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Bimetal-Catalyzed Cascade Reaction for Efficient Synthesis of N-isopropenyl 1,2,3-Triazoles via in situ Generated 2-Azidopropenes

Zhenhua Liu*[a], Wenjing Hao[a], Zhixian Liu[a], Wen Gao*[a], Zhihai Zhang[a], Yanan Zhang[a], Xiang Li[a], Lili Tong[a] and Bo Tang*[a]

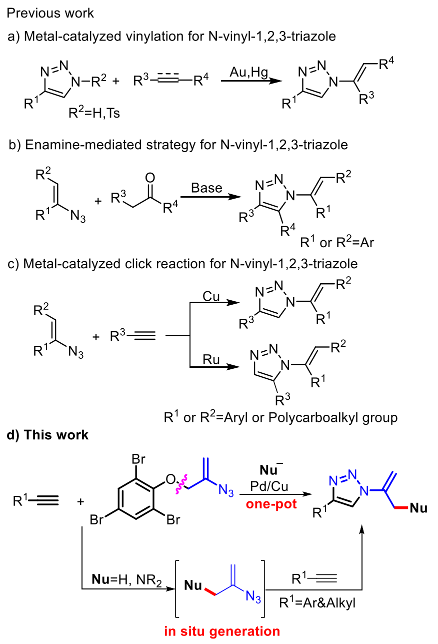
Abstract: A bimetal-catalyzed cascade reaction for high-yielding synthesis of unknown N-isopropenyl 1,2,3-triazoles is reported. This reaction involves, the first example, generation of 2-azidopropenes in situ by C(sp3)-OAr bond cleavage for click reaction with eraesing explosion risk of azides under mild reaction conditions, which was characterized by broad substrate scope, good functional group tolerance and readily available substrates.

Introduction

1,2,3-Triazoles are important structural motifs found in various areas, including organic synthesis[1], materials science[2], chemical biology[3], and medicinal development[4]. As a subset of them, N-vinyl substituted 1,2,3-triazoles are one of the most important precursors for industrially functional polymers[5]. Their facile polymerization under free radical conditions motivated chemists for large scale production of electron rich polymers[6]. Conventionally, two approaches for the construction of N-vinyl-1,2,3-triazoles were developed via the post-modification of NH/sulfonyl-triazoles with suitable electrophile[7] and the cycloaddition between vinyl azides and compounds having an active methylene[8-11] (Figure 1a,1b). However, the application of these methods is fettered by narrow substrate scope, redundant preparation steps, the risk of explosion/toxicity of the reagents. Therefore, a powerful, sustainable, costeffective route to access diverse vinyl-triazoles are highly desirable.

With the advent of click chemistry popularized by Meldal[12a] and Sharpless,[12b] the click reaction between azides and alkynes under copper(I) and ruthenium(II)[13] catalyst has been evolved into alternatively powerful strategies for the regioselective construction of N-vinyl 1,2,3-triazoles by vinyl azides as reaction parameter (Figure 1c). However, the substituent (R^1 or R^2) of vinyl azides are merely restricted to aryl and polycarboalkyl groups because of their potentially explosive equation[13b,14]. To obtain the readily explosive azidoethenes from substituted alkanes, hypothermia and strong base were indispensable[13b,15]. The above requirements detract the significant role of N-vinyl 1,2,3-triazoles especially in drug discovery because drug properties strongly associated with their substitution types[16]. Meanwhile, the allyl group has been widely explored as a protecting group for various alcohols and amines in organic synthesis[17], which delivers the deprotected products by selective C(sp3)-OAr bond cleavage with the release of propylene intact. Therefore, we sought to develop benign method that generated the explosive 2-azidopropenes in situ by this flexible protection-deprotection strategy and subsequently reacted with appropriate substrates without further isolation.

Recently, we have developed two cascade reactions with readily available vinyl azides[18] to assemble functionalized N-heterocycles[19] under copper-mediated system. Owing to our ongoing efforts to explore novel reactions based on vinyl azides[15a,20]. We herein report, the first example, a one-pot protocol for the synthesis of N-isopropenyl 1,2,3-triazoles under mild reaction conditions, which involves the generation of 2-azidopropenes in situ by selective C(sp^3)-OAr bond cleavage to conduct click reaction with high yields (Figure 1d). This portable and scalable method exhibited a straightforward and safe pathway to access neotype N-isopropenyl 1,2,3-triazoles under easy operation conditions, thus enriching the toolbox for functionalized 1,2,3-triazoles with the potential application in the drug discovery and materials chemistry. This reaction displayed a broad substrate scope and good functional-group tolerance with uniformly good to excellent yields.


Previous work

a) Metal-catalyzed vinylation for N-vinyl-1,2,3-triazole

b) Enamine-mediated strategy for N-vinyl-1,2,3-triazole

c) Metal-catalyzed click reaction for N-vinyl-1,2,3-triazole

d) This work

Scheme 1. Transformations for N-vinyl-1,2,3-triazoles.

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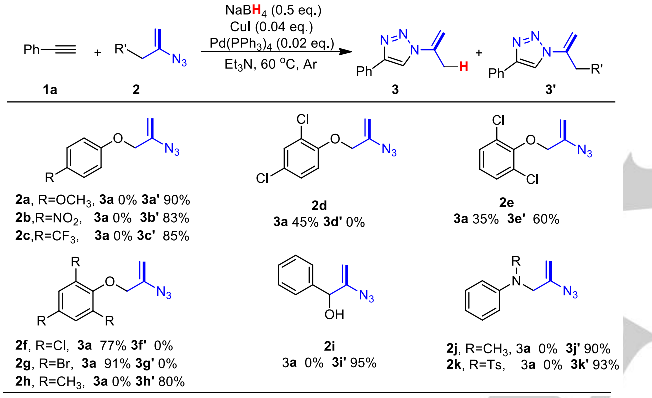
Results and Discussion

Our initial investigations started with dissociation kinetics of vinyl azides bearing different substituents to deliver 2-azidopropene in the presence of NaBH$_4$ in Et$_3$N at 60 ^{o}C (Scheme 2). These results clearly indicated that both position and electronic characteristics of the substituents strongly affected the efficiency of C(sp^3)-OAr bond cleavage. For instance, when electron-donating and -withdrawing groups anchored on the para-position of benzene ring (**2a**-**2c**), good reactivity was observed for the product **3a'**-**3c'** rather than the desired ones. Fortunately, when **2d** was performed in the reaction, the proposed product **3a** could be obtained in a relatively low yield. Encouraged by this initial results, other substituted vinyl azides (**2e**-**2h**) were subjected to the reaction and the substrate **2g** with 2,4,6-tribromophenyl group gave the preferable reactivity for product **3a** via the three-component cascade reaction. Other vinyl azides with adjacent hydroxyl **2i** and nitrogen atom (**2j**, **2k)** displayed as unproductive substrates to deliver the targeted N-isopropenyl 1,2,3-triazole product **3a**.



^{a}Reaction conditions: **1a** (0.24 mmol), **2** (0.2 mmol.), CuI (0.04 eq.), Pd(PPh$_3$)$_4$ (0.02 eq.), NaBH$_4$ (0.5 eq.), Et$_3$N (2 mL), 60 °C, Ar (balloon), 4 h; Isolated yield.

Scheme 2. Scope of vinyl azides^a.

Accordingly, the model reaction was carried out with phenylacetylene **1a**, **2g** and NaBH$_4$ as substrates for the initial reaction optimization by three-component cascade reaction to preparation of N-isopropenyl-1,2,3-triazoles. The reaction was shut down with the sole CuTc or Pd(PPh$_3$)$_4$ as catalyst (Table 1, entries 1 and 2). Taking into consideration of selective C(sp^3)-OAr bond cleavage and subsequent click reaction process, we performed the cascade reaction with the Pd/Cu bimetallic catalysts for the next screening. Notably, the desired transformation was observed and produced **3a** in 83% yield with CH$_3$CN/Et$_3$N as reaction solvents (Table 1, entry 3). Studies of other copper salts (Table 1, entries 4-7) uncovered that CuI significantly improved the efficiency of cascade reaction with the target product **3a** in 93% yield (Table 1, entry 7). The reaction showed inferior reactivity when the alternative Pd sources were used (Table 1, entries 8-9). Furthermore, solvents such as EG, DMF, DMSO, toluene, 1,4-dioxane, afforded lower yields of N-vinyl-1,2,3-triazoles **3a** (Table 1, entries 10-15). The use of open air decreased the yield of the desired product by the cascade transformation (Table 1, entry 16). Product **3a** was only detected in 68% yield when 2.0 eq. Et$_3$N was employed in the three-component reaction (Table 1, entry 17).

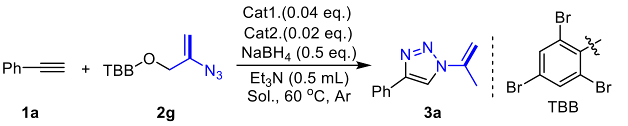


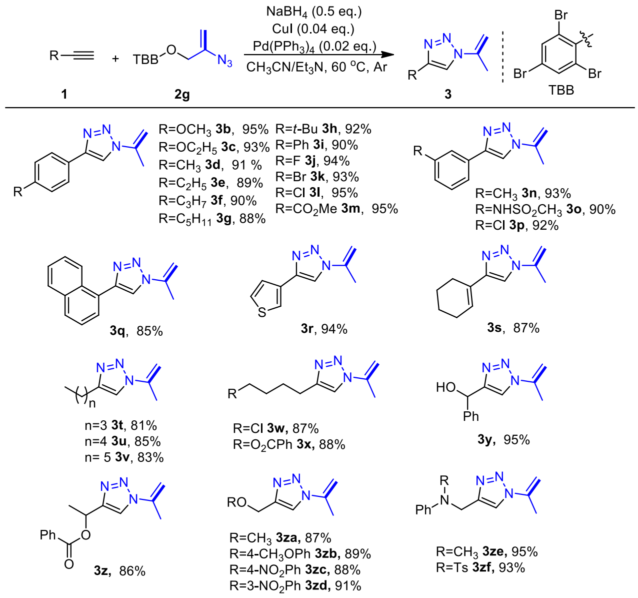
Table 1. Optimization of the reaction conditions. ^{a}

Entry	Cat1	Cat2	Sol.	**3a**/%
1	CuTc	......	CH_3CN	0
2	......	Pd(PPh$_3$)$_4$	CH_3CN	0
3	CuTc	Pd(PPh$_3$)$_4$	CH_3CN	83
4	Cu$_2$O	Pd(PPh$_3$)$_4$	CH_3CN	0
5	CuCl$_2$	Pd(PPh$_3$)$_4$	CH_3CN	88
6	Cu(OAc)$_2$	Pd(PPh$_3$)$_4$	CH_3CN	84
7	CuI	Pd(PPh$_3$)$_4$	CH_3CN	93
8	CuI	Pd(PPh$_3$)$_2$Cl$_2$	CH_3CN	63
9	CuI	Pd(OAc)$_2$	CH_3CN	trace
10	CuI	Pd(PPh$_3$)$_4$	EG	47
11	CuI	Pd(PPh$_3$)$_4$	DMF	64
12	CuI	Pd(PPh$_3$)$_4$	DMSO	66
13	CuI	Pd(PPh$_3$)$_4$	Toluene	55
14	CuI	Pd(PPh$_3$)$_4$	DCE	55
15	CuI	Pd(PPh$_3$)$_4$	1,4-DOE	51
16	CuI	Pd(PPh$_3$)$_4$	CH_3CN	45^b
17	CuI	Pd(PPh$_3$)$_4$	CH_3CN	68^c

[a] Reaction conditions: **1a** (0.24 mmol), **2g** (0.2 mmol.), [cat1] (0.04 eq.), [cat2] (0.02 eq.), NaBH$_4$ (0.5 eq.), Et$_3$N (0.5 mL), Sol. (1.5 mL), 60 °C, Ar (balloon), 4 h; Isolated yield. b) Open air. c) 2.0 eq. Et$_3$N and 1.5 mL CH$_3$CN was used. EG = ethylene glycol, DMSO = dimethyl sulfoxide, DMF = dimethylformamide, DCE = 1,2-dichloroethane, 1,4-DOE=1,4-dioxane.

The optimized reaction conditions in hand, using **1a**, **2g** and NaBH$_4$, were then applied to evaluate the scope of alkynes with various groups in the bimetallic-accelerated sequential reaction (Schemes 3). In general, diverse aromatic and aliphatic alkynes with electron-deficient or -rich substituents were allowed to the corresponding 1,2,3-triazoles (**3b**-**3zf**) in good to excellent yields. For instance, the varied electron-donating groups at para-position of the aromatic ring (**3b**-**3g**) were well-tolerated in this cascade reaction and had no significant influence on the efficiency of the conversion in 88-

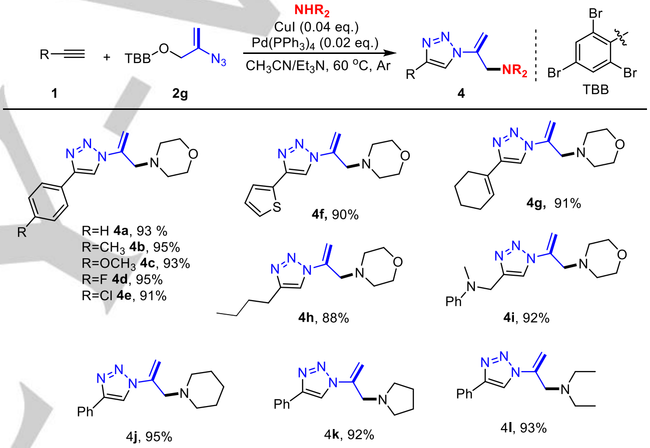
95% yields. The aromatic alkynes with sterically congested para-substituents (**1h**-**1i**) also exhibited satisfactory reactivity to access the product (**3h**-**3i**) in 92% and 90% yield, respectively. Alkynes with electron-withdrawing groups such as fluoro (**1j**), bromo (**1k**), chloro (**1l**) yielded the corresponding products with intact halogen handles for further derivatizations. The structure of **3l** was further corroborated by X-ray diffraction analysis[21] (See the details in SI). Similarly, alkyne substrate with ester group at the para position could smoothly be converted to 1,2,3-triazoles **3m** in 95% yield without showing much of electronic factors. When additional functionality such as methyl, methyl sulfamic or chloro group was at the meta-position of benzene ring, excellent reactivity was furnished with 90-93% yields for the homologous products (**3n**-**3p**). Notably, replacing the phenyl group of **1a** with other rings, including 2-naphthyl (**1q**), 3-thienyl (**1r**) and cyclohexenyl (**1s**), were also compatible for the corresponding triazoles in good yields. Aliphatic alkynes possessing long alkyl substituents (**1t**-**1v**) and functionalized alkyl groups (**1w**-**1x**) worked well to give the expected products. The reaction system also displayed good tolerance toward a range of functional groups such as hydroxyl (**1y**), ester (**1z**), alkoxy (**1za**) and aryloxy (**1zb**-**1zd**) in the three-component click reaction with the satisfactory yields. It is worth noting that aliphatic alkynes anchored nitrogen-atom as reaction partner gave the product **3ze** and **3zf** with the excellent yields.



[a] Reaction conditions: **1a** (0.24 mmol), **2g** (0.2 mmol.), CuI (0.04 eq.), Pd(PPh_3)$_4$ (0.02 eq.), $NaBH_4$ (0.5 eq.), Et_3N (0.5 mL), CH_3CN (1.5 mL), 60 °C, Ar (balloon), 4 h; Isolated yield.

Scheme 3. Scope of alkynes [a].

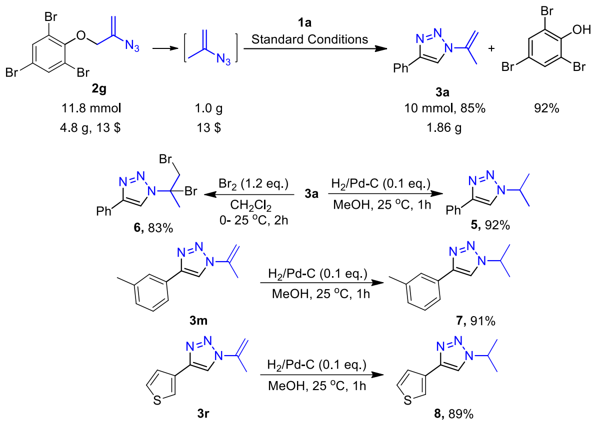
Owing to the good generality of this three-component reaction, we further investigated other nucleophilic reagent to N-substituted 1,2,3-triazoles in one pot via generation of functionalized 2-azidopropenes in situ. Amines with good nucleophilicity were well extended to this cascade reaction by replacing $NaBH_4$. It is noteworthy that the morpholine as reaction parameter well tolerated the defined conditions to provide the corresponding product **4a** in 93% yield. The structure of product **4a** was unambiguously confirmed by X-ray diffraction[21] (See the details in SI). We then examined other functionalized alkynes and secondary amines via in situ generation of 2-azidopropene derivatives for click reaction, which were observed with the good reactivity for the exclusive formation of adorned triazoles (**4b**-**4l**) in good to excellent yields. For example, alkynes decorated with electron-donating and -withdrawing benzene ring were performed with high reactivity to assemble the targeted products **4b**-**4e**. Several functionalized terminal alkynes, such as 2-ethynylthiophene and 1-ethynylcyclohexene could also successfully afford the corresponding **4f** and **4g** in 90% and 91% yield, respectively. Alkynes with long carbon chain and nitrogenous carbon chain were further applied to the cascade click reaction for the preparation of 1,2,3-triazole derivatives (**4h**-**4i**) in good yields. When the reaction was conducted with cyclic and acyclic secondary amines, the pre-set course effectively proceeded to synthesis of the functionalized triazoles (**4j**-**4l**).



[a] Reaction conditions: **1a** (0.24 mmol), **2g** (0.2 mmol.), CuI (0.04 eq.), Pd(PPh_3)$_4$ (0.02 eq.), NHR_2 (2.0 eq.), Et_3N (0.5 mL), CH_3CN (1.5 mL), 60 °C, Ar (balloon), 4 h; Isolated yield.

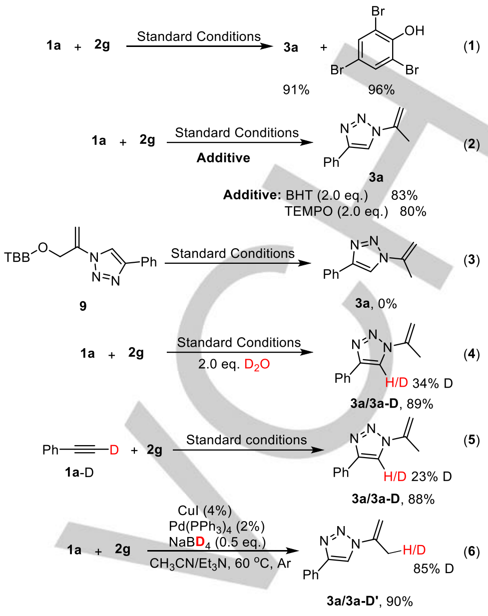
Scheme 4. Scope of alkynes and secondary amines [a].

To further demonstrate the practicability and scalability of this cascade reaction, we carried out the gram-scope conversion with **2g** (11.8 mmol, 13 $) to produce **3a** in 85% yield with the recovery of 2,4,6-tribromophenol after workup. Product **3a** could be further derivatization to dibrominated 1,2,3-triazole **6** in good yield by treating bromine[8b]. N-alkyl-1,2,3-triazoles was isolated with nearly quantitative conversion through hydrogenation of **3a** under H_2 (balloon) in the presence of Pd/C (0.1 eq.) in methanol[8b]. Analogously, other vinyl-triazoles tethered with meta-methyl aromatic ring and thiophene were also amenable to hydrogenation reaction with good yields. These results highlighted the advantages of this cascade reaction for the isolation of N-isopropenyl-1,2,3-triazoles, which opened the door to access various N-alkyl-substituted 1,2,3-triazoles rather than through available CuAAC reaction with explosive and costly 2-azidopropane (1g, > $600) as reaction parameter.



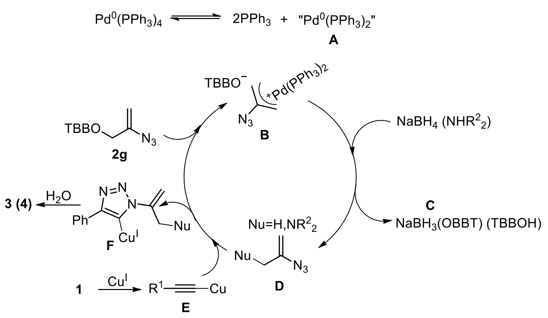
Scheme 5. Gram-scope reaction and further transformations.

Encouraged by these results, we subsequently implemented control reactions for shedding light to the mechanism of this cascade process. Apart from the isolation of the desired product **3a**, 2,4,6-tribromophenol could be recovered after workup in 96% yield under the standard reactions (Scheme 6, Eq.1). This result verified the cleavage of the C(sp^3)-OAr bond during the cascade reaction. Radical scavenger studies were conducted in an effort to find evidence of radical species. When the additive such as 2,6-di-tert-butyl-4-methylphenol (BHT) or 2,2,6,6-tetramethylpiperidinooxy (TEMPO) was added as radical scavengers in the reaction, the tandem course proceeded well and generated product **3a** in 83% and 80% yield, respectively (Scheme 6, Eq. 2). This indicated that ionic pathway was prior over the radical pathway in the standard reaction process. To illuminate the fracture sequence of C(sp^3)-OAr bond, we performed the cascade reaction using the reactant **9** as substrate under the optimal conditions. Yet the desired product **3a** was not observed after 4 h and 100% of **9** was recovered. This showed that the C(sp^3)-OAr bond cleavage for 2-azidopropene was in preference to click reaction under the standard conditions. When 2.0 eq. D_2O was added to the reaction under the optimalized conditions, deuterium-incorporated product **3a**-D was obtained with a 34% of D/H ratio at the triazole ring. Not surprisingly, **1a**-D as reaction partner was allowed to the targeted product **3a**/**3a**-D in 88% total yield with a deuterium content of 23%. The two results implied that the click reaction underwent through the previous process[13b] and both H_2O and the substrate **1a** did not provide hydrogen source for constructing methyl group of targeted product **3**. We suspected that $NaBH_4$ in the reaction system offered hydrogen atom for the methyl group of 2-azidopropene. We then introduced $NaBD_4$ into the cascade reaction and isolated the product **3a**-D' with a deuterium content of 85% on methyl group. This finding was further confirmed that $NaBH_4$ was the hydrogen source for assembling methyl group in the desired product **3**.



Scheme 6. Mechanistic investigations.

On the basis of the control results and former investigations[12,13b,17], a probable mechanism for the cascade reaction was depicted in Scheme 7. Initially, the $Pd^0(PPh_3)_4$ catalyst underwent ligand dissociation and formed the dual-ligand palladium species **A**, which proceeded oxidative addition with **2g** to generate the key cationic π-allylpalladium(II) complex **B**. Subsequently, $NaBH_4(HNR_2^2)$ served as the nucleophile to react with intermediate **B** by delivering the intermediate **D** in situ and deallylated complex **C**. TBBOH could be recovered after the workup. In the meantime, the activation of alkynes **1** was by formation of Cu(I) acetylides **E** from substrate **1** and Cu(I). Eventually, 2-azidopropene intermediate **D** without any isolation occurred the subsequent cyclization reaction with the active species **E** for preparation of Cu(I) triazolides **F**, which underwent site-selective protonation to release the final product **3(4)** and regenerated the copper(I) catalyst.



Scheme 7. Possible mechanism for the reaction.

Conclusions

In conclusion, we have disclosed a mild and efficient tandem reaction for the formation of new-type N-isopropenyl 1,2,3-triazoles from safe and easy-to-handle reagents. This reaction process involves in situ generation of explosive 2-azidopropenes by artful cleavage of C(sp^3)-OAr bond, which subsequently participate in the click reaction for the unique 1,2,3-triazole skeleton by eliminating tedious isolation. This one-pot protocol is successfully achieved with broad substrate scope and good functional-group compatibility and readily costeffective substrates. This reaction enables an ideal and efficient strategy to convey volatile 2-azidopropenes under mild reaction conditions for the first time, which erases the explosive danger of vinyl azides to furnish 1,2,3-triazole scaffolds. Their synthetic application has been demonstrated by gram-scope reaction and secondary modifications for useful molecules. Meanwhile, a possible reaction pathway is tentatively proposed based on our preliminary tests and previous literatures. Further applications will facilitate a broad set of potential building blocks for the development of pharmaceuticals and new materials.

Experimental Section

Typical synthetic procedure for the synthesis 3 (with **3a** as an example): To a schlenk tube was added phenylacetylene (**1a**, 0.027 mL, 0.24 mmol), (**2g**, 82.4 mg, 0.2 mmol), $NaBH_4$ (3.8 mg, 0.1mmol), $Pd(PPh_3)_4$ (4.7 mg, 0.004 mmol) , CuI (1.5 mg, 0.008 mmol) ,CH_3CN (1.5 mL) and Et_3N (0.5 mL). Then the tube was charged with Ar (1 atm), and was stirred at 60 ºC (oil bath temperature) for the indicated time (about 4 h) until complete consumption of starting material as monitored by TLC. The resulting reaction mixture was cooled to room temperature and taken up by dichloromethane (3 × 15 mL). The organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was further purified by flash column chromatography (silica gel) using petroleum ether/ethyl acetate as an eluent and concentration in vacuo afforded **3a** in 91% yield.

Typical synthetic procedure for the synthesis 4 (with **4a** as an example): To a schlenk tube was added phenylacetylene (**1a**, 0.027 mL, 0.24 mmol), (**2g**, 82.4 mg, 0.2 mmol), morpholine (0.035 mL, 0.4 mmol), $Pd(PPh_3)_4$ (4.7 mg, 0.004 mmol) , CuI (1.5 mg, 0.008 mmol) ,CH_3CN (1.5 mL) and Et_3N (0.5 mL). Then the tube was charged with Ar (1 atm), and was stirred at 60 ºC (oil bath temperature) for the indicated time (about 4 h) until complete consumption of starting material as monitored by TLC. The resulting reaction mixture was cooled to room temperature and taken up by dichloromethane (3 × 15 mL). The organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was further purified by flash column chromatography (silica gel) using petroleum ether/ethyl acetate as an eluent and concentration in vacuo afforded **4a** in 93% yield.

Acknowledgements

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Keywords: bimetal-catalyzed • vinyl azides • alkynes •1,2,3-triazoles

[1] a) H. M. L. Davies, J. S. Alforda, *Chem. Soc. Rev.* **2014**, *43*, 5151-5162; b) D. Huang, P. Zhao, D. Astruc, *Coordin. Chem. Rev.* **2014**, *272*, 145-165; c) S. Hosseyni, L. Wojtas, M. Li, X. Shi, *J. Am. Chem. Soc.* **2016**, *138*, 3994-3997; d) X. Ye, C. Xu, L. Wojtas, N. G. Akhmedov, H. Chen, X. Shi, *Org. Lett*. **2016**, *18*, 2970-2973; e) A. Goitia, E. Gómez-Bengoa, A. Correa, *Org. Lett.* **2017**, *19*, 962-965; f) Q. Gu, H. H. Al Mamari, K. Graczyk, E. Diers, L. Ackermann, *Angew. Chem. Int. Ed.* **2014**, *53*, 3868-2871.

[2] a) B. L. Wilkinson, L. F. Bornaghi, T. A. Houston, Poulsen in *Drug Design Research Perspectives* (Ed.: S. P. Kaplan), Nova, Haupauge, **2007**, p. 57; (b) K. Kacprzak, I. Skiera, M. Piasecka, Z. Paryzek, *Chem. Rev.* **2016**, *116*, 5689-5743; c) H. C. Kolb, K. B. Sharpless, *Drug Discovery Today*, **2003**, *8*, 1128-1137; d) M. Whiting, J. C. Tripp, Y. C. Lin, W. Lindstrom, A. J. Olson, J. H. Elder, K. B. Sharpless, V. V. Fokin, *J. Med. Chem*. **2006**, *49*, 7697-7710; e) C. C. Chrovian, D. J. Gallacher, A. Bhattacharya, M. A. Letavic, *J. Med. Chem.* **2018**, *61*, 207-223.

[3] a) Y. Zheng, X. Ji, B. Yu, K. Ji, D. Gallo, E. Csizmadia, M. Zhu, M. R. Choudhury, L. K. C. De La Cruz, V. Chittavong, Z. Pan, Z. Yuan, L. E. Otterbein, B. Wang, *Nat. Chem*. **2018**, *10*, 787-794; b) V. K. Tiwari, B. B. Mishra, K. B. Mishra, N. Mishra, A. S. Singh, X. Chen, *Chem. Rev.* **2016**, *116*, 3086-3240; c) W. G. Kim, B. Choi, H.-J. Yang, J.-A. Han, H. Jung, H. Cho, S. Kang, S. Y. Hong, *Bioconjugate Chem.* **2016**, *27*, 2007-2013; d) P. Thirumurugan, D. Matosiuk, K. Jozwiak, *Chem. Rev.* **2013**, *113*, 4905-4979; e) W. Tang, M. L. Becker, *Chem. Soc. Rev.* **2014**, *43*, 7013-7039; f) H. Tian, A. Fürstenberg, T. Huber, *Chem. Rev.* **2017**, *117*, 186-245; g) W. Gao, S. Li, Z. Liu, Y. Sun, W. Cao, L. Tong, G. Cui, B. Tang, *Biomaterials* **2017**, 139, 1-11.

[4] a) M. G. Finn, V. V. Fokin, *Chem. Soc. Rev*. **2010**, *39*, 1221-1408; b) A. S. Kumar, V. D. Ghule, S. Subrahmanyam, A. K. Sahoo, *Chem.-Eur. J.* **2013**, *19*, 509-518; c) C. J. Hawker, V. V. Fokin, M. G. Finn, K. B. Sharpless, *Aust. J. Chem*. **2007**, *60*, 381-383; d) C. Chu, R. Liu, *Chem. Soc. Rev*. **2011**, *40*, 2177-2188; e) D. Astruc, L. Liang, A. Rapakousiou, J. Ruiz, *Acc. Chem. Res*. **2012**, *45*, 630-640; f) P. Leophairatana, S. Samanta, C. C. De Silva, J. T. Koberstein, *J. Am. Chem. Soc*. **2017**, *139*, 3756-3766.

[5] N. G. Rogov, E. P. Kabanova, I. G. Gruzdeva, Ross. *Khim. Zh.* **1997**, *41*, 115-118.

[6] a) S. Beghdadi, I. A. Miladi, D. Addis, H. Ben Romdhane, J. Bernard, E. Drockenmuller, *Polym. Chem*. **2012**, *3*, 1680-1692; b) E. V. Khavula, V. A. Kuznetsov, V. N. Verezhnikov, G. V. Shatalov, *Polym. Sci*. *Ser. B* **2003**, *45*, 26-30; c) V. N. Kizhnyaev, F. A. Pokatilov, L. I. Vereshchagin, *Polym. Sci., Ser. C* **2008**, *50*, 1-7; d) V. N. Kizhnyaev, N. A. Tsypina, A. I. Smirnov, *Polym. Sci., Ser. A* **2003**, *45*, 735-741; e) N. A. Tsypina, V. N. Kizhnyaev, F. A. Pokatilov, A. I. Smirnov, *Polym. Sci., Ser. B* **2003**, *45*, 41-47.

[7] a) V. N. Kizhnyaev, F. A. Pokatilov, N. A. Tsypina, G. V. Ratovskii, L. I. Vereshchagin, A. I. Smirnov, *Russ. J. Org. Chem*. **2002**, *38*, 1056-1059; b) B. A. Trofimov, O. A. Tarasova, M. A. Shemetova, A. V. Afonin, L. V. Klyba, L. V. Baikalova, A. I. Mikhaleva, *Russ. J. Org. Chem*. **2003**, *39*, 408-414; c) H. F. Duan, W. M. Yan, S. Sengupta, X. Shi, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3899-3902; d) C. Sun, X. Yuan, Y. Li, X. Li, Z. Zhao, *Org. Biomol. Chem*. **2017**, *15*, 2721-2724.

[8] a) G. Labbe, A. Hassner, *J. Heterocycl. Chem*. **1970**, *7*, 361-366; b) D. B. Ramachary, J. Gujral, S. Peraka, G. S. Reddy, *Eur. J. Org. Chem.* **2017**, 459-464; c) D. B. Ramachary, G. S. Reddy, S. Peraka, J. Gujral, *ChemCat Chem* **2017**, *9*, 263-267.

[9] a) M. Kavitha, B. Mahipal, P. S. Mainkar, S. Chandrasekhar, *Tetrahedron Lett.* **2011**, *52*, 1658-1662; b) L. Kupracz, J. Hartwig, J. Wegner, S. Ceylan, A. Kirschning, *Beilstein J. Org. Chem*. **2011**, *7*, 1441-1448; c) G.

Labbe, J. E. Galle, A. Hassner, *Tetrahedron Lett*. **1970**, 303-306; d) F. Shi, J. P. Waldo, Y. Chen, R. C. Larock, *Org. Lett*. **2008**, *10*, 2409-2412.

[10] E. P. J. Ng, Y. F. Wang, B. W. Q. Hui, G. Lapointe, S. Chiba, *Tetrahedron* **2011**, *67*, 7728-7737.

[11] P. Ykman, G. Smets, G. Mathys, G. Labbe, *J. Org. Chem.* **1972**, *37*, 3213-3216.

[12] a) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed*. **2002**, *41*, 2596-2599; b) C. W. Tornoe, C. Christensen, M. Meldal, *J. Org. Chem*. **2002**, *67*, 3057-3064.

[13] a) V. V. Fokin, in *Organic Chemistry-Breakthroughs and Perspectives*, (Eds.: K. Ding, L. -X. Dai) Wiley-VCH, Weinheim, Germany, **2012**, p. 247; b) K. Banert in *Organic Azides: Syntheses and Applications* (Eds.: S. Bräse, K. Banert,), Wiley, Chichester, **2010**; c) F. Wei, W. Wang, Y. Ma, C.-H. Tung, Z. Xu, *Chem. Commun.* **2016**, *52*, 14188-14199; d) C. O. Kappe, E. V. Eycken, *Chem. Soc. Rev*. **2010**, *39*, 1280-1290; e) J. R. Johansson, T. Beke-Somfai, A. S. Stalsmeden, N. Kann, *Chem. Rev.* **2016**, *116*, 14726-14768; f) Z. Wang, B. Li, X. Zhang, X. Fan, *J. Org. Chem*. **2016**, *81*, 6357-6363; g) Q. Wang, X. Shi, X. Zhang and X. Fan, *Org. Biomol. Chem*., **2017**, *15*, 8529-8534; h) W. G. Kim, M. E. Kang, J. B. Lee, M. H. Jeon, S. Lee, J. Lee, B. Choi, P. M. S. D. Cal^{II}, S. Kang, J.-M. Kee, G. J. L. Bernardes^{II}, J.-U. Rohde, W. Choe, S. Y. Hong, *J. Am. Chem. Soc.* **2017**, *139*, 12121-12124.

[14] F.-L. Zhang, Y.-F. Wang, G. H. Lonca, X. Zhu, S. Chiba, *Angew. Chem. Int. Ed.* **2014**, *53*, 4390-4394.

[15] a) J. Fu, G. Zanoni, E. A. Anderson, X. Bi, Chem. Soc. Rev. **2017**, *46*, 7208; b) H. Choi, H. J. Shirley, P. A. Hume, M. A. Brimble, D. P. Furkert, *Angew. Chem. Int. Ed.* **2017**, *56*, 7420-7424.

[16] a) For the applications of 1,2,3-triazoles, see: a) L. S. Kallander, et al. *J. Med. Chem.,* **2005**, *48*, 5644-5647; b) S. Ito, A. Satoh, Y. Nagatomi, Y. Hirata, G. Suzuki, T. Kimura, A. Satow, S. Maehara, H. Hikichi, M. Hata, H. Kawamoto, H. Ohta, *Bioorg. Med. Chem.* **2008**, *16*, 9817-9829; c) S. Ito, Y. Hirata, Y. Nagatomi, A. Satoh, G. Suzuki, T. Kimura, A. Satow, S. Maehara, H. Hikichi, M. Hata, H. Ohta, H. Kawamoto, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5310-5313; d) T. Tsuritani, H. Mizuno, N. Nonoyama, S. Kii, A. Akao, K. Sato, N. Yasuda, T. Mase, *Org. Process Res. Dev.* **2009**, *13*, 1407-1412; e) S. G. Agalave, S. R. Maujan, V. S. Pore, *Chem. Asian J.,* **2011**, *6,* 2696-2718; f) see also: *Chem. Asian J.* **2011**, *6,* Issue 10. Special edition devoted to click chemistry; g) M. Fujinaga, T. Yamasaki, K. Kawamura, K. Kumata, A. Hatori, J. Yui, K. Yanamoto, Y. Yoshida, M. Ogawa, N. Nengaki, J. Maeda, T. Fukumura, M. -R. Zhang, *Bioorg. Med. Chem.* **2011**, *19*, 102-110; h) A. Lauria, R. Delisi, F. Mingoia, A. Terenzi, A. Martorana, G. Barone, A. M. Almerico, *Eur. J. Org. Chem.* **2014**, 3289-3306; i) S. Li, Y. Huang, *Curr. Med. Chem.* **2014**, *21*, 113-123.

[17] a) S Chandrasekhar, C. R. Reddy, R J Rao, *Tetrahedron* **2001**, *57*, 3435-3438; b) J.-N. Lemercier, B. W.Meier, J. D. Gomez, J. A. Thompso, *Bio. Med. Chem.* **2018**, *26*, 50-64; c) R. J. Smith, D. Nhu, M. R. Clark, S. Gai, N. T. Lucas, B. C. Hawkins, *J. Org. Chem.* **2017**, *82*, 5317-5327; d) H. E. Pelish, N. J. Westwood, Y. Feng, T. Kirchhausen, M. D. Shair, *J. Am. Chem. Soc*. **2001**, *123*, 6740-6741. e) N. W. Polaske, M. L. Szalai, C. S. Shanahan, D. V. McGrath, *Org. Lett*. **2010**, *12*, 4944-4947; f) R. Beugelmans, S. Bourdet, A. Bigot, J. Zhu, *Tetrahedron Lett.* **1994**, *35*, 4349-4350; g) S. Li, M. L. Szalai, R. M. Kevwitch, D. V. McGrath, *J. Am. Chem. Soc.* **2003**, *125*, 10516-10517.

[18] a) M. O. Forster, S. H. Newman, *J. Chem. Soc., Trans*.**1910**, *97*, 2570-2579; b) M. O. Forster, S. H. Newman, *J. Chem. Soc., Trans.* **1911**, *99*, 1277-1282; c) A. Hassner, L. A. Levy, *J. Am. Chem. Soc*. **1965**, *87*, 4203-4204; d) F. W. Fowler, A. Hassner, L. A. Levy, *J. Am. Chem. Soc*. **1967**, *89*, 2077-2082; e) A. Hassner, F. W. Fowler, *J. Org. Chem*. **1968**, *33*, 2686-2691; f) Liu, P. Liao, X. Bi, *Org. Lett.* **2014**, *16*, 3668--3671; g) Z. Liu, J. Liu, L. Zhang, P. Liao, J. Song, X. Bi, *Angew. Chem., Int. Ed.* **2014**, *53*, 5305-5309; h) X. Li, S. Liao, Z. Wang, L. Zhang, *Org. Lett*. **2017**, *19*, 3687-3690.

[19] a) Z. Liu, H. Ji, W. Gao, G. Zhu, L. Tong, F. Lei, B. Tang, *Chem. Commun.* **2017**, *53*, 6259-6262; b) Z. Liu, G. Zhu, W. Gao, L. Yang, H. Ji, L. Tong, Bo Tang, *Org. Chem. Front*. **2019**, *6*, 468-473.

[20] a) B. Hu, S. G. DiMagno, *Org. Biomol. Chem*. **2015**, *13*, 3844-3855; b) V. Kanchupalli, S. Katukojvala, *Angew. Chem. Int. Ed.* **2018**, *57*, 5433-5437; c) J. Cen, J. Li, Y. Zhang, Z. Zhu, S. Yang, H. Jiang, *Org. Lett.* **2018**, *20*, 4434-4438; d) G. Fang, Z. Liu, S. Cao, H. Yuan, J. Zhang, L. Pan, *Org. Lett*. **2018**, *20*, 7113-7116; e) J. Cen, J. Li, Y. Zhang, Z. Zhu, S. Yang, H. Jiang, *Org. Lett*. **2018**, *20*, 4434-4438; f) V. Kanchupalli, S. Katukojvala, *Angew. Chem. Int. Ed.* **2018**, *57*, 5433-5437.

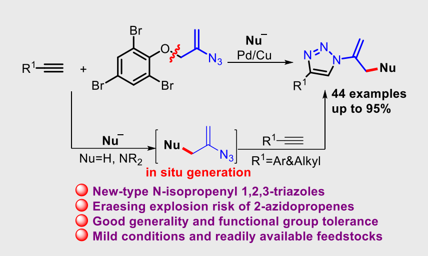
[21] CCDC 1887508 of **3l** and CCDC 1887511 of **4a** contain the supplementary crystall-ographic data for this paper from Cambridge Crystallographic Data Centrehttp: //www.ccdc.cam.ac.uk/.

Entry for the Table of Contents (Please choose one layout)

Layout 1:

FULL PAPER

Bimetal-catalyzed cascade reaction for high-yielding synthesis of unknown N-isopropenyl 1,2,3-triazoles is described. This reaction involves, the first example, generation of 2-azidopropenes in situ by C(sp3)-OAr bond cleavage for click reaction with eraesing explosion risk of azides under mild conditions, which was achieved with broad substrate scope, good functional group tolerance and readily available substrates



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