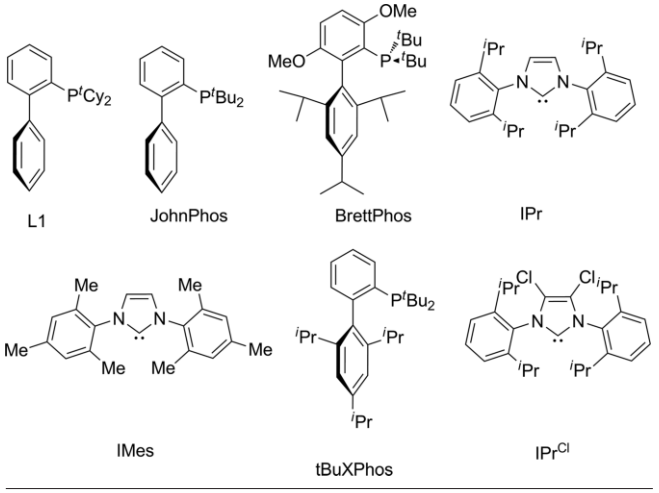
Table 1. Initial reaction conditions optimization.[a]



1a 2a 3aa

Entry	[Au] (2 mol-%)	MX (2 mol-%)	Yield [%][b]
1[c]	$IPrAuNTf_2$		0
2[d]	$IPrAuNTf_2$		22
3[e]	$IPrAuNTf_2$		41
4	$IPrAuNTf_2$		79
5[f]	$IPrAuNTf_2$		67
6	$Ph_3PAuOTf$		29
7	$Ph_3PAu\ NTf_2$		38
8	$Et_3PAuNTf_2$		47
9	L_1AuNTf_2		60
10	JohnphosAuCl	$AgNTf_2$	80
11	IMesAuCl	$AgNTf_2$	63
12	*t*BuXPhosAuCl	$AgNTf_2$	70
13	**BrettPhosAuCl**	**$AgNTf_2$**	**85**
14	IPrClAuCl	$AgNTf_2$	75
15	BrettPhosAuCl	NaBARF	13
16	BrettPhosAuCl	AgOTf	76
17	BrettPhosAuCl	$AgSbF_6$	68
18[g]	BrettPhosAuCl	$AgNTf_2$	79

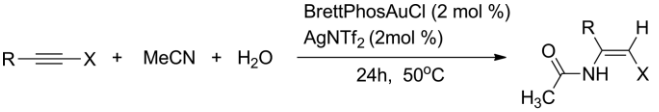


[a] Reaction conditions: phenylethynyl chloride **1a** (0.4 mmol), MeCN **2a** (0.5 mL), water 0.4 mmol, [Au] (2 mol-%), MX (2 mol-%), 50 °C. [b] Isolated yield. [c] No water added. [d] Water 0.1 mmol. [e] Water 0.2 mmol. [f] Water 0.5 mmol. [g] 70 °C.

Ritter reaction, albeit less efficient than its chloro counterpart (Table 2, entries 15–18). However, the corresponding iodoalkyne led to no corresponding product **3sa** (Table 2, entry 16).

To further determine the scope of the procedure, the next various nitriles were investigated, and the results are shown in Table 3. Considering that other nitriles are not as cheap as acetonitrile, we used 1,2-dichloroethane as solvent to reduce the amount of nitrile to 0.1 mL. Table 3 showed that most nitriles could react with phenylethynyl chloride (**1a**) to afford the corresponding (*Z*)-β-chlorogenated enamides **3** with excellent to good yields. It was found that 2-bromoacetonitrile afforded the corresponding (*Z*)-β-chlorogenated enamide (**3ac**) in a slightly low yield with 75 % (Table 3, entry 2). It may be that the electron-withdrawing effect of bromine reduces the nucleophilicity of nitrile. Similarly, we also found that 2-methylbenzonitrile afforded the corresponding compound (**3aj**) in a low yield with 69 % (Table 3, entry 2). This may be due to the steric hindrance of *ortho*-position (Table 3, entry 9).

Table 2. Gold catalyzed Ritter reaction of haloalkyne **1** with acetonitrile **2a**.[a]



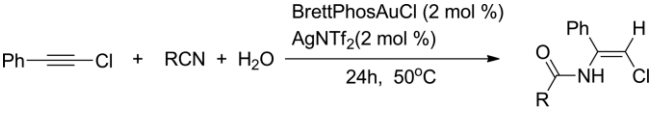
1 2a 3

Entry	**1**, R	X	**3**	Yield [%][b]
1	**1a**, C_6H_5	Cl	**3aa**	85
2	**1b**, 2-Cl C_6H_4	Cl	**3ba**	69
3	**1c**, 2-Br C_6H_4	Cl	**3ca**	61
4	**1d**, 2-MeC_6H_4	Cl	**3da**	80
5	**1e**, 4-Me C_6H_4	Cl	**3ea**	90
6	**1f**, 4-MeO C_6H_4	Cl	**3fa**	86
7	**1g**, 4-Ph C_6H_4	Cl	**3ga**	92
8	**1h**, 4- BrC_6H_4	Cl	**3ha**	83
9	**1i**, 3,5-$Cl_2C_6H_3$	Cl	**3ia**	80
10	**1j**, 2,4,6-Me_3 C_6H_2	Cl	**3ja**	70
11	**1k**, 2-naphthyl	Cl	**3ka**	95
12	**1l**, 1-cyclohexenyl	Cl	**3la**	80
13	**1m**, BnOCOCH=CH	Cl	**3ma**	82
14	**1n**, cyclopropyl	Cl	**3na**	79
15	**1o**, C_6H_5	Br	**3oa**	68
16	**1p**, 4-Ph C_6H_5	Br	**3pa**	77
17	**1q**, 2-naphthyl	Br	**3qa**	84
18	**1r**, 1-cyclohexenyl	Br	**3ra**	60
19	**1s**, C_6H_5	I	**3sa**	0

[a] Reaction conditions: Chloroalkyne **1** (0.40 mmol), MeCN **2a** (0.50 mL), water 0.4 mmol, BrettphosAuCl (2 mol-%), $AgNTf_2$ (2 mol-%), 50 °C. [b] Isolated yield.

On the basis of our results and previous relevant mechanistic studies,[10d, 11, 12] a mechanism for the gold-catalyzed Ritter reaction of haloalkynes with nitriles was proposed, as shown in Scheme 1. The gold-activated haloalkyne **4** or its polarized resonance structure **4′** is attacked by the nitrogen atom of nitrile from the direction of small steric hindrance. The alkenyl gold

Table 3. Gold catalyzed Ritter reaction of phenylethynyl chloride **1a** with nitrile **2a**.[a]

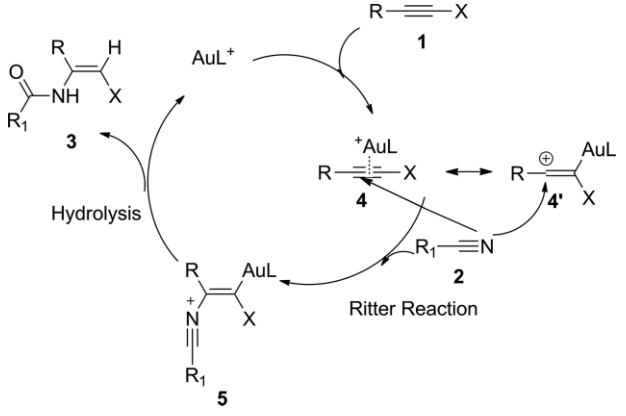


1a 2 3

Entry	**2**, R	**3**	Yield [%][b]
1	**2b**, C_2H_5	**3ab**	88 %
2	**2c**, $BrCH_2$	**3ac**	75 %
3	**2d**, $ClCH_2CH_2$	**3ad**	83 %
4	**2e**, $BrCH_2CH_2$	**3ae**	87 %
5	**2f**, *i*Pr	**3af**	81 %
6	**2g**, cyclohexyl	**3ag**	90 %
7	**2h**, C_6H_5	**3ah**	92 %
8	**2i**, 4-BrC_6H_4	**3ai**	84 %
9	**2j**, 2-$CH_3C_6H_4$	**3aj**	69 %

[a] Reaction conditions: phenylethynyl chloride **1a** (0.40 mmol), nitrile **2** (0.10 mL), water 0.4 mmol, 1,2-dichloroethane (0.4 mL), BrettphosAuCl (2 mol-%), $AgNTf_2$(2 mol-%), 50 °C. [b] Isolated yield.

intermediate **5** is generated, then followed a hydrolysis and proton transfer to afford (*Z*)-β-halogenated enamide **3** and regenerate the Au(I) catalyst. We believe the terminal halo group is critical for the Ritter reaction of haloalkynes with nitriles. As the inductively electron-withdrawing nature of X makes the alkyne gold complex **4**/**4′** more polarized and hence more reactive to react with nitriles.



Scheme 1. Proposed mechanism for Au-catalyzed Ritter reaction of haloalkynes with nitriles.

Conclusions

In conclusion, we developed an efficient and stereoselective protocol for the synthesis (*Z*)-β-halogenated enamide via gold catalyzed Ritter reaction. In the presence of 2 mol-% BrettPhosAuCl and 2 mol-% $AgNTf_2$, a variety of (*Z*)-β-halogenated enamide bearing different functional groups can be prepared in excellent to good yields. The current study is focusing on the synthesis of biologically important N-containing molecules using this method.

Experimental Section

General Information: ^1H and ^{13}C NMR Spectra were recorded on a Bruker AC-500 FT spectrometer (500 MHz and 100 MHz, respectively) using tetramethylsilane as internal reference. Chemical shifts (δ) and coupling constants (*J*) were expressed in ppm and Hz, respectively. IR spectra were recorded on a Perkin-Elmer 2000 FTIR spectrometer. High resolution mass spectra were recorded on a LC-TOF spectrometer (Micromass). the UV detection was monitored at 254 nm. Melting points were uncorrected.

General Procedure for the Gold Catalyzed Ritter Reaction of Haloalkynes with Acetonitrile (Table 2)**:** To a solution of haloalkyne **1** (0.40 mmol) in acetonitrile (0. 14 mL) were added BrettPhosAuCl (6.24 mg, 0.0080 mmol) and $AgNTf_2$ (3.11 mg, 0.0080 mmol) subsequently. The mixture was stired at 50 °C for 10 min. MeCN/H_2O (0.37 mL, 50:1) was then added dropwise over 20 minutes. The resulting mixture was stirred at 50 °C for 23.5 h. The mixture was cooled to room temperature, and purified by silica gel column chromatography, eluting with petroleum ether/ethyl acetate (10:1 to 4:1), to give β-halogenated enamides **3**.

General Procedure for the Gold Catalyzed Ritter Reaction of Phenylethynyl Chloride with Nitriles (Table 3)**:** To a solution of phenylethynyl chloride **1a** (0.40 mmol) in DCE (0.40 mL) were added BrettPhosAuCl (6.24 mg, 0.0080 mmol) and $AgNTf_2$ (3.11 mg, 0.0080 mmol) subsequently. The mixture was stired at 50 °C for 10 min. Nitrile/H_2O (0.11 mL, 14:1) was then added dropwise over 20 minutes. The resulting mixture was stirred at 50 °C for 23.5 h. The mixture was cooled to room temperature, and purified by silica gel column chromatography, eluting with petroleum ether/ethyl acetate (10:1 to 4:1), to give β-chlorogenated enamides **3**.

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Keywords: Halogenated enamide · Ritter reaction · Gold catalysis · Stereoselectivity · Chloroalkyne

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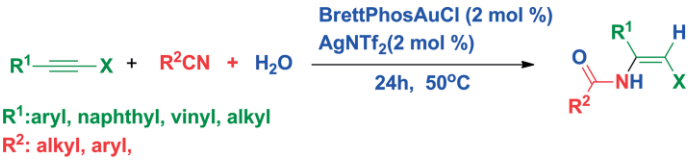

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