Nobel Prize in Chemistry Is Awarded to 3 Scientists for Work 'Snapping Molecules Together'

Carolyn R. Bertozzi, Morten Meldal and K. Barry Sharpless were honored for their advances in "click chemistry," which has played a role in treating and diagnosing illnesses.

Carolyn Bertozzi, Morten Meldal and Barry Sharpless (left to right) developed ways of joining molecules quickly and without unwanted by-products. Credit: James Tensuan/The New York


TEXAS

Click Chemistry: Diverse Chemical Function from a Few Good Reactions

Hartmuth C. Kolb, M. G. Finn, and K. Barry Sharpless*

Dedicated to Professor Daniel S. Kemp

Examination of nature's favorite molecules reveals a striking preference for making carbon–heteroatom bonds over carbon–carbon bonds—surely no surprise given that carbon dioxide is nature's starting material and that most reactions are performed in water. Nucleic acids, proteins, and polysaccharides are condensation polymers of small subunits stitched together by carbon–heteroatom bonds. Even the 35 or so building blocks from which these crucial molecules are made each contain, at most, six contiguous C–C bonds, except for the three aromatic amino acids. Taking our cue from nature's approach, we address here the development of a set of powerful, highly reliable, and selective reactions for the rapid synthesis of useful new compounds and combinatorial libraries through heteroatom links (C–X–C), an approach we call "click chemistry". Click chemistry is at once defined, enabled, and constrained by a handful of nearly perfect "spring-loaded" reactions. The stringent criteria for a process to earn click chemistry status are described along with examples of the molecular frameworks that are easily made using this spartan, but powerful, synthetic strategy.

Keywords: combinatorial chemistry · drug research · synthesis design · water chemistry

2.1. "Click Chemistry"

Following nature's lead, we endeavor to generate substances by joining small units together with heteroatom links (C–X–C). The goal is to develop an expanding set of powerful, selective, and modular "blocks" that work reliably in both small- and large-scale applications. We have termed the foundation of this approach "click chemistry," and have defined a set of stringent criteria that a process must meet to be useful in this context. The reaction must be *modular*, *wide in scope*, give *very high yields*, generate only *inoffensive byproducts* that can be removed by nonchromatographic methods, and be *stereospecific* (but not necessarily enantioselective). The required process characteristics include *simple reaction conditions* (ideally, the process should be insensitive to oxygen and water), *readily available starting materials and reagents*, the use of *no solvent or a solvent that is benign* (such as water) *or easily removed*, and *simple product isolation*. Purification—if required—must be by nonchromatographic methods, such as crystallization or distillation, and the product must be stable under physiological conditions.

Angewandte
Communications

Fluorescence Imaging Hot Paper

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Systemic Fluorescence Imaging of Zebrafish Glycans with Bioorthogonal Chemistry

*Paresh Agarwal, Brendan J. Beahm, Peyton Shieh, and Carolyn R. Bertozzi**

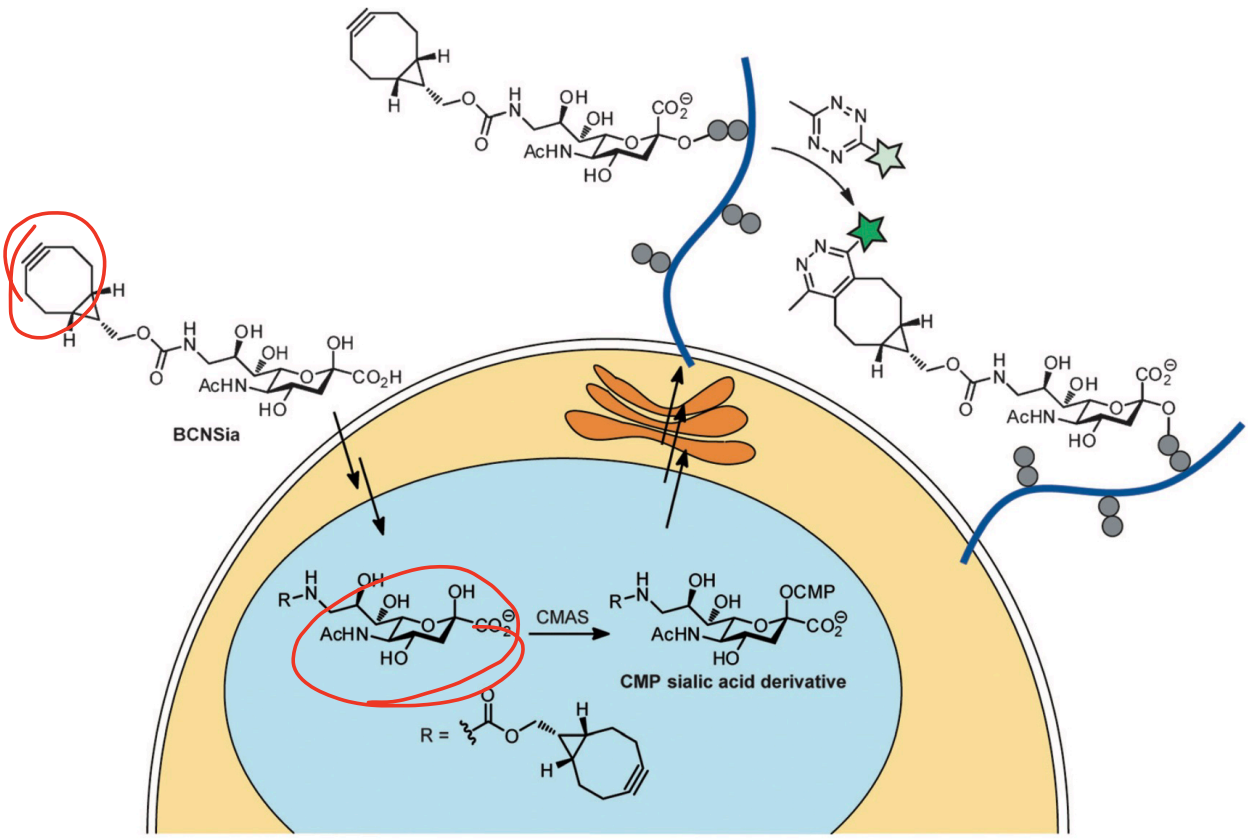
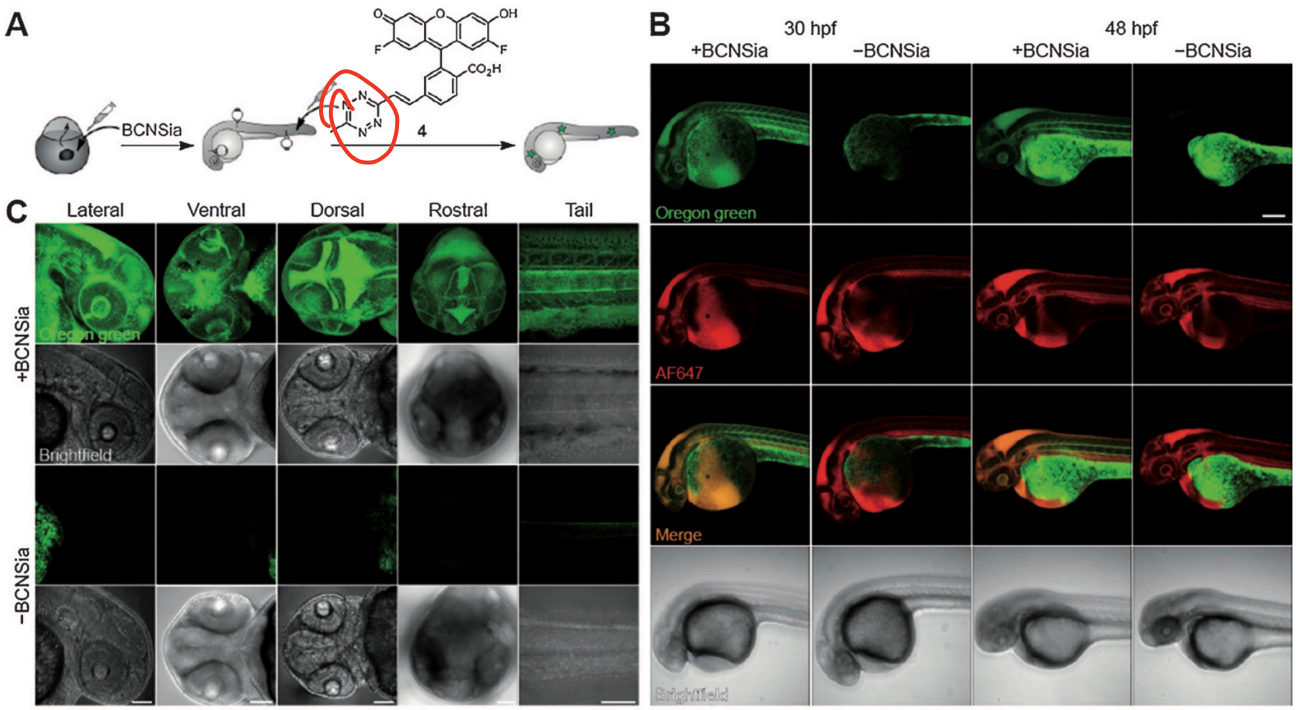


Figure 1. Expected metabolic pathway for the incorporation of BCNSia into cell-surface glycans followed by labeling with a fluorogenic tetrazine probe. CMAS = cytidine monophosphate *N*-acetylneuraminic acid synthetase, CMP = cytidine monophosphate.


A
BCNSia
4
B
30 hpf
48 hpf
+BCNSia
−BCNSia
+BCNSia
−BCNSia
Oregon green
AF647
Merge
Brightfield
C
Lateral
Ventral
Dorsal
Rostral
Tail
+BCNSia
−BCNSia
Oregon green
Brightfield

12/11/2010

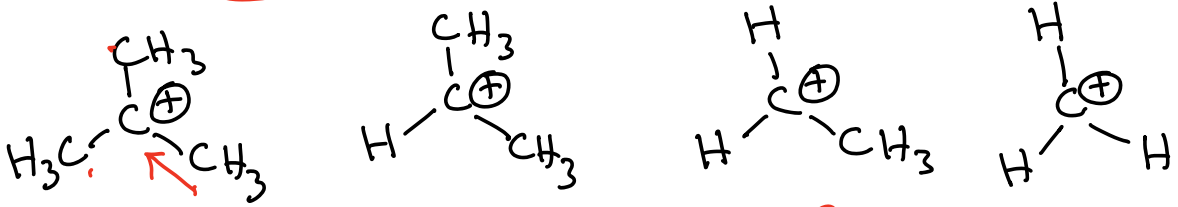
Dear Dr. Iverson,

I have a story you should tell to your class next year when trying to get them to run.

Today I woke up at 9:25. My Genetics final started at 9:00 and the professor has a no-entry policy after @ 30 minutes of the exam. Luckily I sprinted from my apt. over to the room in 3 minutes and got to take my final. Had I not trained for Run for The Water, I probably would have not made it on time and failed my class. So, thanks a million for inspiring me to run! It's already helped my future!!

P.S. Have you read about the Archae recently discovered that uses Arsenic instead of phosphorus for its DNA backbone? Crazy stuff!

Carbocation stability → the more C atoms bonded to the C⊕ the more stable



3° (tertiary) 2° (secondary) 1° (primary) methyl

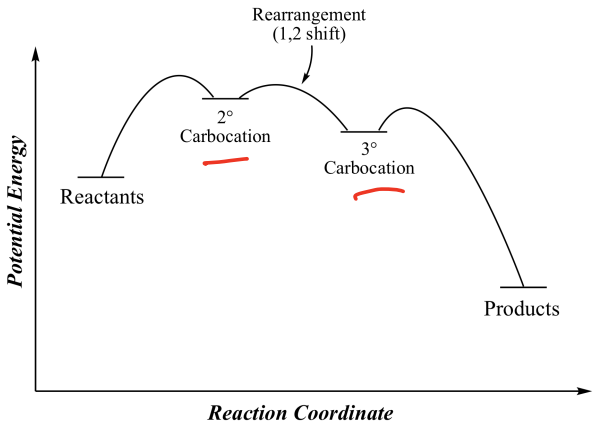
Hyperconjugation stabilization

Inductive effect stabilization

Carbocation Stability

Markovnikov's Rule → For alkene reactions involving a carbocation intermediate the nucleophile (ex. :Br:⊖) will make a bond to the more substituted C atom → derived from the more stable carbocation

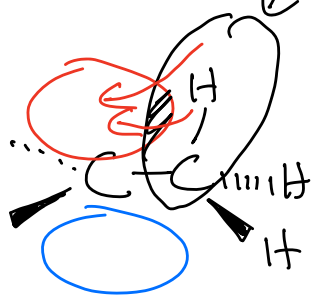
Carbocation intermediates can sometimes rearrange (Called 1,2 Shift) If a carbocation intermediate of equal or greater stability can be produced by shifting an adjacent H atom (or rarely an alkyl group), rearrangement will compete with product formation to give a mixture of products.



Motive → A 3° (tertiary) carbocation is more stable than a 2° (secondary) carbocation

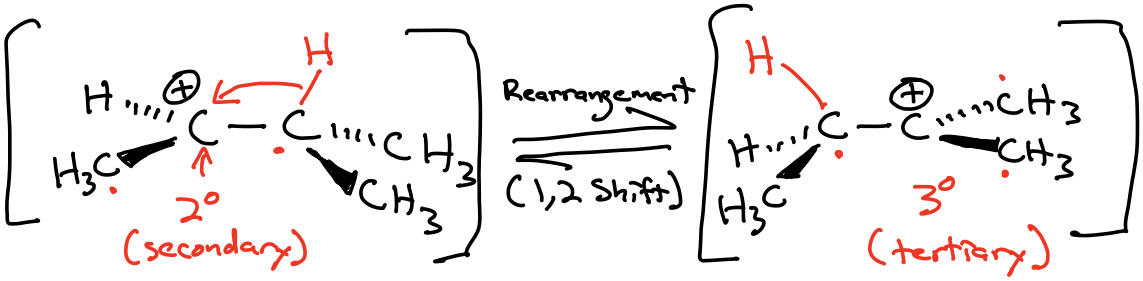
Opportunity → The mechanism is really just hyperconjugation "taken to the extreme"

1) Hyperconjugation → overlap of adjacent σ bonding electron density with the empty 2p orbital of a carbocation



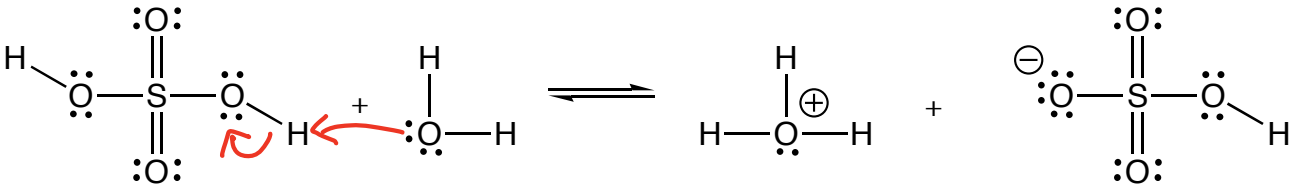
delocalizes the ⊕ charge

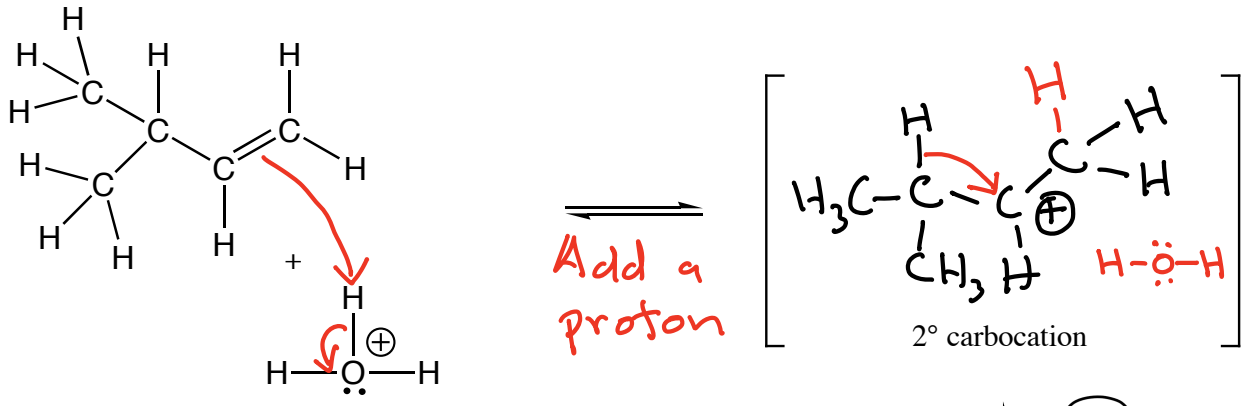
Some electron density of the C–H σ bond is pulled into the empty 2p orbital (red arrows in the figure)

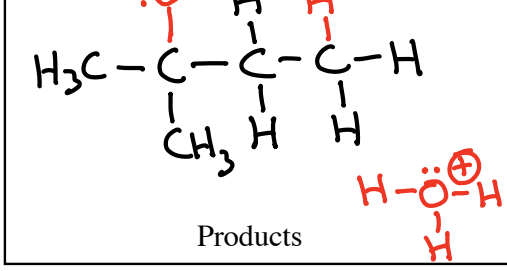


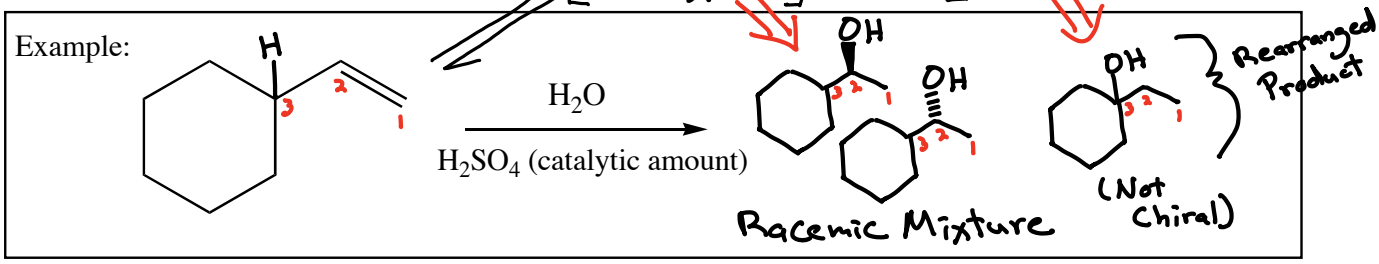
More Stable Carbocation

Cation Rearrangement

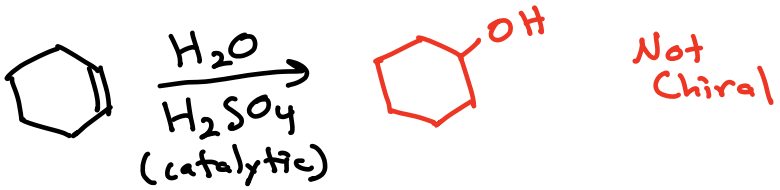




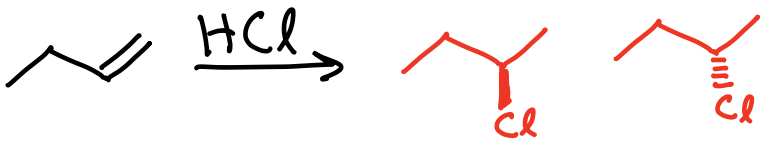




Examples



Not Chiral



Racemic Mixture

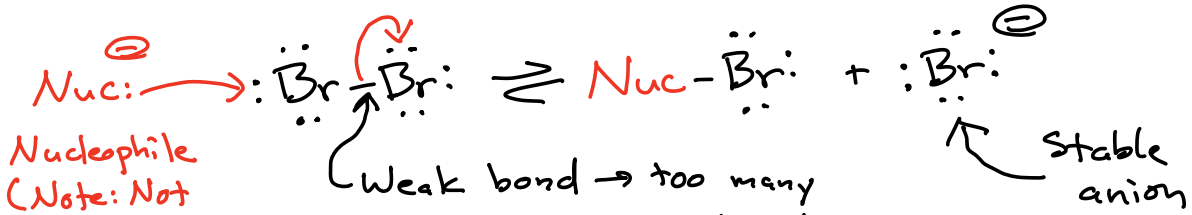
Not Chiral

(Only draw the rearranged product)

Not Chiral

New definition of an electrophile →

a relatively weak bond that can break to create a stable anion



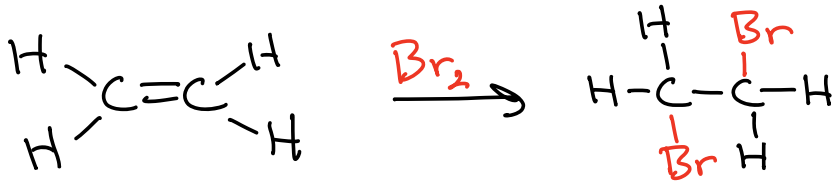
Nucleophile (Note: Not all nucleophiles have a ⊖ charge)

Weak bond → too many lone pairs close to each other

Cl_2, Br_2, I_2 (not F_2)

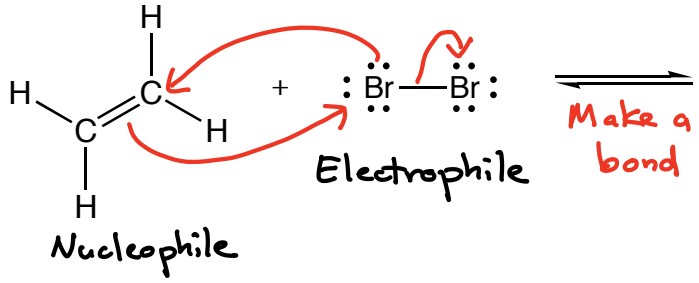
Electrophiles

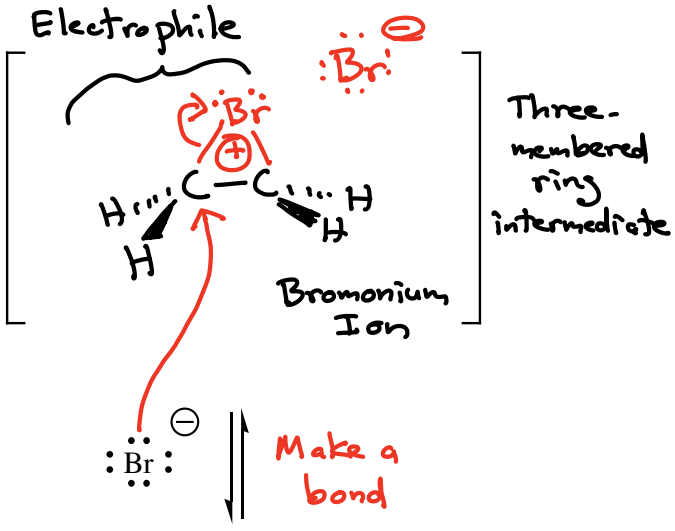
Overall New Reaction



"adjacent" → Vicinal Dihalide

Alkene Halogenation

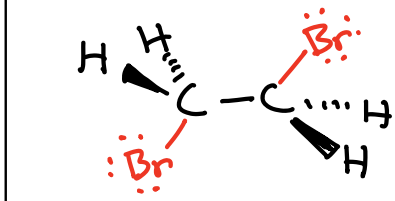




Called "anti" addition stereochemistry

The top face of the intermediate is "blocked" by the Br atom, so the :Br:⊖ nucleophile must react from the opposite face

Gives only a "trans" product – never "cis"

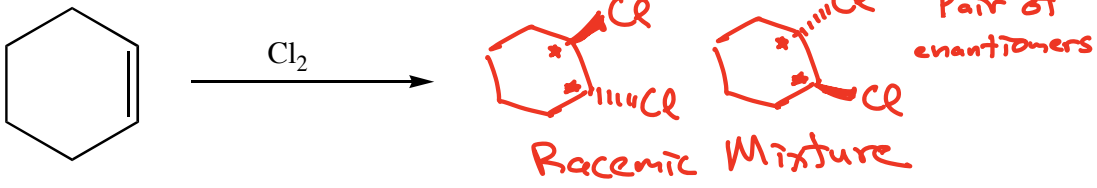


Summary: Alkenes react with X_2 to give a three-membered ring intermediate, then a new bond is made by $X^{\ominus}$ reacting from behind the C-X bond of the intermediate.

Regiochemistry: Not applicable → Br is on both atoms

Stereochemistry: Anti addition geometry → trans products

Example:



Alkene Reaction Stereochemistry Possibilities

Anti → groups add to opposite faces of the original double bond

Syn → groups add to the same face of the original double bond

Mixed → groups add both anti and syn in the reaction