Modular Click Chemistry Libraries for Functional Screens Using a Diazotizing Reagent

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Click chemistry – a term coined by 2001 Chemistry Nobel Prize Laureate Professor Barry Sharpless, at Scripps Research (USA) – aims to be a quick and modular synthesis concept for finding new molecules with desirable properties. Professor Sharpless had the intention of connecting 2 or 3 modules together in solution, in sequence, within a few hours and submitting the mixture directly to screening. "This original hope seemed absurd until his lab discovered the CuAAC triazole annulation reaction in 2002," said Professor Dong, who remarked: "This one perfect reaction instantly solved nearly all of our needs for intermolecular ligation. Compared with known combinatorial chemistry strategies based on solid-phase synthesis, this ideal click chemistry plan in solution takes advantage of the near-perfect reactivity of CuAAC and does not involve protecting groups. More importantly, and almost uniquely among combinatorial chemistry strategies, it can make any compound of interest pure on a milligram to gram scale in a day or less, very soon after the biologist has revealed the screening results."

Professor Dong joined Professor Sharpless' laboratory in 2009 as a research associate and paid tribute to him, saying: "Barry is more than a mentor for me. His visionary lecture about click chemistry at SIOC in 2004 was really inspiring for me as a young chemist there, while others simply thought that he had lost his mind! I have been fortunate to work closely with him in the last ten years, in Scripps and now at SIOC."

In the first six years, synthesizing and collecting azides or alkynes had become Professor Dong's daily work. During that time, he noticed at least three aspects having key importance for the aim of generating such a library:

1. The number of commercially accessible azide and alkyne modules is very low.

2. While collecting terminal alkyne molecules, it became evident that usually those molecules hardly tolerated other functional groups or protecting groups, which were generally difficult and laborious to incorporate. Therefore, the alkyne chemical space was limited for this particular application, especially for low-molecular-weight modules.

3. Although many procedures are known for the synthesis of azides, the synthesis of low-molecular-weight azides was even more complicated than the synthesis of alkynes.

Firstly, there were significant safety concerns regarding their reactions and purifications; secondly, azides are unstable, especially in solution. The so-called "Diazotransfer process" was already well known at that time. However, the two standard reagents used for this procedure (TfN_3 and imidazole-1-sulfonyl azide hydrochloride) require metal catalysts, excess azide reagent, and sometimes risky purification steps (as mentioned in this *Nature* article). An excess of diazotransfer reagents would affect the CuAAC reaction if both reactions were run in sequence in one-pot.

Professor Dong explained: "It has been known for years that the CuAAC reaction is unusually predictable; however, it relies on the power of two highly energetic functional groups nature did not use, which kills the accessibility aspect. The commercial availability of both groups is very low compared to those that medicinal chemists often use. While ready availability of azides/alkynes would be highly desirable, in reality this option is simply too difficult to achieve and too expensive."

The exciting discovery of this methodology has an interesting origin, partially based on serendipity. In fact, during their experiments, the group wanted to use FSO_2N_3 for the SuFEx reaction and accidentally discovered the abnormal diazotransfer process. Professor Dong said: "Mistakes are the portals of discovery! We were trying to make FSO_2N_3 from our imidazolium fluorosulfuryl triflate salt **1**, but we knew from our previous publication (*Angew. Chem. Int. Ed.* **2018**, *57*, 2605–2610) that the salt would be hydrolyzed very quickly in water. Therefore, three of my students used organic solvents but failed to produce anything. However, our research associate, Genyi Meng, used water and succeeded at the first attempt! So I asked him: "Why did you use water? Didn't you know the reagent would hydrolyze even without a base?" His answer was, "No, I didn't know that." And that is how we found this excellent procedure for making FSO_2N_3."

Ever since working with Professor Sharpless at Scripps, Professor Dong had wondered how predictable the ligand-

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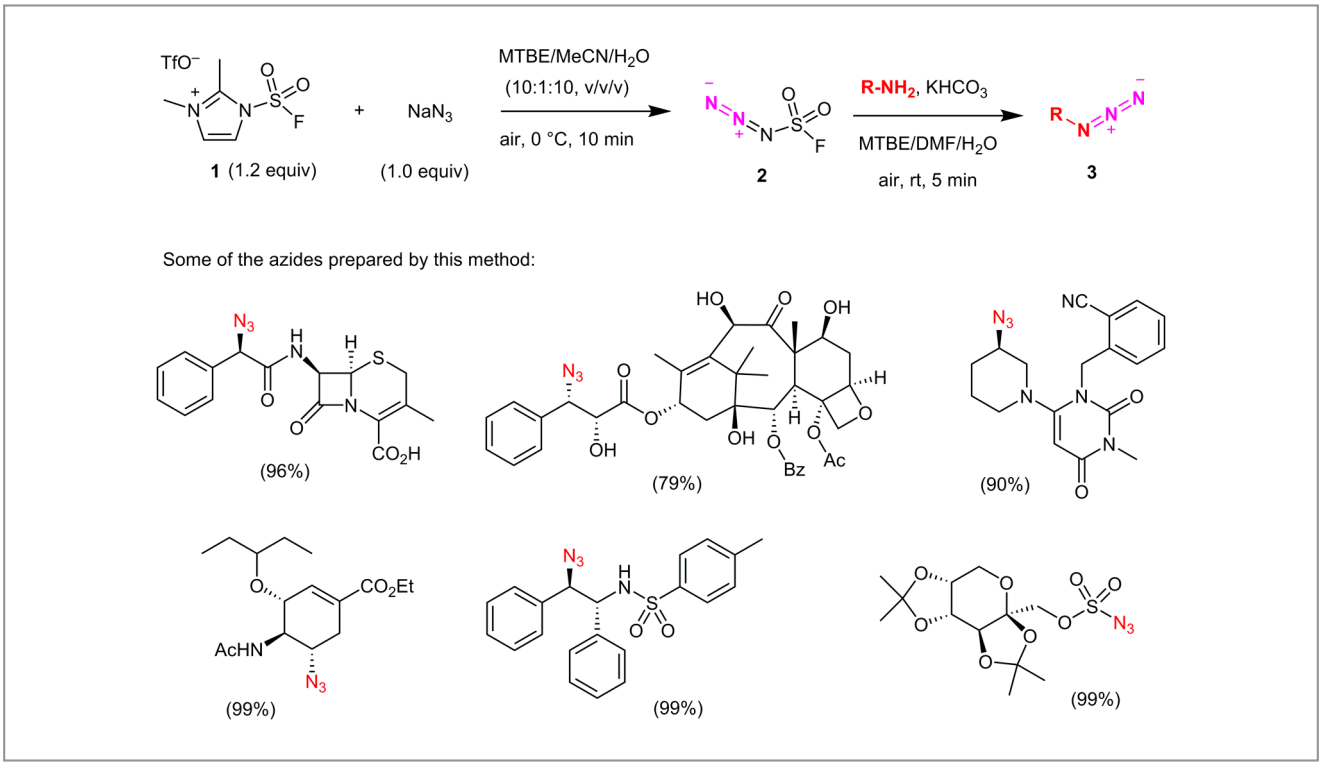


Scheme 1

accelerated CuAAC could be and whether it would be possible to find one SOP to fit every substrate in CuAAC and build a modular synthetic platform. "This discovery inspired me, and we suddenly realized we could have thousands of modules to try this idea now," remarked Professor Dong. He continued: "But it turned out to be surprisingly harder than we thought! PhD student Tiancheng Ma worked hard on it though and we finally figured out a good set of conditions in plates."

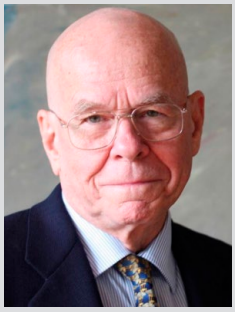
Concerning the future applications of this new methodology, Professor Dong noted that since its discovery, CuAAC has become the most powerful tool to connect two molecular entities chemically. However, its potential as a powerful synthetic tool to produce new compounds has been overlooked. "With this dramatically improved diazotransfer reaction between primary amines and FSO_2N_3, enormous azide libraries are suddenly a reality," said Professor Dong. Even more excitingly, Professor Dong considers this reaction to be a powerful leverage of CuAAC or even SuFEx chemistry, not just any new reaction. "It enables a modular synthesis platform based on the most accessible building blocks in medicinal chemistry and on the most predictable connecting method ever known. Just imagine: one could do 1000, even 10000 modifications on a given lead in a predictable fashion without purification, with just one employee in one day or even less!" said Professor Dong.

"In the last two years, we have collaborated with different groups in China and the U.S.; more than a dozen different 1000-mer triazole libraries have been or are going through phenotypic screens aimed at finding useful activity relevant to human diseases," said Professor Dong. He concluded: "None of the biology results are included in this manuscript. We hope this reaction can help click chemistry towards its goal of speeding up discoveries of useful new molecules, especially much-needed medicines. We are now working on the next version of this azide library: Taijie Guo – a co-author of this study – scaled up our salt to 5 kg and we purchased more than 5000 primary amines. We hope we can hit 4016 pieces soon (LEGO Death Star 75159 had 4016 pieces) and, eventually, a platform with more than 10000 azides."

About the authors

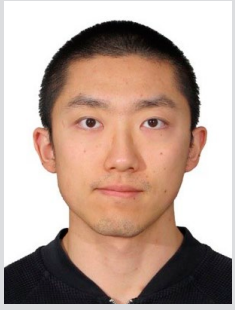
Prof. J. Dong

Jiajia Dong was born in P. R. of China and received his BA from Xiamen University (P. R. of China) in 2000. Prof. Biao Jiang supervised his 2006 PhD in organic chemistry from Shanghai Institute of Organic Chemistry (SIOC, P. R. of China). He was a senior scientific researcher at Egret Pharma, Shanghai (P. R. of China), before becoming a postdoctoral associate in 2009–2015 with Prof. K. Barry Sharpless' group at The Scripps Research Institute (USA). He is currently a research professor at SIOC. His research interests include the main-group fluoride chemistry and click chemistry.



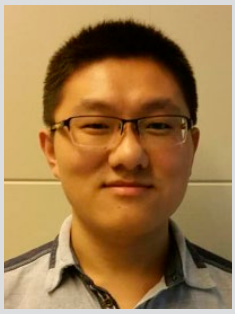
Prof. K. B. Sharpless

Nobel Laureate K. Barry Sharpless became W. M. Keck Professor of Chemistry at The Scripps Research Institute and The Skaggs Institute of Chemical Biology (USA) in 1990. Previously a professor at MIT and Stanford (USA), he was educated at Dartmouth College, USA (BA 1963), Stanford (PhD 1968 with E. E. van Tamelen; postdoc 1969 with J. P. Collman), and Harvard, USA (postdoc 1970, K. E. Bloch). He joined the Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, CAS (P. R. of China) as an adjunct professor in 2016.



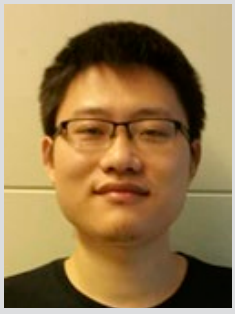
G. Meng

Genyi Meng obtained his BA and MSc in natural sciences from University of Cambridge (UK) in 2016. From 2016 to 2019, he worked under the supervision of Prof. K. Barry Sharpless at Shanghai Institute of Organic Chemistry (P. R. of China) as a research assistant. In 2019, he started his PhD program at the Scripps Research Institute (USA).



T. Guo

Taijie Guo was born in P. R. of China and obtained his B.E. in Chemical Engineering and Technology in 2013 at Jining University (P. R. of China). He received his Master's degree in chemical engineering from Shanghai Normal University (P. R. of China) in 2019. From 2016 to 2019, he studied as a joint student under the supervision of Prof. Jiajia Dong at Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences (P. R. of China). He is currently a research assistant at SIOC with Prof. Jiajia Dong.



T. Ma

Tiancheng Ma was born in 1993 in Hefei, P. R. of China. He received his BSc in chemistry in 2015 at Tongji University, Shanghai (P. R. of China). In September 2015, he started his MSc studies at Shanghai Institute of Organic Chemistry (P. R. of China) under the supervision of Prof. Jiajia Dong. In 2017, he transferred to the PhD program.

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