CLICK CHEMISTRY

"Olefins, spring-loaded electrophiles, and heteroatom connections are key elements in a fast, modular, process-driven approach to molecular discovery."

"…powerful, highly reliable, and selective reactions for the rapid synthesis of useful new compounds and combinatorial libraries through heteroatom links (C-X-C), …"

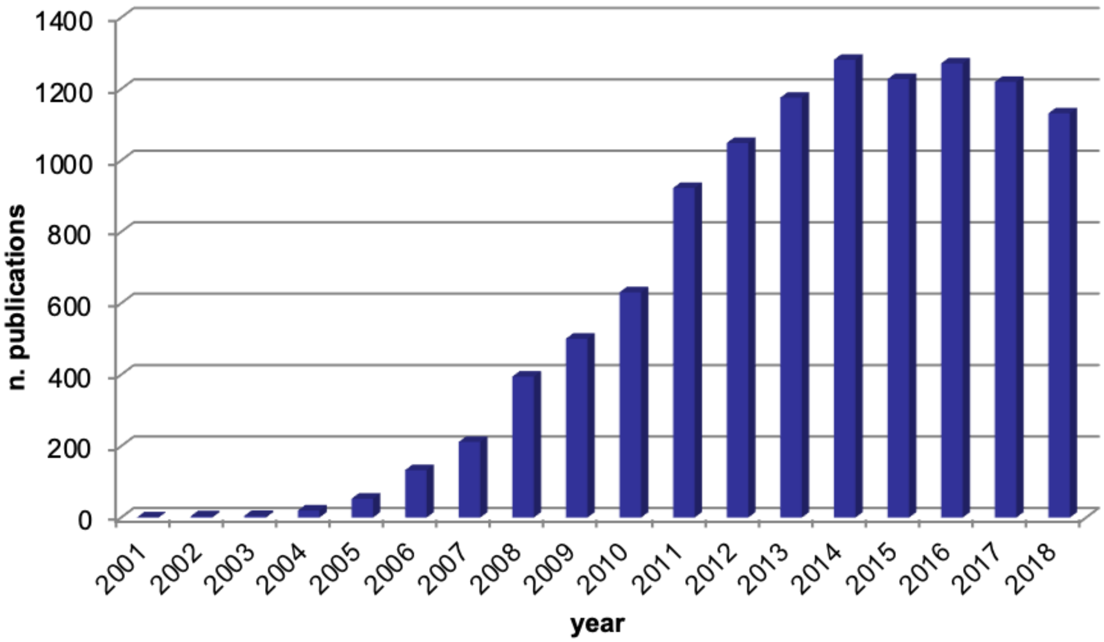
Criteria: the reaction must be modular, wide in scope, give very high yields, generate only inoffensive byproducts …, and be stereospecific

Process Characteristics: simple reaction conditions,
readily available starting materials and reagents
the use of non solvent or a solvent that is begnin
and simple product isolation

Kolb, H. C.; M. G. Finn, K. Barry Sharpless *Angew. Chem. Int. Ed.* 2001, *40*, 2004-2021.

CLICK CHEMISTRY

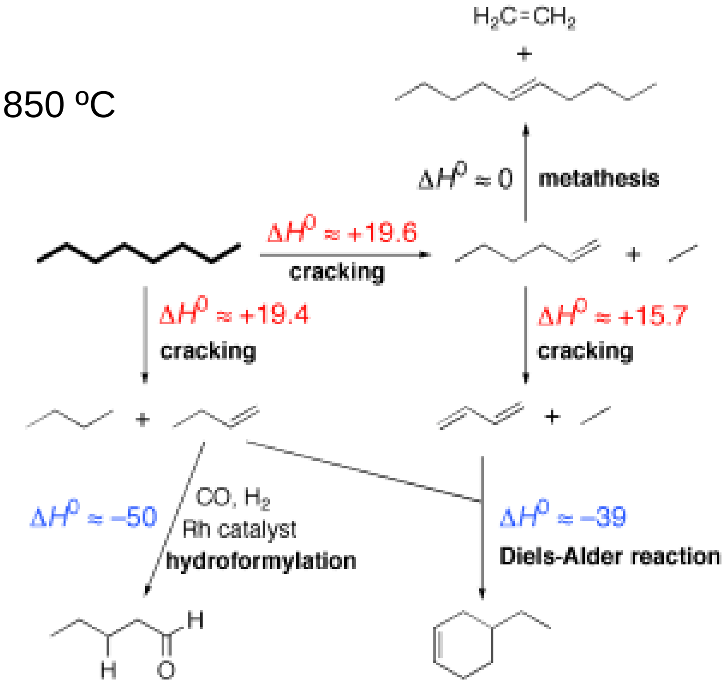
letteratura



CLICK CHEMISTRY

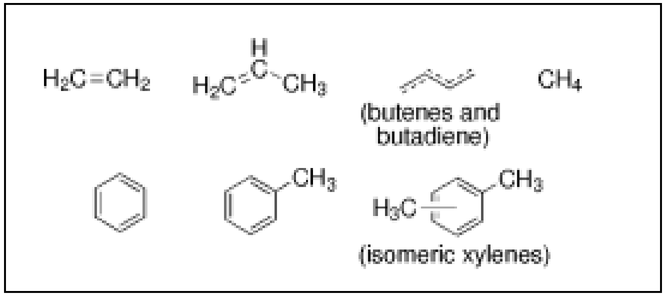
Sintesi organica basata su olefine

Il craking viene condotto a 850 ºC

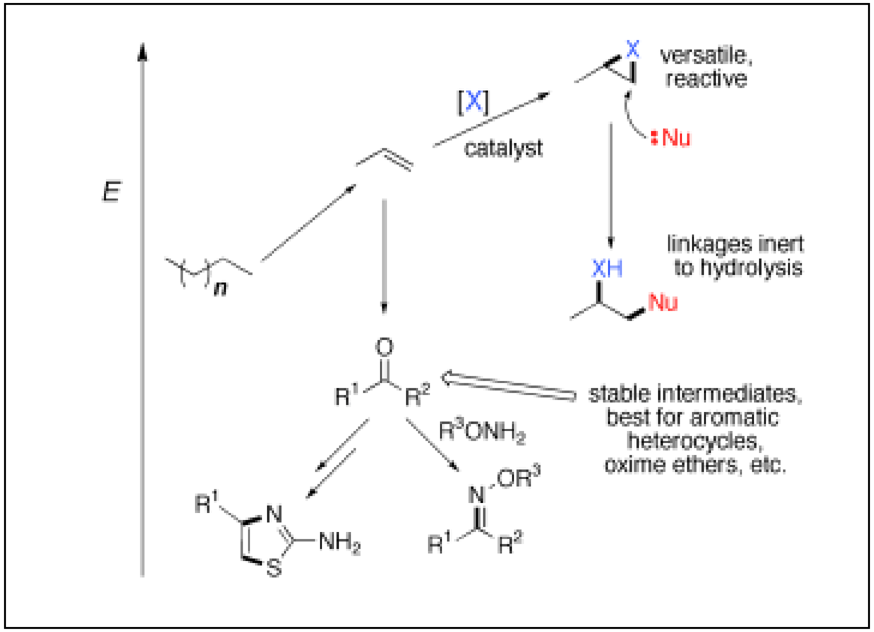


“olefins are the most attractive starting materials available to the synthetic chemist, readily accessible in large quantities and in many varieties, especially if one includes the naturally abundant terpenes.’”

“the chemistry of olefins provides for the creation of diverse scaffolds and the attachment and display of myriad of functionality through oxidative addition of heteroatoms to specifically placed olefinic sites”



Small carbon building blocks from petroleum

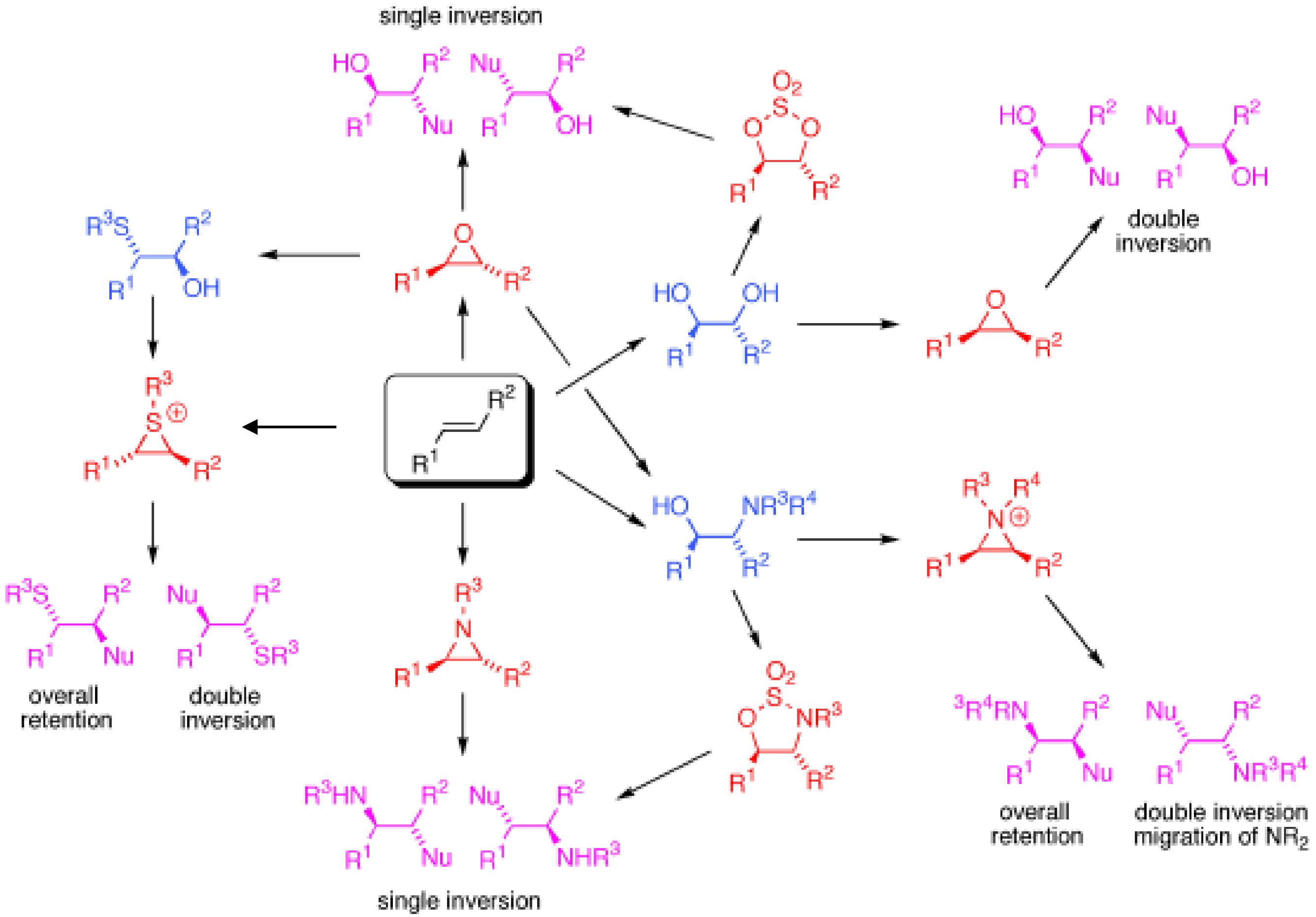


Nu = nucleophile

Examples of the genesis and relative energetics of click chemistry components.
New bonds made with click reactions are in bold.

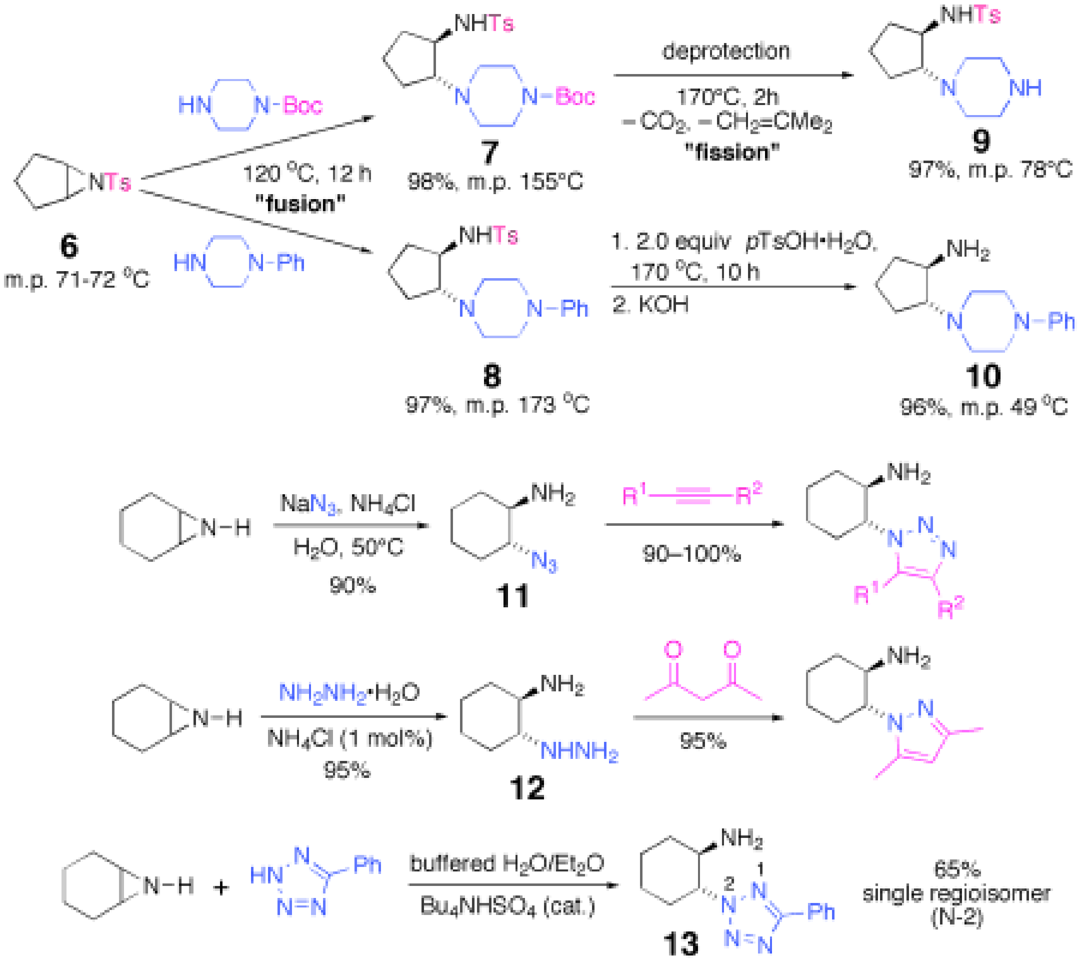
Nucleophilic opening of spring-loaded rings

The S_N2 ring-opening reactions of epoxides, aziridines, cyclic sulphates, cyclic sulfamidates, aziridinium ions and episulfonium ions are reliable, stereospecific, often hygly regioselective, and nearly quantitative.



- Competing elimination processes are stereoelectronically disfavored
- Most of these reactions can be performed in absence of solvent or in water, alcohol, or water/alcohol mixture

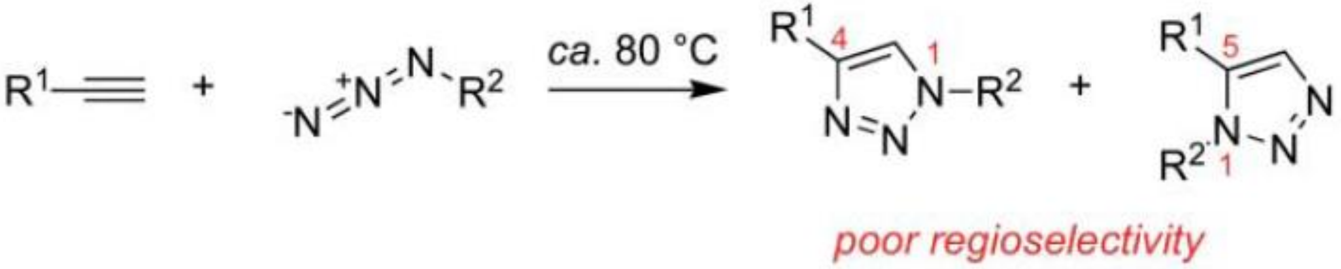
- **Aziridines** are stable under basic conditions
- They can be readily opened by heteroatom nucleophiles under buffered conditions in various solvent including water or neat



Use of activated and nonactivated aziridines as building blocks

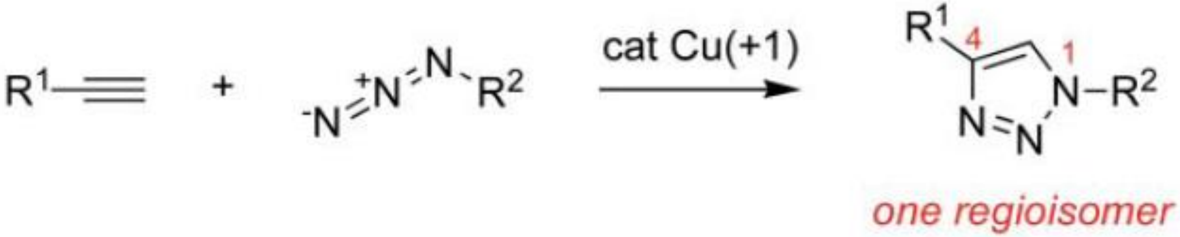
Boc = tert-butoxycarbonyl

Huisgen 1,3-dipolar cycloaddition reactions of alkynes and organic azides



(reaction1)

R. Huisgen, G. Szeimies and L. Moebius, *Chem. Ber.,* **1967**, *100*, 2494–2507.

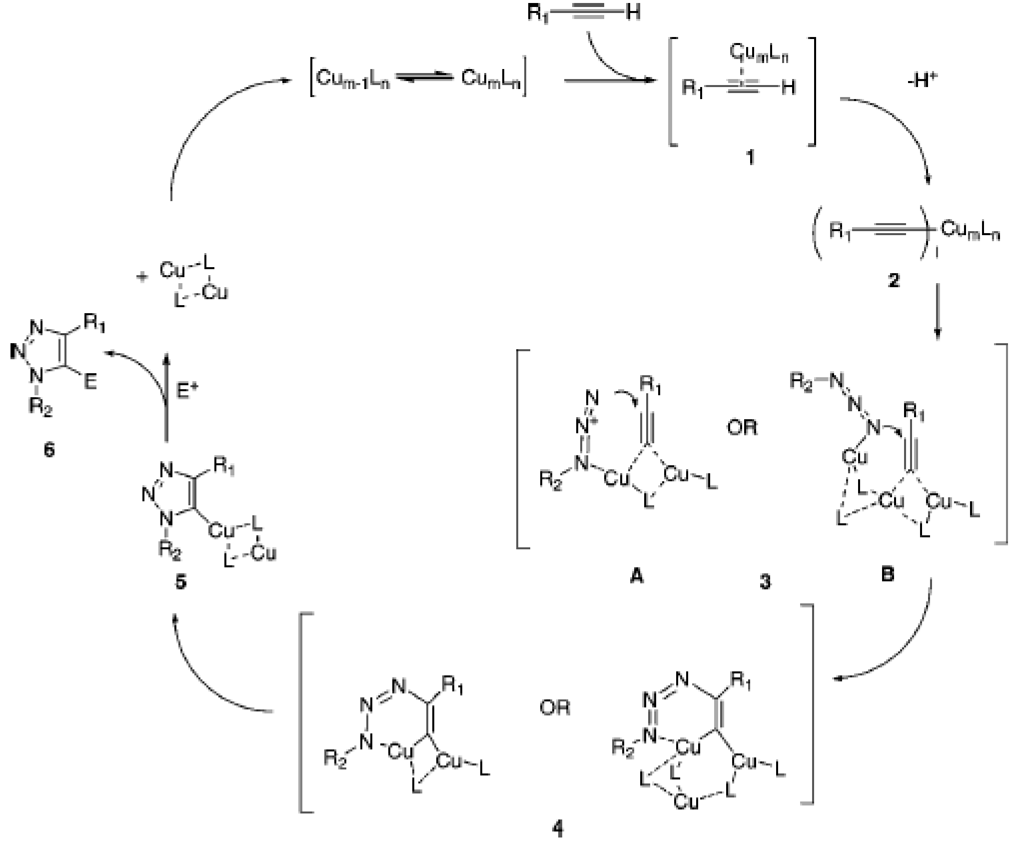


high Δ*G* of the reaction

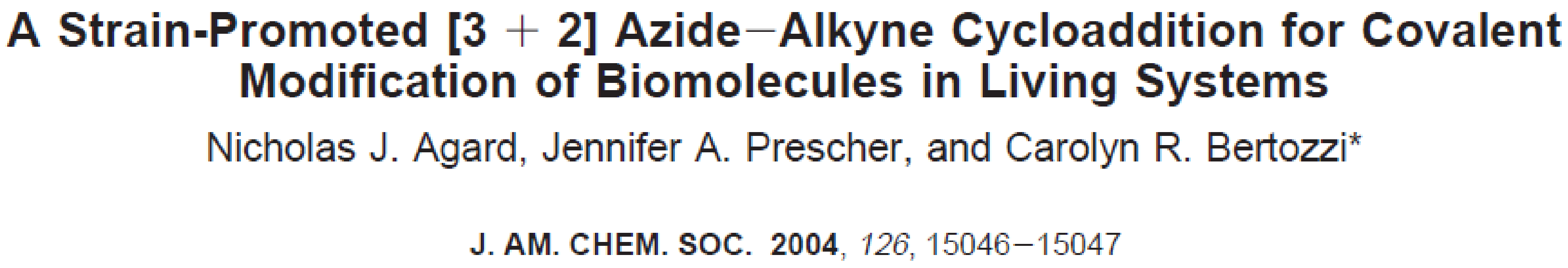
(reaction2)

C. W. Tornoe, C. Christensen and M. Meldal, *J. Org. Chem.,* **2002**, *67*, 3057–3064.
V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.,* **2002**, *7*, 2596–2599.

Scheme 1. Outline of Plausible Mechanisms for the Cu(1) Catalyzed Reaction between Organic Azides and Terminal Alkynes[a]



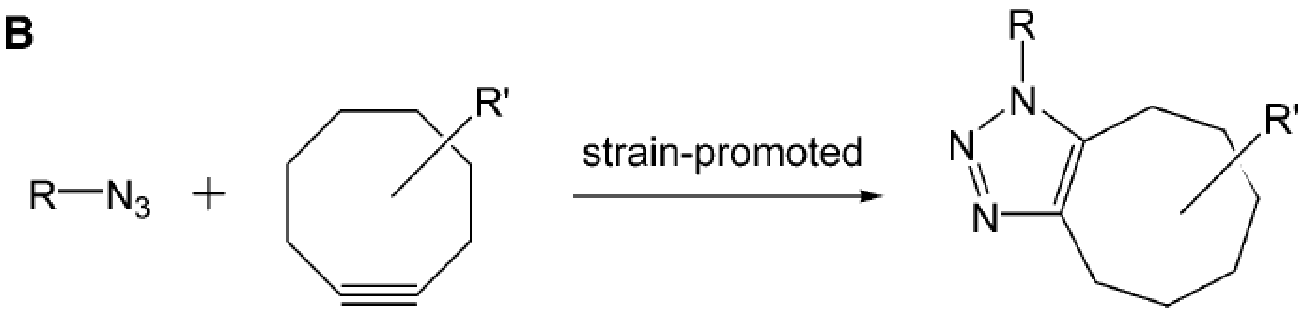
[a] Intermediate A is generally assumed to be the intermediate; however, it fails to explain much of the observed behavioral data of the reaction, and alternatively, intermediate B could explain most observations.



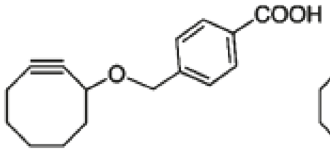
A Strain-Promoted [3 + 2] Azide−Alkyne Cycloaddition for Covalent Modification of Biomolecules in Living Systems

Nicholas J. Agard, Jennifer A. Prescher, and Carolyn R. Bertozzi*

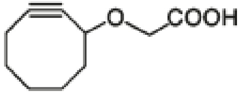
J. AM. CHEM. SOC. **2004**, *126*, 15046−15047



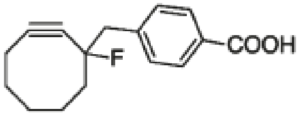
In 1961, Wittig and Krebs reported that cyclooctyne, the smallest stable cycloalkyne, reacted “like an explosion” with phenyl azide (Chem. Ber. 1961, 94, 3260). We inferred from this statement that a good portion of the ~18 kcal/mol of ring strain associated with cyclooctyne was released in the transition state of the cycloaddition reaction. (ACR 2011, C.R. Bertozzi).



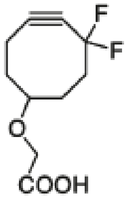
12, OCT
$k = 0.0024\ \mathrm{M^{-1}s^{-1}}$



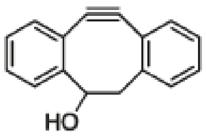
13, ALO
$k = 0.0013\ \mathrm{M^{-1}s^{-1}}$



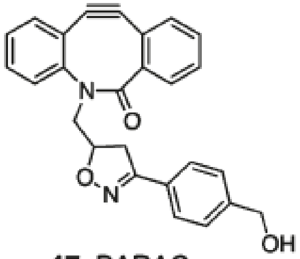
14, MOFO
$k = 0.0043\ \mathrm{M^{-1}s^{-1}}$



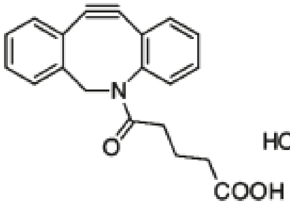
15, DIFO
$k = 0.076\ \mathrm{M^{-1}s^{-1}}$



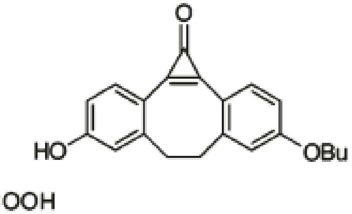
16, DIBO
$k = 0.057\ \mathrm{M^{-1}s^{-1}}$



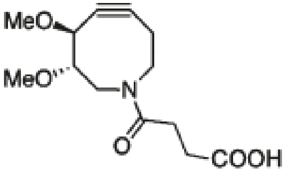
17, BARAC
$k = 0.96\ \mathrm{M^{-1}s^{-1}}$



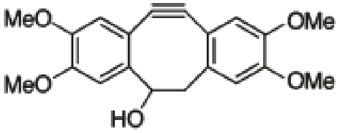
18, DIBAC (ADIBO)
$k = 0.31\ \mathrm{M^{-1}s^{-1}}$



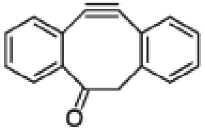
19
$k = 0.076\ \mathrm{M^{-1}s^{-1}}$



22, DIMAC
$k = 0.0030\ \mathrm{M^{-1}s^{-1}}$



20, TMDIBO
$k = 0.094\ \mathrm{M^{-1}s^{-1}}$



21, keto-DIBO
$k = 0.26\ \mathrm{M^{-1}s^{-1}}$

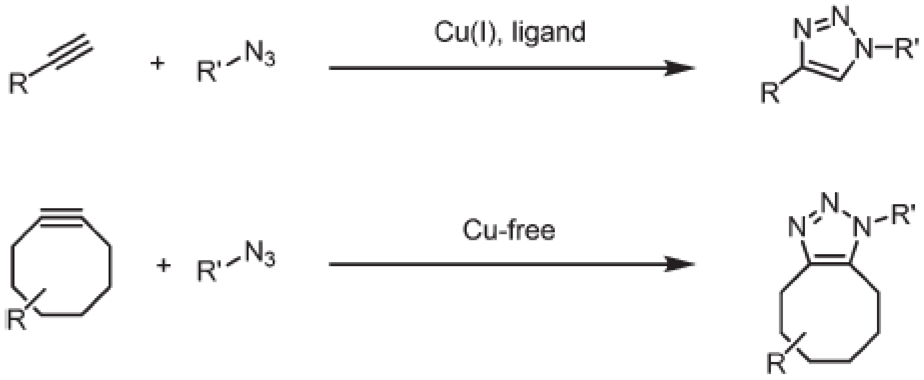
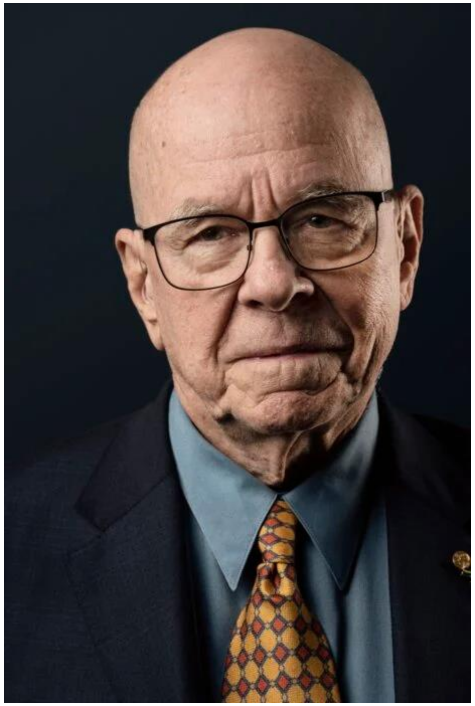


Fig. 8 The copper-catalyzed and copper-free click reactions between alkynes and azides to form triazoles.

The Nobel Prize in Chemistry 2022

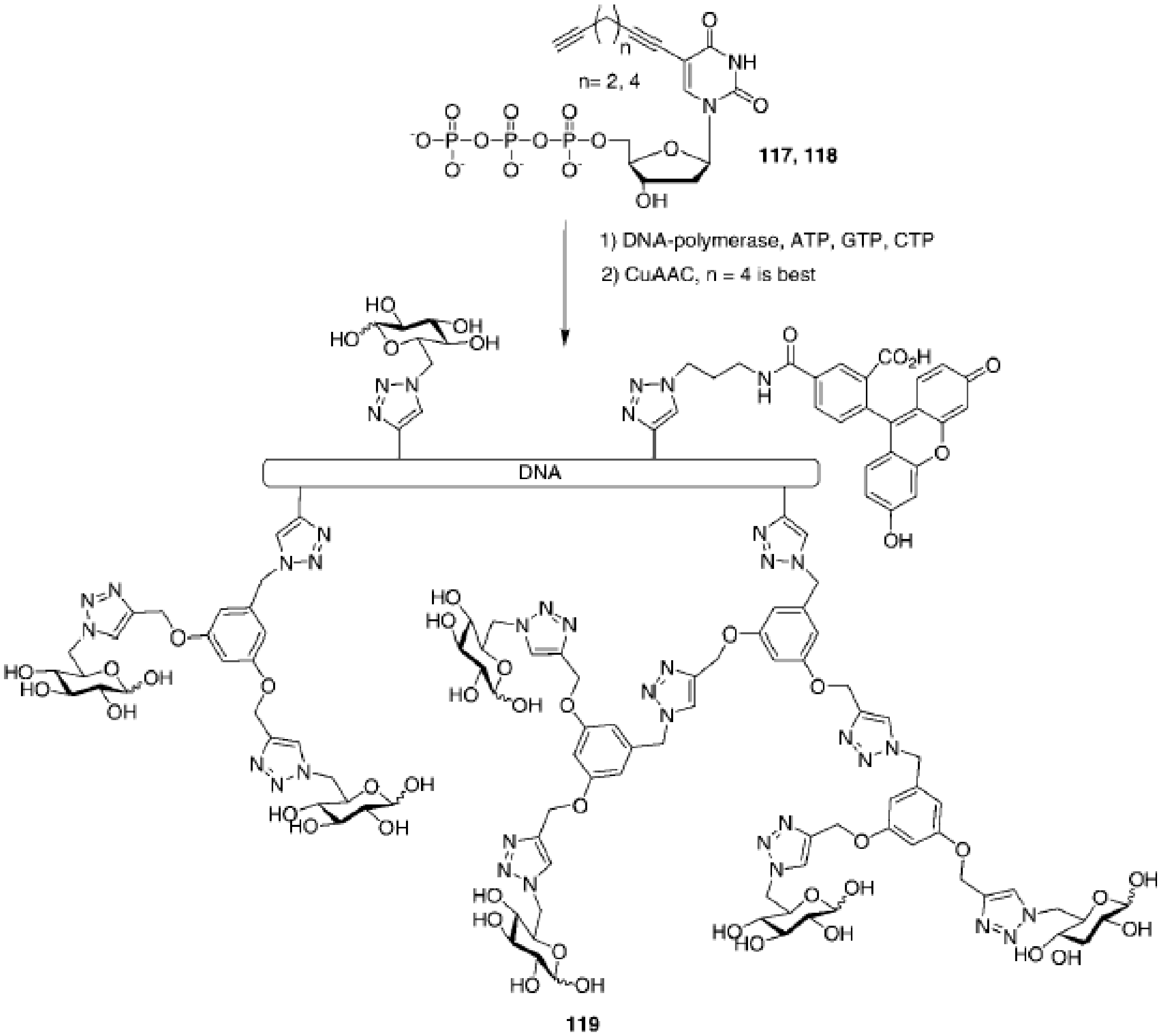
Carolyn R. Bertozzi

Morten Meldal



K. Berry Sharpless

The Nobel Prize in Chemistry 2022 was awarded jointly to Carolyn R. Bertozzi, Morten Meldal and K. Barry Sharpless "for the development of click chemistry and bioorthogonal chemistry"



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The triazole formed is essentially chemically inert to reactive conditions, e.g. oxidation, reduction, and hydrolysis.

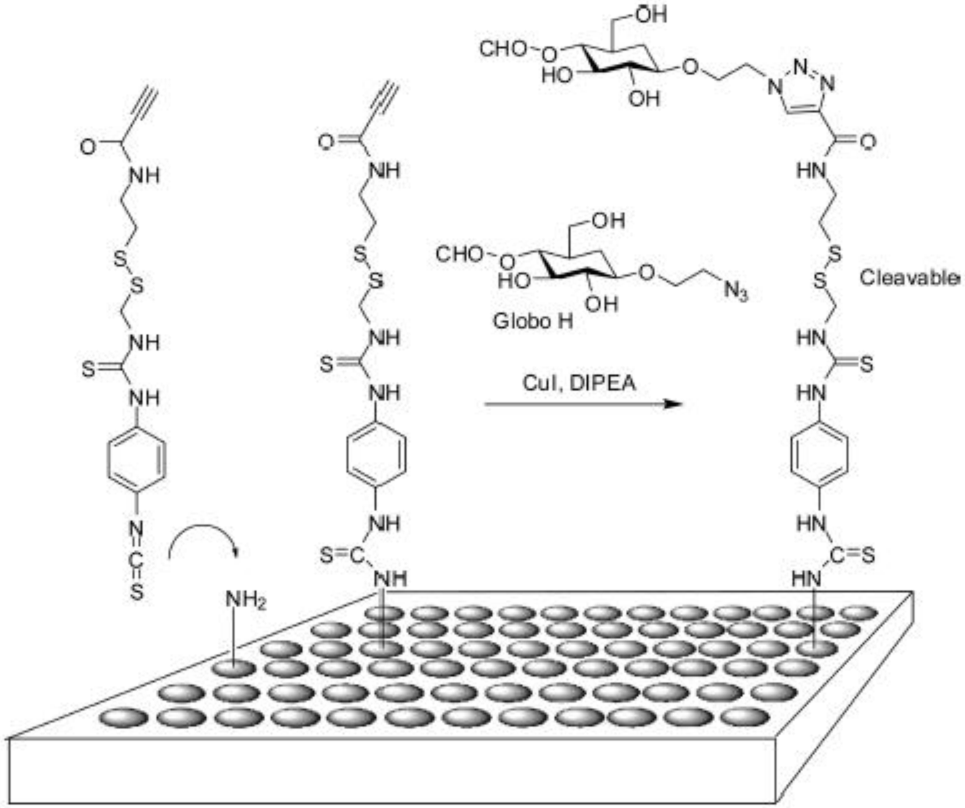

Figure 53. Immobilization by covalent attachment to titer wells is an important technique, and CuAAC may add considerably to this field by its virtue of being quantitative and selective.

Zhang, Y.; Luo, S.; Tang, Y.; Yu, L.; Hou, K. Y.; Cheng, J. P.; Zeng, X.; Wang, P. G. *Anal. Chem.* **2006**, *78*, 2001.

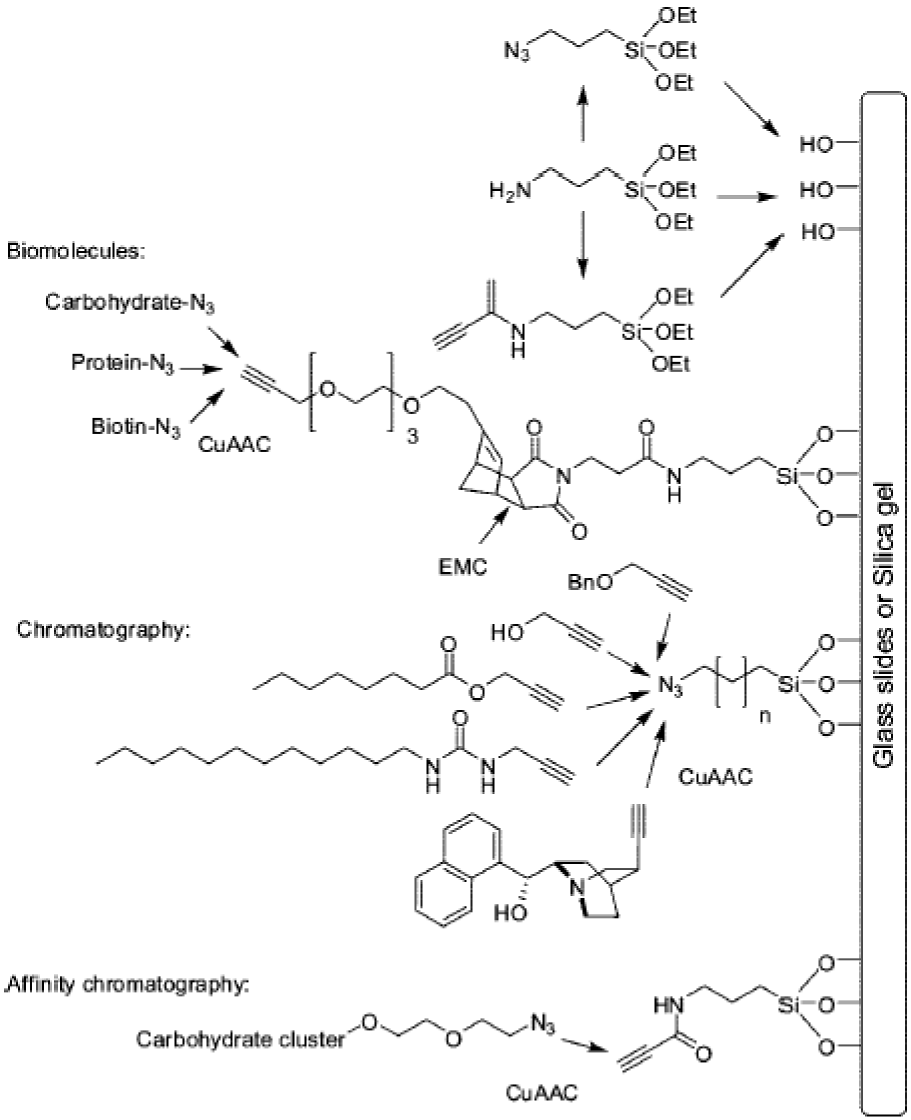

Figure 54. Glass surfaces are used extensively to produce microarrays of compounds. Both these and surface modified silica gels are available through CuAAC.

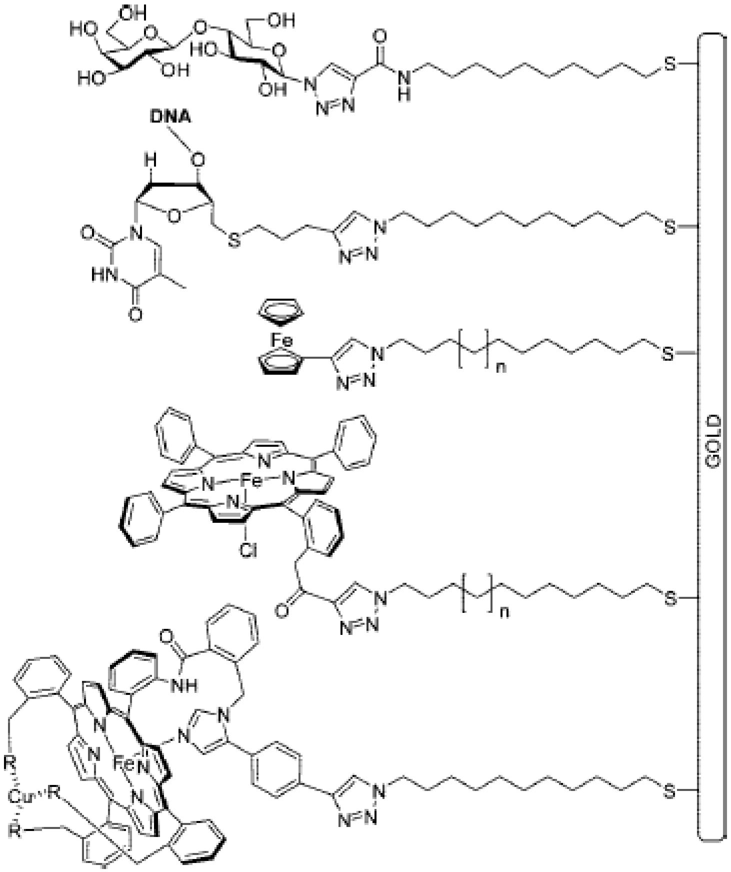

Figure 55. Gold surfaces have been modified with complex molecular entities for voltametric measurements and plasmon resonance. A special application is that of controlling the derivatization locally through reduction of Cu(2) to Cu(1) over a microelectrode kept at −300 mV with reference to the solution.

Scheme 32. Gold Nanoparticles and Nanorods Have Been Surface Modified with Biologically Active Protein and Signalling Peptides for Targeting