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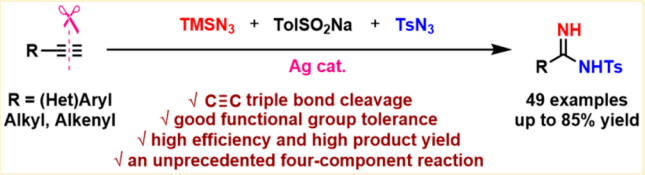
Direct Transformation of Terminal Alkynes into Amidines by a Silver-Catalyzed Four-Component Reaction

Binbin Liu,[†,⊥] Yongquan Ning,[†,⊥] Matteo Virelli,[§] Giuseppe Zanoni,[§] Edward A. Anderson,[∥] and Xihe Bi*[,†,‡]

[†]Department of Chemistry, Northeast Normal University, Changchun 130024, China
[‡]State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China
[§]Department of Chemistry, University of Pavia, Viale Taramelli 12, 27100, Pavia, Italy
[∥]Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford OX1 3TA, United Kingdom

Supporting Information

ABSTRACT: An unprecedented conversion of terminal alkynes into *N*-sulfonimidamides (amidines) is reported by a silver-catalyzed, one-pot, four-component reaction with $TMSN_3$, 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 $TMSN_3$, and retro-1,3-dipolar cycloaddition, is proposed. $TMSN_3$ 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.[1] 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^{-1}) poses a challenge to the transformation of this functionality into other motifs.[2] Most of the known examples of alkyne cleavage processes are involved in the construction of heterocycles and carbocycles.[3,4] Far fewer strategies are available for the transformation of C≡C triple bonds into other functional groups such as ketones,[5,3g] carboxylic esters and (thio)amides,[6] olefins,[7] alkynes,[8] and nitriles[9] (Figure 1a). Nevertheless, these procedures often require the use of activated alkynes or expensive and/or toxic transition metals.[5−9] The development of functional group transformations starting from nonactivated alkynes remains highly appealing.

Our group has recently developed a silver-catalyzed hydroazidation of terminal alkynes, which provided a method for the direct transformation of terminal alkynes to α-substituted vinyl azides.[10] We subsequently reported a silver-catalyzed three-component reaction of terminal alkynes, trimethylsilyl azide ($TMSN_3$), and sodium sulfinate, which enables the synthesis of β-sulfonyl enamines (Figure 1b).[11] 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.[12] In the case of β-sulfonyl enamines, $TMSN_3$ was found to play a crucial regulative role in the reaction of the in situ formed aminotriazole intermediate: in the absence of $TMSN_3$, the anticipated triazole product was obtained, whereas in the presence of $TMSN_3$, an amidine was unexpectedly isolated as the major product (Figure 1c). Numerous reactions to make amidines from N-substituted enamines have been reported; however, the amidination of free enamines with azides is unknown,[13] despite the importance of amidines in azaheterocycle synthesis,[14] molecular recognition,[15] and pharmacophores in medicinal chemistry.[16] Therefore, the development of an efficient synthetic method for amidines, especially for the iminyl-unprotected amidines, would be of great value.[17] 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 $TMSN_3$, 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 1d).[17b,18] To the best of our knowledge, this is the first report of the direct transformation of alkynes into amidines.[19]

RESULTS AND DISCUSSION

In an initial study, *p*-tolylacetylene **1a**, $TMSN_3$, sodium sulfinate **2a**, tosyl azide **3a**, and water were reacted in the presence of Ag_3PO_4 catalyst in DMSO at 70 °C, giving 4-methyl-*N*-tosylbenzimidamide **4a** in 80% yield (Table 1, entry 1). This discovery prompted us to further optimize the

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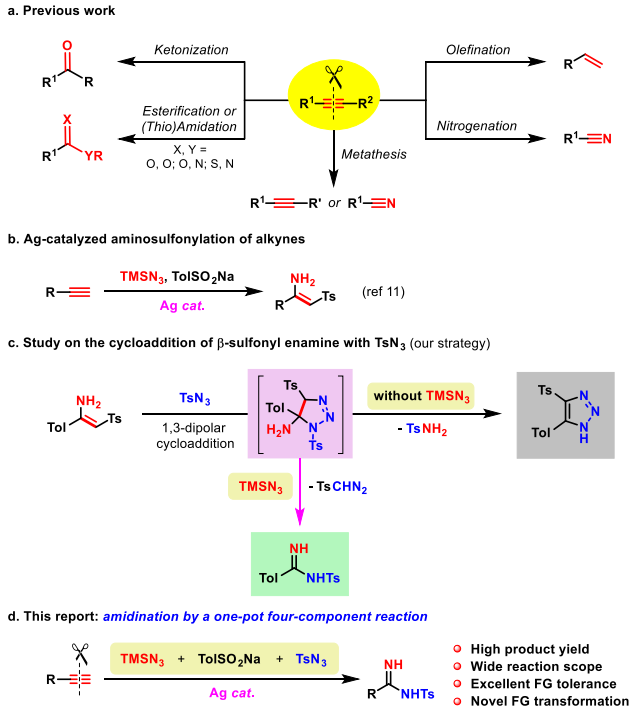
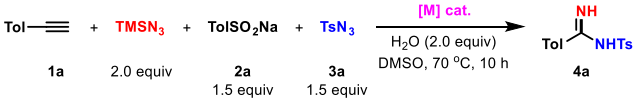


Figure 1. (a) Previous transformations of alkynes into other functional groups. (b) Previous work from our group on alkyne aminosulfonylation. (c) Transformation of *β*-sulfonyl enamine into an amidine. (d) Reaction blueprint for the development of the direct transformation of terminal alkynes into amidines.

Table 1. Optimization of the Reaction Conditions[a]



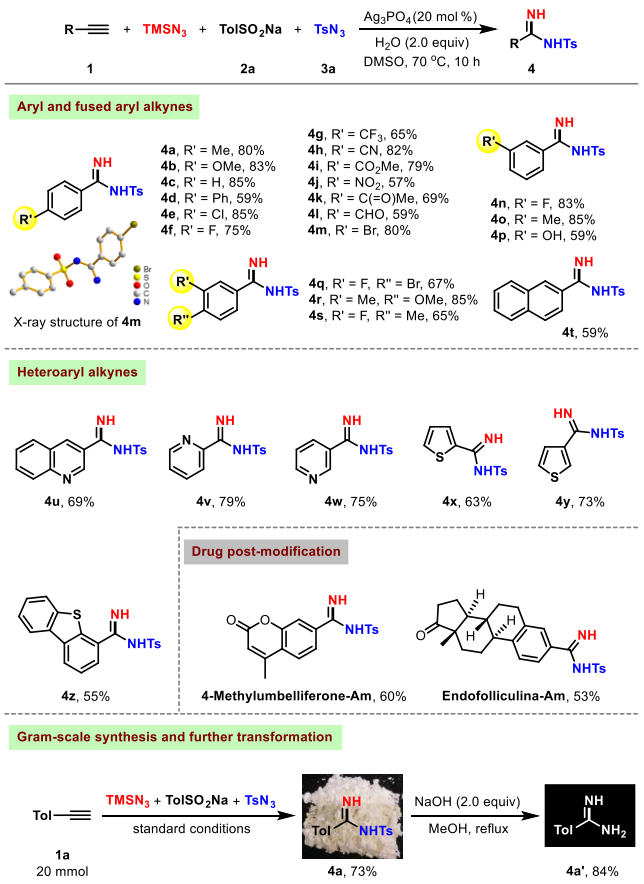
entry	[M] cat.	amount (mol %)	solvent	yield (%)[b]
1	Ag_3PO_4	20	DMSO	80
2	Ag_2CO_3	20	DMSO	47
3	$AgNO_3$	20	DMSO	62
4	AgF	20	DMSO	55
5	$Pd(OAc)_2$	5	DMSO	0
6	CuI	20	DMSO	0
7	$Au(PPh_3)Cl$	10	DMSO	0
8	Ag_3PO_4	20	DMF	43
9	Ag_3PO_4	20	CH_3CN	0
10	Ag_3PO_4	20	DCE	0
11	Ag_3PO_4	20	1,4-dioxane	0

[a]Reaction conditions: **1a** (0.5 mmol), $TMSN_3$ (1.0 mmol), H_2O (1.0 mmol), $TolSO_2Na$ **2a** (0.75 mmol), TsN_3 **3a** (0.75 mmol), catalyst (5–20 mol %) in solvent (3 mL) at 70 °C under air for 10 h. [b]Isolated yields.

reaction conditions for this C≡C triple bond cleavage. In the absence of any one of the three reagents ($TMSN_3$, $TolSO_2Na$, and TsN_3), no product was obtained. When Ag_3PO_4 was replaced by other common silver salts such as Ag_2CO_3, $AgNO_3$, and AgF (entries 2–4), no improvement in yield was recorded. Other transition-metal-based catalysts, such as $Pd(OAc)_2$, CuI, and $Au(PPh_3)Cl$, did not show any activity (entries 5–7). The reaction outcome proved highly solvent dependent with no detection of the desired product in CH_3CN, 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_3PO_4 resulted in lower product yields. The conditions listed in entry 1 were therefore optimal and are termed "standard conditions".

With the 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

Scheme 1. Reaction Scope of Aromatic Terminal Alkynes[a]



[a]Reaction conditions: **1** (0.5 mmol), $TMSN_3$ (1.0 mmol), $TolSO_2Na$ (0.75 mmol), TsN_3 (0.75 mmol), and Ag_3PO_4 (0.1 mmol) in DMSO (3 mL) at 70 °C under air for 10 h. Yields of isolated products.

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**.[20] The *meta*-substituted aryl alkynes as well as substrates with two substituents on the phenyl ring also afforded the desired products in 59–85% 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-quinolinyl, 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 55–79% yield. As an example of the application to the late-stage modification of more complex molecules, the methodology was successfully applied to 4-methylumbelliferone and endofolliculina, afford-

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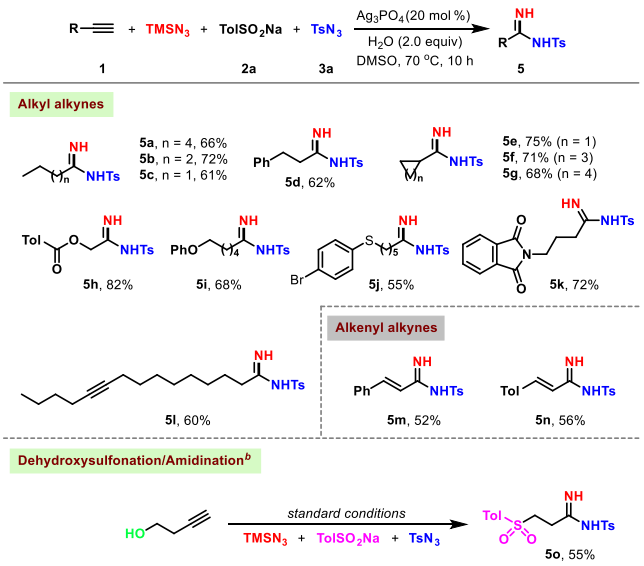
ing the corresponding amidine-modified derivatives in moderate yield.

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.[21]

Our attention next turned to the reaction scope for aliphatic alkynes. As illustrated in Scheme 2, this class of substrates also

Scheme 2. Reaction Scope of Aliphatic Terminal Alkynes[a]

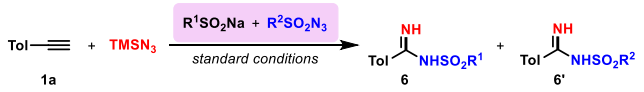


[a]Reaction conditions: **1** (0.5 mmol), $TMSN_3$ (1.0 mmol), $TolSO_2Na$ (0.75 mmol), and Ag_3PO_4 (0.1 mmol) in DMSO (2 mL) at 70 °C for 4 h, then TsN_3 (0.75 mmol, dissolved in 1 mL of DMSO), at 70 °C under air for another 4–6 h. Yield of isolated products. [b]2 equiv of $TolSO_2Na$ was used.

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, still afforded the corresponding amidines (**5h–5l**) in 55–82% 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-butyn-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,[22] followed by the amidination reaction.

The scope for sodium sulfinate and sulfonyl azide was 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 ($R^1 = R^2$, aryl or alkyl), the target amidines (**6a–6f**) were obtained in 67–85% yield. When we performed the reaction with different groups on the sulfinate and sulfonate azide (i.e., $R^1 \neq R^2$), amidines **4a** and **6c** were obtained as the sole products, with no detectable trace of the possible

Table 2. Reaction Scope of Sodium Sulfinates and Sulfonyl Azides[a]



entry	$R^1 = R^2$		6 = 6′	yield (%)[b]
1	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**6a**	74
2	Ph	Ph	**6b**	67
3	4-ClC_6H_4	4-ClC_6H_4	**6c**	75
4	4-FC_6H_4	4-FC_6H_4	**6d**	78
5	Oct	Oct	**6e**	82
6	Me	Me	**6f**	85

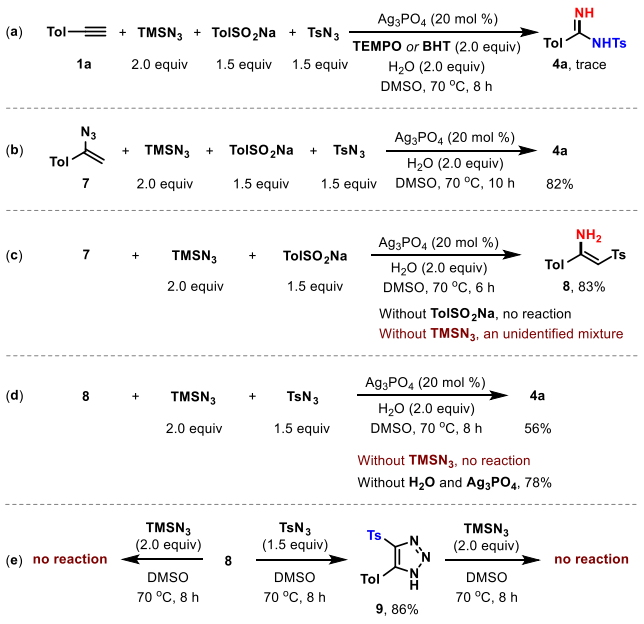
entry	$R^1 \neq R^2$		6	yield (%)[b]	6′	yield (%)[b]
7	Me	4-MeC_6H_4	**6f**	0	**4a**	80
8	4-MeC_6H_4	4-ClC_6H_4	**4a**	0	**6c**	75

[a]Reaction conditions: **1** (0.5 mmol), $TMSN_3$ (1.0 mmol), R^1SO_2Na **2** (0.75 mmol), $R^2SO_2N_3$ **3** (0.75 mmol), and Ag_3PO_4 (0.1 mmol) in DMSO (3 mL) at 70 °C under air for 8–10 h. [b]Yields of isolated products.

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)

Scheme 3. Mechanistic Investigations



Addition 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 (cf. 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

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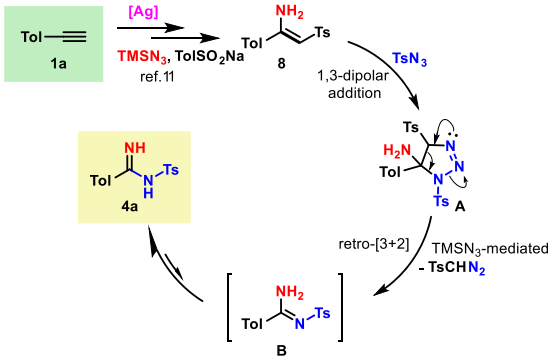
conditions but in the absence of TsN_3, the aminosulfonylated product **8** was obtained in 83% yield and amidine **4a** was not detected. Moreover, no product **8** could be observed when the reaction was carried out in the absence of either $TolSO_2Na$ or $TMSN_3$. (d) When **8** was subjected to the 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 $TMSN_3$, 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) No reaction occurred when treating **8** with $TMSN_3$, whereas the cycloaddition of enamine **8** with TsN_3, but in the absence of $TMSN_3$, led to triazole product **9** in 86% yield. Further, no reaction was observed on treatment of **9** with $TMSN_3$, so **9** is not an intermediate in the formation of amidine product.

Based on the above results and related precedent,[12a,23] a plausible mechanism for the amidination of tolylacetylene **1a** is outlined in Scheme 4. As demonstrated in Scheme 3c, tosyl

Scheme 4. Proposed Mechanism



enamine **8** is first formed from the reaction of **1a** with $TMSN_3$ and $TolSO_2Na$ under silver catalysis, through sequential hydroazidation of the terminal alkyne and aminosulfonylation by sulfonyl radical addition to the in situ generated vinyl azide.[11] 1,3-Dipolar cycloaddition with TsN_3 gives 1,2,3-triazoline intermediate **A**,[12a] which undergoes retro-[3 + 2]-cycloaddition to yield the imidamide **B**, with elimination of $TsCHN_2$.[13] In light of the result in Scheme 3e, $TMSN_3$ 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. 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 of hydroazidation, sulfonyl radical addition, 1,3-dipolar cycloaddition, and 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

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b11039.

Experimental procedures, analytical data, and copies of NMR spectra (PDF)

X-ray data for **4m** (CIF)

AUTHOR INFORMATION

Corresponding Author

*bixh507@nenu.edu.cn

ORCID

Edward A. Anderson: 0000-0002-4149-0494

Xihe Bi: 0000-0002-6694-6742

Author Contributions

⊥B.L. and Y.N. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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