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General Silver-Catalyzed Hydroazidation of Terminal Alkynes by Combining TMS-N_3 and H_2O: Synthesis of Vinyl Azides

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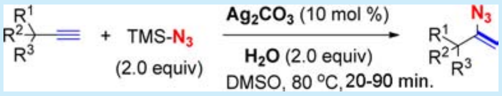
Ⓢ *Supporting Information*

ABSTRACT: A general hydroazidation of unactivated alkynes using silver catalysis is reported. The reactions of diverse terminal alkynes with trimethylsilyl azide (TMS-N_3) in the presence of H_2O afforded the corresponding vinyl azides in good to excellent yields. This reaction has a broad substrate scope, good functional group tolerance, simple operation, and high reaction efficiency, thus providing an easy access to various functionalized vinyl azides.



Vinyl azides have been known for 100 years, since the first report by Forster and Newman in 1910.[1] These compounds are versatile synthetic intermediates for numerous transformations,[2] particularly in recently developed transition-metal-catalyzed azaheterocyclization reactions.[3] However, the synthetic potency of vinyl azides remains largely underexplored because of the intrinsic high reactivity and limited general and efficient methods available for their preparation.[2] Therefore, the development of practical synthetic methods for the convenient preparation of newly functionalized vinyl azides is still highly appealing. Alkynes are easily available building blocks, and the hydroelementation of alkynes is a powerful method to access various functionalized alkenes.[4] The hydroazidation of alkynes is an ideal route to vinyl azides.[5] Such reactions have been rarely reported and almost all have been limited to the Michael addition of azide anions to electron-deficient alkynes. Regarding unactivated alkynes, only two examples have been known: (1) Banert reported the reaction of butadiyne with lithium azide (LiN_3) to give 1-azidoenyne,[5d] and (2) Jiao and co-workers isolated a vinyl azide intermediate during the mechanistic studies of the nitrogenation of alkynes to nitriles (Figure 1, *a*).[6] Recently, the chemoselective reactions of alkynes with TMS-N_3 were reported by the Jiao[6,7a] and Echavarren[7b] research groups by varying the catalysts. In our ongoing efforts to develop novel organic reactions using functionalized alkynes,[8] we accomplished a chemo- and regioselective silver-catalyzed hydroazidation of ethynyl carbinols with TMS-N_3, affording diverse 2-azidoallyl alcohols (Figure 1, *b*).[8b] The hydroxyl group of ethynyl carbinols played a critical role as the proton source, and a trace amount of water in DMSO was necessary for the reaction. Therefore, we envisaged that the presence of a stoichiometric amount of H_2O would avoid the dependence of the hydroxyl group, thus *establishing a general hydroazidation reaction of unactivated alkynes in a real sense*. The experimental results confirmed this hypothesis, and we found that diverse terminal alkynes could react with trimethylsilyl azide (TMS-N_3) by means of silver catalysis in the presence of H_2O to afford the corresponding vinyl azides in excellent yields (Figure 1, *c*). Herein, we report this powerful method for the synthesis of vinyl azides.

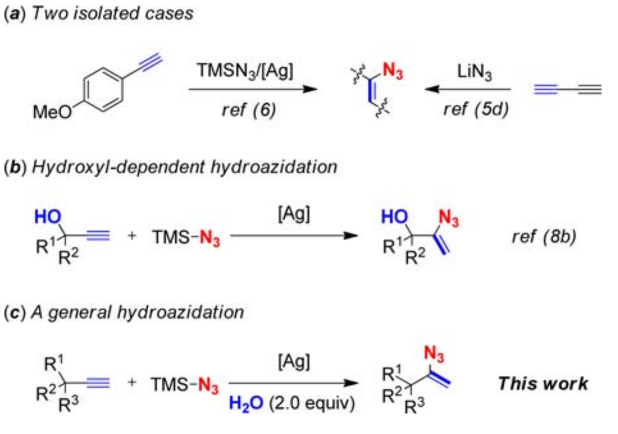


Figure 1. Hydroazidation of unactivated alkynes.

First, the effect of the amount of H_2O in the solvent was investigated using the reaction of 4-bromophenylacetylene (**1a**) and TMS-N_3 as the model. In dry DMSO, a mixture of **2a** and substrate **1a** was obtained at a ratio of 1:3 determined by ^1H NMR analysis of the reaction mixture. Once H_2O (2.0 equiv) was added to the reaction system, a single product **2a** was obtained. However, increasing the amount of H_2O to 1 mL resulted in a large amount of substrate **1a** left in the reaction, and only a trace amount of the vinyl azide **2a** was detected. These results demonstrated that an appropriate amount of H_2O was essential for the hydroazidation of terminal alkynes with TMS-N_3, in which the role of H_2O might react with TMS-N_3 to generate HN_3.[8b,9]

Further, a detailed study on the conversion of **1a** into **2a** in the presence of 2.0 equiv of H_2O was carried out in a time course. An aliquot of the reaction mixture was taken out at regular intervals (ca. 10 min) and directly analyzed by ^1H NMR spectra. As shown

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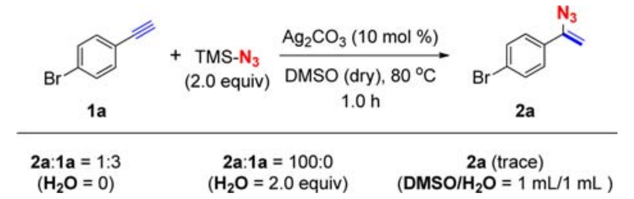


in Figure 2, a proportional increase of product **2a** and consummation of substrate **1a** was observed. This result proved the clean transformation from **1a** to **2a** in the reaction with TMS-N_3. However, once the reaction time ws prolonged, the 4-bromobenzonitrile could be detected like Jiao's report.[6] Consequently, the strict control of the reaction time was necessary in order to avoid the further conversion of vinyl azides to nitriles.

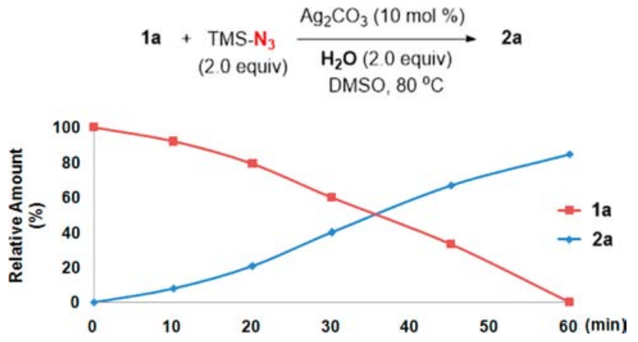
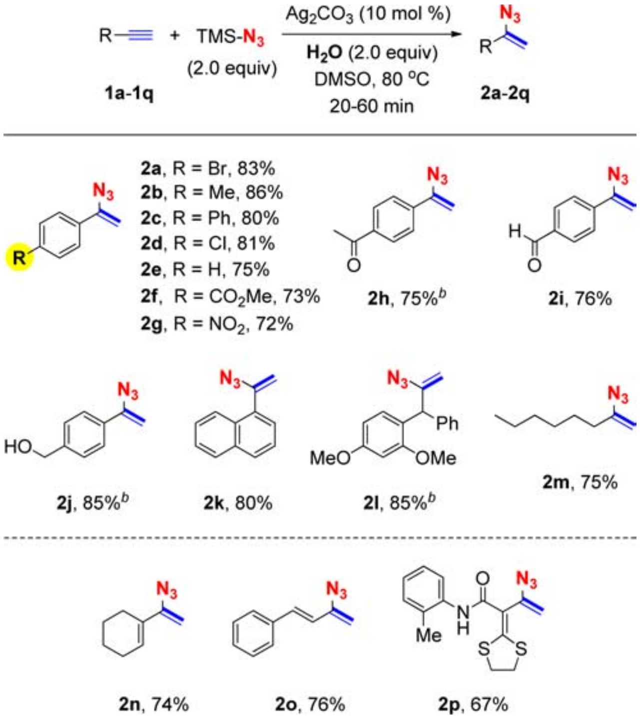


Figure 2. Time course of the reaction of **1a** with TMS-N_3 in the presence of 2.0 equiv of H_2O.

The silver-catalyzed hydroazidation of terminal alkynes with TMS-N_3 in the presence of two equivalents of H_2O was first investigated using various aryl-, alkyl-, and alkenylalkynes (Scheme 1). In general, the substrate scope was quite broad, and diverse aryl-, alkyl-, and alkenylalkynes could be applied to this silver-catalyzed procedure, thus affording the corresponding vinyl azides (**2a**−**p**) chemoselectively and in good-to-high yields (67−86%). All the reactions proceeded smoothly and were complete within 20−60 min. Various substitutents on the benzene ring of phenylacetylene were well tolerated such as electron-donating (Me, and Ph) and -withdrawing groups (Cl, Br, CO_2Me, NO_2, CH_3CO, and HCO). Some of these functional groups are useful for further synthetic diversification. Similar to aryl alkynes, aliphatic alkynes (**1l**, and **1m**) were also applicable. Notably, the reaction of sterically bulky alkyne **1l** reacted with TMS-N_3 smoothly afforded the corresponding vinyl azide, **2l**, in 85% yield, albeit requiring a slightly large amount of the silver catalyst (30 mol %). The reactivity of several alkenyl alkynes (**1n**, **1o**, and **1p**) was investigated, and the corresponding 2-azidobuta-1,3-dienes (**2n**, **2o**, and **2p**) were obtained in good yields. Notably, the reaction of a terminal alkyne sterically encumbered in a complex molecular skeleton such as α-ethynyl ketene dithioacetal (**1p**) with TMS-N_3 smoothly afford vinyl azide **2p** in a good yield (67%).

Functionalized allylamines are not only useful building blocks in organic synthesis[10a,b] but also possess remarkable biological activity.[10c,d] Therefore, we next applied the silver-catalyzed, H_2O-participating hydroazidation of terminal alkynes to synthesize 2-azidoallyl amines. To the best of our knowledge, such compounds are unknown.[11] As summarized in Scheme 2, diverse *N*-protected allylamines participated in this silver-catalyzed method to afford the desired 2-azidoallyl amines (**4a**−**p**) in good-to-excellent yields (66−89%). The functional groups on the *N*-atom were well tolerated, including electron-rich and -poor aryl, fused aryl, tosyl, benzyl, benzoyl, and alkenyl groups (**4a**−**h**). The variation in the substituents at the 3-position of allylamines had no influence on the reaction outcome (**4i**−**p**). Notably, the reactions of substrates (**3j** and **3k**) containing a sterically bulky quaternary carbon center with TMS-N_3 also smoothly afforded the corresponding products (**4j** and **4k**) in 76% and 66% yields, respectively. Next, other heteroatoms such as oxygen and sulfur instead of nitrogen were investigated. To our delight, propargyl ethers (**5a**−**i**) and thioether (**5j**) participated in this hydroazidation reaction, affording diverse functionalized vinyl azides (**6a**−**j**) in good yields. Notably, the products, **2**, **4**, and **6** are highly functionalized and thus of great interest for further synthetic exploitation.

Scheme 1. Hydroazidation of Aryl, Alkyl, and Alkenyl Terminal Alkynes[a,b]

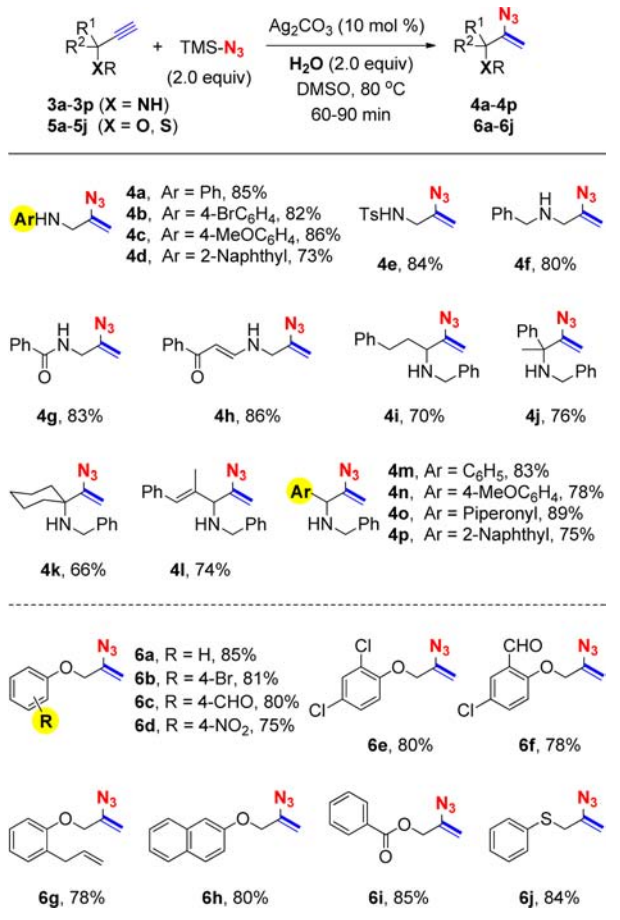


[a] Reaction conditions: **1** (0.5 mmol), H_2O (1.0 mmol), Ag_2CO_3 (0.05 mmol), DMSO (2 mL), 80 °C, 20−60 min. [b] 30 mol % Ag_2CO_3 was used.

Encouraged by these results, we further investigated the hydroazidation of other types of easily accessible terminal alkynes. 4-Alkynones can be easily prepared by the base-catalyzed nucleophilic substitution of β-dicarbonyl compounds with propargyl bromides. Previously, we investigated the synthetic potency of these functionalized alkynes in the [4C + 1N] annulation with primary amines, leading to polysubstituted pyrroles.[8j] When they were subjected to the silver-catalyzed hydroazidation reaction (Scheme 3), to our delight, the corresponding vinyl azides (**8a**−**d**) were obtained in high yields (80−86%) within a short reaction time (60−90 min). These novel multifunctionalized vinyl azides have great potential for further synthetic utilization.

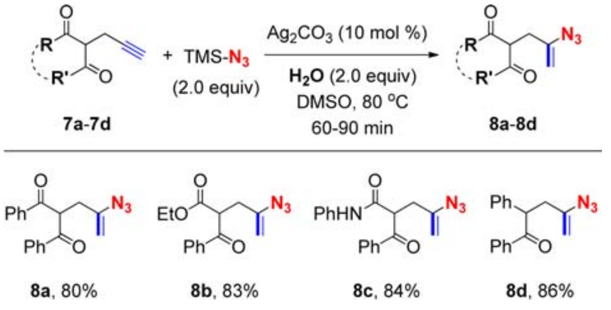
The substrate scope of the hydroazidation of terminal alkynes can be extended to dialkynes such as *N*,*N*-di(prop-2-yn-1-yl)aniline (**9a**) and 1,7-octadiyne (**9b**). Under the slightly

Scheme 2. Hydroazidation of Propargyl Compounds.[a]



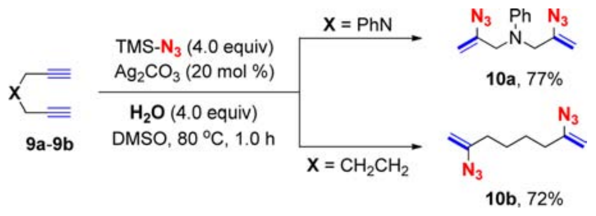
[a]Reaction conditions: **3**/**5** (0.5 mmol), H_2O (1.0 mmol), Ag_2CO_3 (0.05 mmol), DMSO (2 mL), 80 °C, 60−90 min.

Scheme 3. Hydroazidation of 4-Alkynones[a]



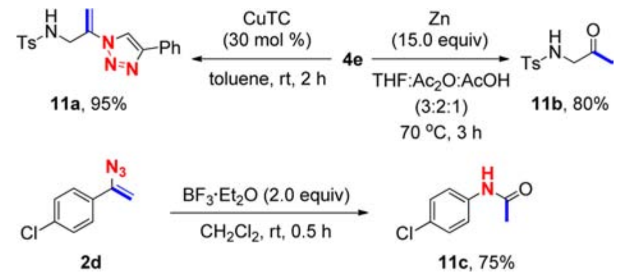
[a]Reaction conditions: **7** (0.5 mmol), H_2O (1.0 mmol), Ag_2CO_3 (0.05 mmol), DMSO (2 mL), 80 °C, 60−90 min.

modified reaction conditions, i.e., using double the amount of silver catalyst, H_2O, and TMS-N_3, the desired divinyl azides (**10a** and **10b**) could be obtained in 77% and 72% yields, respectively.



To demonstrate the synthetic utility of this hydroazidation reaction, we conducted the reaction on a gram scale, which provided **4e** in 78% yield (Scheme 4). Subsequently, we also showed that **4e** can be converted to the desired 1,2,3-triazole (**11a**)[12] and the α-amino ketone[13] (**11b**) in 95% and 80% yields, respectively, using the known transformations.[14] Meanwhile, a rearrangement of vinyl azide (**2d**) to yield the amide (**11c**) in 75% yield was realized.[15]

Scheme 4. Synthetic Transformation of Vinyl Azides



In summary, we have developed a novel and practical silver-catalyzed hydroazidation of terminal alkynes by combining TMS-N_3 and H_2O. This reaction represents the general hydroazidation of unactivated alkynes in a real sense. The reaction has a broad substrate scope of terminal alkynes, affording the corresponding vinyl azides in good-to-excellent yields. Easy access to these highly functionalized vinyl azides has paved a way in organic synthesis to explore their synthetic potency in the future.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectra copies. 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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■ REFERENCES

(1) (a) Forster, M. O.; Newman, S. H. *J. Chem. Soc.* **1910**, *97*, 2570−2579. (b) Forster, M. O.; Newman, S. H. *J. Chem. Soc.* **1911**, *99*, 1277−1282.

(2) For a general review on the synthesis and reactions of vinyl azides, see: Banert, K. in *Organic Azides: Syntheses and Applications*; Bräse, S.; Banert, K.; Eds., John Wiley & Sons Ltd.: Chichester, 2010.

(3) For recent examples, see: (a) Farney, E. P.; Yoon, T. P. *Angew. Chem., Int. Ed.* **2014**, *53*, 793−797. (b) Zhang, G.; Ni, H.; Chen, W.; Shao, J.; Liu, H.; Chen, B.; Yu, Y. *Org. Lett.* **2013**, *15*, 5967−5969. (c) Chen, F.; Shen, T.; Cui, Y.; Jiao, N. *Org. Lett.* **2012**, *14*, 4926−4929. (d) Wang, Y.-F.; Toh, K. K.; Lee, J.-Y.; Chiba, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 5927−5931. (e) Wang, Y.-F.; Toh, K. K.; Ng, E. P. J.; Chiba, S. *J. Am. Chem. Soc.* **2011**, *133*, 6411−6421. (f) Wang, Y.-F.; Chiba, S. *J. Am. Chem. Soc.* **2009**, *131*, 12570−12572. (g) Stokes, B. J.; Dong, H.;

Leslie, B. E.; Pumphrey, A. L.; Driver, T. G. *J. Am. Chem. Soc.* **2007**, *129*, 7500−7501. (h) Hu, B.; Wang, Z.; Ai, N.; Zheng, J.; Liu, X.-H.; Shan, S.; Wang, Z. *Org. Lett.* **2011**, *13*, 6362−6365. (i) Chen, W.; Hu, M.; Wu, J.; Zou, H.; Yu, Y. *Org. Lett.* **2010**, *12*, 3863−3865. (j) Stokes, B. J.; Vogel, C. V.; Urnezis, L. K.; Pan, M.; Driver, T. G. *Org. Lett.* **2010**, *12*, 2884−2887. (k) Chiba, S.; Zhang, L.; Ang, G. Y. B.; Hui, W.-Q. *Org. Lett.* **2010**, *12*, 2052−2055. (l) Wang, Y.-F.; Toh, K. K.; Chiba, S.; Narasaka, K. *Org. Lett.* **2008**, *10*, 5019−5022. (m) Chiba, S.; Wang, Y.-F.; Lapointe, G.; Narasaka, K. *Org. Lett.* **2008**, *10*, 313−316. (n) Dong, H.; Shen, M.; Redford, J. E.; Stokes, B. J.; Pumphrey, A. L.; Driver, T. G. *Org. Lett.* **2007**, *9*, 5191−5194.

(4) For general reviews on the hydroelementation of alkynes, see: (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079−3159. (b) Zeng, X. *Chem. Rev.* **2013**, *113*, 6864−6900.

(5) (a) Hyatt, I. F. D.; Croatt, M. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 7511−7514. (b) Palacios, F.; Aparicio, D.; de los Santos, J. M.; Perez de Heredia, I.; Rubiales, G. *Org. Prep. Proced. Int.* **1995**, *27*, 171−178. (c) Haddach, M.; Pastor, R.; Riess, J. G. *Tetrahedron* **1993**, *49*, 4627−4638. (d) Banert, K. *Chem. Ber.* **1989**, *122*, 1175−1178. (e) Kitamura, T.; Stang, P. J. *Tetrahedron Lett.* **1988**, *29*, 1887−1889. (f) Ochiai, M.; Kunishima, M.; Fuji, K.; Nagao, Y. *J. Org. Chem.* **1988**, *53*, 6144−6145. (g) Ostroverkhov, V. G.; Shilov, E. A. *Ukrain. Khim. Zhur.* **1957**, *23*, 615−622.

(6) Shen, T.; Wang, T.; Qin, C.; Jiao, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 6677−6680.

(7) (a) Qin, C.; Feng, P.; Ou, Y.; Shen, T.; Wang, T.; Jiao, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 7850−7854. (b) Gaydou, M.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 13468−13471.

(8) (a) Fang, Z.; Liu, J.; Liu, Q.; Bi, X. *Angew. Chem., Int. Ed.* **2014**, DOI: 10.1002/anie.201403014. (b) Liu, Z.; Liu, J.; Zhang, L.; Liao, P.; Song, J.; Bi, X. *Angew. Chem., Int. Ed.* **2014**, *53*, 5305−5309. (c) Liu, J.; Liu, Z.; Wu, N.; Liao, P.; Bi, X. *Chem.—Eur. J.* **2014**, *20*, 2154−2158. (d) Fang, Z.; Liao, P.; Yang, Z.; Wang, Y.; Zhou, B.; Yang, Y.; Bi, X. *Eur. J. Org. Chem.* **2014**, 924−927. (e) Liu, J.; Fang, Z.; Zhang, Q.; Liu, Q.; Bi, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 6953−6957. (f) Fang, G.; Li, J.; Wang, Y.; Gou, M.; Liu, Q.; Li, X.; Bi, X. *Org. Lett.* **2013**, *15*, 4126−4129. (g) Liu, Y.; Barry, B.-D.; Yu, H.; Liu, J.; Liao, P.; Bi, X. *Org. Lett.* **2013**, *15*, 2608−2611. (h) Fang, Z.; Yuan, H.; Liu, Y.; Tong, Z.; Li, H.; Yang, J.; Barry, B.-D.; Liu, J.; Liao, P.; Zhang, J.; Liu, Q.; Bi, X. *Chem. Commun.* **2012**, *48*, 8802−8804. (i) Wang, K.; Bi, X.; Xing, S.; Liao, P.; Fang, Z.; Meng, X.; Zhang, Q.; Liu, Q.; Ji, Y. *Green Chem.* **2011**, *13*, 562−565. (j) Wang, Y.; Bi, X.; Li, D.; Liao, P.; Wang, Y.; Yang, J.; Zhang, Q.; Liu, Q. *Chem. Commun.* **2011**, *47*, 809−811.

(9) (a) Jin, T.; Kamijo, S.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 9435−9437. (b) Jin, T.; Kamijo, S.; Yamamoto, Y. *Eur. J. Org. Chem.* **2004**, 3789−3791.

(10) (a) Jiang, Z.; Zhang, L.; Dong, C.; Cai, Z.; Tang, W.; Li, H.; Xu, L.; Xiao, J. *Adv. Synth. Catal.* **2012**, *354*, 3225−3230. (b) Trost, B. M.; Spagnol, M. D. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2083−2097. (c) Birnbaum, J. E. *J. Am. Acad. Dermatol.* **1990**, *23*, 782−785. (d) Ryder, N. S. *Biochem. Soc. Trans.* **1990**, *18*, 45−46.

(11) For one report regarding the preparation and reaction of 3-azidoallyl amines, see: Alajarín, M.; Vidal, A.; Orenes, R.-A. *Eur. J. Org. Chem.* **2002**, 4222−4227.

(12) Raushel, J.; Fokin, V. V. *Org. Lett.* **2010**, *12*, 4952−4955.

(13) For synthetic applications of α-amino ketones, see: (a) Fujita, M.; Hiyama, T. *J. Am. Chem. Soc.* **1984**, *106*, 4629−4630. (b) Takahashi, H.; Sakuraba, S.; Takeda, H.; Achiwa, K. *J. Am. Chem. Soc.* **1990**, *112*, 5876−5878.

(14) Nitta, M.; Kobayashi, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1035−1039.

(15) (a) Hassner, A.; Ferdinandi, E. S.; Isbister, R. J. *J. Am. Chem. Soc.* **1970**, *92*, 1672−1675. (b) Zhang, F.-L.; Wang, Y.-F.; Lonca, G. H.; Zhu, X.; Chiba, S. *Angew. Chem., Int. Ed.* **2014**, *53*, 390−4394.