SCIENCE CHINA
Chemistry

•ARTICLES•

https://doi.org/10.1007/s11426-019-9455-0

Silver-catalyzed three-component reaction: synthesis of N^2-substituted 1,2,3-triazoles via direct benzylic amination

Zhenhua Liu[†], Wenjing Hao[†], Wen Gao[*], Guangyu Zhu, Xiang Li, Lili Tong & Bo Tang[*]

College of Chemistry, Chemical Engineering and Materials Science, Collaborative Innovation Center of Functionalized Probes for Chemical Imaging in Universities of Shandong, Key Laboratory of Molecular and Nano Probes, Ministry of Education, Shandong Provincial Key Laboratory of Clean Production of Fine Chemicals, Shandong Normal University, Jinan 250014, China

Received January 22, 2019; accepted March 4, 2019; published online April 25, 2019

A novel Ag(I)-catalyzed benzylic amination reaction with *in situ* generation of NH-1,2,3-triazoles for N^2-substituted 1,2,3-triazole scaffolds is described. This protocol is achieved with easily accessible substrate, broad functional group, good regioselectivity, thus providing the efficient and practical method to diverse N^2-substituted 1,2,3-triazole rings with moderate to good yields.

silver-catalyzed, alkynes, 1,2,3-triazoles, amination

Citation: Liu Z, Hao W, Gao W, Zhu G, Li X, Tong L, Tang B. Silver-catalyzed three-component reaction: synthesis of N^2-substituted 1,2,3-triazoles via direct benzylic amination. *Sci China Chem*, 2019, 62, https://doi.org/10.1007/s11426-019-9455-0

1 Introduction

1,2,3-Triazoles with interesting properties have been omnipresent in organic synthesis [1], medicinal chemistry [2], chemical biology [3] and materials science [4]. The pioneered synthesis of 1,2,3-triazoles by Huisgen 1,3-dipolar cycloaddition reaction [5] suffered from elevated temperature and poor regioselectivity. This smaller heterocyclic unit has drawn little attention as "sleeper" until the premier copper(I)-catalyzed examples of "click chemistry" [6] by Sharpless and Meldal's groups [7]. Nowadays, the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) and subsequent ruthenium(II)-catalyzed azide-alkyne cycloaddition (RuAAC) (Figure 1(a)) [8] have been established as reliable strategies for the efficient and regioselective assembly of N^1-substituted 1,2,3-triazoles. Recently, Hong and co-workes [9] introduced alternatively synthetic route to access 1,5-substituted 1,2,3-triazoles using complex Ni(II) catalyst in water (Figure 1(a)). Compared with well developed methods for synthesis of N^1-substituted triazoles, available approaches for N^2-substituted ones were nearly all limited to two-step strategy via presynthesis and post-functionalization of NH-1,2,3-triazoles with suitable electrophiles as the reactant [10] (Figure 1(b)). Another common route to the N^2-substituted triazoles [11] was obtained by the oxidative cyclization of bishydrazones or bissemicarbazones. However, tedious pre-modified process of the substrates was pre-requisite in those reactions, which severely hampered a broader utility of N^2-substituted triazoles in different fields of chemical science. Recently, Yamamoto *et al.* [12] and Fokin *et al.* [13] have made good progress toward the synthesis of N^2-allyl and N^2-hydroxymethyl triazoles via the elegant three-component coupling by the restrictive electrophiles (Figure 1(c)). Therefore, novel method for synthesis of N^2-substituted triazoles with diverse substitution patterns of commodity chemicals under simple and mild conditions is still rare and sorely needed so far.

The carbon-carbon triple bonds of alkynes are among the most valuable chemical skeletons because of their abundance

---

†These authors contributed equally to this work.
*Corresponding authors (email: gaowen@sdnu.edu.cn; tangb@sdnu.edu.cn)

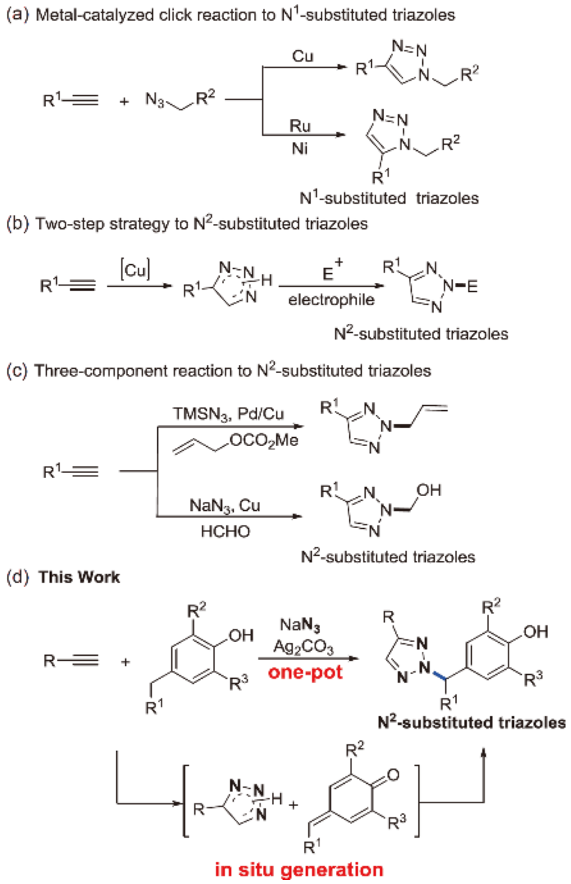


Figure 1 Synthesis of disubstituted 1,2,3-triazoles (color online).

and rich reactivities [9,14]. These fundamental chemicals have been disclosed as significant and extensive applications in organic transformations. Especially, "Silver Rush" in the various transformations of alkynes and their derivatives has flourished gradually over the past decade [15]. Meanwhile, 2,6-di-*tert*-butyl-4-methylphenol (BHT) was all restricted to radical scavenger [16] and has been ignored in organic synthesis [17]. Herein, we reported a silver-catalyzed click/alkylation sequence reaction by direct benzylic amination for N^2-substituted 1,2,3-triazoles with easily available substrates through three-component reaction in one-pot (Figure 1(d)), in which amination source and the electrophile were both generated *in situ*.

2 Experimental

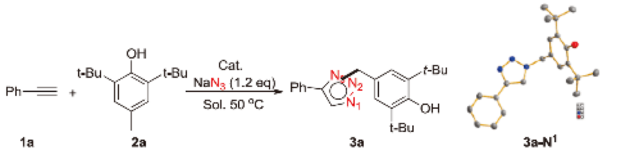
Typical synthetic procedure for compounds **3**, **4** (with **3a** as an example): to a solution of phenylacetylene (**1a**) (0.055 mL, 0.5 mmol), 2,6-di-*tert*-butyl-4-methylphenol (BHT) (**2a**) (133 mg, 0.6 mmol), NaN_3 (39 mg, 0.6 mmol) and KF (58 mg, 1.0 mmol) in DMF (1 mL) at 50 °C, Ag_2CO_3 (41 mg, 0.15 mmol) was added. The reaction mixture was then stirred for 6 h when TLC conformed that substrate **1a** was consumed. The resulting reaction mixture was cooled to room temperature and extracted by dichloromethane (3×15 mL). The organic layer was washed with brine (3×40 mL), dried over $MgSO_4$ and concentrated. Purification of the crude product via flash column chromatography (silica gel; petroleum ether) and concentratinon in vacuo afforded the desired product of **3a-**N^2/**3a-**N^1 in 91% yield.

3 Results and discussion

Based on our continuous interest in alkyne reactions, our investigation began with the reaction of two easily accessible phenylacetylene **1a** and BHT **2a** as the model substrates to verify our hypothesis of the extensive screening of transition-metal catalysts and solvents (Table 1 and Supporting Information online). Gratifyingly, we could obtain the desired isomeric triazole **3a** with 65% yield in 3.3:1 ratio of **3a-**N^2 and **3a**-N^1 by employing AgCl as the catalyst and DMF as the solvent (Table 1, entry 1). The two isomers were clearly confirmed by single-crystal X-ray analysis [18a] of 1,4-disubstituted product **3a**-N^1 (see Supporting Information online), assisted by the ^{13}C chemical shifts of the triazole CH [19]. Guided by this exciting result, other silver salts such as AgF, $AgNO_3$ and Ag_2CO_3 were then examined using model substrates for 1,2,3-triazoles by *in-situ* C(sp^3) –H/N–H cross-coupling (Table 1, entries 2–4). A good yield of product **3a** was achieved with Ag_2CO_3 as catalyst under air atmosphere. Diminished or no catalytic activity was exhibited when the reaction was performed with other commercially available metal sources such as CuI, $Cu(OAc)_2$, $NiCl_2$ (Table 1, entries 5–7). The click/coupling tandem reaction employing DCE, EG, H_2O, DMSO and toluene as solvent was investigated and furnished **3a** in the unsatisfactory outcome (Table 1, entries 8–12). We further examined base as additives in the tandem reaction (Table 1, entries 13, 14). KF was proved to be beneficial for the reaction and delivered 1,2,3-triazole product **3a** in the highest yield with a ratio of N^2-substituted/N^1-substituted (N^2/N^1**)** 1,2,3-triazoles up to 9.1:1.

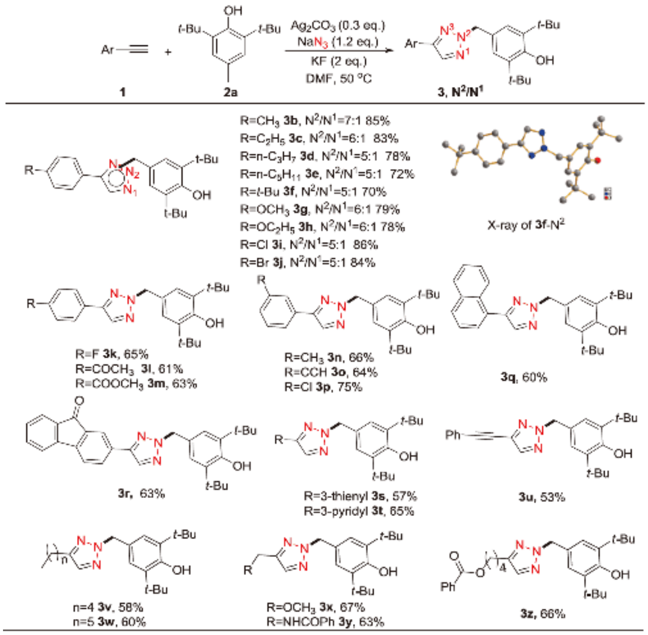
Having identified optimal reaction conditions, we next turned our attention to evaluate the scope of various terminal alkynes for this sequential reaction. As shown in Scheme 1, diverse electron-deficient or -rich aromatic alkynes proceeded smoothly under the optimization conditions, affording the desired 1,2,3-triazoles with moderate to good yields. For instance, arylacetylenes with various *para*-substituted groups such as alkyl, alkoxyl, halogen (**1b**–**1j**) were suitable for this silver-catalyzed click/amination cascade reaction, generating the corresponding N^2/N^1-substituted 1,2,3-triazoles (**3b**–**3j**) in 70%–85% yields. The structure of **3f**-N^2 was confirmed by single-crystal X-ray [18b] (see more details in Supporting Information online). We were pleased to find that regioselectivity was significantly increased when fluoro,

Table 1 Optimization of the reaction conditions[a)]

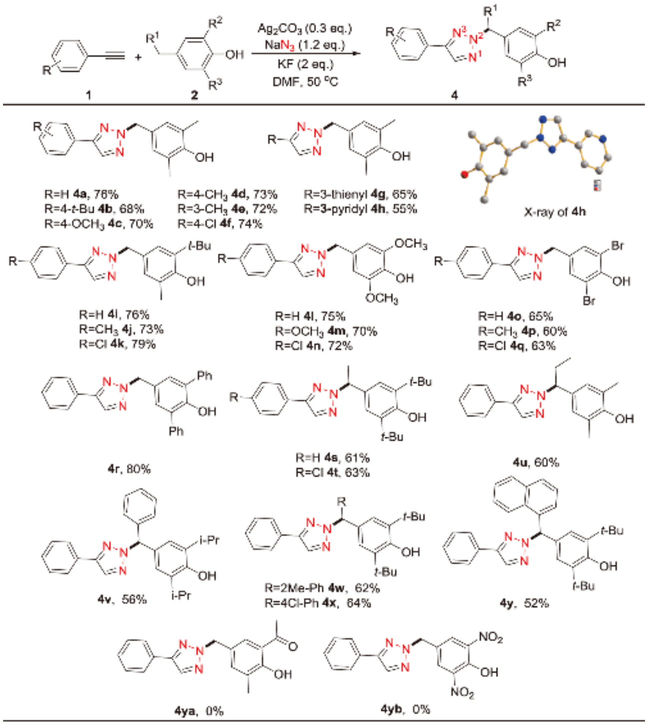


Entry	Cat.	Sol.	**3a** (N^2/N^1) (%)[b)]
1	AgCl	DMF	50:15
2	AgF	DMF	trace
3	$AgNO_3$	DMF	50:15
4	Ag_2CO_3	DMF	70:10
5	CuI	DMF	30:0
6	$Cu(OAc)_2$	DMF	33:0
7	$NiCl_2$	DMF	0
8	Ag_2CO_3	DCE	trace
9	Ag_2CO_3	EG	30:55
10	Ag_2CO_3	H_2O	trace
11	Ag_2CO_3	DMSO	57:21
12	Ag_2CO_3	Toluene	0
13	Ag_2CO_3	DMF	80:10[c)]
14	Ag_2CO_3	DMF	82:9[d)]

a) Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol.), NaN_3 (0.6 mmol), Cat. (0.3 eq.), Sol. (1 mL), 50 °C, 6 h. b) Isolated yield. c) 2.0 eq. $NaHCO_3$ was added. d) 2.0 eq. KF was added. DMF=*N*,*N*-dimethylformamide; DCE=1,2-dichloroethane; EG=ethylene glycol; DMSO=dimethyl sulfoxide.



Scheme 1 Scope of alkynes. Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol.), NaN_3 (0.6 mmol), Ag_2CO_3 (0.3 eq.), KF (2.0 eq.), DMF (1 mL), 50 °C, 6 h, and isolated yield (color online).



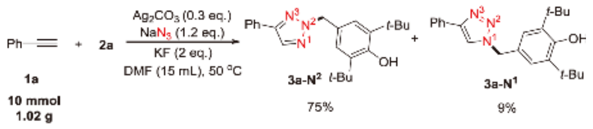
Scheme 2 Scopes of trisubstituted phenol. Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol.), NaN_3 (0.6 mmol), Ag_2CO_3 (0.3 eq.), KF (2.0 eq.), DMF (1 mL), 50 °C, 6 h, and isolated yield (color online).

acetyl and ester group on benzene ring (**1k**–**1m**) were used, delivering the sole N^2-substituted products in moderate yields. This could be attributed to the stabilization of the proposed intermediates **C** with electron effect. Similarly, *meta*-substituted groups including methyl, ethynyl and chloro on the benzene ring (**1n**–**1p**) also gave the desired triazoles (**3n**–**3p**) in a good regioselective manner with 64%–75% yields. Fused or heteroaryl alkynes (**1q**–**1t**) were also compatible with corresponding products (**3q**–**3t**) in a 57%–65% yields under the optimized reaction conditions. Furthermore, a variety of aliphatic alkynes (**1v**–**1z**) could be used in the reaction to the sole triazoles (**3v**–**3z**) in moderate yields. The structure of **3x** was confirmed by single-crystal X-ray [18c] (see more details in Supporting Information online).

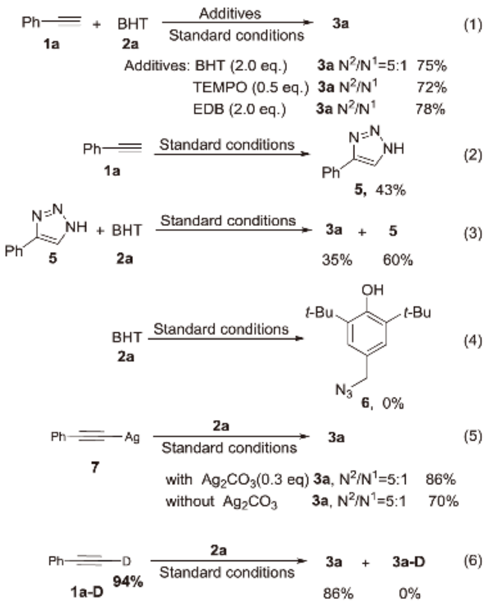
Subsequently, the range of multisubstituted phenols **2** was estimated and summarized in Scheme 2. 2,4,6-trimethylphenol **2b** with **1a** as reaction partner smoothly generated the desired product **4a** in 76% yield. Other electron-deficient or -rich aromatic alkynes were also examined and afforded corresponding products **4b**–**4h** in 55%–74% yields. The structure of **4h** was verified by single-crystal X-ray [18d] (see Supporting Information online). The reaction using other *ortho*-disubstituted *p*-cresols with electron-deficient and -rich aromatic acetylenes analogously showed good reactivity and delivered the products **4i**–**4r** with 60%–80% yields, in which **4n** was verified by single-crystal [18e] (see more details in Supporting Information online). It is worth noting that replacement of *para*-methyl with ethyl on the **2a** also worked well by constructing a chiral center in the targeted product, which was potential for asymmetric amination in one-pot. Subsequently, other *para*-substituent groups such as *n*-propyl (**2u**), aryl (**2v**–**2x**), naphthyl (**2y**) were considered and the corresponding desired products (**4u**–**4y**) were successfully obtained by this three-component reaction. Regretfully, when electron-deficient group such as acetyl or nitryl was introduced into the substrate of trisubstituted phenol, no corresponding product was isolated (**4ya**–**4yb**).

To further demonstrate the practicality of this methodology, we carried out the gram-scale reaction in Scheme 3. The efficiency was not significantly affected by scaling up, and the corresponding product **3a**-N^2 and **3a**-N^1 was obtained in one-pot with 75% and 9% yield, respectively.

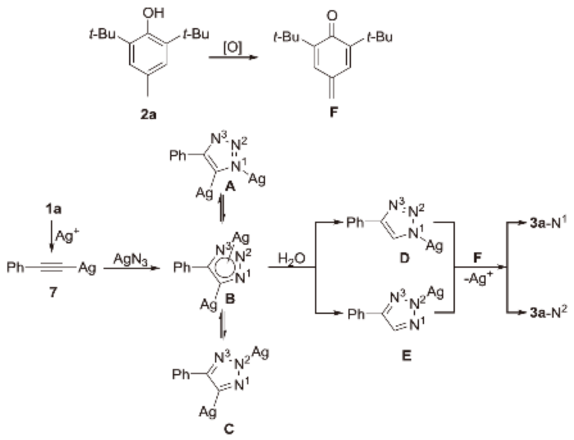
To learn more about the mechanism of tandem reaction, several control experiments were performed as Scheme 4. Firstly, increasing the loading of **2a** to 3.2 equiv. decreased the yield of **3a** to 75%. While 0.5 equiv. 2,2,6,6-*tetra*-methylpiperidinooxy (TEMPO) was added as additives, the reaction yielded 1,2,3-triazole **3a** in 72% (Eq. (1)). When 2.0 equiv. ethene-1,1-diyldibenzene (EDB) as radical scavenger was used under the standard conditions, the yield of the desired product was obtained in 78%. These results suggested that the transformation did not involve a radical process. In the absence of 1.2 equiv. **2a**, the reaction gave the phenyl-1*H*-1,2,3-triazole **5** (Eq. (2)) [20]. While **5** was used as the substrate, the desired product **3a** was yielded in 35% with 60% recovery of the reactant **5** (Eq. (3)). It meant that **5** could be a key intermediate in the reaction. When the reaction was conducted in the absence of **1a**, the presupposed product **6** was not detected (Eq. (4)). It indicated that the silver-catalyzed click reaction between **1a** and **6** in cascade reaction was excluded. Silver acetylide **7** [21] was introduced into the reaction with **2a** under the standard conditions. In the presence of 0.3 equiv. Ag_2CO_3, product **3a** was obtained in 86% yield. In the absence of 0.3 equiv. Ag_2CO_3, a lower yield was afforded (Eq. (5)). These results implied that **7** was an intermediate in the reaction. **1a**-**D** was subjected to the cascade reaction as the reactant and product **3a** was isolated without D atom (Eq. (6)). This indicated that Ag-catalyst activated the triple bond by the generation of silver acetylide **7**.



Scheme 3 Gram-scale of the Ag(I)-catalyzed reaction (color online).



Scheme 4 Mechanistic investigations.



Scheme 5 Possible mechanism for the reaction.

On the basis of the above results and precedent literature [17], a preliminary catalytic cycle for click/alkylation cascade reaction was illustrated in Scheme 5. Initially, the activation of alkyne **1a** took place by producing acetylene silver **7**, and subsequently the 1,3-dipolar cycloaddition proceeded between Ag(I)-species **7** and AgN_3, which was generated *in situ* by anion exchange of NaN_3 with Ag_2CO_3 [15c]. This resulted in the formation of Ag(I) complex **A** [8b], which would be in dynamic equilibrium with the thermodynamically more stable intermediate [13] **C** through intervention of complex **B**. The intermediates **A** and **C** were rapidly captured by H_2O to deliver **D** and **E**, respectively. The coupling reaction subsequently underwent between **D**/**E** and quinone methide **F** from oxidation of **2a** by Ag^+ and oxygen to generate isomer **3a-**N^1/**3a-**N^2 by consecutive loss of Ag^+ for the next cycle.

4 Conclusions

In summary, we have developed a novel and efficient Ag-catalyzed tandem reaction for the preparation of diverse N^2-

substituted 1,2,3-triazoles under simple and mild reaction conditions. This reaction involved the click reaction for NH-1,2,3-triazoles *in situ* and subsequently participated in benzylic C(sp^3)–H amination of easily accessible *p*-cresol derivatives without further isolation. This regioselective and practical protocol enabled operational simplicity, good functional group tolerance and broad substrate scope with simple silver catalyst by three-component reaction in one-pot. The practicality and the synthetic application of this reaction were demonstrated by the large-scale experiments. Meanwhile, a speculated reaction pathway was tentatively proposed based on our preliminary tests and reported literature. Further applications and mechanistic studies of the reaction are ongoing in our laboratory.

Acknowledgements This work was supported by the National Natural Science Foundation of China (21535004, 91753111, 21605097, 21775092, 21390411), the Key Research and Development Program of Shandong Province (2018YFJH0502), the Natural Science Foundation of Shandong Province of China (ZR2016BQ01, ZR2018JL008) and the China Postdoctoral Science Foundation (2017M610442).

Conflict of interest The authors declare that they have no conflict of interest.

Supporting information The supporting information is available online at http://chem.scichina.com and http://link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

1 (a) Davies HML, Alford JS. *Chem Soc Rev*, 2014, 43: 5151–5162; (b) Huang D, Zhao P, Astruc D. *Coordin Chem Rev*, 2014, 272: 145–165; (c) Hosseyni S, Wojtas L, Li M, Shi X. *J Am Chem Soc*, 2016, 138: 3994–3997; (d) Ye X, Xu C, Wojtas L, Akhmedov NG, Chen H, Shi X. *Org Lett*, 2016, 18: 2970–2973; (e) Goitia A, Gómez-Bengoa E, Correa A. *Org Lett*, 2017, 19: 962–965

2 (a) Kacprzak K, Skiera I, Piasecka M, Paryzek Z. *Chem Rev*, 2016, 116: 5689–5743; (b) Kolb HC, Sharpless KB. *Drug Discovery Today*, 2003, 8: 1128–1137; (c) Whiting M, Tripp JC, Lin YC, Lindstrom W, Olson AJ, Elder JH, Sharpless KB, Fokin VV. *J Med Chem*, 2006, 49: 7697–7710; (d) Wilkinson BL, Bornaghi LF, Houston TA, Poulsen SA. In: Kaplan S P, ed. *Drug Design Research Perspectives*. Nova: Haupauge, 2007. 57; (e) Chrovian CC, Soyode-Johnson A, Peterson AA, Gelin CF, Deng X, Dvorak CA, Carruthers NI, Lord B, Fraser I, Aluisio L, Coe KJ, Scott B, Koudriakova T, Schoetens F, Sepassi K, Gallacher DJ, Bhattacharya A, Letavic MA. *J Med Chem*, 2018, 61: 207–223

3 (a) Zheng Y, Ji X, Yu B, Ji K, Gallo D, Csizmadia E, Zhu M, Choudhury MR, De La Cruz LKC, Chittavong V, Pan Z, Yuan Z, Otterbein LE, Wang B. *Nat Chem*, 2018, 10: 787–794; (b) Tiwari VK, Mishra BB, Mishra KB, Mishra N, Singh AS, Chen X. *Chem Rev*, 2016, 116: 3086–3240; (c) Kim WG, Choi B, Yang HJ, Han JA, Jung H, Cho HJ, Kang S, Hong SY. *Bioconjugate Chem*, 2016, 27: 2007–2013; (d) Thirumurugan P, Matosiuk D, Jozwiak K. *Chem Rev*, 2013, 113: 4905–4979; (e) Tang W, Becker ML. *Chem Soc Rev*, 2014, 43: 7013–7039; (f) Tian H, Fürstenberg A, Huber T. *Chem Rev*, 2017, 117: 186–245

4 (a) Finn MG, Fokin VV. *Chem Soc Rev*, 2010, 39: 1231; (b) Kumar AS, Ghule VD, Subrahmanyam S, Sahoo AK. *Chem Eur J*, 2013, 19: 509–518; (c) Hawker CJ, Fokin VV, Finn MG, Sharpless KB. *Aust J Chem*, 2007, 60: 381–383; (d) Chu C, Liu R. *Chem Soc Rev*, 2011, 40: 2177–2188; (e) Astruc D, Liang L, Rapakousiou A, Ruiz J. *Acc Chem Res*, 2012, 45: 630–640; (f) Leophairatana P, Samanta S, De Silva CC, Koberstein JT. *J Am Chem Soc*, 2017, 139: 3756–3766

5 Huisgen R. *Angew Chem Int Ed Engl*, 1963, 2: 565–598

6 Kolb HC, Finn MG, Sharpless KB. *Angew Chem Int Ed*, 2001, 40: 2004–2021

7 (a) Rostovtsev VV, Green LG, Fokin VV, Sharpless KB. *Angew Chem Int Ed*, 2002, 41: 2596–2599; (b) Tornøe CW, Christensen C, Meldal M. *J Org Chem*, 2002, 67: 3057–3064

8 (a) Fokin VV. In: Ding K, Dai L-X, eds. *Organic Chemistry-Breakthroughs and Perspectives*. Weinheim: Wiley-VCH, 2012. 247–277; (b) Banert K. In: Bräse S, Banert K, Eds. *Organic Azides: Syntheses and Applications*. Chichester: Wiley, 2010; (c) Wei F, Wang W, Ma Y, Tung CH, Xu Z. *Chem Commun*, 2016, 52: 14188–14199; (d) Kappe CO, Van der Eycken E. *Chem Soc Rev*, 2010, 39: 1280–1290; (e) Johansson JR, Beke-Somfai T, Said Stålsmeden A, Kann N. *Chem Rev*, 2016, 116: 14726–14768; (f) Wang Z, Li B, Zhang X, Fan X. *J Org Chem*, 2016, 81: 6357–6363; (g) Wang Q, Shi X, Zhang X, Fan X. *Org Biomol Chem*, 2017, 15: 8529–8534

9 Kim WG, Kang ME, Lee JB, Jeon MH, Lee S, Lee J, Choi B, Cal PMSD, Kang S, Kee JM, Bernardes GJL, Rohde JU, Choe W, Hong SY. *J Am Chem Soc*, 2017, 139: 12121–12124

10 (a) Zhu L, Zhang H, Wang C, Chen Z. *Chin J Org Chem*, 2018, 38: 1052–1064; (b) Chen Y, Liu Y, Petersen JL, Shi X. *Chem Commun*, 2008, 2: 3254–3256; (c) Kalisiak J, Sharpless KB, Fokin VV. *Org Lett*, 2008, 10: 3171–3174; (d) Wang XJ, Sidhu K, Zhang L, Campbell S, Haddad N, Reeves DC, Krishnamurthy D, Senanayake CH. *Org Lett*, 2009, 11: 5490–5493; (e) Wang X, Zhang L, Krishnamurthy D, Senanayake CH, Wipf P. *Org Lett*, 2010, 12: 4632–4635; (f) Yan W, Wang Q, Chen Y, Petersen JL, Shi X. *Org Lett*, 2010, 12: 3308–3311; (g) Liu Y, Yan W, Chen Y, Petersen JL, Shi X. *Org Lett*, 2008, 10: 5389–5392; (h) Zhang Y, Ye X, Petersen JL, Li M, Shi X. *J Org Chem*, 2015, 80: 3664–3669; (i) Wang X, Zhang L, Lee H, Haddad N, Krishnamurthy D, Senanayake CH. *Org Lett*, 2009, 11: 5026–5028; (j) Ueda S, Su M, Buchwald SL. *Angew Chem Int Ed*, 2011, 50: 8944–8947; (k) Ueda S, Ali S, Fors BP, Buchwald SL. *J Org Chem*, 2012, 77: 2543–2547

11 (a) Guru MM, Punniyamurthy T. *J Org Chem*, 2012, 77: 5063–5073; (b) Stewart S, Harris R, Jamieson C. *Synlett*, 2014, 25: 2480–2484; (c) Wu L, Guo S, Wang X, Guo Z, Yao G, Lin Q, Wu M. *Tetrahedron Lett*, 2015, 56: 2145–2148; (d) Gavlik KD, Lesogorova SG, Sukhorukova ES, Subbotina JO, Slepukhin PA, Benassi E, Belskaya NP. *Eur J Org Chem*, 2016, 2016: 2700–2710; (e) Zhou J, He J, Wang B, Yang W, Ren H. *J Am Chem Soc*, 2011, 133: 6868–6870; (f) Ryu T, Min J, Choi W, Jeon WH, Lee PH. *Org Lett*, 2014, 16: 2810–2813; (g) Li J, Zhou H, Zhang J, Yang H, Jiang G. *Chem Commun*, 2016, 52: 9589–9592

12 Kamijo S, Jin T, Huo Z, Yamamoto Y. *J Org Chem*, 2003, 69: 2386–2393

13 Kalisiak J, Sharpless KB, Fokin VV. *Org Lett*, 2008, 10: 3171–3174

14 (a) Peshkov VA, Pereshivko OP, Nechaev AA, Peshkov AA, Van der Eycken EV. *Chem Soc Rev*, 2018, 47: 3861–3898; (b) Boyarskiy VP, Ryabukhin DS, Bokach NA, Vasilyev AV. *Chem Rev*, 2016, 116: 5894–5986; (c) Yang L, Huang H. *Chem Rev*, 2015, 115: 3468–3517; (d) Dorel R, Echavarren AM. *Chem Rev*, 2015, 115: 9028–9072; (e) Asiri AM, Hashmi ASK. *Chem Soc Rev*, 2016, 45: 4471–4503; (f) Zeng X. *Chem Rev*, 2013, 113: 6864–6900; (g) Müller DS, Marek I. *Chem Soc Rev*, 2016, 45: 4552–4566

15 (a) Fang G, Bi X. *Chem Soc Rev*, 2015, 44: 8124–8173; (b) Sekine K, Yamada T. *Chem Soc Rev*, 2016, 45: 4524–4532; (c) Ning Y, Ji Q, Liao P, Anderson EA, Bi X. *Angew Chem Int Ed*, 2017, 56: 13805–13808; (d) Sadamitsu Y, Komatsuki K, Saito K, Yamada T. *Org Lett*, 2017, 19: 3191–3194; (e) Wang H, Mi P, Zhao W, Kumar R, Bi X. *Org Lett*, 2017, 19: 5613–5616; (f) Liu Z, Li Q, Liao P, Bi X. *Chem Eur J*, 2017, 23: 4756–4760; (g) Barve IJ, Thikekar TU, Sun CM. *Org Lett*, 2017, 19: 2370–2373; (h) Tang J, Sivaguru P, Ning Y, Zanoni G,

Bi X. *Org Lett*, 2017, 19: 4026–4029; (i) Liu JQ, Shen X, Wang Y, Wang XS, Bi X. *Org Lett*, 2018, 20: 6930–6933

16 (a) Liu Z, Ji H, Gao W, Zhu G, Tong L, Lei F, Tang B. *Chem Commun*, 2017, 53: 6259–6262; (b) Xu T, Hu X. *Angew Chem Int Ed*, 2015, 54: 1307–1311; (c) Shen T, Wang T, Qin C, Jiao N. *Angew Chem Int Ed*, 2013, 52: 6677–6680

17 (a) Meier BW, Gomez JD, Zhou A, Thompson JA. *Chem Res Toxicol*, 2005, 18: 1575–1585; (b) Lemercier JN, Meier BW, Gomez JD, Thompson JA. *Chem Res Toxicol*, 2004, 17: 1675–1683; (c) Kupfer R, Dwyer-Nield LD, Malkinson AM, Thompson JA. *Chem Res Toxicol*, 2002, 15: 1106–1112; (d) Zhou Q, Turnbull KD. *J Org Chem*, 2001, 66: 7072–7077

18 (a) CCDC 1849952 of **3a-N**^{1} (b) CCDC 1881654 of **3f-N**$^{\mathbf{2}}$ (c) CCDC 1898986 of **3x** (d) CCDC 1881653 of **4h** (e) CCDC 1898987 of **4n**. All the supplementary crystallographic data for this paper are from Cambridge Crystallographic Data Centre http://www.ccdc.cam.ac.uk/

19 Creary X, Anderson A, Brophy C, Crowell F, Funk Z. *J Org Chem*, 2012, 77: 8756–8761

20 Jin T, Kamijo S, Yamamoto Y. *Eur J Org Chem*, 2004, 2004: 3789–3791

21 Vitérisi A, Orsini A, Weibel JM, Pale P. *Tetrahedron Lett*, 2006, 47: 2779–2781