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$Bi(OTf)_3$-catalyed one-pot synthesis of α-halo-β-amino ketones and acyl aziridines from 3-aryl propargyl alcohols

Qinglin Zhang,[a] Yongbin Duan,[a] Huifeng Guo,[a] Hong Yang,[a] Jiulong Zhai,[a] Tiantian Li,[a] Zhihai, Wang,[a] Xiaolei Lu,[a] Yan Wang[a] and Yan Yin[a,b]*

[a] Department of Chemical and Environmental Engineering, Shanghai Institute of Technology, 201418, 100 Hai Quan Rd., Shanghai, PR China.
[b] Shanghai Key Laboratory of Chemical Assessment and Sustainability, Tongji University, 200092, 1239 Si Ping Rd, Shanghai, PR China.
Email: yinyan@sit.edu.cn (Y. Yin)

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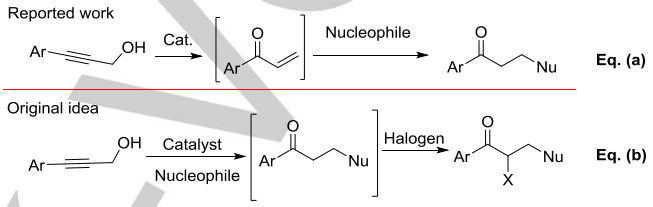
Abstract: $Bi(OTf)_3$-catalyed reaction of 3-aryl propargyl alcohols with sulfonamide and halogen source was firstly investigated, which provided a facile route for the synthesis of a large variety of α-halo-β-amino ketones. The key intermediates, β-amino ketones, were obtained through tandem Meyer-Schuster rearrangement reaction of propargyl alcohols and intermolecular Michael addition of α, β-unsaturated ketones and sulfonamide. Then the in situ generated α-halo-β-amino ketones underwent the base-promoted intramolecular cyclization to give diverse acyl aziridines in a one-pot fashion. These transformations are reliable on a large scale. The high yields and convenient experimental operations make it a valuable method for the construction of α-halo-β-amino ketones and acyl aziridine derivatives.

Introduction

Aziridinyl ketone is a versatile building block for it undergo various transformation to provide diverse amine derivatives.[1] Thus, a large number of methods for its synthesis have been developed, such as aziridination of vinyl ketones using $SESN_3$,[2] synthesis of NH aziridines from 2-azidoallyl alcohols,[3] direct transformation of propargylic N-hydroxylamines to acylaziridines,[4] rearrangement of isoxazolines,[5] and aziridination of chalcones[6] or vicinal haloamines.[7] Although chemists have made great achievements in the synthesis of acyl aziridines in the past few decades, but these methods have more or less defects. It is still of great significance to develop a simple and efficient method to synthesize them.

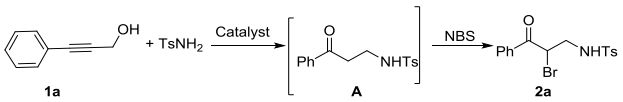
Acyl vicinal haloamine is a versatile building block in organic synthesis by replacement of halogen with multifarious nucleophiles.[8] A number of synthetic strategies have been developed to furnish this functionality.[9] Undoubtedly, the synthesis of vicinal haloamino carbonyl compounds from chalcones have been well documented in the last decades, but the examples of regioselective aminohalogenation of chalcones to deliver α-halo-β-amino carbonyl compounds are seldom reported.[10]

Previously, our group reported the synthesis of acyclic/cyclic β-aminoketones and β-carbonyl thioethers from 3-aryl propargyl alcohols, which probable proceeded a acid-catalyzed Meyer-Schuster rearrangement of 3-aryl propargyl alcohols, followed by a inter/intramolecular addition between nucleophiles and α, β-unsaturated ketones[11] (**Scheme 1, Eq. (a)**). It is well known that β-aminoketones are easy to undergo halogenation reaction at α postion of carbonyl group. We guess that the addition of halogen source to in situ generated β-aminoketones will extremely access the versatile α-halo-β-amino ketones as the sole product (**Scheme 1. Eq. (b)**).



Scheme 1. Conversion of propargyl alcohols

As a continuous efforts on the transformation of propargyl alcohols, we refluxed the mixture of 3-phenyl propargylic alcohol **1a**, catalyst, $TsNH_2$, and NBS. Unfortunately, this treatment only led to a small amount of halogenated product **2a**. We then delay the addition of NBS until the complete conversation of **1a** to β-amino ketone derivative **A**. As expected **2a** was accessed in good yield probably through a sequence rearrangement, addition, and halogenation reaction (**Scheme 2**). Herein, we describe a new, versatile, and general synthetic method of α-halo-β-amino ketones from propargyl alcohols, as well as the further conversion applications of α-halo-β-amino ketones to acyl aziridines.



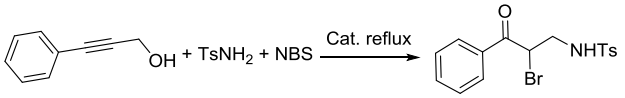
Scheme 2. Synthesis of α-halo-β-amino ketones from propargyl alcohols

Results and Discussion

For the efficient access to α-halo-β-amino ketone derivatives, the reaction conditions were optimized with **1a**, $TsNH_2$, and NBS as the model reaction substrates (Table 1). Optimization indicated that 2 equivalence of $TsNH_2$ as the nitrogen nucleophile, 1.5 equivalence of NBS as the halogen source, and dioxane as solvent were good. Catalyzed with 20 mol% of acids including TfOH, AgOTf, $Cu(OTf)_2$, or $Sc(OTf)_3$ **2a** were separated in moderate yields (entries 1-4). Treating with 20 mol% of $Bi(OTf)_3$ or $Fe(OTf)_3$, **2a** were obtained in 92% and 90% yields after 22hs and 42hs, respectively (entries 5 and 6). Catalyst loading studies showed that 3 mol% of $Bi(OTf)_3$ cause lower yield of **2a,** and 20 mol% and 10 mol% of $Bi(OTf)_3$ had the

similar yields and times of reaction as 5 mol% of $Bi(OTf)_3$ (entries 6, 7, and 9 vs. 8). Out of our expectation, no dimeric diketone was separated while decreasing catalyst loading to 5 mol%. So the optimized reaction conditions for this transformation were: **1a** (1 equiv.), $TsNH_2$ (2 equiv.), $Bi(OTf)_3$ (0.05 equiv.), dioxane (0.5 mL), reflux; then NBS (1.5 equiv.), reflux.

Table 1. Optimization of the reaction conditions [a]



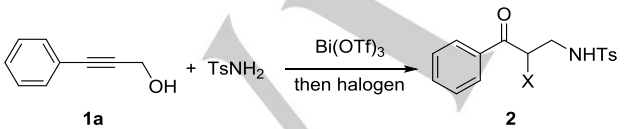
1a **2a**

Entry	Catalyst	Catalyst loading (mol%)	Time (h)	Yield of **2a**[b]
1	TfOH	20	42	58
2	AgOTf	20	42	55
3	$Cu(OTf)_2$	20	42	55
4	$Sc(OTf)_3$	20	42	50
5	$Fe(OTf)_3$	20	42	90
6	$Bi(OTf)_3$	20	20	92
7	$Bi(OTf)_3$	10	21	92
8	**$Bi(OTf)_3$**	**5**	**22**	**92**
9	$Bi(OTf)_3$	3	48	86

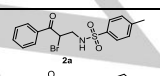
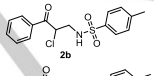
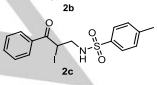
[a]Reaction conditions: **1a** (0.2 mmol), $TsNH_2$ (0.4 mmol), dioxane (0.5 mL), reflux; then NBS (0.3 mmol), reflux. [b]Isolated yield after flash chromatography.

The effect of halogen sources on the transformation of **1a** to α-halo-β-amino ketones was then investigated. Although α-chloro and α-iodo substituted β-amino ketones were obtained in 90% yield while NCS and NIS were treated as the halogen sources, the halogenation rates among them were obvious different, and 16 h, 22h, and 25 h were needed for **2c** with I, **2a** with Br, and **2b** with Cl, respectively (entries 1-3). However, no expected α-fluoro product was separated while N-fluorobisphenylsulfonamide (NFSI) was used (entry 4). The reaction with I_2 and Br_2 gave **2c** and **2a** in both 85% yields (entries 5 and 6). Considering the convenience of operation and environmental friendliness, NBS was used as the halogen sources for the further investigations although the halogenation reaction with NBS is not so fast as halogen elements.

Table 2. The effect of halogen sources on the transformation of **1a** to α-halo-β-amino ketones [a]



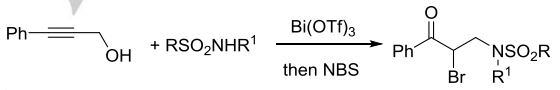
1a **2**

Entry	Halogen	Product	Time (h)	Yield (%)[b]
1	NBS		22	92
2	NCS		25	90
3	NIS		16	90
4	NFSI	NR	30	
5	I_2	**2c**	8	60
6	Br_2	**2a**	8	60

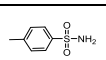
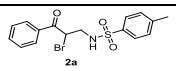
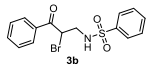
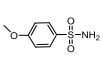
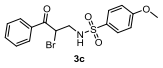
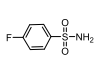
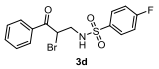
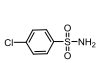
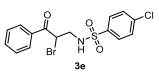
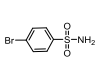
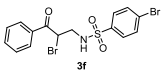
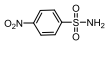
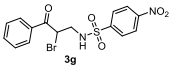
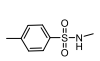
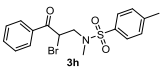
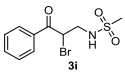
[a] Reaction conditions: **1a** (0.2 mmol), $TsNH_2$ (0.4 mmol), $Bi(OTf)_3$ (0.01mmol), dioxane (0.5 mL), reflux. Then halogen (0.3 mmol), reflux. [b] Isolated yield after flash chromatography.

Our previous studies on the acid-catalyzed reaction of propargyl alcohols and nitrogen nucleophilis indicated that nucleophilicity of nitrogen nucleophilis had dominant effect on the reaction, and only sulfonamides were well tolerated and afforded the corresponding β-amino ketones in high yields.[11b] So, the effec of sulfonamides on the transformation of **1a** to α-bromo-β-amino ketones was then invesigated, and the resutls indicated that all sulfonamides underwent this reaction smoothly and led to corresponding α-bromo-β-amino ketones in 51-92% yields (Table 3). Although increasing the nucleophilicity of benzenesulfonamides resulted in higher reaction rate in both the formation and transformation stages of β-amino ketones, but benzenesulfonamides with 4-OCH_3 gave much lower yield compared with benzenesulfonamides with 4-CH_3, 4-H, 4-F, 4-Cl, and 4-Br. Benzenesulfonamides with 4-NO_2 exhibited the worst time and yield of reaction. Bulky secondary arylsulfonamides could be employed for this reaction as the primary arylsulfonamides, and $TsNHCH_3$ gave **3h** in 92% yield after refluxing 28 h. $CH_3SO_2NH_2$, an alkyl sulfonamide, also underwent this reaction smoothly and gave **3i** in the yield of 85%.

Table 3. Effect of sulfonamides on the transformation of **1a** to α-bromo-β-amino ketones [a]

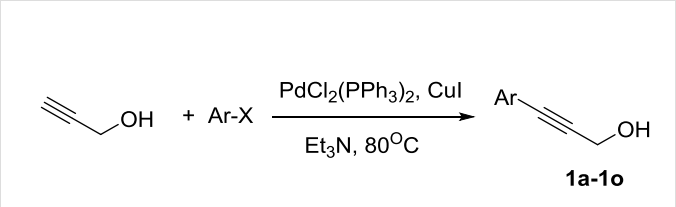


1a **2a, 3b-3i**

Entry	RSO_2NHR^1	Product	Time (h)	Yield (%)[b]
1		 **2a**	22	92
2		 **3b**	24	91
3		 **3c**	3	65
4		 **3d**	26	68
5		 **3e**	24	75
6		 **3f**	24	78
7		 **3g**	41	51
8		 **3h**	28	92
9		 **3i**	25	85

[a]Reaction conditions: **1a** (0.2 mmol), sulfonamide (0.4 mmol), $Bi(OTf)_3$ (0.01 mmol), dioxane (0.5 mL), reflux. Then NBS (0.3 mmol), reflux. [b]Isolated yield after flash chromatography.

Previous studies also indicated that only primary 3-aryl propargyl alcohols underwent the transformation smoothly and led to β-amino ketones in high yields. Propargyl alcohols with bulky group α to -OH, and 3-phenylprop-2-yn-1-ols with 4-NO_2 or 4-CN were not tolerated for this trasformation of β-amino ketones.[11b] So, a series of primary 3-aryl propargyl alcohols **1a**-**1o** were prepared through a Pd^{2+}-catalyzed Sonogashira coupling reaction of Ar-X and commercial available prop-2-yn-1-ol (Scheme 3),[11, 12] and the scope was explored for the one-pot synthesis of α-bromo-β-amino ketones from propargyl alcohols **1** with $TsNH_2$ as the nucleophile and NBS as the halogen source (Table 4).

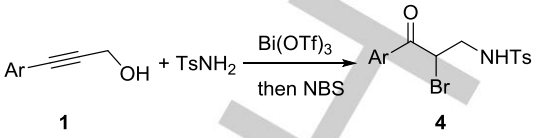


Scheme 3. Synthesis of 3-aryl propargyl alcohols **1**

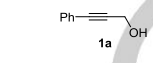
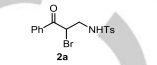
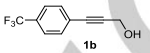
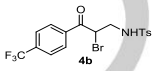
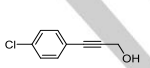
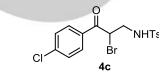
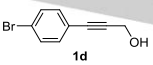
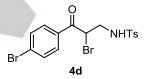
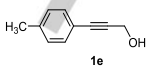
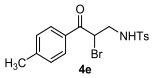
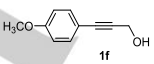
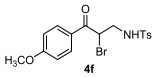
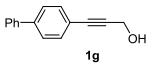
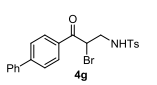
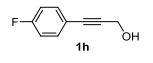
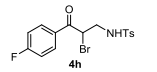
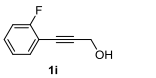
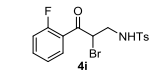
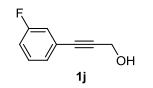
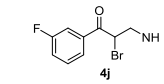
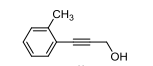
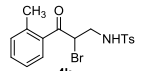
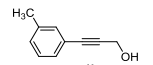
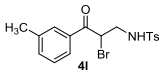
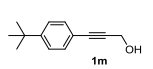
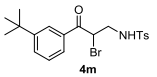
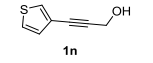
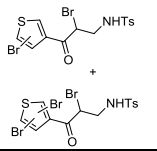
The substituents at the 4-position of the phenyl ring had obvious effects on the times and yields of reaction. The reaction of **1b** with CF_3 was mess and **4b** was obtained in only 20% yield, and a dimeric diketone via self-coupling of intermediate α, β-unsaturated ketones was detected. **1c** with para chlorine, **1d** with para bromine, and **1i** with ortho fluorine finished the conversation in good yields after refluxing longer times compared with **1a** (85% yield for **1c** in 33 h, 85% yield for **1d** in 30 h, and 80% yield for **1i** in 28 h). Substrates (**1e**, **1k**, and **1l**) with para, ortho, and meta methyl group showed similar reactivity to **1a**. Methoxyl and phenyl groups at para position of the phenyl ring were favorable for the reaction rate because of the higher electron density of carbon-carbon triple bond, and **4f** and **4g** were achieved in 2 h and 3 h, respectively. It is worth noting that the reaction of **1h** and **1j** with para and meta fluorine proceeded faster than **1c** and **1d** probably because of the complex interactions existing in **1h** and **1j**.[13] Steric hindrance group at the para position of the phenyl ring did no decrease the reaction, and **4m** was separated in yield of 90% after 6 h. Changing the aromatic group at the carbon-carbon triple bond from phenyl group to naphthyl, and thienyl groups were tolerated and led to **4n** and **4o** in high yields, although **4o** were brominated products on the thiophene ring. However, the expected products were not detected when the Ar groups in **1** were replaced by pyridyl, methyl, or ethyl groups. The reaction of 2-methyl-4-phenylbut-3-yn-2-ol was mess according to TLC detection and no targeted product was separated.

The reaction times should be highly dependent on the substituent of aryl propargyl alcohol. Indeed, the competition experiments between propargyl alcohol **1e** with an electron-donating CH_3 group and **1d** with an electron-withdrawing Br group under standard reaction conditions indicated that the reaction rate of **1e** is faster than that of **1d**, the ratio of yield was **4d**:**4e** =2:3 after 15 hours while **1d**:**1e** = 1:1 equiv.

Table 4: Scope investigation on the transformation of propargyl alcohols **1** to α-bromo-β-amino ketones[a]



1 4

Entry	Alcohols	Products	Time (h)	Yield (%)[b]
1			22	92
2			45	20
3			33	85
4			30	85
5			15	90
6			2	50
7			3	55
8			4	85
9			28	80
10			11	83
11			14	89
12			14	90
13			6	90
14			10	79

[a]Reaction conditions: Alcohol **1** (0.2 mmol), $TsNH_2$ (0.4 mmol), $Bi(OTf)_3$ (0.01 mmol), dioxane (0.5 mL), reflux. Then NBS (0.3 mmol), reflux. [b]Isolated yield after flash chromatography.

Fortunately, the product **4d** was recrystallized from a mixture of petroleum ether and ethyl acetate as a colorless crystal, and the X-ray crystallography of **4d** confirmed the molecular structure of α-bromo-β-amino enones (Figure 1).

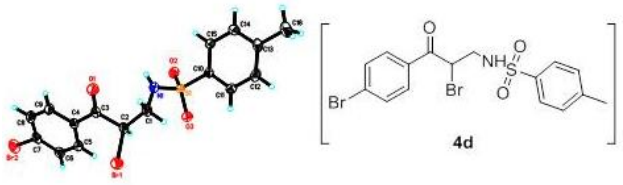
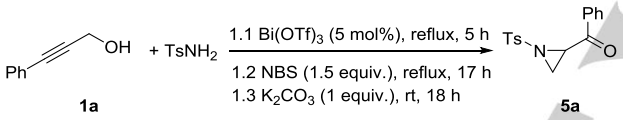


Figure 1 Crystal structure of **4d**

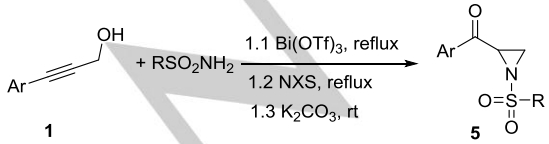
The halogen in the α-halo-β-amino ketones can be substituted by nucleophilic reagents. So a series of chemicals, such as malononitrile, thiourea, hydroxylamine, hydrazine hydrate, and inorganic base, were added to the mixture of in situ generated **4a** to explore the synthetic utility of propargyl alcohols. To our excited, aziridinyl ketone derivative **5a** was obtained in 87% yield while 1 equivalence of K_2CO_3 was added (Scheme 4).

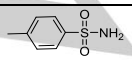
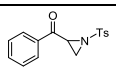
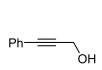
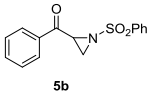
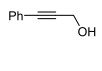
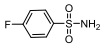
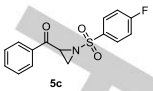
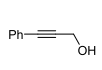
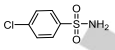
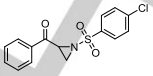
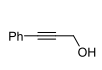
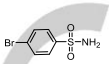
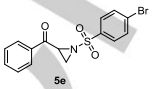
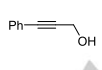
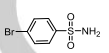
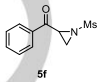
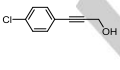
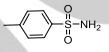
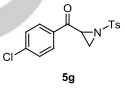
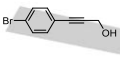
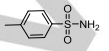
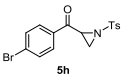
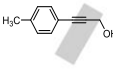
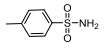
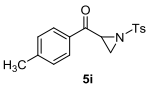
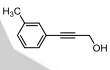
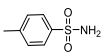
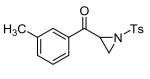
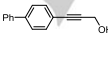
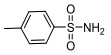
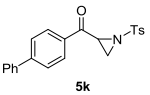
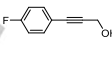
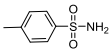
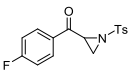
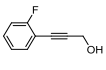


Scheme 4 One-pot synthesis of **5a** from **1a**

Encouraged by the successful synthesis of **5a**, we tried more one-pot synthesis of acyl aziridines **5** with propargyl alcohols **1**, sulfonamides, and NXS as the reaction materials (Table 5). NBS, NCS, NIS proved to be suitable for this transformation and gave the desired 5a product in high yields (87% yield for NBS in 40 h, 85% yield for NCS in 47 h, 83% yield for NIS in 19 h). Both alkyl and aryl sulfonamides worked well, affording **5a**-**5f** in 65-87% yields. Propargyl alcohols (**1c**-**1e**, **1g**-**1m**), which showed good reactivity in the one-pot transformation of propargyl alcohols to α-bromo-β-amino ketones, were subjected the investigated, and **5g**-**5o** were obtained in 50%-87% yields after 9-50 hours.

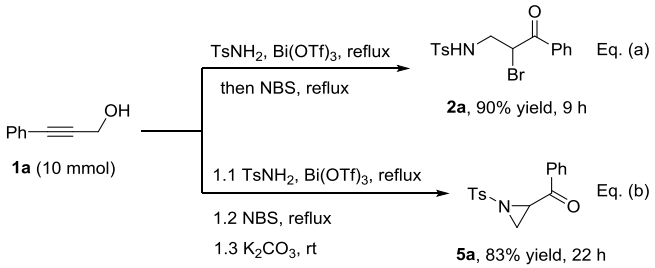
Table 5: One-pot synthesis of acyl aziridines **5** from propargyl alcohols **1**[a]



Entry	Alcohols	RSO_2NHR^1	Product	Time (h)	Yield (%)[b]
1			 5a	40	87[c]
2			 5b	31	77
3			 5c	50	65
4			 5d	46	65
5			 5e	40	65
6			 5f	32	77
7			 5g	50	55
8			 5h	48	72
9			 5i	33	86
10			 5j	33	72
11			 5k	9	50
12			 5l	10	78
13			5m	38	69
14			5n	21	56
15			5o	28	87

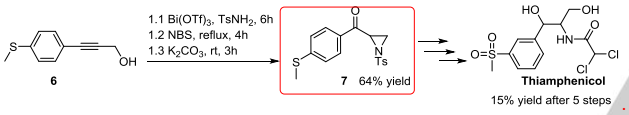
[a]Reaction conditions: Alcohol (0.2 mmol), sulphonamide (0.4 mmol), $Bi(OTf)_3$ (0.01 mmol), dioxane (0.5 mL), reflux. Then NBS (0.3 mmol), reflux. Then K_2CO_3 (0.2 mmol), rt. [b]Isolated yield after flash chromatography. [c]NBS, 87%, 40 h; NCS, 85%, 47 h; NIS, 83%, 19 h.

To demonstrate the scalability of this reaction protocol, reactions with **1a** as the starting material were conducted on a 10 mmol scale, wherein the products **2a** and aziridine **5a** were obtained in 90% and 83% yields, respectively. Unexpectly, shorter times were needed in the scale-up reactions. This suggested the realistic possibility of future larger scale-ups (Scheme 5).



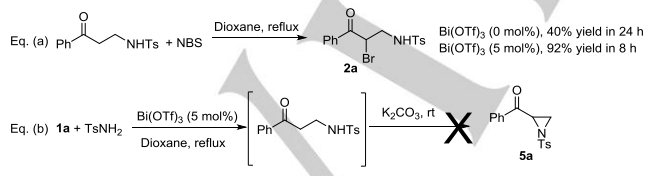
Scheme 5. Scale-up reactions

Florfenicol (FF) and thiamphenicol (TAP) are two typical pharmaceuticals used widely as therapeutica antibiotic agents in aquaculture. (4-(Methylthio)phenyl)(1-tosylaziridin-2-yl)methanone **7** was the key intermediate for the synthesis of the common intermediate of FF and TAP.[14] To show versatility and feasibility of aziridines, further transformation of aziridinyl ketones to TAP was investigated. Finally, racemic Thiamphenicol was obtained through sequent 5 steps reactions with 3-(4-(methylthio)phenyl)prop-2-yn-1-ol **6** as starting material (scheme 6).



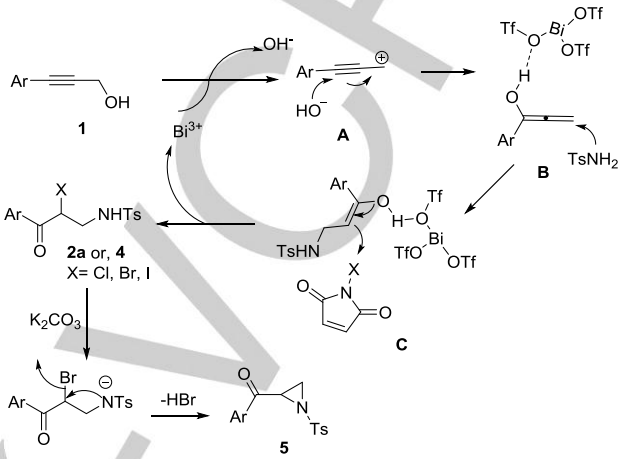
Scheme 6. Synthesis of racemic Thiamphenicol

Further experiments were carried out to gain more insights into the mechanism of this sequential MS rearrangement/halogenation/intramolecular cyclization (Scheme 7). Halogenation reaction underwent slowly without $Bi(OTf)_3$, and the transformation discontinued after one day to give **2a** in 40% yield; yet, the expected α-bromo-β-amino carbonyl compound **2a** was obtained in 92% yield within 8 h using 5 mol% $Bi(OTf)_3$ (Eq. (a)), showing that catalyst was necessary in halogenation step. Additionally, the stirring of in situ generated **A** in the presence of 1 equivalence of K_2CO_3 gave no expected product **5a** (Eq. (b)), which disclosed that **2a** should be the key intermediate for this reaction.



Scheme 7. Mechanism verification experiment

On the basis of the aforementioned observations and our previous work on the MS rearrangement of propargyl alcohols to β-aminoketones, a plausible mechanism for the synthesis of α-bromo-β-amino ketones and acyl aziridines from propargyl alcohols is depicted in Scheme 8. The lose and addition of a molecule of water in the presence of catalytic amounts of $Bi(OTf)_3$ led to intermediate **B**. Coordination of the O atom of intermediate **B** to $Bi(OTf)_3$ followed by nucleophilic addition of $TsNH_2$ afforded coordinated enol intermediate **C**. Electrophilic addition of enol intermediate **C** provided α-bromo-β-amino carbonyl compounds **2a** or **4**, and regenerated the catalyst $Bi(OTf)_3$. Finally, base-promoted intramolecular cyclization gave aziridinyl ketones **5**.



Scheme 8. Plausible Mechanism.

Conclusion

In summary, we reported a novel and efficient $Bi(OTf)_3$-catalyzed reaction of 3-aryl propargyl alcohols with sulfonamides as the nitrogen source to give α-halo-β-amino ketones and aryl aziridinyl ketones in a one-pot fashion. The $Bi(OTf)_3$ catalyst probably played a multi role in the sequencial MS rearrangement of propargyl alcohols, intermolecular addition of sulfonamides to unsaturated ketones, and halogenation at α position of carbonyl group. Our studies indicated a low catalyst loading, mild condition, and easy operation reaction, making it a potentially attractive method for the construction of α-halo-β-amino ketones and aryl aziridinyl ketones. More transformations beginning with the MS rearrangement of propargyl alcohols are underway in our lab and will be published in due course.

Experimental Section

The reagents used in the experiment are all purchased from commercial source without further drying and purification, unless there are special instructions for processing. Thin-layer chromatography (TLC) was used to detect the progress of the reaction under ultraviolet light. The ^{1}H NMR and ^{13}C NMR spectra of the targeted compounds were measured on a Bruker 500 MHz instrument with TMS as the internal standard. The infrared spectra (KBr) was recorded on the FT-IR spectrometer in the range of 400-4000cm^{-1}. The melting point was measured on the SGWX-4 instrument. High resolution mass spectrometry (HRMS electrospray ionization) was performed using the Solaril X70 FT-MS instrument. Compounds **1a-1o, and 6**[11] were synthesized according to the literature.

General procedure for the synthesis of 2, 3, and 4

Propynol **1** and **6** (0.2 mmol), sulfonamide (0.4 mmol 2 eq), and $Bi(OTf)_3$ (0.01 mmol), and dioxane (0.5 mL) were added into a 15 mL sealed tube.

The mixture was stirred under reflux temperature until complete conversion of propynol to give the intermediate β-amino ketone detected by TLC analysis. Then halogen source (0.3 mmol) was added to the reaction system , and the resulted mixture was sequentially stirred under reflux temperature until the complete conversion of intermediate β-amino ketone detected by TLC analysis. Finally, the reaction was quenched with saturated sodium bicarbonate solution, extracted with EtOAc (3×5 mL), washed with saturated brine (3×5 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a residue. The residue was purified by silica gel with petroleum ether/EtOAc as the elute to afford products **2**, **3**, and **4**.

General procedure for the synthesis of 5 and 7

K_2CO_3 (0.2 mmol) was added to a reaction system of in situ generated **2**, **3**, and **4** at room temperature, and the resulted mixture was stirred at room temperature until complete conversation of **2**, **3**, and **4** detected by TLC analysis. Finally, the reaction was quenched with saturated sodium bicarbonate solution, extracted with EtOAc (3×5 mL), washed with saturated brine (3×5 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a residue. The residue was purified by silica gel with petroleum ether/EtOAc as the elute to afford acyl aziridines **5**.

Acknowledgements

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Keywords: Meyer-Schuster rearrangement reaction • Acyl vicinal haloamines • Propargyl alcohols • α-Iodo-β-amino carbonyl compounds • Aryl aziridinyl ketones

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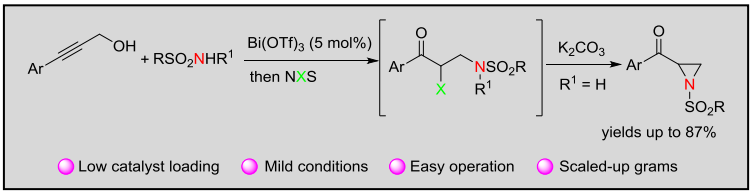

A synthetic route to construct α-halo-β-amino ketones and acyl aziridines from propargyl alcohols with diverse halogen source and sulfonamides in a one-pot fashion was investigated. This method is mild conditions, easy operation, low catalyst loading, and scaled-up grams. Notably, catalyst $Bi(OTf)_3$ is found to play a multi role in the cascade sequence.