

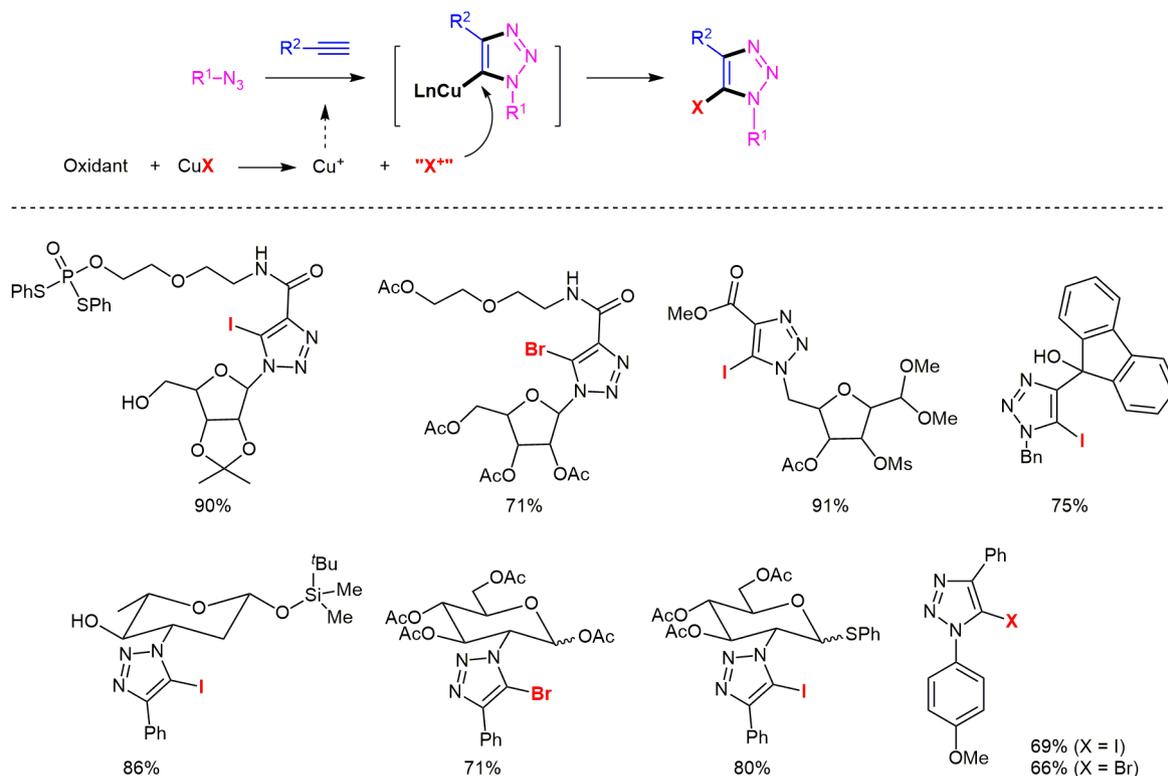
## 4-Trimethylsilyl-5-iodo-1,2,3-triazole: A Key Precursor for the Divergent Syntheses of 1,5-Disubstituted 1,2,3-Triazoles

*Synlett* 2015, 26, 695–699

The investigation of synthetic methods involving 5-substituted 1,2,3-triazoles began several years ago when Professor Lingjun Li was a PhD candidate under the supervision of Professor Lihe Zhang at Peking University (Beijing, P. R. of China). At that time, they applied 4-amide-1,2,3-triazole as the bioisostere of purine nucleobase for the design and synthesis of cyclic ADP-ribose (cADPR, known as a cellular signaling molecule) analogues (*J. Med. Chem.* 2004, 47, 5674). Professor Li said: “However, we could not find an existing method to efficiently incorporate an iodine atom to the 5-position of 4-amide-1,2,3-triazole nucleobase at that time. Thus, we decided to explore new methods.” Based on the study of a 1,2,3-triazolyl copper intermediate in the literature, they

developed a new tandem oxidative iodination and copper-catalyzed alkyne azide cycloaddition (CuAAC) strategy, by which the 5-iodo-4-amide-1,2,3-triazole nucleobase could be constructed directly from two building blocks without touching the other functional groups (*J. Org. Chem.* 2008, 73, 3630). Then, the Li group extended this strategy to ‘tandem oxidative bromination and CuAAC’ (*Synlett* 2011, 874). “The above protocols provided mild, efficient and one-pot synthetic routes to 5-halo-1,4-disubstituted 1,2,3-triazoles from readily prepared terminal alkynes, azides and halide, for a wide scope of substrates, especially various sugar moieties (Scheme 1),” said Professor Li.

Tandem oxidative halogenation and CuAAC strategy: one-pot preparation of 5-halo-1,2,3-triazole



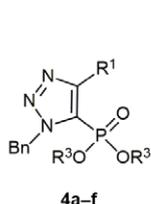
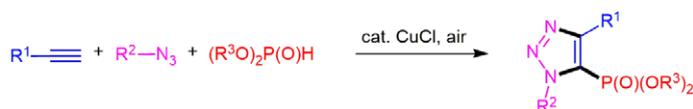
Scheme 1

"To our delight, our methods were soon applied for the synthesis of carbonic anhydrase inhibitor libraries, focusing on the diverse modification of the 1,2,3-triazole pharmacophore (*J. Med. Chem.* **2011**, *54*, 6905)," said Professor Li. "Besides, the one-pot preparative protocol for 5-iodo-triazole-containing cADPR analogues was considered to open new prospects for further interesting modifications of this molecule (*Chem. Rev.* **2009**, *109*, 4207)." This success prompted the Li group to continue pursuing more concise synthetic methodologies that would allow for the straightforward incorporation of various functional groups into the 5-position of the 1,2,3-triazole moiety from alkyne and azide building blocks as starting materials. "As an example, we recently reported another oxidative tandem protocol to prepare 1,2,3-triazolyl-5-phosphonates from terminal alkynes, azides and H-phosphates (*Chem. Eur. J.* **2013**, *19*, 14403, Scheme 2)," explained Professor Li.

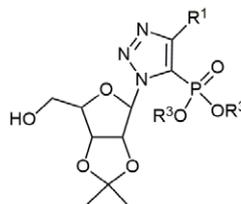
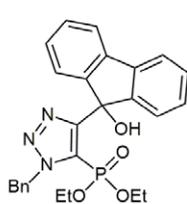
"Compared with the extensive research on the synthesis of 1,4-disubstituted 1,2,3-triazoles, effective methods for the preparation of 1,5-disubstituted 1,2,3-triazoles were fairly limited," said Professor Li. "Therefore, we hope to explore some

practical synthetic protocols for 1,5-disubstituted 1,2,3-triazoles, especially biologically relevant derivatives that are difficult to prepare through other known methods. In the current paper (*Synlett* **2015**, *26*, 695), we developed a novel divergent synthetic protocol for 1,5-disubstituted 1,2,3-triazoles (Scheme 3)." 4-Trimethylsilyl-5-iodo-1,2,3-triazoles (TMSIT), that are prepared successfully from an inexpensive TMS-alkyne and an azide, as the versatile precursors, along with copper(I) iodide, can be conveniently transformed into 5-phenoxy-, 5-arythio-, 5-alkynyl-, and 5-aryl-1,2,3-triazoles. The directing effects of the TMS group allow iodine atoms to be incorporated into the 5-position of the 1,2,3-triazole regioselectively using a tandem oxidative iodination and CuAAC strategy. "TMS groups can then be deprotected smoothly, under conditions compatible with classic Cu/Pd-catalyzed cross-coupling reactions, and thus can give 1,5-disubstituted 1,2,3-triazoles in one pot from TMSIT," said Professor Li. "Moreover, 1-benzyl TMSIT, which is a light-brown crystalline solid (mp 96–98 °C) and stable enough to be stored in air for several months, can be prepared on gram scale.

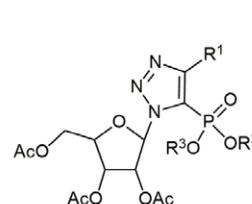
One-pot assembly of 1,2,3-triazolyl-5-phosphonates from azides, alkynes, and H-phosphates



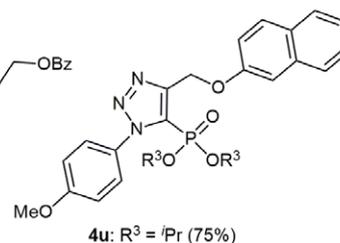
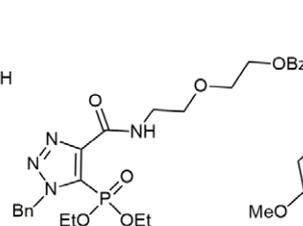
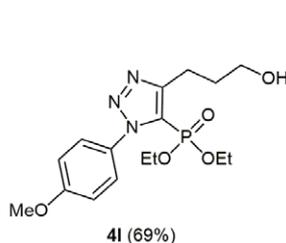
- 4a: R<sup>1</sup> = Ph, R<sup>3</sup> = Et (78%)  
 4b: R<sup>1</sup> = 4-MeC<sub>6</sub>H<sub>4</sub>, R<sup>3</sup> = Et (82%)  
 4c: R<sup>1</sup> = 4-FC<sub>6</sub>H<sub>4</sub>, R<sup>3</sup> = Et (83%)  
 4d: R<sup>1</sup> = 2-pyridinyl, R<sup>3</sup> = Et (73%)  
 4e: R<sup>1</sup> = Ph, R<sup>3</sup> = <sup>i</sup>Pr (80%)  
 4f: R<sup>1</sup> = Ph, R<sup>3</sup> = Bn (62%)



- 4p: R<sup>1</sup> = Ph, R<sup>3</sup> = Et (76%)  
 4q: R<sup>1</sup> = Ph, R<sup>3</sup> = <sup>i</sup>Pr (69%)

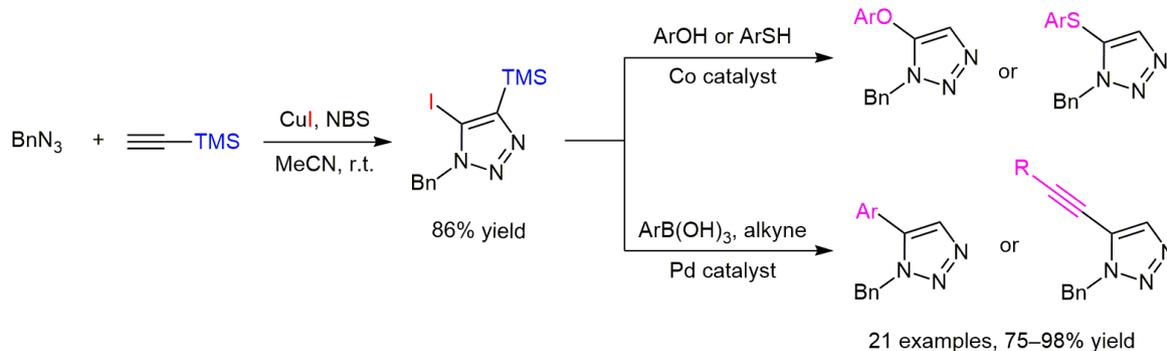


- 4r: R<sup>1</sup> = Ph, R<sup>3</sup> = Et (73%)  
 4s: R<sup>1</sup> = Ph, R<sup>3</sup> = <sup>i</sup>Pr (75%)



Scheme 2

## Divergent syntheses via 4-trimethylsilyl-5-iodo-1,2,3-triazoles



Scheme 3

Together with the concise synthesis routes and the stability of the key precursors, this work provides an attractive alternative for the preparation of structurally diverse 1,5-disubstituted 1,2,3-triazoles.”

Professor Li concluded: “The exploration of more convenient methodologies for the preparation of 5-functionalized 1,2,3-triazoles, and further application of these synthetic methods in the design of bioactive molecules are currently ongoing in our lab.”

*Lucretia Fenske*

## About the authors



Prof. L. Li

**Lingjun Li** was born in Henan (P. R. of China) in 1979. He defended his PhD in 2007 under the supervision of Professor Lihe Zhang (Peking University, P. R. of China), working on the design and synthesis of nucleotide cellular signaling molecules. Subsequently, he worked as a teacher at Henan Normal University (P. R. of China). He carried out postdoctoral training at The Scripps Research Institute (USA) in Professor Floyd E. Romesberg’s

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T.-P. Shang

**Tong-Peng Shang** was born in Henan (P. R. of China) in 1989. He received his BSc in applied chemistry from Huanghuai University (P. R. of China) in 2013 and is currently performing research under the guidance of Professor Li Lingjun in Henan Normal University as a postgraduate student. His research interest concerns triazole chemistry.

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*Prof. G. Zhang*

**Guisheng Zhang** was born in Henan (P. R. of China) in 1965 and obtained his Bachelor's degree in organic chemistry in 1986 from Jilin University (P. R. of China). After receiving his Master's degree at Jilin University in 1989, he immediately joined the Faculty of Henan Normal University. He was promoted to Full Professor of Chemistry in 1999. In 2002, he completed his PhD under the supervision

of Professor Li-He Zhang in Peking University. He then joined Professor Peng George Wang at Ohio State University (USA) as a postdoctoral associate. At the beginning of 2006, he returned to China as an Eminent Professor at Henan Normal University, and he was appointed as the Dean of School of Chemistry and Chemical Engineering in 2012. His research interests are in the fields of synthetic methodology and medicinal synthesis.