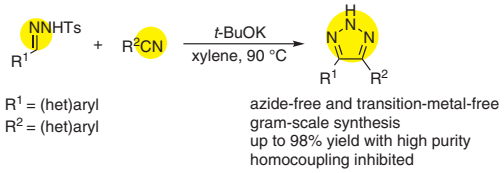
Synlett S. Qiu et al. Letter

Potassium *tert*-Butoxide Promoted Synthesis of 4,5-Diaryl-2*H*-1,2,3-triazoles from Tosylhydrazones and Nitriles

Shanguang Qiu
Yuxue Chen
Xinming Song
Li Liu
Xi Liu
Luyong Wu*

Key Laboratory of Tropical Medicinal Resource Chemistry of Ministry of Education, Hainan Normal University, No. 99, Longkun South Road, Haikou 571158, P. R. of China
wuluyong@hainnu.edu.cn



Received: 24.07.2020
Accepted after revision: 14.09.2020
Published online: 12.10.2020
DOI: 10.1055/s-0040-1707321; Art ID: st-2020-l0415-l

Crowd-Reviewed

Abstract Intermolecular cycloaddition of tosylhydrazones with nitriles was investigated. *t*-BuOK was shown to be an excellent base for increasing the effectiveness of the reaction in this protocol, and homocoupling of the tosylhydrazones was significantly inhibited by using xylene as a solvent. Through this transformation, a variety of 4,5-diaryl-2*H*-1,2,3-triazoles were prepared in good to excellent yields and with high purities. The process is azide-free and transition-metal-free.

Key words triazoles, tosylhydrazones, cycloaddition, potassium butoxide

NH-1,2,3-Triazoles, as a class of special 1,2,3-triazoles, are found in a number of bioactive molecules (for examples, see Figure 1).[1] Consequently, their synthesis has become an important issue in 1,2,3-triazole chemistry and medicinal chemistry.[2] Since the discovery of the copper-catalyzed Huisgen cycloaddition of azides and alkynes for the synthesis of 1,2,3-triazoles with exclusive regioselectivity and high efficiency,[3] several elegant protocols have been used to prepare *NH*-1,2,3-triazoles from azides through cycloaddition reactions of azides,[4] multicomponent reactions,[5] and other reactions.[6] Although various *NH*-1,2,3-triazole motifs have been synthesized, 4,5-diaryl-*NH*-1,2,3-triazoles have received little attention.

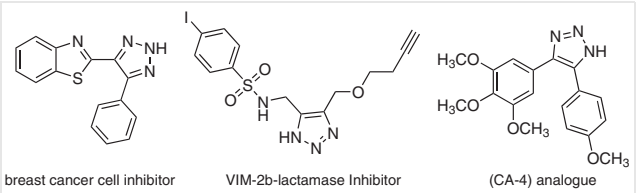
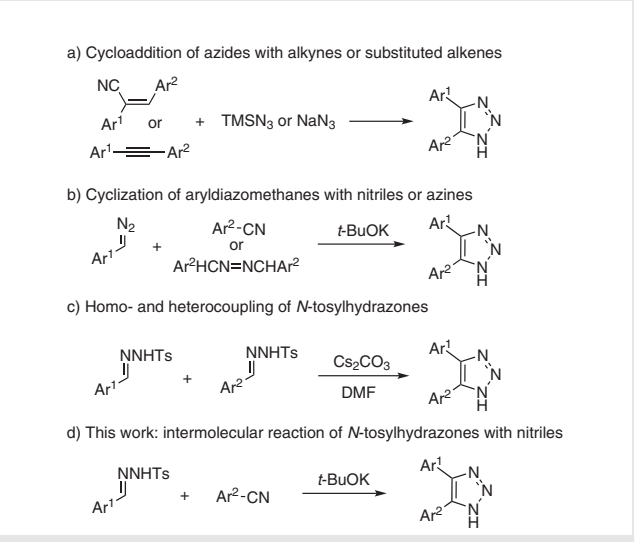


Figure 1 Bioactive molecules containing *NH*-1,2,3-triazole structures

Generally, 4,5-diaryl-*NH*-1,2,3-triazoles have been synthesized by [3+2]-cycloaddition of diarylalkynes with trimethylsilyl azide[7] or sodium azide[8] (Scheme 1a). Because of the potential explosivity and toxicity of azides,[9] the concept of azide-free synthesis has been widely adopted in the synthesis of 1,2,3-triazoles.[10] This progress has also influenced the synthesis of *NH*-1,2,3-triazoles.[11] It is therefore imperative to explore azide-free protocols for the synthesis of 4,5-diaryl-1,2,3-triazoles. In 1988, Grundon and Khan reported that the reactions of aryldiazomethanes with arylaldehyde azines or aryl nitriles gave the corresponding 4,5-diaryl-*NH*-1,2,3-triazoles in moderate yields (Scheme 1b).[12] Perhaps, the instability, hazardous nature, and difficulty in handling of diazo compounds has restricted the use of this cycloaddition reaction and, consequently, this work is rarely mentioned in the literature on 1,2,3-triazoles.



Scheme 1 Synthetic approaches to 4,5-diaryl-*NH*-1,2,3-triazoles

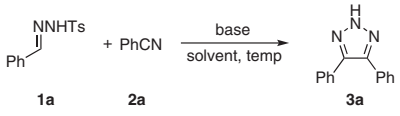
Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

In recent decades, tosylhydrazones have attracted intense interest from the organic-synthesis community,[4d,5b,13] and they have been widely used in many reactions as excellent and safe precursors of diazo compounds.[14] Furthermore, the use of tosylhydrazones as versatile synthons has been explored in many novel reactions to afford various heterocycles, including 1,2,3-triazoles.[15] Recently, the groups of Sakač and Mani reported a synthesis of *NH*-1,2,3-triazoles through 1,3-dipolar cycloadditions of diazo compounds generated in situ from tosylhydrazones.[16] Obviously, the preparation of 4,5-diaryl-*NH*-1,2,3-triazoles by 1,3-dipolar cycloadditions of nitriles with diazo compounds generated in situ from tosylhydrazones would constitute an elegant protocol.

In 2017, the group of Maity and Manna described regioselective syntheses of 1,2,3-triazoles and pyrazoles from tosylhydrazones.[17] They succeeded in synthesizing 4,5-diaryl-*NH*-1,2,3-triazoles in moderate to good yields by coupling tosylhydrazones. They also showed that the electronic nature of tosylhydrazone influenced the coupling process. As the results, when cross-couplings of different tosylhydrazones were carried out, the corresponding homocoupled *NH*-triazoles were obtained as byproducts and reduced the purity of the desired products. The authors also explored the intermolecular reactions of tosylhydrazones with nitriles to provide two 4,5-diaryl-*NH*-1,2,3-triazoles,[17] in which homocoupling of the tosylhydrazones similarly decreased the yields and the purities of the products (Scheme 1c).[17] The challenge therefore remained of inhibiting the homocoupling cyclization of tosylhydrazones to provide 4,5-diaryl-*NH*-1,2,3-triazoles with high efficiency and high purity. Because of our continuing interest in 1,2,3-triazoles,[18] we decide to explore further the azide-free reaction of tosylhydrazones with nitriles (Scheme 1d).

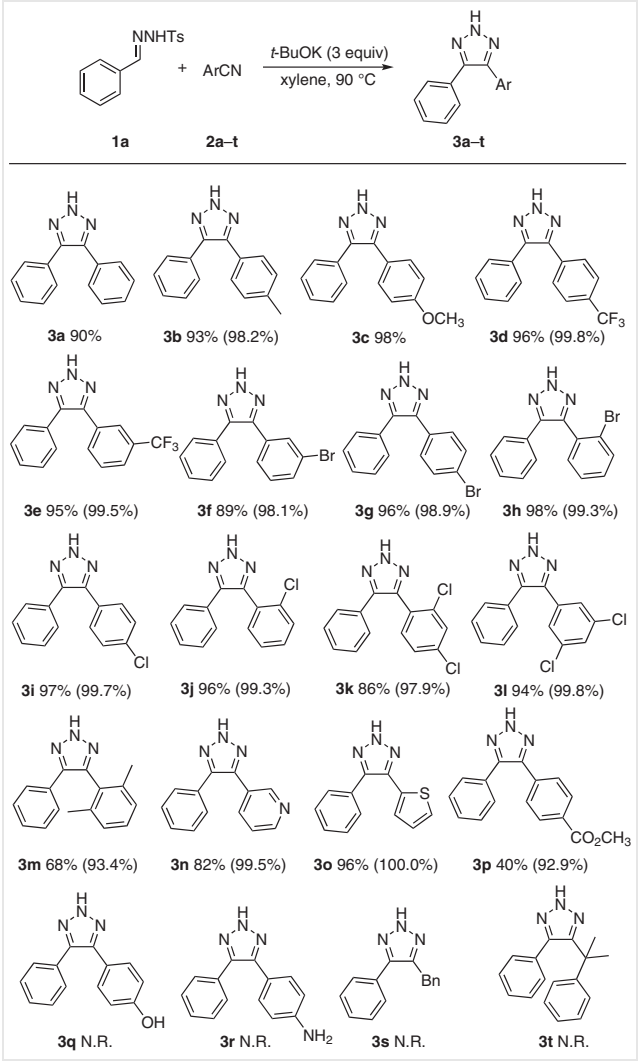
Initially, we chose benzaldehyde tosylhydrazone (**1a**) and benzonitrile (**2a**) as model substrates for the optimization of the reaction conditions (Table 1). K_2CO_3, generally suitable as a base in intramolecular cycloadditions,[16] did not facilitate the intermolecular reaction. However, when 2.0 equivalents of *t*-BuOK were used as the base, the desired product was isolated in 38% yield, along with benzaldehyde azine[19] as a byproduct in a yield of 35% (entry 3). Encouraged by this result, and with the aim of restraining the formation of the benzaldehyde azine byproduct, we increased the amount of *t*-BuOK to 3.0 equivalents, and this gave the desired product in an excellent yield of 90%. Cs_2CO_3 as a base gave a lower yield of 30%. When we screened other

Table 1 Optimization of the Intermolecular Cyclization[a]



Entry	Base (equiv)	Yield[b] (%)
1	K_2CO_3 (2.0)	n.d.
2	DBU (2.0)	n.d.
3	*t*-BuOK (2.0)	38
4	Cs_2CO_3 (3.0)	30
5	*t*-BuOK (3.0)	90

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), DMF (6 mL), 90 °C, 4 h, under Ar.
[b] Isolated yield; n.d. = not detected.

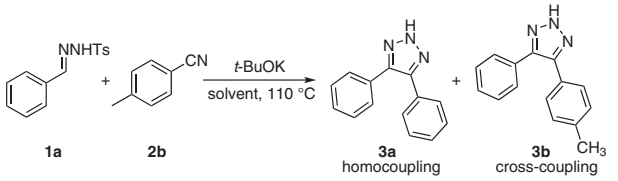


Scheme 2 Reactions of benzaldehyde tosylhydrazone (**1a**) with various nitriles under the optimized conditions. *Reaction conditions*: **1a** (1.0 mmol), 2 (1.2 mmol), xylene (6 mL), 90 °C, 4 h. The yields of the cross-coupling products were calculated from the combined isolated yields of the mixtures of the homocoupled 1,2,3-triazole and the cross-coupled 1,2,3-triazole. The figures in parentheses are the purities of the cross-coupled 1,2,3-triazole, determined by reverse-phase HPLC. N.R. = No reaction.

bases (see Supporting Information), we found that the use of *t*-BuOK as a strong base is critical in improving the efficiency of this intermolecular reaction.

Having increased the efficiency of the intermolecular reaction of the tosylhydrazone and nitrile, we turned our interest to the inhibition of the homocoupling of the tosylhydrazone. When the reaction of benzaldehyde tosylhydrazone (**1a**) and 4-methylbenzonitrile **2b** was carried out, the 4,5-diphenyl- 2*H*-1,2,3-triazole (**3a**) homocoupling byproduct could not be separated from the desired product **3b** by flash column chromatography on silica gel. When DMF was used as the solvent, the isolated product contained 6.1% of homocoupling product. When toluene or xylene was used, however, the proportion of **3a** (as determined by HPLC) was significantly reduced, and xylene was found to give the best result in terms of the yield and the selectivity. We surmised that, in comparison with Cs_2CO_3, the greater basicity of *t*-BuOK is a critical factor in relation to the deprotonation of the tosylhydrazone to transfer anions or diazo compounds, thereby markedly inhibiting the homocoupling of the tosylhydrazone. Therefore the optimal reaction conditions are: tosylhydrazone (1.0 mmol), nitrile (1.2 mmol), *t*-BuOK (3.0 mmol) for four hours at 90 °C under an Ar atmosphere.

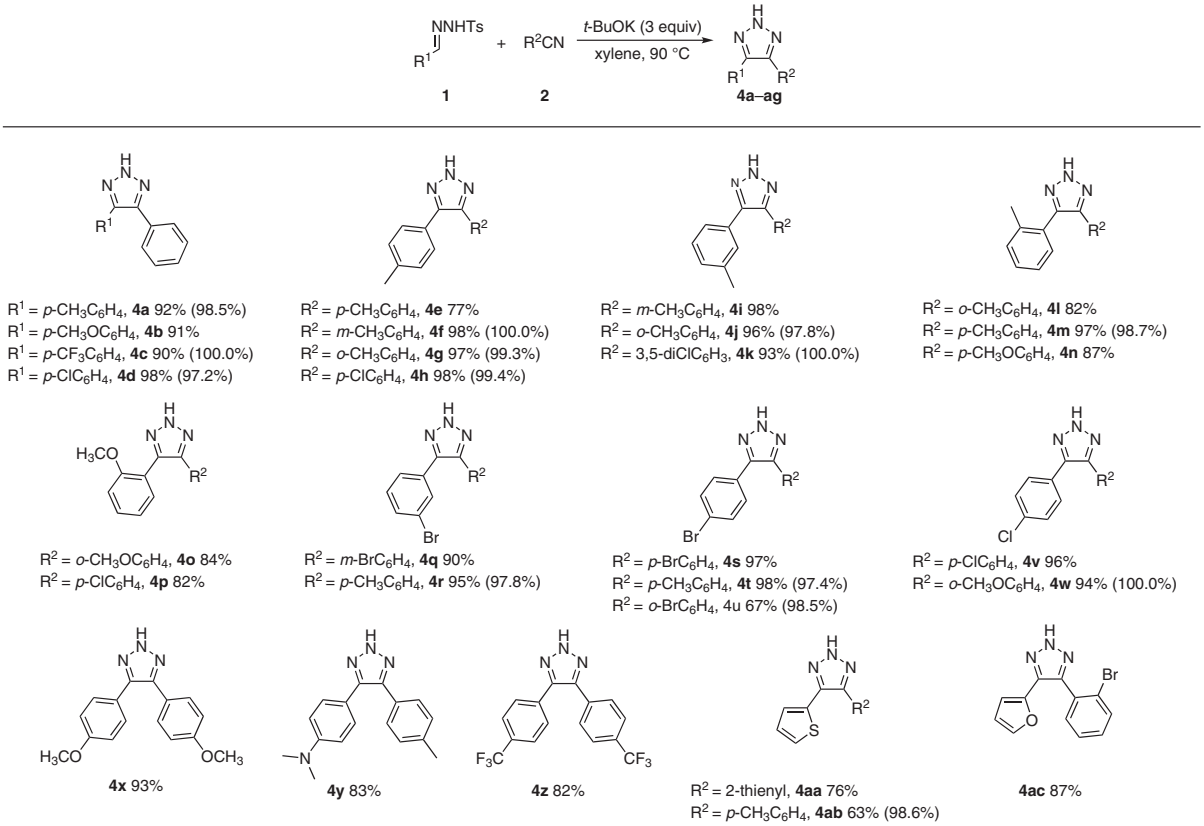
Table 2 Optimization of the Inhibition of Homocoupling of the *N*-Tosylhydrazone[a]



Entry	Solvent	Yield[b] of **3b** (%)	**3a**/**3b**[c]
1	DMF	90	6.1: 93.9
2	toluene	93	0.7: 99.3
3	xylene	93	0.5: 99.5

[a] Reaction conditions: **1a** (1.0 mmol), **2b** (1.2 mmol), solvent (6 mL), 4 h, under Ar.
[b] Based on the isolated mixture of **3a** and **3b**.
[c] Determined by HPLC.

With these optimized conditions in hand, we extended the scope of the method to the reactions of **1a** with various nitriles **2** (Scheme 2). The intermolecular cyclization reaction was found to tolerate various substituents on the aryl nitrile **2**, and gave the desired products **3a–o** in good to ex-

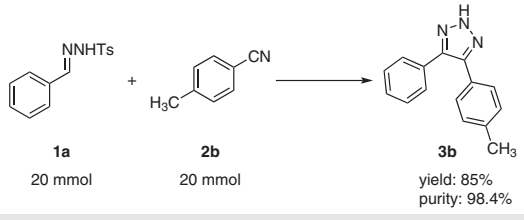


Scheme 3 Reaction scope of tosylhydrazones **1** with nitriles **2** under the optimized conditions. *Reaction conditions*: **1a** (1.0 mmol), **2** (1.2 mmol), xylene (6 mL), 90 °C, 4 h, under Ar. The yields of the cross-coupling products were calculated from the combined isolated yields of the mixtures of the homocoupled 1,2,3-triazole and the cross-coupled 1,2,3-triazole. The figures in parentheses are the purities of the cross-coupled 1,2,3-triazole, determined by reverse-phase HPLC.

cellent yields of 68–98%; however, the methoxycarbonyl-substituted product **3p** was obtained in only 40% yield. Only small amounts of the corresponding homocoupling products of the tosylhydrazones were formed, and the cross-coupling products of the tosylhydrazone with the nitrile were formed in high ratios. The yields were little affected by the presence of electron-withdrawing or electron-donating groups on the nitriles. Moreover, the presence of steric hindrance at the *ortho*-position had little effect on the yields in this transformation (**3h**, **3j**, and **3k**). However, an aryl nitrile bearing two methyl groups at the two *ortho*-positions gave the corresponding 1,2,3-triazole **3m** in a lower yield and a lower cross-coupling ratio. Heterocyclic aryl nitriles also worked well under optimized conditions, and gave good yields of corresponding 1,2,3-triazoles **3n** and **3o** with a high cross-coupling ratio. Unfortunately, when a hydroxy or amino group was present in the benzonitrile, the desired product was not obtained and the unreacted nitrile was recovered by column chromatography (**3q**, **3r**). Nonaromatic nitriles **2s** and **2t** also failed to give the desired products **3s** and **3t**. When phenylacetonitrile was used, the benzaldehyde azine was isolated.

To further expand the scope of this reaction, a series of tosylhydrazones were explored in reactions with various nitriles under the optimized conditions (Scheme 3). Generally, the corresponding 1,2,3-triazoles were obtained in good to excellent yields with high purities. The cyclization was highly tolerant of various functional groups on the benzene rings. When electron-rich or electron-deficient phenyl tosylhydrazones reacted with benzonitrile, the 1,2,3-triazoles **4a**–**d** were obtained in excellent yields and high purities. The reaction also permitted the use of other substituted benzaldehyde tosylhydrazones with substituted benzonitriles (**4e**–**z**). Additionally, hetaryl aldehyde tosylhydrazones were also well tolerated, affording corresponding 1,2,3-triazoles **4aa**–**ac** in good yields.

To demonstrate the synthetic utility of the reaction, we performed a gram-scale reaction (Scheme 4). When **1a** and **2b** were used as substrates, the corresponding product **3b** was isolated by column chromatography in 85% yield and a purity of 98.4%.



Scheme 4 Gram-scale reaction of **1a** and **2b** to give **3b**

In summary, an intermolecular reaction of tosylhydrazones with nitriles is described.[20] This reaction proceeded smoothly when promoted by potassium *tert*-butoxide in xylene; these conditions were beneficial to intermolecular cyclization and inhibited the homocoupling of the tosylhydrazone. The reaction provides an efficient and convenient method for the synthesis of *NH*-1,2,3-triazoles, and a wide range of 4,5-diaryl-2*H*-1,2,3-triazoles were obtained in good to excellent yields.

Funding Information

This work was supported by the Natural Science Foundation of Hainan Province (219MS044) and the National Natural Science Foundation of China (NSFC-21562019).

Acknowledgment

We are grateful to our colleagues in the Centre for Instrumental Analysis for providing services.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707321.

References and Notes

(1) (a) Weide, T.; Saldanha, S. A.; Minond, D.; Spicer, T. P.; Fotsing, J. R.; Spaargaren, M.; Frère, J.-M.; Bebrone, C.; Sharpless, K. B.; Hodder, P. S.; Fokin, V. V. *ACS Med. Chem. Lett.* **2010**, *1*, 150. (b) Madadi, N. R.; Penthala, N. R.; Howk, K.; Ketkar, A.; Eoff, R. L.; Borrelli, M. J.; Crooks, P. A. *Eur. J. Med. Chem.* **2015**, *103*, 123. (c) Cheng, Z.-Y.; Li, W.-J.; He, F.; Zhou, J.-M.; Zhu, X.-F. *Bioorg. Med. Chem.* **2007**, *15*, 1533. (d) Röhrig, U. F.; Majjigapu, S. R.; Grosdidier, A.; Bron, S.; Stroobant, V.; Pilotte, L.; Colau, D.; Vogel, P.; Van den Eynde, B. J.; Zoete, V.; Michielin, O. *J. Med. Chem.* **2012**, *55*, 5270. (e) Röhrig, U. F.; Awad, L.; Grosdidier, A.; Larrieu, P.; Stroobant, V.; Colau, D.; Cerundolo, V.; Simpson, A. J. G.; Vogel, P.; Van den Eynde, B. J.; Zoete, V.; Michielin, O. *J. Med. Chem.* **2010**, *53*, 1172. (f) Penthala, N. R.; Madhukuri, L.; Thakkar, S.; Madadi, N. R.; Lamture, G.; Eoff, R. L.; Crooks, P. A. *Med. Chem. Commun.* **2015**, *6*, 1535.

(2) (a) Zhang, W.; Kuang, C.; Yang, Q. *Youji Huaxue* **2011**, *31*, 54. (b) Tomé, A. C. In *Science of Synthesis, Vol. 13*; Storr, R. C.; Gilchrist, T. L., Ed.; Thieme: Stuttgart, **2004**, Chap. 13, 415. (c) Krivopalov, V. P.; Shkurko, O. P. *Russ. Chem. Rev.* **2005**, *74*, 339.

(3) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596. (b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.

(4) (a) Quan, X.-J.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Org. Lett.* **2014**, *16*, 5728; corrigendum: Org. Lett. 2015, 17, 393. (b) Li, J.; Wang, D.; Zhang, Y.; Li, J.; Chen, B. *Org. Lett.* **2009**, *11*, 3024. (c) Roshandel, S.; Suri, S. C.; Marcischak, J. C.; Rasula, G.; Prakash, G. K. S. *Green Chem.* **2018**, *20*, 3700. (d) Gao, Y.; Lam, Y. *Org. Lett.* **2006**, *8*, 3283. (e) Augustine, J. K.; Boodappa, C.; Venkatachaliah, S. *Org. Biomol. Chem.* **2014**, *12*, 2280.

(5) (a) Wu, G.-L.; Wu, Q.-P. *Synthesis* **2018**, *50*, 2768. (b) Wu, G.-L.; Wu, Q.-P. *Adv. Synth. Catal.* **2018**, *360*, 1949. (c) Xu, C.; Jiang, S.-F.; Wu, Y.-D.; Jia, F.-C.; Wu, A.-X. *J. Org. Chem.* **2018**, *83*, 14802.

(6) (a) Loren, J. C.; Sharpless, K. B. *Synthesis* **2005**, 1514. (b) Barluenga, J.; Valdés, C.; Beltrán, G.; Escribano, M.; Aznar, F. *Angew. Chem. Int. Ed.* **2006**, *45*, 6893. (c) Zhang, H.; Tanimoto, H.; Morimoto, T.; Nishiyama, Y.; Kakiuchi, K. *Org. Lett.* **2013**, *15*, 5222. (d) Ramachary, D. B.; Shashank, A. B. *Chem. Eur. J.* **2013**, *19*, 13175. (e) Liu, Y.; Yan, W.; Chen, Y.; Petersen, J. L.; Shi, X. *Org. Lett.* **2008**, *10*, 5389. (f) Chai, H.; Guo, R.; Yin, W.; Cheng, L.; Liu, R.; Chu, C. *ACS Comb. Sci.* **2015**, *17*, 147. (g) Zhang, W.; Kuang, C.; Yang, Q. *Synthesis* **2010**, 283.

(7) Kim, D.-K.; Kima, J.; Park, H.-J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2401.

(8) (a) Tsai, C.-W.; Yang, S.-C.; Liu, Y.-M.; Wu, M.-J. *Tetrahedron* **2009**, *65*, 8367. (b) Madadi, N. R.; Penthala, N. R.; Song, L.; Hendrickson, H. P.; Crooks, P. A. *Tetrahedron Lett.* **2014**, *55*, 4207.

(9) (a) Chang, S.; Lamm, S. H. *Int. J. Toxicol* **2003**, *22*, 175. (b) Bräse, S.; Banert, K. *Organic Azides: Syntheses and Applications*; Wiley: Chichester, **2010**.

(10) (a) van Berkel, S. S.; Brauch, S.; Gabriel, L.; Henze, M.; Stark, S.; Vasilev, D.; Wessjohann, L. A.; Abbas, M.; Westermann, B. *Angew. Chem. Int. Ed.* **2012**, *51*, 5343. (b) Wan, J.-P.; Hu, D.; Liu, Y.; Sheng, S. *ChemCatChem* **2015**, *7*, 901. (c) Chen, Z.; Yan, Q.; Liu, Z.; Xu, Y.; Zhang, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 13324. (d) Cai, Z.-J.; Lu, X.-M.; Zi, Y.; Yang, C.; Shen, L.-J.; Li, J.; Wang, S.-Y.; Ji, S.-J. *Org. Lett.* **2014**, *16*, 5108. (e) Liu, H.-N.; Cao, H.-Q.; Cheung, C.-W.; Ma, J.-A. *Org. Lett.* **2020**, *22*, 1396. (f) Guru, M. M.; Punniyamurthy, T. *J. Org. Chem.* **2012**, *77*, 5063. (g) Gu, J.; Fang, Z.; Yang, Z.; Li, X.; Zhu, N.; Wan, L.; Wei, P.; Guo, K. *RSC Adv.* **2016**, *6*, 89073. (h) Chen, Z.; Yan, Q.; Liu, Z.; Zhang, Y. *Chem. Eur. J.* **2014**, *20*, 17635. (i) Wang, S.; Yang, L.-J.; Zeng, J.-L.; Zheng, Y.; Ma, J.-A. *Org. Chem. Front.* **2015**, *2*, 1468. (j) Ahamad, S.; Kant, R.; Mohanan, K. *Org. Lett.* **2016**, *18*, 280.

(11) He, Y.; Sun, E.; Zhao, Y.; Hai, L.; Wu, Y. *Tetrahedron Lett.* **2014**, *55*, 111.

(12) Grundon, M. F.; Khan, E. A. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2917.

(13) (a) Li, D.; Liu, L.; Tian, Y.; Ai, Y.; Tang, Z.; Sun, H.-b.; Zhang, G. *Tetrahedron* **2017**, *73*, 3959. (b) Hu, L.; Mück-Lichtenfeld, C.; Wang, T.; He, G.; Gao, M.; Zhao, J. *Chem. Eur. J.* **2016**, *22*, 911. (c) Hu, Q.; Liu, Y.; Deng, X.; Li, Y.; Chen, Y. *Adv. Synth. Catal.* **2016**, *358*, 1689. (d) Jin, T.; Kamijo, S.; Yamamoto, Y. *Eur. J. Org. Chem.* **2004**, *2004*, 3789.

(14) Shu, W.-M.; Zhang, X.-F.; Zhang, X.-X.; Li, M.; Wang, A.-J.; Wu, A.-X. *J. Org. Chem.* **2019**, *84*, 14919.

(15) (a) Guru, M. M.; De, S.; Dutta, S.; Koley, D.; Maji, B. *Chem. Sci.* **2019**, *10*, 7964. (b) Shen, X.; Gu, N.; Liu, P.; Ma, X.; Xie, J.; Liu, Y.; He, L.; Dai, B. *RSC Adv.* **2015**, *5*, 63726.

(16) (a) Sakač, M. N.; Gaković, A. R.; Csanádi, J. J.; Djurendić, E. A.; Klisurić, O.; Kojić, V.; Bogdanović, G.; Gaši, K. M. P. *Tetrahedron Lett.* **2009**, *50*, 4107. (b) Mani, N. S.; Fitzgerald, A. E. *J. Org. Chem.* **2014**, *79*, 8889.

(17) Panda, S.; Maity, P.; Manna, D. *Org. Lett.* **2017**, *19*, 1534.

(18) (a) Wu, L.-Y.; Xie, Y.-X.; Chen, Z.-S.; Niu, Y.-N.; Liang, Y.-M. *Synlett* **2009**, 1453. (b) Wu, L.; Chen, Y.; Tang, M.; Song, X.; Chen, G.; Song, X.; Lin, Q. *Synlett* **2012**, *23*, 1529. (c) Wu, L.; Chen, Y.; Luo, J.; Sun, Q.; Peng, M.; Lin, Q. *Tetrahedron Lett.* **2014**, *55*, 3847. (d) Wu, L.; Guo, S.; Wang, X.; Guo, Z.; Yao, G.; Lin, Q.; Wu, M. *Tetrahedron Lett.* **2015**, *56*, 2145. (e) Wu, L.; Wang, X.; Chen, Y.; Huang, Q.; Lin, Q.; Wu, M. *Synlett* **2016**, *27*, 437. (f) Wu, L.; Chen, Y.; He, W.; An, M.; Yan, G.; Fu, Q.; Chen, M. CN 108794412, **2018**.

(19) Sha, Q.; Wei, Y. *Tetrahedron* **2013**, *69*, 3829.

(20) **4,5-Diaryl-2*H*-1,2,3-triazoles 3a–t, 4a–ag; General Procedure**

A mixture of the appropriate tosylhydrazone **1** (1.0 mmol), nitrile **2** (1.2 mmol), and *t*-BuOK (3.0 mmol) in xylene (6 mL) was stirred at 90 °C for 4 h under Ar. The mixture was then cooled to r.t. and diluted with EtOAc (40 mL). The organic layer was washed with water (3 × 40 mL) and brine (30 mL), then dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuum, and the crude product was purified by column chromatography (silica gel, PE–EtOAc).

4,5-Bis(4-methoxyphenyl)-2*H*-1,2,3-triazole (4x)

White solid; yield: 261.3 mg (93%); mp 121.9–124.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 8.8 Hz, 4 H), 6.79 (d, *J* = 8.9 Hz, 4 H), 3.74 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.5, 140.6, 129.3, 122.2, 113.9, 55.0.