Carbon–Carbon Bond Cleavage

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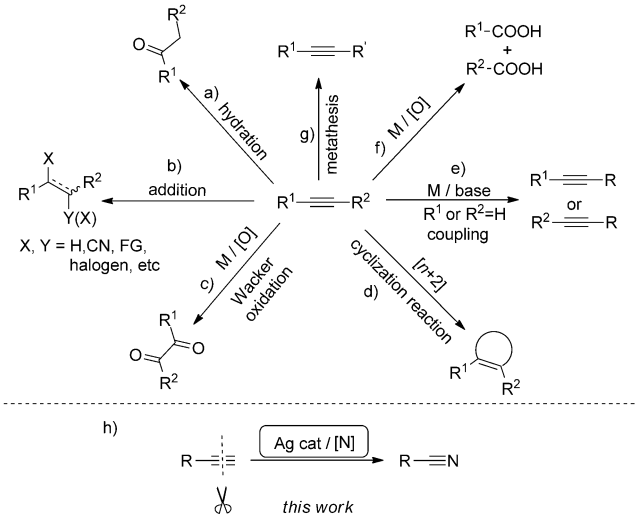
Silver-Catalyzed Nitrogenation of Alkynes: A Direct Approach to Nitriles through C≡C Bond Cleavage**

*Tao Shen, Teng Wang, Chong Qin, and Ning Jiao**

Dedicated to Professor Manfred T. Reetz on the occasion of his 70th birthday

The transformation of alkynes is a fundamental method that has been widely used in organic synthesis.[1–11] Alkyne chemistry can be dated back to the early nineteenth century. The hydration of alkynes to ketones[1] (Scheme 1 a) and the addition reactions of alkynes[2] (Scheme 1 b) are early examples. Subsequently, various catalytic systems were developed. For example, the Pd-catalyzed Wacker-type oxidation[3,4] to generate 1,2-diketones (Scheme 1 c) is one of the most important industrial processes. The development of cyclization reactions[5] such as click chemistry (Scheme 1 d)[6] has established new perspectives for the use of alkynes in drug discovery, materials science, supramolecular chemistry, polymer chemistry, and biotechnology.[7] Furthermore, the coupling of terminal alkynes, such as the Sonogashira coupling (Scheme 1 e), provides important methods for C–C bond formation.[8] The catalytic cleavage of C≡C bonds to produce carboxylic acids[9] and new alkynes[10] has also been disclosed (Scheme 1 f,g). Because of the significance and wide applications of such chemistry in organic synthesis, the exploration for new types of alkyne transformations is very attractive to researchers.



Scheme 1. Direct transformations of alkynes.

Nitriles[11] are one of the most common structural motifs in nature, and are versatile building blocks in the synthesis of natural products, pharmaceuticals, agricultural chemicals, materials, and dyes. Their importance in synthetic and medicinal chemistry has attracted considerable attention for the development of new synthetic strategies for these compounds.[12–15] Azides have been widely used in organic reactions,[16–18] but recent progress on the direct transformation of simple hydrocarbons into N-containing compounds[18] through a nitrogenation strategy encouraged us to try the direct transformation of alkynes. Although metal-catalyzed C≡C bond cleavage involving alkyne metathesis has been disclosed,[9,10] direct C≡C bond cleavage to form nitriles (Scheme 1 h) is still unknown and remains both challenging and of great value.

Herein, we report a novel and direct silver-catalyzed nitrogenation reaction of alkynes to nitriles through C≡C bond cleavage (Scheme 1 h). The significance of the present chemistry is threefold: 1) It is the first example of a direct transformation from terminal alkynes to nitriles. 2) The application of selective C–C bond cleavage in organic synthesis presents one of the most attractive and challenging projects. This chemistry provides a novel means of C–C bond cleavage. 3) Compared to traditional gold salt π-acid catalysts,[19] the silver catalyst plays a key role in this transformation. This research not only provides a new application for alkynes in organic synthesis, but also offers valuable mechanistic insights into this novel nitrogenation chemistry, which may promote the discovery of other new types of nitrogenation reactions for the construction of N-containing compounds.

The initially investigated substrate for the direct nitrogenation of acetylenes was *para*-methoxy phenylacetylene. When the reaction is performed in the presence of Ag_2CO_3 using azidotrimethylsilane ($TMSN_3$) as the nitrogen source, *p*-methoxy-benzonitrile (**2a**) was obtained in 58% yield (Table 1, entry 1). Reactions catalyzed by other transition metals, such as $AuCl_3$, $NiCl_2$, $FeCl_2$, $Cu(OAc)_2$, and $Pd(OAc)_2$, either did not proceed or gave poor yields (Table 1, entries 2 and 3; see also the Supporting Information). Product **2a** was obtained in 81% yield when DMSO was employed as the

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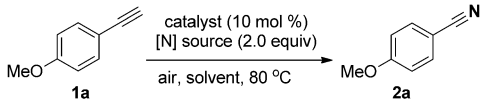
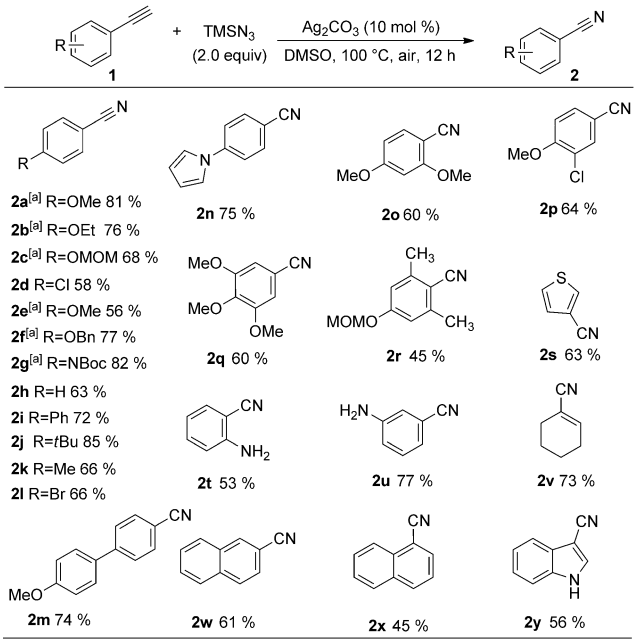
Table 1: Reaction optimization for the direct conversion of *p*-methoxy phenylacetylene **1a** into nitrile **2a**.[a]



Entry	Catalyst	[N] source	solvent	Yield of **2a** [%][b]
1	Ag_2CO_3	$TMSN_3$	DMF	58
2	$AuCl_3$	$TMSN_3$	DMF	0
3	$NiCl_2$	$TMSN_3$	DMF	0
4[c]	Ag_2CO_3	$TMSN_3$	DMSO	68
5	**Ag_2CO_3**	**$TMSN_3$**	**DMSO**	**81**
6	Ag_2CO_3	$TMSN_3$	HOAc	0
7	Ag_2CO_3	$TMSN_3$	TFA	0
8	Ag_2CO_3	NaN_3	DMSO	trace
9	Ag_2CO_3	TsN_3	DMSO	0
10	Ag_2CO_3	DPPA	DMSO	0
11	–	$TMSN_3$	DMSO	0
12[d]	Ag_2CO_3	$TMSN_3$	DMSO	62
13[e]	Ag_2CO_3	$TMSN_3$	DMSO	60
14[f]	Ag_2CO_3	$TMSN_3$	DMSO	84

[a] Reaction conditions: **1a** (0.5 mmol), catalyst (0.05 mmol), $TMSN_3$ (1.0 mmol), solvent (2 mL), stirred at 80 °C under air for 12 h. [b] Yield of isolated products. [c] The reaction was carried out at 130 °C. [d] 5 mol % of Ag_2CO_3 was used. [e] The reaction was carried out under Ar. [f] 4.0 equiv of $TMSN_3$ was used. Ac = acetyl, DMF = dimethylformamide, DMSO = dimethylsulfoxide, DPPA = diphenylphosphoryl azide, TFA = trifluoroacetic acid, TMS = trimethylsilyl.



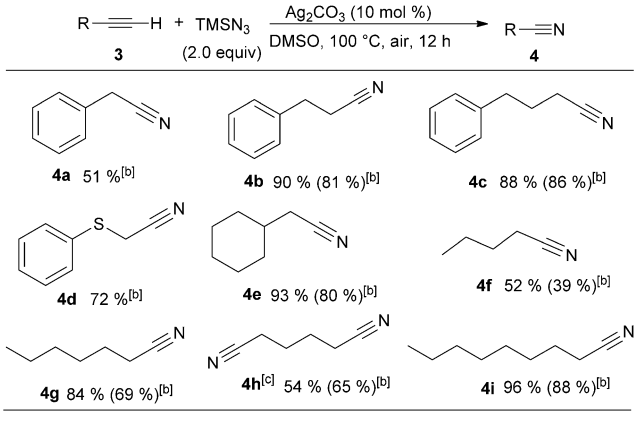
Scheme 2. Direct conversion of aryl alkynes **1** into nitriles **2**. Standard conditions: **1** (0.5 mmol), $TMSN_3$ (1.0 mmol), and Ag_2CO_3 (0.05 mmol) in DMSO (2 mL) at 100 °C under air for 12 h. Yields shown are of isolated products. [a] These reactions were carried out at 80 °C for 24 h. Bn = benzyl, Boc = *tert*-butoxycarbonyl, DMSO = dimethylsulfoxide, MOM = methoxymethyl.

solvent (Table 1, entry 5). In contrast, other solvents such as acetic acid and trifluoroacetic acid (TFA) did not perform well (Table 1, entries 6 and 7). Other azide reagents such as diphenylphosphoryl azide (DPPA), NaN_3, and *p*-tosyl azide did not yield the desired products (Table 1, entries 8–10).

The scope of the transformation was then investigated under the standard conditions (Table 1, entry 5). Phenylacetylenes bearing electron-donating substituents (MeO, EtO, BocN, Me, and *t*Bu) afforded the desired products in good to excellent yields (Scheme 2, **2a**–**2c**, **2e**–**2g**, **2j**, **2k**, and **2n**). Halo-substituted phenylacetylenes worked well to produce the corresponding halo-substituted benzonitriles, which could be used in further coupling reactions (Scheme 2, **2d**, **2l**, and **2p**). Some substrates with unprotected reactive groups, such as NH_2 and NH, are well tolerated (**2t**, **2u**, and **2y**). Heteroaryl-substituted substrates could also be converted into the desired products in moderate yields (**2s** and **2y**). Moreover, the alkenyl nitrile product **2v** was also obtained in 73 % yield.

To our delight, aliphatic alkynes could be smoothly converted into the expected alkyl nitriles in moderate to excellent yields (Scheme 3). A substrate bearing a strongly coordinating sulfur atom did not inhibit this Ag catalysis (Scheme 3, **4d**). Substrates with double C≡C bonds, such as octa-1,7-diyne, produced **4h** in 54 % yield. The long-chain alkyl alkyne dec-1-yne was converted into **4i** in better yield (96 %) than other, shorter chain, alkyl alkynes (**4f** and **4g**).

To further probe the mechanism, control experiments with possible intermediates were designed and investigated. The reactions performed well in the presence of TEMPO or BHT producing the desired product **2a** in 77 % and 72 % yields, respectively (see Eq. (S1-2) in the Supporting Information), which may exclude a radical process in this transformation. During the reaction, a key intermediate, vinyl azide **5**, was observed and characterized (Scheme 4a). This species can be directly transformed into nitrile product **2a** in 81 % yield under the standard conditions (Scheme 4b). In contrast, **2a** was obtained in only 11 % yield in the absence of $TMSN_3$, which indicates that another equivalent of $TMSN_3$ plays an important role in C≡C bond cleavage (Scheme 4b). A catalytic amount of $TMSN_3$ is enough to enable the conversion of **5** into **2a** (Scheme 4b). It can thus be concluded that the conversion from vinyl azide **5** into nitrile **2a** does not



Scheme 3. Direct conversion of alkyl alkynes **3** into aliphatic nitriles **4**.[a] These reactions were carried out at 100 °C under air for 12 h. Unless otherwise noted yields shown are based on NMR spectroscopy. [b]Yield of isolated products. [c] 4.0 equiv of $TMSN_3$ was used.

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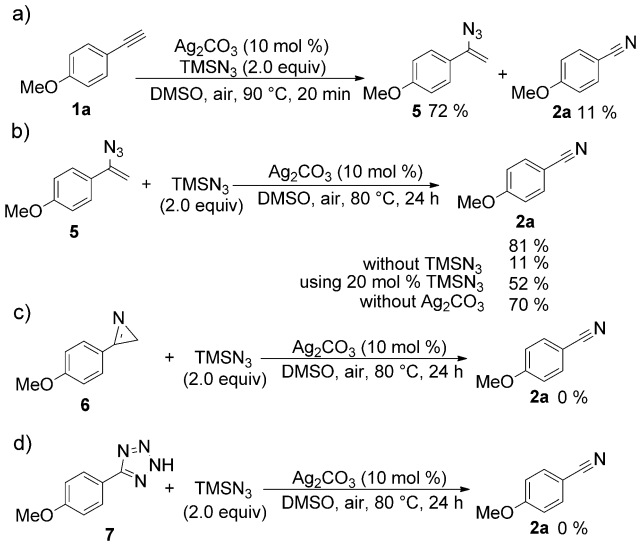


Scheme 4. Mechanistic studies and control experiments.

require the silver catalyst (Scheme 4b). Furthermore, when 3-(4-methoxyphenyl)-2*H*-azirine (**6**), which is potentially generated by the nitrene intermediate,[20] and tetrazole **7** [21,22] were employed as the substrates, the reactions did not proceed (Scheme 4c and d). These results exclude azirine and tetrazole as intermediates in this transformation.

To gain additional insight, the reaction of **1a** under standard reaction conditions in [D_6]DMSO was monitored by ^{1}H NMR spectroscopy (Figure 1). By comparison with standard samples in [D_6]DMSO (see the Supporting Information), the signal at 4.0 ppm (0–1.5 h) was assigned to **1a**. After reacting with $TMSN_3$ for 10 min, the weak signals at 4.93 and 5.53 ppm were assigned to the olefinic hydrogen of vinyl azide **5**, which reached a peak after 1.5 h (Figure 1). The signals at 7.7, 7.1, and 3.8 ppm were assigned to the nitrile product **2a**, which appeared and increased after 10 min along with the decrease of **1a**. The peaks of vinyl azide **5** became weak at 3.5 h, and completely disappeared at 6.5 h as it was converted into nitrile product **2a** (Figure 1).

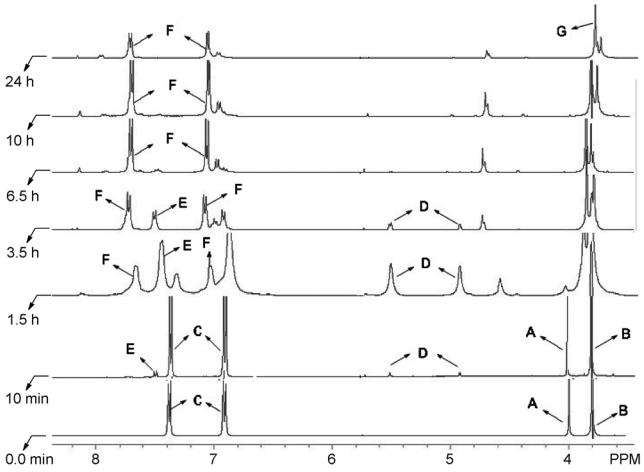
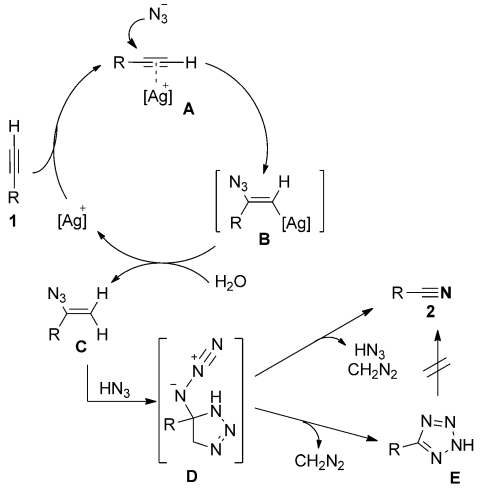


Figure 1. Reaction of **1a** monitored by ^{1}H NMR spectroscopy (400 MHz, [D_6]DMSO). **A** = **1a** alkynyl group, **B** = **1a** methoxy group, **C** = **1a** Ar–H, **D** = **5** alkenyl group, **E** = **5** Ar–H, **F** = **2a** Ar–H, **G** = **2a** methoxy group.



Scheme 5. Proposed mechanism.

On the basis of these preliminary results, possible mechanisms are proposed (Scheme 5). Initially, the alkyne is activated by the silver catalyst. Subsequent attack by azide anion generates *trans*-alkenyl metal complexe **B**. The protonation of **B** generates vinyl azide **C** with a trace amount of H_2O in the DMSO solvent, which was supported by an exchange experiment in the presence of D_2O (see the Supporting Information). Next, vinyl azide **C** cyclizes with azide like traditional click reaction to form the unstable intermediate **D** (Scheme 5).[21] Although the rearrangement of intermediate **D** could occur and produce tetrazole **E** in conjunction with the release of CH_2N_2,[21] the control experiment excludes the conversion of tetrazole **E** into nitrile product **2** under the standard reaction conditions (Scheme 4d). Therefore, the direct transformation of intermediate **D** into nitrile product **2** through a fast rearrangement process that releases HN_3 and CH_2N_2, which were detected by GC-MS (see the Supporting Information), is proposed. In the last step, the HN_3 produced is reused in the cyclization step of **C** to produce **D**.

In summary, we have demonstrated the first direct conversion of alkynes into nitriles by Ag-catalyzed nitrogenation of alkynes through C≡C bond cleavage. From the results of the present study, and on the basis of the proposed mechanism, it should be possible to develop novel chemical transformations through C–C bond cleavage, which should be of interest to both industrial and academic researchers.

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