# Silver-Catalyzed Tandem $C\equiv C$ bond Hydroazidation/Radical Addition/Cyclization of Biphenyl Acetylene: One-pot Synthesis of 6-Sulfonylated Phenanthridines

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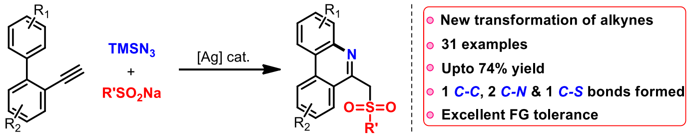
*Supporting Information Placeholder*



New transformation of alkynes through tandem hydroazidation/radical addition/cyclization process

**ABSTRACT:** A silver-catalyzed tandem carbon-carbon triple bond hydroazidation, radical addition and cyclization of biphenyl acetylene is described, leading under mild conditions to 6-sulfonylated phenanthridines in good yields. In this unprecedented tandem reaction, most of the atoms are uninterruptedly incorporated into the product without the cleavage of $C\equiv C$ bond. Mechanistic studies suggest the reaction should proceed through an iminyl radical reactive intermediate.

Alkynes are found in various natural products, bioactive compounds and organic materials.[1] Because they can be readily converted into a variety of other functional groups, alkynes are versatile intermediates in organic synthesis.[2] In recent years, significant attention has been placed on the nitrogenation of carbon-carbon triple bonds ($C\equiv C$) using trimethylsilyl azide ($TMSN_3$) as nitrogenating agent (Figure 1a). In the literature only few reports describe this kind of nitrogenation: Jiao and their coworkers devised a silver-catalyzed synthesis of nitriles by nitrogenation of alkynes using $TMSN_3$;[3] Jiao[4] and Echavarren[5] independently described the direct synthesis of amides[4] and tetrazoles[5] by nitrogenation of alkynes with $TMSN_3$; Yanada et al synthesized diazidoketones by reacting arylalkyl alkynes with *N*-iodosuccinimide (NIS) and $TMSN_3$;[6] Jiao and coworkers developed a gold-catalyzed nitrogenation of alkynes to carbamides and aminotetrazoles.[7] In all reported nitrogenation reactions, the substrate alkyne was cleaved into two or three parts but all the dissection parts were located in a single product and involved the two component process.[3-7] Efficient alternative procedures have been continuously pursued for the synthesis of heterocycles via nitrogenation of $C\equiv C$ using $TMSN_3$ via one-pot tandem processes. In light of this landscape and in consideration of the versatility and convenience of silver-based catalysis,[8] in this report we disclose for the first time a silver-catalyzed nitrogenation of biphenyl acetylene towards the synthesis of phenanthridines by sequential $C\equiv C$ hydroazidation, radical addition and cyclization reactions (Figure 1b). Phenanthridine and their derivatives are common structural components in a variety of natural products and medicinally-relevant synthetic compounds.[9] In addition to their pharmaceutical potency,[10] some of these phenanthridine-based compounds are used as ligands in coordination chemistry.[11] Unlike previous work,[3-7] in the synthethic methodology we describe herein both carbon atom of the alkyne are incorporated in the final phenantridine in the same sequence as in the substrate.

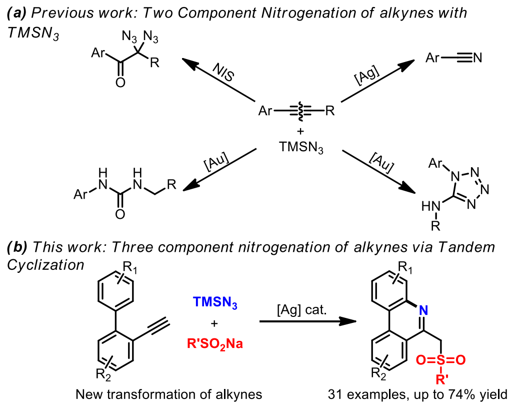
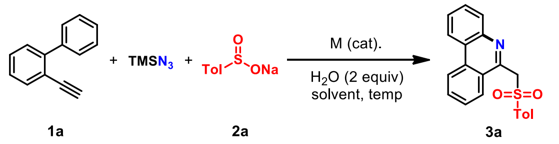


**Figure 1. Nitrogenation of $C\equiv C$ bond using $TMSN_3$**

In the initial design, biphenyl acetylene (**1**) as substrate, $TMSN_3$ and sodium *p*-toluenesulfinate (**2a**) as reagents were utilized for the optimization studies of the reaction conditions (Table 1). In a scouting experiment, **1a** (1 equiv) was reacted for 6 h with $TMSN_3$ (1.5 equiv) and **2a** (1.5 equiv) in DMSO (2 ml) and $H_2O$ (2 equiv)at 70 °C, using 20 mol% of $Ag_2CO_3$ as catalyst, affording the desired phenanthridine was in 36% of yield (entry 1). In order to improve the product yield, other silver salt sources were screened as catalysts; with $Ag_3PO_4$ the product was obtained in an increased 63% yield (entry 2), whereas no improvement was achieved with AgF as catalyst (29% yiled, entry 3). Other metal salts such as Pd(OAc)$_2$, CuI and Mn(OAc) were not productive catalysts for this transformation (entries 4-6). The effect of few polar solvents was also evaluated: in 1,2-dichloroethane (DCE) or 1,4-dioxane only trace amounts of phenanthridine **3a** (entries 7 and 8) were observed, whereas in *N*-methylpyrrolidone (NMP) product **3a** was obtained in moderate yield (48%, entry 9). Finally, we screened the impact of temperature and found that the yield was negatively affected by either increasing or decreasing the reaction temperature (entries 10 and 11).

**Table 1. Optimization of Reaction Conditions**[a]

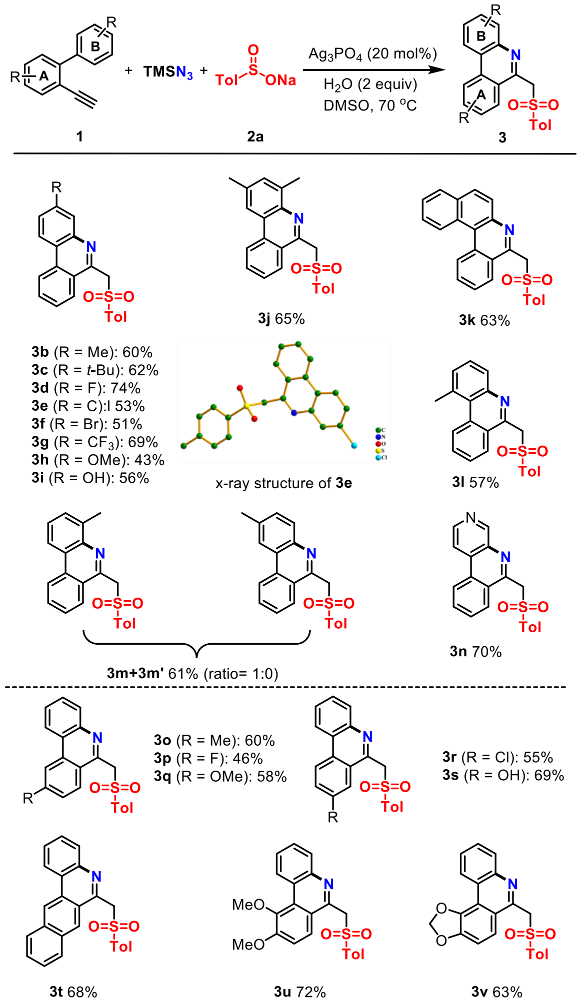


| entry | [M] cat. | amount | solvent | *T* (°C) | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | Ag$_2$CO$_3$ | 20 mol % | DMSO | 70 | 36 |
| 2 | Ag$_3$PO$_4$ | 20 mol % | DMSO | 70 | 63 |
| 3 | AgF | 20 mol % | DMSO | 70 | 29 |
| 4 | Pd(OAc)$_2$ | 20 mol % | DMSO | 70 | 0 |
| 5 | CuI | 20 mol % | DMSO | 70 | 0 |
| 6 | Mn(OAc)$_3$ | 20 mol % | DMSO | 70 | 0 |
| 7 | Ag$_3$PO$_4$ | 20 mol % | DCE | 70 | trace |
| 8 | Ag$_3$PO$_4$ | 20 mol % | 1,4-Dioxane | 70 | trace |
| 9 | Ag$_3$PO$_4$ | 20 mol % | NMP | 70 | 48 |
| 10 | Ag$_3$PO$_4$ | 20 mol % | DMSO | 100 | 55 |
| 11 | Ag$_3$PO$_4$ | 20 mol % | DMSO | 50 | 51 |

[a] Reaction conditions: **1a** (0.5 mmol), TMSN$_3$ (0.75 mmol), **2a** (0.75 mmol) and H$_2$O (1.0 mmol) in solvent (2 ml) for 6 h. [b] Isolated yields.

The scope of the reaction was investigated using substituted biphenyl acetylenes under the optimal conditions identified in the preliminary study (Table 1, entry 2); the results are summarized in Scheme 1. We initially explored the effect of substituents on the **B** ring of the biphenyl acetylene substrate. All substrates with either an electron-donating or electron-withdrawing group on the B ring provided the desired product in moderate to good yields. In particular, fluorine and trifluoromethyl groups at the C-4’ position of the biphenyl acetylenes **1d** and **1g** afforded products **3d** and **3g** in 74% and 69% yield, respectively. Both C-4’ electron-donating substitutents in **1b**, **1c**, **1h**, **1i** and halogens in **1e**, **1f** also reacted efficiently, affording the corresponding products in moderate to good yields (43%–62%). Compound **3e** was further characterized by single crystal X-ray analysis and the structure of the phenantridine product could be unambiguously confirmed (see supporting information). A disubstituted B-ring could also be part of a viable substrate, for instance 3’,5’-dimethyl biphenyl acetylene was transformed into phenanthridine **3j** in good yield.

**Scheme 1. Scope of biphenyl Acetylenes**[a]

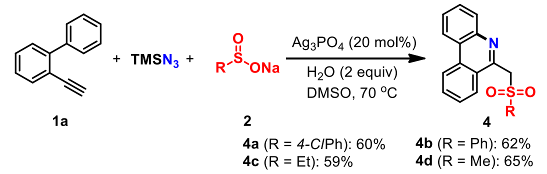


[a] Reaction conditions: **1** (0.5 mmol), TMSN$_3$ (0.75 mmol), **2a** (0.75 mmol), Ag$_3$PO$_4$ (20 mol%) and H$_2$O (1.0 mmol) in DMSO (2 ml) at 70 °C for 6 h. Yields (%) are calculated based on isolated product.

Biphenyl acetylene with a methyl substituent in the more sterically encumbered C-2’ position of the B ring productively reacted to afford product **3l** in 57% yield. When the methyl group was in the C-3’ position, product **3m** was obtained in 61% yield and without any detectable amount of the regioisomer **3m’**. This exquisite selectivity suggests that the cyclization might occur at the more sterically hindered position. Acetylene substrates containing a pyridine and a naphthalene moiety productively reacted and respectively afforded **3k** and **3n** in good yield. Next, we examined the effect of the substitution pattern on the **A** ring of the biphenyl acetylene substrate. Biphenyl acetylenes with substituents at either C-4 or C-5 position were reactive and afforded the corresponding products **3o-3s** in 46% to 69% yield. Biphenyl acetylenes featuring a naphthalene or a benzodioxole based could also resepctively be converted into desired products **3t** and **3v** in good yields. Moreover, 5,6-dimethoxy-substituted biphenyl acetylene also afforded the corresponding product **3u** in high yield (72%).

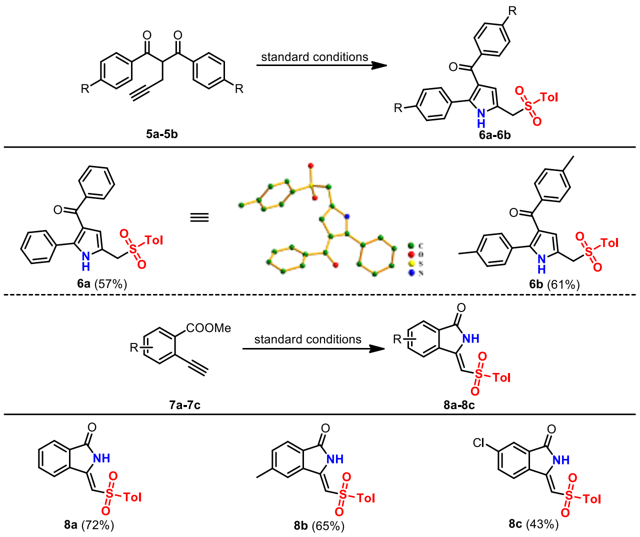
Furthermore, we have explored the scope of different sodium sulfinates, the results are summarized in Scheme 2. Both aryl and alkyl sodium sulfinates were compatible with the optimized conditions, providing the desired phenanthridine derivatives **4a-4d** in yields (59%–65%) that are comparable to that reported for **3a** in Table 1.

**Scheme 2. Scope of Sodium Sulfinates**[a]



[a] Reaction conditions: **1** (0.5 mmol), TMSN$_3$ (0.75 mmol), **2** (0.75 mmol), Ag$_3$PO$_4$ (20 mol%) and H$_2$O (1.0 mmol) in DMSO (2 ml) at 70 °C for 6 h. Yields (%) are calculated based on isolated product.

**Scheme 3. Further developments of the protocol**

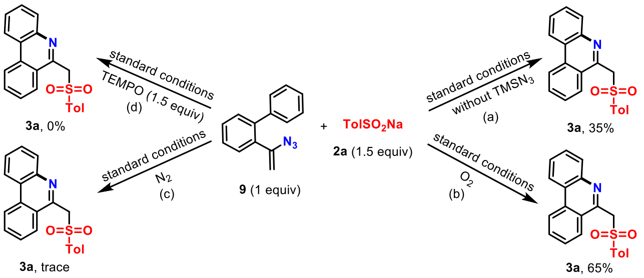


Reaction conditions: Alkyne (0.5 mmol), TMSN$_3$ (0.75 mmol), **2** (0.75 mmol), Ag$_3$PO$_4$ (20 mol%) and H$_2$O (1.0 mmol) in DMSO (2 ml) at 70 °C for 6 h. [a] Isolated Yield

With the purpose of gaining more insights on the versatility of this silver-catalyzed three-component synthetic protocol, we have applied this chemistry toward the synthesis of other rings by (Scheme 3). When alkynes **5a** and **5b** were used as substrates, tri-substituted sulfonated pyrroles **6a** and **6b** were obtained in 57% and 61% yield, respectively. The structure of compound **6a** was confirmed by X-ray crystallographic analysis (see Supporting Information). By this methodology we have finally successfully synthesized a new class of sulfonated isoindolinones **8a-8c** from alkynes **7a-7c** in good yields (43%–72%).

In order to ascertain whether the described sequential reaction proceeds a the radical or an ionic mechanism, we have carried out control experiments whose results are summarized in Scheme 4. In a first experiment, biphenyl vinyl azide **9** was reacted with sodium *p*-toluenesulfinate in the absence of TMSN$_3$ under the optimized conditions, thus delivering product **3a** in a dimished 35% yield (path a). In the presence of TMSN$_3$ (1.5 equiv), the desired product **3a** was formed in a typical good yield (65%, path b), thus confirming the TMSN$_3$ as necessary reactant. However, when performed under a nitrogen atmosphere, the reaction proceeded sluggishly, providing only traces of **3a** (path c), thus suggesting a pivotal role of atmospheric oxygen in this reaction. The sulfonylation reaction was shut down by addition of TEMPO (1.5 equiv) in the mixture (path d), implying the likelyhood of radical process.

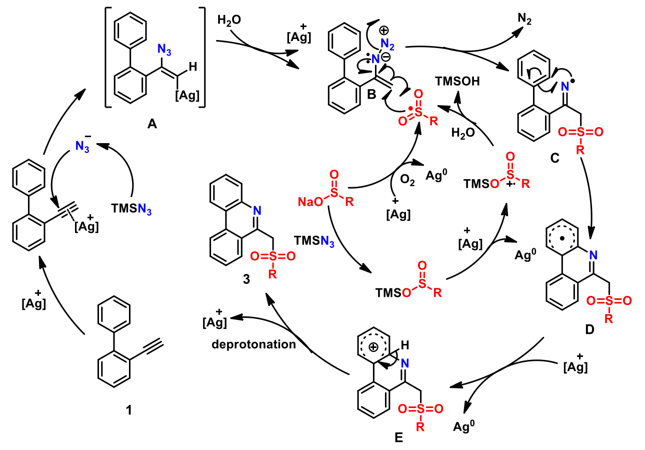
**Scheme 4. Mechanistic Investigations**



Reaction conditions: Vinyl azide **9** (0.5 mmol), TMSN$_3$ (0.75 mmol), **2** (0.75 mmol), Ag$_3$PO$_4$ (20 mol%) and H$_2$O (1.0 mmol) in DMSO (2 ml) at 70 °C for 6 h. The yields are estimated based on $^1$H NMR of crude reaction mixtures.

With reference to literature precedence,[7a,12f,16a] and based on these experimental results, we propose the following possible mechanitic pathway for this transformation (Scheme 5). The azide anion would attack the substrate alkyne **1** that is activated by the silver catalyst, to generate the organosilver complex **A**. The latter would extract a proton from water to produce vinyl azide **B** and release the cationic silver. The sulfonyl radical, which is generated from sodium sulfinate by the action of the silver catalyst and TMSN$_3$ or atmospheric oxygen, would add to vinyl azide **B** to generate the iminyl radical **C** upon loss of nitrogen. The iminyl radical **C** would undergo intramolecular cyclization with the aryl moiety (ring A), yielding radical species **D** that is stabilized by resonance. **D** would be subsequently oxidized by the silver catalyst forming the aryl cation **E**, which would finally deprotonate to product **3**.

**Scheme 5. Plausible Reaction Mechanism**



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In conclusion, we have developed a silver-catalyzed protocol for the construction of 6-sulfonylated phenanthridine through a tandem C≡C bond hydroazidation, radical addition and cyclization of biphenyl acetylenes. In this reaction, the carbon atom sequence of the alkyne substrate was preserved and incorporated into the product. The silver catalyst played a dual role as activator of the nitrogenation of biphenyl acetylene, as well as an oxidant for the generation of the reactive sulfonyl radical species. The synthetic methodology here described features mild reaction conditions, atom-economy, simple operations under ambient atmosphere, broad substrate scope, and good yields of isolated product. Control experiments supported the proposal of consecutive radical addition and cyclization processes. Further exploration of this reaction is ongoing in our laboratory.

## ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, spectral data and copies of $^1H$ and $^{13}C$-NMR spectra were given as a separate supplementary file. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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