

# Direct Transformation of Terminal Alkynes into Amidines by a Silver-Catalyzed Four-Component Reaction

Binbin Liu,<sup>§a</sup> Yongquan Ning,<sup>§a</sup> Matteo Virelli,<sup>c</sup> Giuseppe Zanoni,<sup>c</sup> Edward A. Anderson<sup>d</sup> and Xihe Bi<sup>\*a,b</sup>

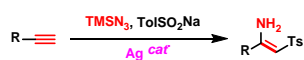
<sup>a</sup> Department of Chemistry, Northeast Normal University, Changchun 130024, China. <sup>b</sup> State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China. <sup>c</sup> Department of Chemistry, University of Pavia, Viale Taraselli 12, 27100, Pavia, Italy. <sup>d</sup> Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford, OX1 3TA, U.K.

**ABSTRACT:** An unprecedented conversion of terminal alkynes into *N*-sulfonimidamides (amidines) is reported, by a silver-catalyzed, one-pot, four-component reaction with TMSN<sub>3</sub>, sodium sulfinate, and sulfonyl azide. The reaction scope includes both aromatic and aliphatic alkynes. A possible cascade reaction mechanism, consisting of alkyne hydroazidation, sulfonyl radical addition, 1,3-dipolar cycloaddition by TMSN<sub>3</sub>, and a concerted C–C and N–N bond cleavage, is proposed. TMSN<sub>3</sub> is found to play an essential role in each step of the reaction.

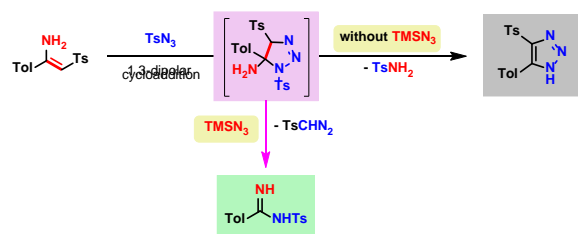
## INTRODUCTION

The development of novel functional group transformations of commonly available chemicals is of great importance in the development of general and readily applied synthetic methodologies.<sup>1</sup> Alkynes are one example of a readily available chemical class; however the large dissociation energy required for the complete cleavage of the C≡C triple bond (~200 kcal mol<sup>-1</sup>) poses a challenge to the transformation of this functionality into other motifs.<sup>2</sup> Most of the known examples of alkyne cleavage processes are involved in the construction of heterocycles and carbocycles.<sup>3,4</sup> Far fewer strategies are available for the transformation of C≡C triple bonds into other functional groups such as ketones,<sup>5,3g</sup> carboxylic esters and (thio)amides,<sup>6</sup> olefins,<sup>7</sup> alkenes,<sup>8</sup> and nitriles<sup>9</sup> (Figure 1a). Nevertheless, these procedures often require the use of activated alkynes or expensive and/or toxic transition metals.<sup>5–9</sup> The development of functional group transformations starting from non-activated alkynes remains of high appeal.

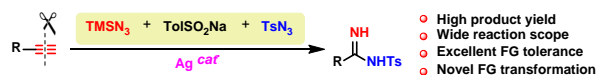
a. Ag-catalyzed aminosulfonylation of alkynes<sup>11cvi, 11v</sup>



b. Study on the cycloaddition of β-sulfonyl enamine with TsN<sub>3</sub> (our strategy)



c. This report: amidination by a four-component reaction



**Figure 1.** a. Previous transformations of alkynes into other functional groups. b. Previous work from our group on alkyne amino-

sulfonylation. c. Transformation of β-sulfonyl enamine into an amidine. d. Reaction blueprint for the direct transformation of terminal alkynes into amidines.

Our group has recently developed a silver-catalyzed hydroazidation of terminal alkynes, which provides a method for the direct transformation of terminal alkynes to α-substituted vinyl azides.<sup>10</sup> We subsequently reported a silver-catalyzed three-component reaction of terminal alkynes, trimethylsilyl azide (TMSN<sub>3</sub>), and sodium sulfinate, which enables the synthesis of β-sulfonyl enamines (Figure 1b).<sup>11</sup> The efficient generation of these enamines from terminal alkynes encouraged us to investigate their synthetic utility. One of the most studied reactions of enamines is their cycloaddition with sulfonyl azides, leading to triazoles.<sup>12</sup> In the case of β-sulfonyl enamines, TMSN<sub>3</sub> was found to play a crucial regulative role in the reaction of the *in situ* formed aminotriazole intermediate: in the absence of TMSN<sub>3</sub> the anticipated triazole product was obtained, whereas in the presence of TMSN<sub>3</sub> an amidine was unexpectedly isolated as the major product (Figure 1c). Notably, the amidination of free enamines with azides is unknown,<sup>13</sup> despite the importance of amidines in azaheterocycle synthesis,<sup>14</sup> molecular recognition,<sup>15</sup> and pharmacophores in medicinal chemistry.<sup>16</sup> Therefore, the development of an efficient synthetic method for amidines, especially for the iminyl-protected amidines, would be of great value.<sup>17</sup> We envisaged that a novel cleavage transformation of the carbon-carbon triple bond functionality into an amidine group could be achieved by a silver-catalyzed four-component reaction, directly starting from terminal alkynes with TMSN<sub>3</sub>, sodium sulfinate, and sulfonyl azide. Here we report the results of this investigation, which enables the synthesis of a wide range of *N*-sulfonimidamides (Figure 1c).<sup>18</sup> To the best of our knowledge, this is the first report of the direct transformation of alkynes into amidines.<sup>19</sup>

## RESULTS AND DISCUSSION

In an initial study, *p*-tolylacetylene **1a**, TMSN<sub>3</sub>, sodium sulfinate **2a**, tosyl azide **3a** and water were reacted in the

**Table 1. Optimization of the Reaction Conditions<sup>a</sup>**

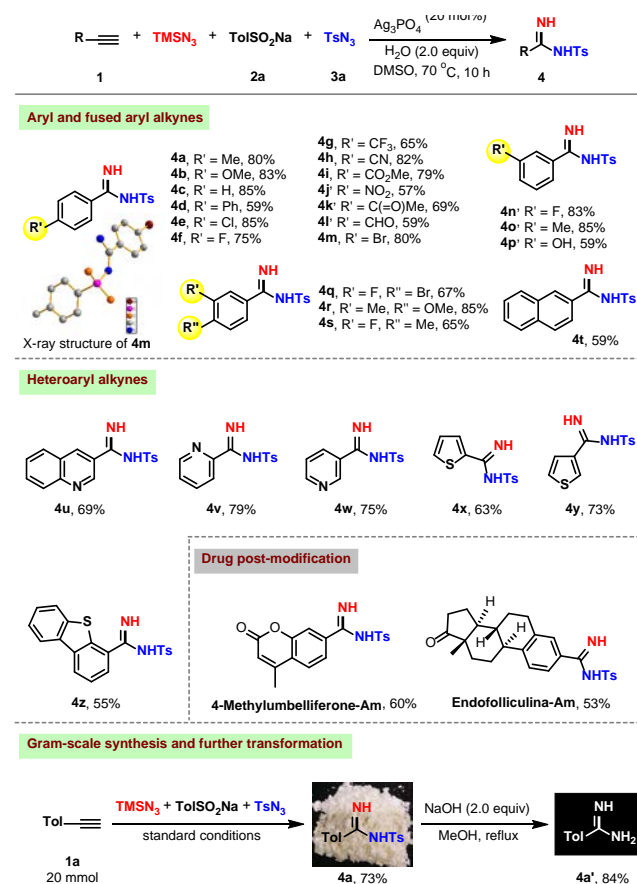
$\text{Tol}\equiv + \text{TMSN}_3 + \text{ToISO}_2\text{Na} + \text{TsN}_3 \xrightarrow[\text{DMSO, 70 }^\circ\text{C, 10 h}]{\text{H}_2\text{O (2.0 equiv) [M] cat.}}$				
entry	[M] cat.	amount	solvent	yield (%) <sup>b</sup>
1	Ag <sub>3</sub> PO <sub>4</sub>	20 mol%	DMSO	80
2	Ag <sub>2</sub> CO <sub>3</sub>	20 mol%	DMSO	47
3	AgNO <sub>3</sub>	20 mol%	DMSO	62
4	AgF	20 mol%	DMSO	55
5	Pd(OAc) <sub>2</sub>	5 mol%	DMSO	0
6	CuI	20 mol%	DMSO	0
7	Au(PPh <sub>3</sub> )Cl	10 mol%	DMSO	0
8	Ag <sub>3</sub> PO <sub>4</sub>	20 mol%	DMF	43
9	Ag <sub>3</sub> PO <sub>4</sub>	20 mol%	CH <sub>3</sub> CN	0
10	Ag <sub>3</sub> PO <sub>4</sub>	20 mol%	DCE	0
11	Ag <sub>3</sub> PO <sub>4</sub>	20 mol%	1,4-Dioxane	0

<sup>a</sup>Reaction conditions: **1a** (0.5 mmol), TMSN<sub>3</sub> (1.0 mmol), H<sub>2</sub>O (1.0 mmol), ToISO<sub>2</sub>Na **2a** (0.75 mmol), TsN<sub>3</sub> **3a** (0.75 mmol), catalyst (0.1 mmol) in solvent (3 mL) at 70 °C under air for 10 h. <sup>b</sup> Isolated yields.

presence of Ag<sub>3</sub>PO<sub>4</sub> catalyst in DMSO at 70 °C, giving 4-methyl-*N*-tosylbenzimidamide **4a** in 80% yield (Table 1). This discovery prompted us to further optimize the reaction conditions for this C≡C triple bond cleavage. In the absence of any one of the three reagents (TMSN<sub>3</sub>, ToISO<sub>2</sub>Na, and TsN<sub>3</sub>), no product was obtained. When Ag<sub>3</sub>PO<sub>4</sub> was replaced by other common silver salts such as Ag<sub>2</sub>CO<sub>3</sub>, AgNO<sub>3</sub>, and AgF (entries 2-4), no improvement in yield was recorded. Other transition-metal based catalysts, such as Pd(OAc)<sub>2</sub>, CuI, and Au(PPh<sub>3</sub>)Cl, did not show any activity (entries 5-7). The reaction outcome proved highly solvent dependent, with no detection of the desired product in CH<sub>3</sub>CN, DCE or 1,4-dioxane, whereas in DMF product **4a** was obtained in a modest 43% yield (entries 8-11). Notably, reducing or increasing the amount of Ag<sub>3</sub>PO<sub>4</sub> resulted in lower product yields. The conditions listed in entry 1 were therefore optimal, and are termed 'standard conditions'.

With optimized conditions in hand, we sought to examine the reaction scope with respect to the alkyne substrate (Scheme 1). Aryl alkynes with either electron-donating or electron-withdrawing groups on the *para*-position of the phenyl ring proved to be competent for the C≡C triple bond cleavage reaction, providing amidines **4a–4m** in uniformly good yields. A variety of functional groups, such as alkoxy, halo, trifluoromethyl, cyano, ester, nitro, and formyl were well tolerated. The structure of the amidine products was further confirmed by X-ray crystallographic analysis of the product **4m**.<sup>20</sup> *Meta*-substituted aryl alkynes, as well as substrates with two substituents on the aryl ring, also afforded the desired products in 59% to 85% yield (**4n–4s**). A phenol (**4p**) was also well tolerated under the cleavage reaction conditions. In addition, a naphthyl group was suitable for the preparation of amidine **4t** (59%). Heteroaryl alkynes, such as 3-quinoliny, 2- and 3-pyridyl, 2- and 3-thienyl, and dibenzo[*b,d*]thiophene-4-yl, also participated in the reaction, affording the desired products (**4u–4z**) in 55% to 79% yield. As an example of application to the late-stage modification of more complex molecules, the methodology was successfully applied to 4-methyl

umbelliferone and endofolliculina, affording the corresponding

**Scheme 1. Reaction Scope of Aromatic Terminal Alkynes<sup>a</sup>**

<sup>a</sup>Reaction conditions: **1** (0.5 mmol), TMSN<sub>3</sub> (1.0 mmol), ToISO<sub>2</sub>Na (0.75 mmol), TsN<sub>3</sub> (0.75 mmol), and Ag<sub>3</sub>PO<sub>4</sub> (0.1 mmol) in DMSO (3 mL) at 70 °C under air for 10 h; Yields of isolated products.

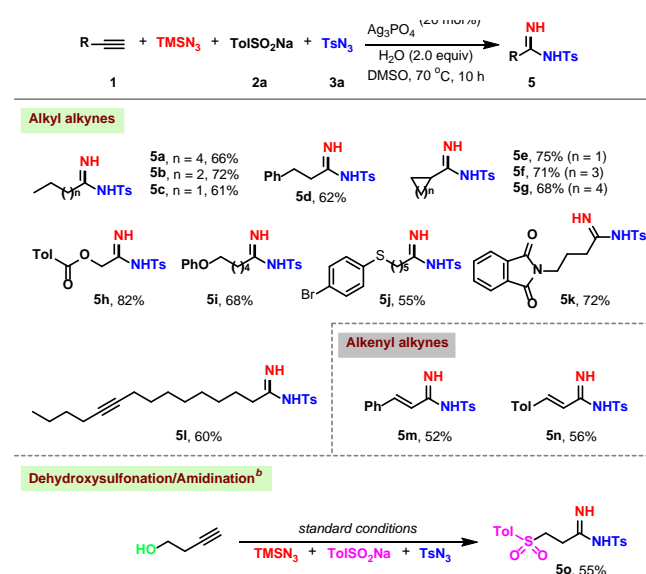
amidine-modified derivatives in moderate yield.

To test the large-scale applicability of this silver-catalyzed transformation, an experiment was performed where 20 mmol of **1a** was subjected to the standard reaction conditions, affording *N*-tosyl amidine **4a** in a slightly reduced yield (73%), which could be easily deprotected to amidine **4a'** in 84% yield on treatment with NaOH.<sup>21</sup>

Our attention next turned to the reaction scope for aliphatic alkynes. As illustrated in Scheme 2, this class of substrates also underwent this transformation with similar efficiency, providing amidines in generally good yields. Terminal linear alkynes of varying chain length gave comparable reaction outcomes (**5a–5d**), as did the underivatized cycloalkylacetylenes (**5e–5g**) of varying ring size. Substrates with a variety of functional groups, such as ester, ether, thioether, phthalimide, and in particular an internal alkyne, also afforded the corresponding amidines (**5h–5l**) in 55% to 82% yield, thus demonstrating chemoselectivity of this silver-catalyzed reaction for the terminal alkyne. The amidination of terminal alkynes was also effective with styryl acetylenes, leading to conjugated products **5m** and **5n** in comparable yields. When 3-butyne-1-ol was used as substrate, the unexpected sulfonylated amidine **5o** was obtained in 55% yield, possibly via a rarely described dehydroxysulfonation of the primary alcohol,<sup>22</sup> followed by the amidination reaction.

The scope for the sodium sulfinate and sulfonyl azide was

## Scheme 2. Reaction Scope of Aliphatic Terminal Alkynes<sup>a</sup>



<sup>a</sup>Reaction conditions: **1** (0.5 mmol), TMSN<sub>3</sub> (1.0 mmol), TolSO<sub>2</sub>Na (0.75 mmol), and Ag<sub>3</sub>PO<sub>4</sub> (0.1 mmol) in DMSO (2 mL) at 70 °C for 4 h, then TsN<sub>3</sub> (0.75 mmol, dissolved in 1 mL DMSO), at 70 °C under air for a further 4–6 h. Yield of isolated products. <sup>b</sup> Two equivalents of TolSO<sub>2</sub>Na were used.

explored by testing the reaction of a small range of these components with *p*-tolylacetylene **1a** (Table 2). When the sodium sulfinate and the sulfonyl azide featured the same substituent (R<sup>1</sup> = R<sup>2</sup>, aryl or alkyl), the target amidines (**6a–6f**) were obtained in 67% to 85% yield. On performing the reaction with different groups on the sulfinate and sulfonyl azide (i.e. R<sup>1</sup> ≠ R<sup>2</sup>), amidines **6g'** and **6h'** were obtained as the sole products, with no detectable trace of the possible alternative product. This finding demonstrates that the sulfonamide unit in the product originates from the sulfonyl azide, rather than from the sulfinate, where the intermediate sulfone group is presumably lost in the course of alkyne cleavage.

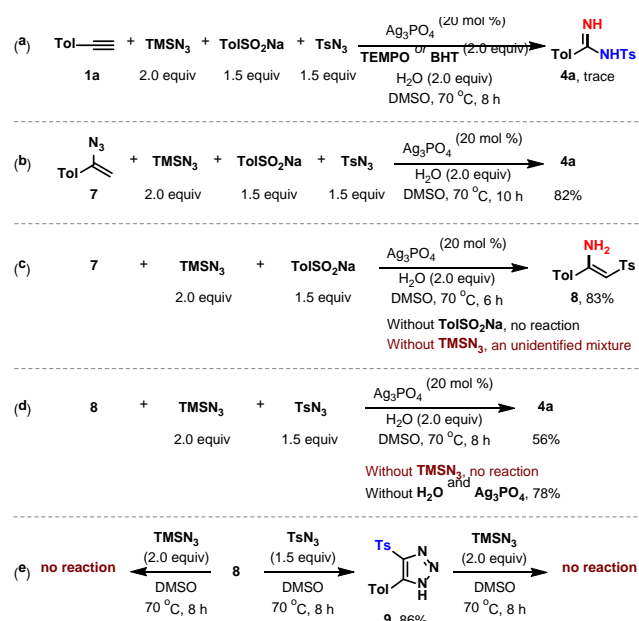
Further experiments were carried out to gain a deeper understanding of the mechanistic pathway (Scheme 3): (a) Addi-

**Table 2. Reaction Scope of Sodium Sulfinites and Sulfonyl Azides<sup>a</sup>**

entry	R <sup>1</sup>	R <sup>2</sup>	<b>6 = 6'</b>	Yield (%) <sup>b</sup>
1	4-MeOC <sub>6</sub> H <sub>4</sub>	4-MeOC <sub>6</sub> H <sub>4</sub>	<b>6a</b>	74
2	Ph	Ph	<b>6b</b>	67
3	4-ClC <sub>6</sub> H <sub>4</sub>	4-ClC <sub>6</sub> H <sub>4</sub>	<b>6c</b>	75
4	4-FC <sub>6</sub> H <sub>4</sub>	4-FC <sub>6</sub> H <sub>4</sub>	<b>6d</b>	78
5	Oct	Oct	<b>6e</b>	82
6	Me	Me	<b>6f</b>	85
7	Me	4-MeC <sub>6</sub> H <sub>4</sub>	<b>6g</b> 0	<b>6g'</b> 80
8	4-MeC <sub>6</sub> H <sub>4</sub>	4-ClC <sub>6</sub> H <sub>4</sub>	<b>6h</b> 0	<b>6h'</b> 75

<sup>a</sup> Reaction conditions: **1** (0.5 mmol), TMSN<sub>3</sub> (1.0 mmol), R<sup>1</sup>SO<sub>2</sub>Na **2** (0.75 mmol), R<sup>2</sup>SO<sub>2</sub>N<sub>3</sub> **3** (0.75 mmol), and Ag<sub>3</sub>PO<sub>4</sub> (0.1 mmol) in DMSO (3 mL) at 70 °C under air for 8–10 h; <sup>b</sup> Yields of isolated products.

## Scheme 3. Mechanistic Investigations

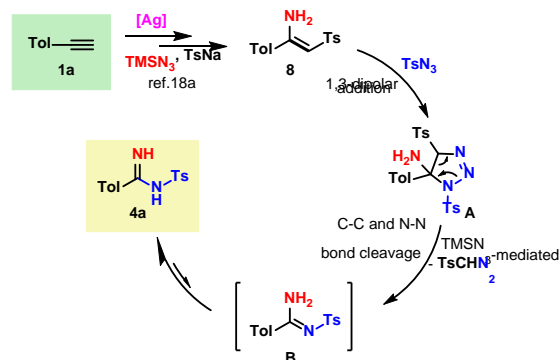


tion of the radical traps 2,2,6,6-(tetramethylpiperidin-1-yl)oxyl (TEMPO) or butylated hydroxytoluene (BHT) to the reaction under the optimized conditions led to the formation of only a trace amount of product **4a**, thus implying the possible involvement of a radical process. (b) When terminal alkyne **1a** was replaced by vinyl azide **7**, **4a** was obtained in a yield (82%) comparable to that in the analogous optimized one-pot conditions (c.f. Table 1, entry 1), thus suggesting the vinyl azide as a potential initial reaction intermediate. (c) When vinyl azide **7** was subjected to the optimized reaction conditions but in the absence of TsN<sub>3</sub>, the aminosulfonylated product **8** was obtained in 83% yield, and amidine **4a** was not detected. Moreover, no product **8** could be observed when the reaction was carried out in the absence of either TolSO<sub>2</sub>Na or TMSN<sub>3</sub>. (d) When **8** was subjected to the optimized conditions (but in the absence of the sulfinate salt), **4a** was isolated in 56% yield, implying **8** also to be a reaction intermediate. No reaction occurred without TMSN<sub>3</sub>, thus confirming this reactant as essential for conversion to the amidine. Moreover, the silver catalyst and water seemed to be detrimental to this particular reaction, with an improved 78% yield of **4a** attained in their absence. (e) The cycloaddition of enamine **8** with TsN<sub>3</sub>, but in the absence of TMSN<sub>3</sub>, led to triazole product **9** in 86% yield. No reaction was observed on treatment of **9** with TMSN<sub>3</sub>, suggesting that **9** is not an intermediate in the formation of the amidine product.

Based on the above results and related precedent,<sup>12a,23</sup> a plausible mechanism for the amidination of tolylacetylene **1a** is outlined in Scheme 4. As demonstrated in Scheme 3c, tosyl enamine **8** is first formed from the reaction of **1a** with TMSN<sub>3</sub> and TolSO<sub>2</sub>Na under silver catalysis, through sequential hydroazidation of the terminal alkyne, and aminosulfonylation by sulfonyl radical addition to the *in situ* generated vinyl azide.<sup>11</sup> 1,3-dipolar cycloaddition with TsN<sub>3</sub> gives 1,2,3-triazoline intermediate **A**,<sup>13a</sup> which undergoes a retro-[3+2] cycloaddition to yield the imidamide **B**, with elimination of

TsCHN<sub>2</sub>.<sup>13b</sup> In light of the result in Scheme 3e, TMSN<sub>3</sub> appears to play a critical role in the chemoselectivity of this cleavage process, favoring the retro-cycloaddition over elimination of ammonia, although the exact mechanism of this step remains unclear.

#### Scheme 4. Proposed Mechanism



Finally, tautomerization of imidamide **B** gives rise to product **4a**.

#### CONCLUSION

In conclusion, we have developed an unprecedented silver-catalyzed C≡C cleavage of terminal alkynes to amidines by a one-pot four-component reaction. The reaction accommodates a wide variety of aryl, heteroaryl, alkyl, and alkenyl-substituted terminal alkynes and tolerates a range of other functional groups. From a mechanistic perspective, a cascade sequence is proposed consisting hydroazidation, sulfonfyl radical addition, 1,3-dipolar cycloaddition, and a retro-1,3-dipolar cycloaddition, resulting in the amidine product. Given the importance of amidines in medicinal chemistry research, this process offers a facile entry to this useful functional group.

#### ASSOCIATED CONTENT

##### Supporting Information

Experimental procedures, analytical data, and copies of NMR spectra are available free of charge via the Internet at (<http://pubs.acs.org/page/jacsat/submission/authors.html>).

#### AUTHOR INFORMATION

##### Corresponding Author

E-Mail: [bixh507@nenu.edu.cn](mailto:bixh507@nenu.edu.cn)

##### Notes

The authors declare no competing financial interest.  
§ These authors contributed equally to this work.

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