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AgN3-Catalyzed Hydroazidation of Terminal Alkynes and Mechanistic Studies

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AgN₃-Catalyzed Hydroazidation of Terminal Alkynes and Mechanistic Studies

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ABSTRACT: The hydroazidation of alkynes is the most straightforward way to access vinyl azides – versatile building blocks in organic synthesis. We previously realized such a fundamental reaction of terminal alkynes using Ag_2CO_3 as a catalyst. However, the high catalyst loading seriously limits its practicality, and moreover the exact reaction mechanism remains unclear. Here, on the basis of X-ray diffraction studies on the conversion of silver salts, we report the identification of AgN_3 as the real catalytic species in this reaction, and therefore developed a AgN_3 -catalyzed hydroazidation of terminal alkynes. AgN_3 proved to be a highly robust catalyst, as the loading of AgN_3 could be as low as 5 mol%, and such a small proportion of AgN_3 is still highly efficient even at a 50 mmol reaction scale. Further, the combination of experimental investigations and theoretical calculations disclosed that the concerted addition mechanism via a six-membered transition state is more favored than the classical silver acetylide mechanism.

■ INTRODUCTION

Alkynes are versatile building blocks for organic synthesis, and the development of catalytic reactions to convert carbon-carbon triple bonds (C≡C) into other functionalities is of great value to a synthetic chemist.¹ The hydrofunctionalization of alkynes is a highly appealing strategy for accessing functionalized alkenes in an atom-economical manner.² In this context, the hydroazidation of alkynes is the most straightforward approach to access α -vinyl azides,³ a class of synthetically useful functionalized alkenes, that have been widely exploited as versatile building blocks in organic synthesis.4 However, the hydroazidation of alkynes is primarily dependent on the Michael addition of azide anions to the activated alkynes.⁵ In terms of more general unactivated alkynes, no efficient method was available⁶ until we reported a Ag₂CO₃-catalyzed hydroazidation reaction of terminal alkynes in 2014 (Figure 1a).7 Since then, our group and others have further demonstrated the power of this method by developing a wide variety of tandem reactions involving such a silver-catalyzed reaction as a critical step.^{4a,4b,8} However, this fundamental reaction has not yet been well developed because of the following significant issues: 1) the reaction mechanism is unclear; 2) the loading of silver salt is high (equal to 20 mol% Ag), which has seriously limited the practicality of this method. Hence, addressing these issues is essential for eventually establishing this fundamental reaction.

The isolation and identification of organometallic intermediates in a transition-metal-catalyzed reaction would provide most usefull information of their possible involvement in a reaction mechanism. However, this is

challenging for silver-catalyzed reactions, because in situformed organosilver intermediates readily undergo demetallation-protonation. In such situations, а technique capable of identifying the silver intermediate in a reaction process would be highly desirable. X-ray diffraction (XRD) is useful for identifying metal catalysts and their activation and/or deactivation behavior during reaction.9 Herein, for the first time, we applied XRD to study a silver-catalyzed organic reaction and found that Ag₂CO₃ underwent a rapid conversion to AgN₃, thus identifying AgN, as the actual catalytic species (Figure 1b). Although AgN₃ has been proposed as a plausible intermediate in some silver-catalyzed nitrogenation reactions,10-13 no spectroscopic evidence was available to support its existence. AgN₃ itself proved to be a highly robust catalyst for the hydroazidation of alkynes, with low catalyst loading (5 mol%) and efficiency at large scale reaction (up to 50 mmol). Finally, experimental investigations and theoretical calculations clarified the catalytic mechanism by AgN₃.





AgN₃ identified by XRD • Ag as an azido group shuttle • AgN₃ as catalyst and reactant
 Low AgN₃ catalyst loading • Unusual concerted addition mechanism

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Figure 1. Silver-catalyzed hydroazidation of terminal alkynes.

■ COMPUTATIONAL METHODS

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All of the DFT calculations were performed with the Gaussian 09 package.14 The B3LYP15 functional with the standard 6-31G(d,p) basis set (SDD¹⁶ basis set for Ag) was used for geometry optimizations. The vibrational frequencies were computed at the same level of theory to check whether each optimized structure is an energy minimum or a transition state and to evaluate its zeropoint vibrational energy (ZPVE). Intrinsic reaction coordinate (IRC)17 calculations were carried out to ascertain the true nature transition states. Mo6 functional proposed by Truhlar et al.¹⁸ with the 6-31++G(d, p) basis set (SDD basis set for Ag) was used to calculate the singlepoint energies, because it has been widely used in recent literature to account for noncovalent interactions in transition metal system,19 including silver,20 Solvent effects (solvent = Dimethylsulfoxide) was evaluated by single-point energy calculations of the solution-phase stationary points with SMD solvation model.²¹ Unless other noted, all the discussions in the text are presented using the $SMD_{(DMSO)}/Mo6/6-31++G(d,p)-SDD(Ag)$ level of theory.

RESULTS AND DISCUSSION

Identification of AgN₃ as the real catalyst. We initially conducted an XRD study on the Ag₂CO₃-catalyzed hydroazidation reaction (Figures 2 and S1). p-Tolylacetylene (1a) was chosen as a model reactant. XRD analysis of the crude insoluble reaction mixture clearly showed a rapid and complete conversion of Ag₂CO₂ to AgN₃ within 5 min. Notably, vinyl azide 2a was not observed in that time, but was after 20 min, as evidenced by 'H NMR analysis (see SI, Figure S2). Several experiments were conducted in parallel under the same reaction conditions, and the insoluble catalytic mixture was removed at different times from each reaction and analyzed by XRD. For comparison, pure AgN₃ was separately prepared by the reaction of AgNO₃ with NaN3.22 The diffraction peaks of these solids were consistent with those of pure AgN₂ (Figure 2), indicating that the catalytic species in this reaction is AgN₃ rather than Ag₂CO₃. To our knowledge, this is the first time XRD was used to study a silver salt-catalyzed organic reaction.23



Figure 2. Reaction monitoring by powder XRD. Patterns at different times of the solid material generated from the Ag₂CO₃-catalyzed hydroazidation reaction, the prepared AgN₃ (blue line) and β -Ag₂CO₃ (orange line). *Safety Notice:* AgN₃ should be avoided to be subjected to stimuli, such as impact, heat (> 273 °C), friction using metal spoon, or discharge. The explosion temperature generally needs to reach 273 °C.

To further confirm the unexpected conversion of Ag,CO₂ to AgN₂, treatment of Ag,CO₂ with trimethylsilyl azide (TMSN₂) was performed in the absence of alkyne and water (Figure 3a). To our surprise, a rapid and complete transformation from Ag₂CO₃ to AgN₃ was observed, as indicated by XRD analysis of the reaction mixture (See SI, Figure S₃). The side product hexamethyldisiloxane $[(CH_3)_3Si-O-Si(CH_3)_3]$ was confirmed by ¹H, ¹³C, and ²⁹Si NMR spectroscopy and MS analysis. To the best of our knowledge, the conversion of Ag₂CO₂ with TMSN₂ to yield AgN₂ represents a new inorganic reaction of silver salts. To rationalize the reaction process, DFT calculations were performed (Figure 3b). Three sequential reaction steps were disclosed, including first Si-O bond formation, decarboxylation, and second Si-O bond formation, for which the energy barriers are 4.6, 9.5, and 11.7 kcal/mol, respectively, suggesting that the conversion from Ag₂CO₃ to AgN₂ proceeds quickly and smoothly under standard conditions.

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Figure 3. a) The reaction of Ag_2CO_3 with TMSN₃ in absence of alkyne and water. b) Mo6/6-31++G(d,p)-SDD (Ag) computed free energy profile for the conversion of Ag_2CO_3 to AgN_3 . DMSO acts as ligands.

On the basis of this conversion, we envisage AgN₃ should be the real catalyst for the hydroazidation of terminal alkynes. To confirm this, AgN₂ was prepared separately and examined in the hydroazidation reaction of p-tolylacetylene (1a) and TMSN₃ in the presence of water at 80 °C (Figure 4a). Encouragingly, the transformation efficiency increased with increasing AgN₃ loading amount, and even as little as 5 mol% of AgN₃ could catalyze a complete transformation affording the desired vinyl azide 2a in 89% NMR vield. These results clearly suggested that AgN₃ was the real catalytic species with high catalytic activity. Furthermore, the effect of solvent on this AgN₃-catalyzed reaction was examined (Figure 4b). The solvent appeared to have significant influence: use of DMSO gave an 86% yield of isolated vinyl azide 2a, and, with the exception of DMF (54% yield), other solvent such as CH₃CN, THF, and 1,4-dioxane were all ineffective.



Figure 4. a) Effect of the amount of AgN_3 on the reaction efficiency: **1a** (0.5 mmol), TMSN₃ (1.0 mmol), AgN_3 (0~5 mol%), DMSO, 80 °C, 90 min. b) Effect of solvent: **1a** (0.5 mmol), TMSN₃ (1.0 mmol), AgN_3 (5 mol%) in different solvents, 80 °C, 90 min. Yields refer to isolated products.

AgN, is a robust catalyst for the hydroazidation of terminal alkynes. We then investigated the scope of the AgN₃-catalyzed hydroazidation reaction at a small scale. A variety of aryl alkynes, bearing either electron-donating or electron-withdrawing substituents at either the para or *meta* positions of the phenyl ring, all smoothly reacted to give corresponding vinyl azides 2a-2k in good-toexcellent yields (82-93%, Scheme 1). Likewise, two heteroaryl alkynes, 2-pyridyl and 2-thienyl acetylenes, were reactive and converted into expected heteroarylvinyl azides 2l and 2m in 81% and 70% yields, respectively. The scope of this hydroazidation reaction was not limited to aryl alkynes, as alkyl-substituted alkynes were also viable substrates. For example, *n*-hexyl-, phenylethyl-, and benzyl-substituted alkynes furnished expected products 2aa-2ac in 82%, 86%, and 83% yields, respectively. Moreover, alkyl alkynes bearing potentially sensitive functional groups, such as hydroxy, chloro, carboxyl, ether, thioether, and amino groups, all smoothly underwent this reaction, delivering target products 2ad-2aj in good-to-excellent yield (75-94%). In addition, cyclohexylacetylene was suitable for this reaction, affording 2ak in 73% yield. Notably, this strategy was also applied to the direct postmodification of bioactive compounds, clodinafop-propargyl (1al) and ethisterone (1am), which afforded the corresponding vinyl azides 2al and 2am in 85% and 78% yields, respectively. Overall, these results clearly demonstrate the excellent catalytic activity of AgN₃ in the hydroazidation of terminal alkynes.

To our knowledge, this is the first time to exploit AgN_3 in an organic reaction.²²

Encouraged by the above results, we further evaluated the practicality of the AgN₃-catalyzed hydroazidation reaction on a multigram scale (Scheme 2). We were pleased to find that the reactions of aryl alkynes **1a**, **1b**, and **1g** could be performed on an approximate 30~50 mmol scale, affording the corresponding products **2a**, **2b**, and **2g** in 89%, 77%, and 79% yield, respectively. Additionally, functionalized aliphatic alkynes having ether (**2ag**), thioether (**2ah**), hydroxy (**2aj**), protected amino (**2an**), or cyclohexenyl (**2ao**) groups were amenable to large-scale reactions, giving the desired vinyl azides with good-to-high yields. Note that 5 mol% AgN₃ was used in these reactions, thus further demonstrating AgN₃ is a robust catalyst for the hydroazidation reaction of terminal alkynes.

Scheme 1. Scope of AgN₃-catalyzed hydroazidation of terminal alkynes on a small scale



To avoid the direct operation of potentially explosive AgN_3 , we try to develop a one-pot two-step protocol to achieve similar high catalytic efficiency starting from the employment of Ag_2CO_3 as catalyst (Scheme 3). Through extensive investigations on the factors that could influence the reaction outcome in such a one-pot two-step protocol (See SI, Schemes S1-S2), we found that water should be added after the in situ formation of AgN_3 , otherwise the catalytic activity would be significantly inhibited due to some kind of silicon-containing floc simultaneously formed during the conversion from Ag_2CO_3 to AgN_3 and covered on the surface of AgN_3 particles (See SI, Figures S5-6). Eventually, we established

a low catalyst-loading Ag_2CO_3 -catalyzed hydroazidation reaction in a one-pot two-step operation. The reaction scope is quite broad and afforded the corresponding vinyl azides in 70–81% yield.

Scheme 2. Multigram-scale synthesis of vinyl azides



Scheme 3. Ag₂CO₃-catalyzed hydroazidation of alkynes in a one-pot two-step protocol



Experimental investigations and DFT studies on the **AgN₃-catalyzed reaction mechanism.** To gain mechanistic insights into the AgN₃-catalyzed reaction, control experiments were designed and performed. As summarized in Scheme 4, in the presence of two equivalents of deuterium oxide (D_2O) , the reaction of **1b** with TMSN₃ afforded a deuterated product [D]-2b in 85% yield, and we identified that the di-deuterated, two kinds of mono-deuterated and non-deuterated [D]-2b products were forming in 36%, 36%, 14% and 14% of overall mixture (Eq. 1). When starting from deuterated substrate [D]-1b, [D]-2b was obtained in a similar yield (86%), albeit with a low 10% and 6% mono-deuterated products (Eq. 2). These two results implied that a silver-acetylide intermediate formed from the alkyne by cleavage of the C_{sp}-H bond during the reaction. Then, using silver acetylide [Ag]-1b as a reactant under reaction conditions, albeit in the absence of AgN₂, which resulted in a mixture of vinyl azide 2b and alkyne 1b with a ratio of 1:2.8, thus silver acetylide could be converted to alkyne in turn (Eq. 3). The results support that there exists a fast equilibrium between alkyne and silver-acetylide, which was also verified by the DFT calculations. In contrast, no reaction

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occurred if internal alkyne **1b**-Me was used as the substrate under the same conditions (Eq. 4).

Scheme 4. Control experiments

Terminal alkyne ____ Ph-1b AgN₃ (5 mol% 1) + **D_O** (2.0 equiv) TMSN₃ °Ċ. DMSO 80 2.0 equiv 36% 36% 14% 14% The ratio detected by ¹H NMR 93% Ph _ [D]-1b AaN₂ (5 mol% 2) + H₂O (2.0 equiv TMSN₃ 80 °C, DMSO 2.0 equiv 84% 10% 6% The ratio detected by ¹H NMR TMSN₃ (1.5 equiv) Ph Ph-== H₂O (2.0 equiv) 80 °C. DMSO 2b:1b, 1:2.8 [Ag]-1b (The ratio detected by ¹H NMR) Internal alkvne AgN₃ (5 mol%) TMSN₃ Ph -Me no reaction H₂O (2.0 equiv) DMSO, 80 °C 1a-Me

With the above experimental results in hand, density functional theory (DFT) calculations were conducted to gain more insights into the reaction mechanism. Initially, the alkynes must coordinate with the AgN₃ catalyst to form an active complex. It was found that A1, the complex representing double AgN₃ activation, is more stable than A1' by 16.9 kcal/mol. Gibbs free energies of the formation of different likely active species (A1', A1, and A1-Me) computed with respect to the separated reactants (substrates, AgN₃, and DMSO).²⁴ Two activation models, A1' and A1, were considered for the coordination of terminal alkyne **1b** with 1 or 2 molecules of AgN_3 (Scheme 5a). Furthermore, natural population analysis (NPA) charge analysis showed that the charge on the terminal C2 in A1 (-0.438) is more negative than that in A1' (-0.314), indicating that the C=C triple bond of A1 is more polarized and activated than that of A1'; therefore, the silver ion preferentially attacks at C2 of A1, which is an important driving force for the reaction. The C=C triple bond of the internal alkyne A1-Me is not polarized by AgN₃, as supported by the similar NPA charge on the C1 and C2 atoms. Therefore, the electrophilic attack of silver ion at the C2 atom of A1-Me is unfavorable and therefore does not occur, which is consistent with the experimental observation (Scheme 4, Eq. 4).

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Figure 5. Mo6/6-31++G(d,p)-SDD (Ag) computed free energy profiles of two possible pathways for the AgN_3 -catalyzed hydroazidation of terminal alkynes and the computed structures of the key transition sates (distances in Å).

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Scheme 5. Computed skeletons of three types of silver-alkyne complexes and two types of reaction modes^a



^{*a*} The relative free energies in parentheses are given in kcal/mol and the solvent ligand (DMSO) is omitted for clarity.

Furthermore, based on the double activation mode A1, two possible reaction pathways were proposed (Scheme 5b). One proceeds through the classical silver acetylide intermediate (Mode I). As suggested by the results of the deuteration studies (Scheme 4), silver acetylide is formed during the reaction, which could react with the HN₃ generated in situ to achieve hydroazidation. This is a stepwise procedure involving C_{sp}-H bond cleavage. In another possible pathway (Mode II), the Ag ion activates the terminal carbon atom (C2) and leads to the polarization of the C=C triple bond, which might induce a concerted addition, that is, the azide anion of coordinated AgN₂ simultaneously attacks the internal carbon atom (C1), resulting in the formation of the crucial alkenylsilver intermediate. Based on the results of these experimental studies and theoretical calculations, we carried out further DFT calculations on these two possible reaction pathways.

Silver acetylide mechanism. Silver acetylides are commonly proposed as intermediates in silver-catalyzed reactions of terminal alkynes.25,4b Therefore, we first investigated the classical silver acetylide mechanism (Figure 5, Path A). From the stable complex A1, one molecule of AgN₃ first activates the C-H bond of 1b via the six-membered ring transition state TSA1 (6.2 kcal/mol) to form a AgN₃-silver-acetylide-HN₃ complex A2. Notably, the free energy of complex A₂ is 0.9 kcal/mol higher than that of complex A1, which indicates that the C(sp)-H bond activation is an endergonic and reversible process. It is feasible that the alkyne complex A1 and silveracetylide-HN₃ complex A2 are in a fast equilibrium, due to similar energies and small activation barriers between these two species, which is consistent with experimental observations (Scheme 4). Note that similar behavior has been reported for copper-catalyzed C_{sp}-H activation of terminal alkynes by the formation of a copper acetylide.²⁶ Next, the nucleophilic addition of HN₃ to the triple bond of the silver acetylide (TSA2, 11.9 kcal/mol relative to A1) produces alkenylsilver intermediate A3. The nucleophilic addition of AgN₃ to the silver acetylide was also

considered, but it could be excluded due to the high energy barrier (**TSA2-1**, 26.3 kcal/mol). Intermediate **A3** then undergoes proto-demetallation assisted by HN₃ (**TSA3**, 5.2 kcal/mol) to provide vinyl azide product **2b**. In addition to the pathway of the reaction between terminal alkyne and AgN₃, HN₃ can also be generated by the silvercatalyzed reaction of water with TMSN₃, which has a low energy barrier (4.8 kcal/mol) (see SI, Figures S13-14). In Path A, **TSA2** is the highest stationary point and overall kinetic barrier with 11.9 kcal/mol. Thus the silver acetylide pathway is energetically feasible under the experimental conditions.

Concerted addition mechanism. one of the bound molecules of AgN₃ (labeled 1 in Figure 5) undergoes concerted addition across the triple bond of 1b via a sixmembered-ring transition state TSB1 (8.1 kcal/mol), in which another molecule of AgN₃ (labeled 2 in Figure 5) is π -coordinated to **1b** (Figure 5, Path B). This could significantly reduce the energy barrier, thereby resulting in alkenylsilver intermediate B1. This is the ratedetermining step in Path B (TSB1, 8.1 kcal/mol). In TSB1, the attack of silver ions (Ag1) to terminal carbon atom C2 leads to further polarization of the C=C triple bond, thus favoring the addition of azido ion to the internal carbon atom C1. In contrast, the concerted addition of internal alkyne **1b**-Me (**TSB1**-Me, 23.1 kcal/mol) is energetically disfavored (see SI, Figure S15), which is also consistent with the experimental results and NPA charge analysis (Schemes 4 and 5a). Then, the demetallation-protonation of alkenylsilver B1 with HN3 occurs via transition state TSB2 (7.4 kcal/mol), affording product 2b, with the regeneration of two molecules of AgN₃ and three molecules of DMSO. Note that the possibilities of demetallation-protonation process assisted by water, instead of HN₃, were also considered: TSB2-2w is calculated to be the most favored one among the transition states assisted by different numbers of water, but the energy barrier is too high (21.9 kcal/mol) to proceed under this reaction conditions (see SI, Figures S16-S17).

Taken together, the overall energy barrier in Path B is 3.8 kcal/mol more favored than that in Path A. In both pathways, silver serves as an azido group shuttle to transfer the azido functional group from TMSN₂ to α vinyl azide products. In the meantime, DFT methods Mo6-2X and ω B97XD with the same basis set 6-31++G(d,p)-SDD(Ag) were employed to calculate the solvation single point energies of the two Paths A and B for comparison (Figures S18-19 and Table S1 in Supporting Information). Our computational results indicated that Mo6, Mo6-2X and $\omega B_{97}XD$ functionals give the same trend in the relative energies of transition states and intermediates. The relative energies of transition states and intermediates on the potential energy surfaces in Paths A and B at Mo6/6-31++G(d,p)-SDD(Ag) level are much lower than those at Mo6-2X(ω B97XD)/6-31++G(d,p)-SDD(Ag) levels, the differences of Gibbs free energy values between TSA2 and TSB1 using these three methods are 3.8 (Mo6), 2.1 (Mo6-2X) and 4.5 (ω B97XD). Note that

the activation of alkyne by one molecule of AgN₃ in Mode I and Mode II were considered, but finally was excluded due to the high energy demands (See SI, Figures S20-22).

NCI analysis of TSA2 and TSB1

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Figure 6. Noncovalent interaction (NCI) plots for TSA₂ and TSB₁.

To get more information about the differences between these two pathways, we carried out noncovalent interaction (NCI) analysis²⁷ for the critical transition states, **TSA2** and **TSB1**. NCI analysis shows that the coordination of the C \equiv C triple bond (a2) and one molecule of solvent (b2) to silver center Ag2 and two molecules of solvent to Ag1 (c2, d2), as well as the electrostatic interactions between the Ag1 and the azide ion (e), effectively stabilize the structure of **TSB1**, thereby promoting this step (Figure 6). However, in **TSA2**, the strong electrostatic interaction e is absent. Overall, the calculation results revealed that this concerted addition mechanism (Path B) is favored over the silver acetylide mechanism (Path A).

On the basis of the experimental and calculation results, we propose two plausible reaction pathways A and B (Scheme 6). A silver– π complex A1 with two molecules of AgN₂ is first formed from alkyne **1** in the presence of the AgN₃ catalyst. A1 may undergo cleavage of the C_{sp} -H bond of alkyne to get a AgN₂-silver-acetylide-HN₂ complex A₂, and this process was proved to be in a fast equilibrium during the reaction. Then, the nucleophilic addition step produces alkenylsilver intermediate A3 (Path A). Alternatively, from A1, the slightly more favorable concerted addition of cationic silver and azido anion to the triple bond of alkyne 1 could also produce an alkenylsilver intermediate B1 (A3 and B1 are isomers, Path B). Subsequently, protonation of A₃ or B₁ by HN₃ formed in situ occurs and delivers the vinyl azide product 2, in which the generation of HN₃ proceeds through the reaction of water with TMSN₃ catalyzed by AgN₃.

Scheme 6. Proposed mechanism for the AgN₃catalyzed hydroazidation of terminal alkynes



CONCLUSION

A highly efficient AgN₂-catalyzed hydroazidation of terminal alkynes is reported. The reaction mechanism has been elucidated by the combined use of experimental investigations and theoretical calculations. XRD studies revealed AgN₃ is the real and robust catalyst in the Ag₂CO₃-catalyzed protocol. Furthermore, a new inorganic reaction between Ag₂CO₃ and TMSN₃ to yield AgN₃ was demonstrated and further rationalized by DFT calculation. The AgN₃-catalyzed hydroazidation of terminal alkynes was efficient and practical because of the low catalyst loading (5 mol%) and scalable reaction (up to 30~50 mmol). DFT calculations disclosed an unusual concerted addition mechanism is more favorable than the stepwise silver-acetylide mechanism. We therefore have developed a fundamental AgN₃-catalyzed hydroazidation reaction of terminal alkynes and further clarified the catalytic mechanism. Moreover, AgN3 was for the first time exploited in organic synthesis, thus opening an avenue to the exploration of its synthetic potency as a promising azido reagent. Taken together, the significance of these findings would not be only restricted to the specific hydroazidation of alkynes, but also have important inspiration on other silver-catalyzed reactions.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, additional figures, details of DFT calculations, and NMR spectra are available free of charge *via* the Internet at (http://pubs.acs.org/page/jacsat/submission/authors.html).

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