Discovery of catalytic click reactions and the 2022 Nobel Prize in Chemistry

A reaction or concept becomes vital when it has wide applicability. Scientists developing these concepts are honoured with the Nobel Prize every year. The 2022 Nobel Prize in Chemistry was awarded to Morten Meldal, K. Barry Sharpless and Carolyn R. Bertozzi for their outstanding contribution to the 'development of click reactions and bioorthogonal chemistry'.

During the early years of this millenium, Sharpless at The Scripps Research Institute, San Diego, USA, and Meldal at the Carlsberg Research Laboratory, Copenhagen, Denmark, independently discovered a new copper-catalysed [3+2]-cycloaddition of terminal alkynes with different azides for synthesizing highly regioselective 1,4-disubstituted 1,2,3-triazoles. During the development of this catalytic reaction, Sharpless coined the term for the copper-catalysed [3+2]-cycloadditions as 'click reactions'.

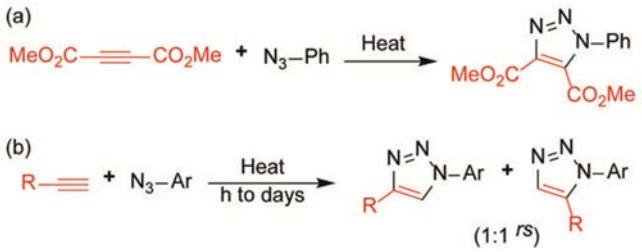
The [3+2]-cycloadditions of alkyne and azide were known since 1893, they were proposed by Michael[1] and expanded by Huisgen[2]. Since the reaction is thermally induced, the chemistry worked well with respect to symmetrical activated alkynes, whereas unsymmetrical alkynes took hours to days to undergo the [3+2]-cycloaddition furnishing a mixture of regioisomers, namely 1,4-disubstituted and 1,5-disubstituted 1,2,3-triazoles, which were difficult to separate (Scheme 1). Due to its least selectivity and slow reaction rates, this thermally induced protocol failed to grab the attention of the scientific community.

In 2001, Sharpless came up with the concept of click reactions[3]. He proposed a set of principles which a reaction must satisfy for it to be categorized as a click reaction. They are as follows: the reaction must (a) be highly selective, (b) be high-yielding; (c) be performed in biofriendly solvents such as water, DMSO, etc. and (d) yield the products at room temperature. In 2002, Sharpless made a pathbreaking discovery by achieving the regioselective copper-catalysed [3+2]-cycloaddition of terminal alkynes with azides[4].

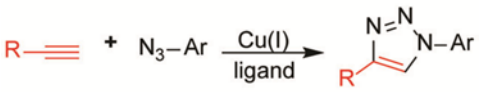
Meanwhile, Meldal at the Carlsberg Research Laboratory developed peptidotriazoles through a solid-phase copper catalysed [3+2]-cycloaddition of different terminal alkynes with azides[5]. This solution and solid-phase click discovery solved the age-old regioselective synthesis of 1,2,3-triazoles and opened a new window for the scientific community (Scheme 2).

Soon after this discovery, Sharpless and co-workers revealed the importance of this concept by synthesizing a potent and highly selective inhibitor of human α-1,3-fucosyltransferase using click chemistry[6]. At about the same time, Benzamin F. Cravatt, a young scientist from The Scripps Research Institute realized the importance of the copper-catalysed click reaction in biological sciences[7]. He took copper-catalysed click reaction as the bioorthogonal probe for the activity-based protein profiling *in vivo*. However, there was cytotoxic effect of copper sulphate on the cell[7]. Addressing this issue, Bertozzi (Stanford University, USA) discovered the strain-promoted copper-free click reaction, for which she chose highly strained alkyne such as cyclooctyne and azide[8]. Soon she started utilizing this copper-free, strain-promoted click reaction as a bioorthogonal reaction *in vivo*[9]. Bertozzi explored different varieties of substituted cyclooctynes for better reaction rates and yields. This reaction takes place well at ambient temperature without disturbing the cell environment, thus making it bioorthogonal (Scheme 3)[10]. However, the methodology is limited to bioorthogonal reactions, because it does not have many applications in medicinal chemistry due to the poor regioselectivity.

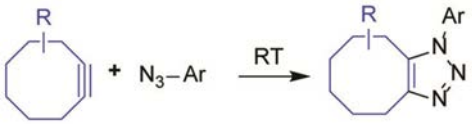
The discovery of copper catalysed [3+2]-cycloaddition for the selective synthesis of 1,2,3-triazoles evoked the interest among organic, medicinal, pharma, biomedical, polymer, material and theoretical chemists. Constructing various functionalized 1,2,3-triazoles and studying their properties became popular in the scientific community. The main reason for this was that '1,2,3-triazoles are considered to be bioisosteres of amide bond'. Also 1,2,3-triazoles have numerous advantages of stability over the amide bond, including thermal stability. Even though this click reaction has wide utility, it has some drawbacks. This copper-catalysed [3+2]-cycloaddition works only for the terminal alkynes, but not for the internal alkynes. To solve this problem, scientists came up with different metal catalysers, including ruthenium, rhodium, gold, silver, etc. for reacting the internal alkynes with azides, but none of them was as efficient as the copper-catalysed click reactions[11]. Since copper-catalysed click reactions work only for the terminal alkynes and the strain-promoted click reactions are limited to bioorthogonal systems and lack regioselectivity, the present authors made an effort to develop a common metal-free green click



Scheme 1. Thermally induced [3+2]-cycloaddition: Michael and Huisgen.



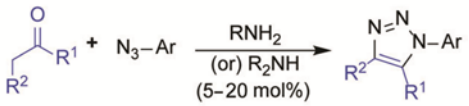
Scheme 2. Copper catalysed click reaction: Meldal and Sharpless.



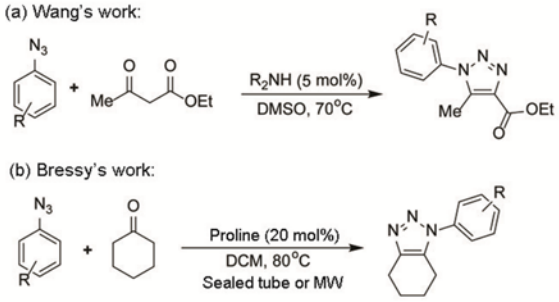
Scheme 3. A strain-promoted click reaction: Bertozzi.

reaction for the synthesis of 1,4-disubstituted, 1,5-disubstituted and 1,4,5-trisubstituted 1,2,3-triazoles in a more sustainable manner way. The present authors chose alpha-methylene carbonyl compounds (because of their wide availability, stability and acidity) as the dipolarophile source to react with aryl/alkyl-azides in [3+2]-cycloaddition fashion, using the amine/amino acid catalysis (Scheme 4)[12].

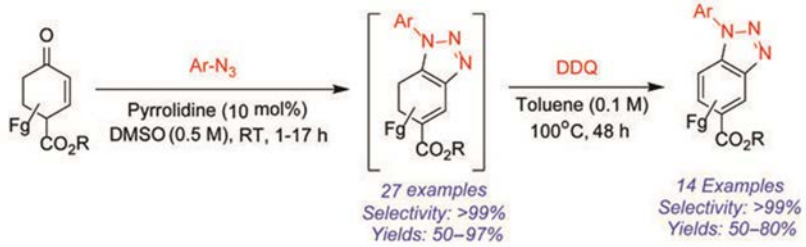
In 2008, under proline catalysis, Ramachary *et al.*[12] discovered the click reaction between cyclohexenones and tosyl azide in DMSO at room temperature and succeeded in achieving the N*H*-1,2,3-triazoles with excellent yield. In one-pot, they achieved both the [3+2]-cycloaddition and the tosyl deprotection reactions in a stepwise manner. It was a metal-free, biofriendly green, organocatalytic click reaction for synthesizing 1,2,3-triazoles. This has led to a novel green, metal-free, organocatalytic, azide-carbonyl-based click pathway for the scientific community. With this motivation, in 2011, Wang[13] from National University of Singapore, Singapore and Bressy[14] from Institut des Sciences Molécularies de Marseille, France demonstrated the [3+2]-cycloaddition of less activated alpha-methylene carbonyl species such as cyclohexanone and activated alkyl carbonyls such as beta-keto esters with various azides, to synthesize the corresponding 1,2,3-triazoles in good to excellent yields with high selectivity (Scheme 5).



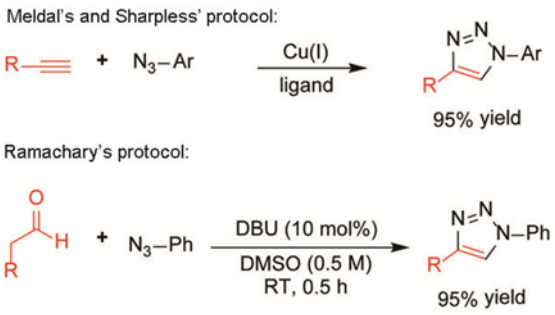
Scheme 4. Amine-catalysed, enamine-mediated click reaction: Ramachary.



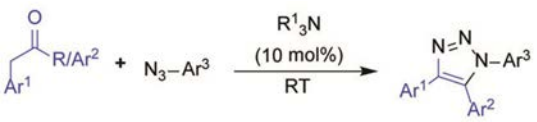
Scheme 5. Amine-catalysed, enamine-mediated click reactions: Wang and Bressy.



Scheme 6. Regioselective synthesis of benzotriazoles through enamine-mediated click reactions and oxidative aromatization reactions: Ramachary.



Scheme 7. DBU-catalysed, enolate-mediated click reaction: Ramachary.



Scheme 8. Amine-catalysed, enolate-mediated synthesis of functionalized 1,2,3-triazoles: Ramachary.

Literature review shows that 1,4,5-trisubstituted 1,2,3-triazoles have more medicinal applications compared to 1,4- or 1,5-disubstituted 1,2,3-triazoles. However, there was no direct protocol for their synthesis. The present authors applied the same enolate-mediated organocatalytic methodology on various ketones and azides to make 1,4,5-trisubstituted 1,2,3-triazoles with excellent yields and regioselectivities (Scheme 8)[17]. They also demonstrated the utility of this metal-free click reaction by synthesizing mGluR1 antagonist with excellent yield[17].

In 2014, these two reactions opened the door for the high yielding, green, metal-free organocatalytic click reaction for the synthesis of 1,4-disubstituted and 1,4,5-trisubstituted 1,2,3-triazoles. Ramachary[18,19] further demonstrated the efficiency of the reaction by choosing various functionalized ketones as dipolarophile source and reacting with different azides such as vinyl azides to make a variety of 1,2,3-triazoles, which are medicinally important. Soon after this discovery, many research groups started utilizing this green concept in various disciplines such as medicinal chemistry, material chemistry,

In 2013, the present authors proposed an *in situ* approach for the synthesis of biologically important benzotriazoles using organocatalytic [3+2]-cycloaddition followed by oxidative aromatization, which are drug-like molecules (Scheme 6)[15].

In 2014, they also developed the new enolate-mediated, amine-catalysed [3+2]-cycloaddition, where different azides were reacted with acetaldehyde in DMSO at room temperature to access 1,4-disubstituted 1,2,3-triazoles within 30 min in excellent yields with high regioselectivity, which is superior to metal catalysis (Scheme 7)[16].

etc. for the synthesis of 1,4-disubstituted and 1,4,5-trisubstituted 1,2,3-triazoles through organocatalysis. Especially in drug synthesis, attaining 1,2,3-triazoles using this organocatalytic, metal-free [3+2]-cycloaddition of carbonyls with azides would be preferable to the copper-mediated [3+2]-cycloaddition of terminal alkynes with azides. Exchange of the terminal alkynes with acetaldehydes, which are low-cost, stable, and abundant in nature, makes the protocol proposed by the present authors appealing. In pharmaceutical chemistry, getting rid of metal impurities such as rhodium, ruthenium, etc. will be a challenging task, whereas amino acids are bio-friendly molecules[20].

There are also other scientists in India working on click chemistry. Vinod K. Tiwari (Banaras Hindu University, Varanasi) works on copper-catalysed sugar-based 1,2,3-triazoles synthesis. Hotha Srinivas (IISER Pune) has synthesized pseudo-oligosaccharides using copper chemistry, Kana M. Sureshan (IISER, Trivandrum) works on topochemical azide–alkyne cycloaddition reactions. Pintu K. Mandal (CDRI, Lucknow) has synthesized fully substituted 1,2,3-triazolyl glycoconjugates using metal-free click reactions, Vandana S. Pore (NCL, Pune) has synthesized fully substituted 1,2,3-triazoles as pharmacophores. A. K. Sinha (CDRI, Lucknow) has worked on thio-ene click reactions.

These foregoing studies in India as elsewhere show the significance of click reactions in various disciplines. Utilization of click reactions in various fields of science may reveal the secrets of nature. The present authors strongly contend that the organocatalytic, metal-free click reactions will become an important tool for drug synthesis in the future.

1. Michael, A., *J. Prakt. Chem*., 1893, **48**, 94.
2. Huisgen, R., *Angew. Chem*., 1963, **75**, 604; *Angew. Chem. Int. Ed*., 1963, **2**, 565–598.
3. Kolb, H. C., Finn, M. G. and Sharpless, K. B., *Angew. Chem. Int. Ed.*, 2001, **40**, 2004–2021.
4. Rostovtsev, V. V., Green, L. G., Fokin, V. V. and Sharpless, K. B., *Angew. Chem. Int. Ed.*, 2002, **41**, 2596–2599.
5. Tornoe, C. W., Christensen, C. and Meldal, M., *J. Org. Chem.*, 2002, **67**, 3057–3064.
6. Lee, L. V., Mitchell, M. L., Huang, S. J., Fokin, V. V., Sharpless, K. B. and Wong, C. H., *J. Am. Chem. Soc*., 2003, **125**, 9588–9589.
7. Speers, A. E., Adam, G. C. and Cravatt, B. F., *J. Am. Chem. Soc*., 2003, **125**, 4686–4687.
8. Agard, N. J., Preschner, J. A. and Bertozzi, C. R., *J. Am. Chem. Soc*., 2004, **126**, 15046–15047.
9. Agard, N. J., Baskin, J. M., Prescher, J. A., Lo, A. and Bertozzi, C. R., *ACS Chem. Biol*., 2006, **1**, 644.
10. Codelli, J. A., Baskin, J. M., Agard, N. J. and Bertozzi, C. R., *J. Am. Chem. Soc*., 2008, **130**, 11486.
11. Johansson, J. R., Beke-Somfai, T., Said Stålsmeden, A. and Kann, N., *Chem. Rev.*, 2016, **116**, 14726.
12. Ramachary, D. B., Ramakumar, K. and Narayana, V. V., *Chem. Eur. J*., 2008, **14**, 9143–9147.
13. Danence, L. J. T., Gao, Y., Li, M., Huang, Y. and Wang, J., *Chem. Eur. J*., 2011, **17**, 3584–3587.
14. Belkheira, M., Abed, D. E., Pons, J.-M. and Bressy, C., *Chem. Eur. J*., 2011, **17**, 12917–12921.
15. Ramachary, D. B. and Shashank, A. B., *Chem. Eur. J*., 2013, **19**, 13175–13181.
16. Ramachary, D. B., Shashank, A. B. and Karthik, S., *Angew. Chem. Int. Ed.*, 2014, **53**, 10420–10424.
17. Ramachary, D. B., Shashank, A. B., Karthik, S., and Madhavachary, R., *Chem. Eur. J*., 2014, **20**, 16877–16881.
18. Ramachary, D. B., Jagjeet, G., Swamy, P. and Surendra Reddy, G., *Eur. J. Org. Chem*., 2017, **3**, 459–464.
19. Ramachary, D. B., Surendra Reddy, G., Swamy, P. and Jagjeet, G., *ChemCatChem*, 2017, **9**, 263–267.
20. Anebouselvy, K. and Ramachary, D. B., *Click Reactions in Organic Synthesis* (ed. Srinivasan Chandrasekaran), Wiley-VCH Verlag GmbH & Co. KGaA, Germany, 2016, pp. 99–140; doi: 10.1002/97835-27694174.ch4.

Anugam V. Krishna, Revoju Sravanthi and **Dhevalapally B. Ramachary*,** Catalysis Laboratory, School of Chemistry, University of Hyderabad, Hyderabad 500 046, India.
*e-mail: ramsc@uohyd.ac.in