New Mechanistic Insight into the Copper(I)-Catalysed Azide-Alkyne Cycloaddition

B. T Worrell, J. A. Malik and V. V. Fokin, *Science*, **2013**, ASAP;
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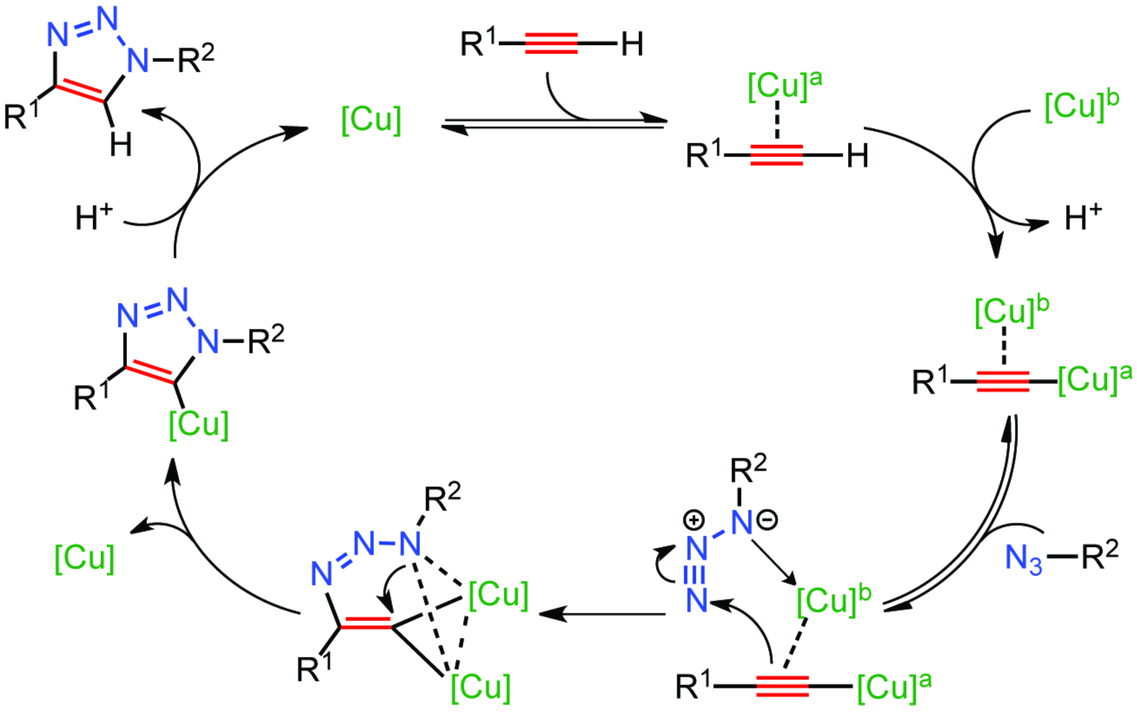

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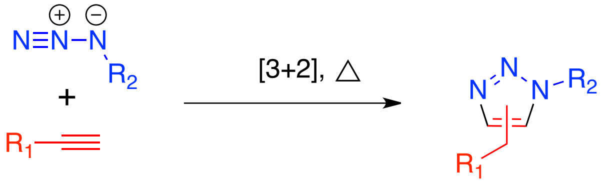
20 March 2013

Historical Context/ Background

1964 – origins

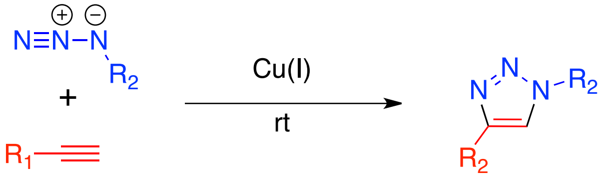
Huisgen reaction – 1,3-dipolar [3+2] cycloaddition between an azide and alkyne



mixture of 1,4 and 1,5-disubstituted-1,2,3-triazoles

2002 – catalytic version

CuAAC reaction introduced independently by the groups of Meldal and Sharpless



1,4-disubstituted-1,2,3-triazoles

- Rate acceleration up to 10^7 (compared to the thermal process)
- Selective
- Good functional group tolerance
- Stable in a wide range of solvents, temperatures and pH values and in the presence of oxygen

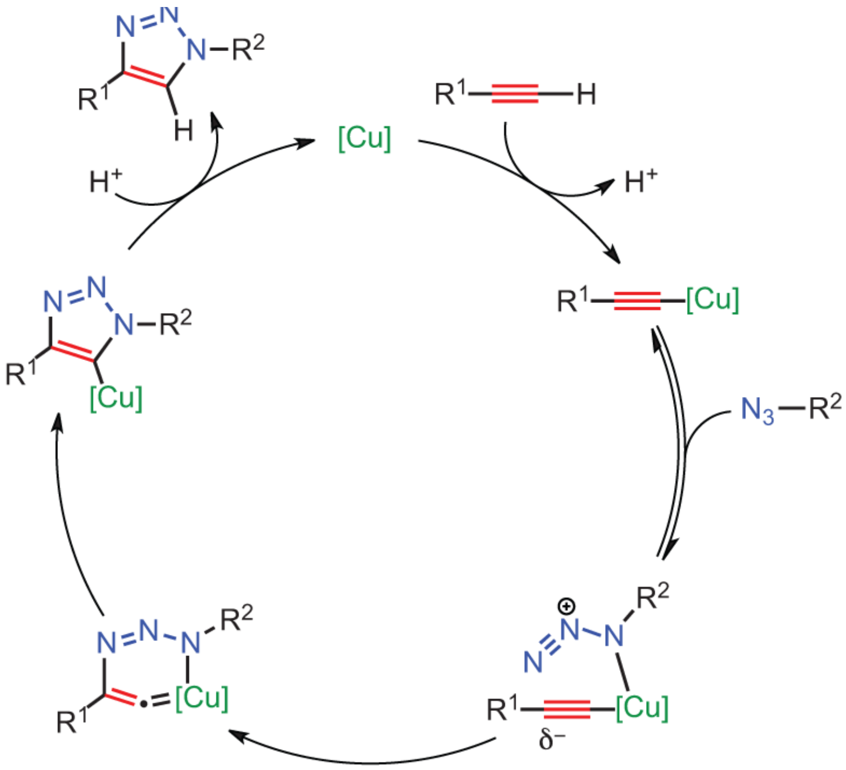
Wide application

- bioconjugation
- synthesis
- materials and surface science
- combinatorial chemistry

R. Huisgen, R. Grashey, J. Sauer in *Chemistry of Alkenes*, Interscience, New York, **1964**, 806-877
V. V. Rostovstev, L. G. Green, V. V Fokin and K. B. Sharpless, *Angew. Chem. Int. Ed.*, **2002**, *41*, 2596-2599
C. W. Tornoe, C. Christensen and M. Meldal. et al. *J. Org. Chem.* **2002**, *67*, 3057-3064

Early Mechanistic Studies

- Original Catalytic Cycle for CuAAC proposes a stepwise mechanism involving mono-nuclear copper (I) intermediates
- DFT studies suggest a stepwise mechanism is favoured



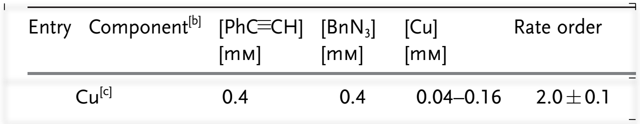
Rate limiting step

V. V. Rostovstev, L. G. Green, V. V Fokin and K. B. Sharpless, *Angew. Chem. Int. Ed.*, **2002**, *41*, 2596-2599
F. Himo et al., *J. Am. Chem. Soc*, **2005**, *127*, 210-216

Recent Work Inspires a New Mechanistic Proposal

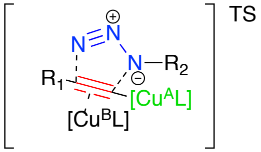
KEY OBSERVATIONS

- Kinetic studies by Finn *et al* (2005) find the reaction between benzyl azide and phenylacetylene is second order in copper suggesting the involvement of two copper centres in the catalytic cycle.

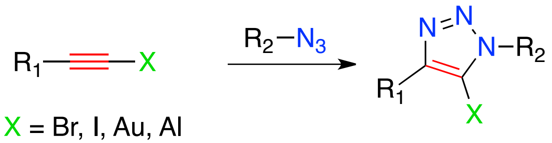


Entry	Component[b]	[PhC≡CH] [mM]	[BnN$_3$] [mM]	[Cu] [mM]	Rate order
	Cu[c]	0.4	0.4	0.04–0.16	2.0±0.1

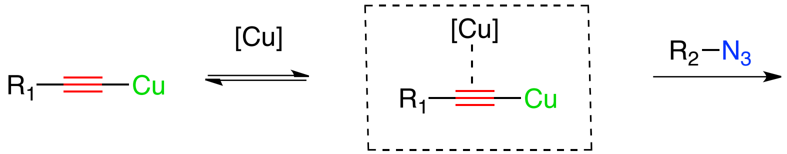
- DFT studies by Fokin *et al* (2007*)* support the observed second order rate law in copper .



- Reactive σ-acetylides react with azide to form 1,4-disubstituted-1,2,3-triazoles, suggesting that copper catalyst may act through weak π-interactions with the formally internal alkyne



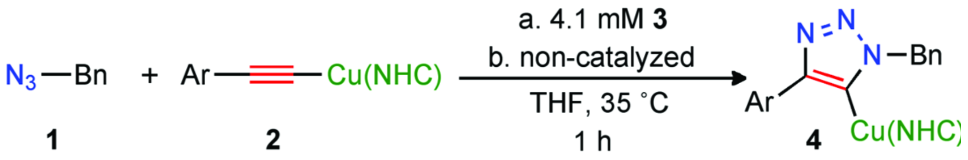
HYPOTHESIS:

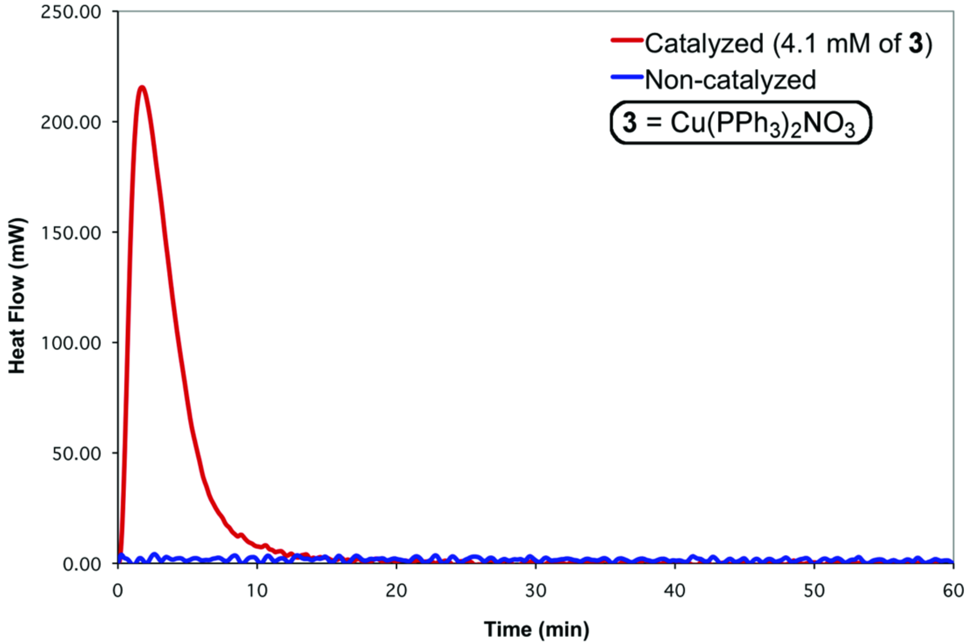


Active catalytic complex?

V. O. Rodionov, V. V. Fokin and M. G. Finn, *Angew. Chem. Int. Ed.*, **2005**, *44*, 2210-2215
M. Ahlquist and V. V. Fokin*, Organometallics*, **2007**, *26*, 4389-4391
B. H. M. Kuijpers et al ., *Synlett*, **2005**, 3059
J. E. Hein, J. C. Tripp, L. B Krasnova, K. B. Sharpless and V. V. Fokin, *Angew. Chem. Int. Ed.*, **2009**, *48*, 8018
D. V. Partyka et al., *Organometallics*, **2009**, *28*, 6171
Y. Zhou et al., *Angew. Chem. Int. Ed.*, **2010**, *49*, 2607

‘Non-classical’ Reaction Progress Kinetic Analysis Using Calorimetry Provides Evidence an Exogenous Copper Atom is Required



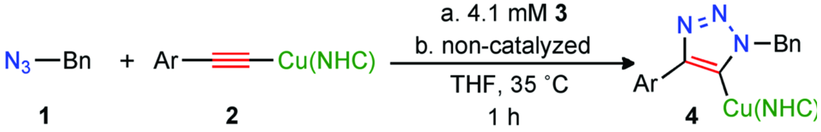


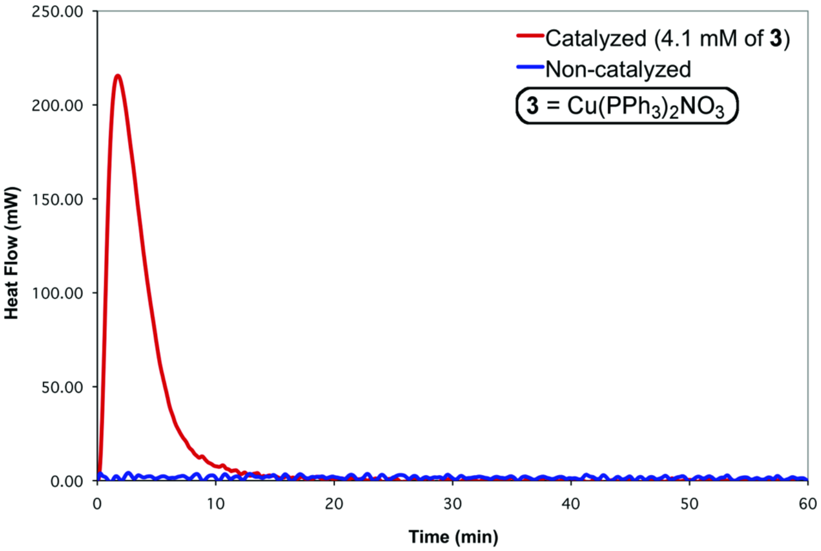
$$q = \Delta H_{rxn} \cdot V \cdot r$$

Where
q = reaction heat flow (*W*)
ΔH_{rxn} = heat of reaction (*J/mol*)
V = reaction volume (*L*)
r = reaction rate (*M/s*)

Trend is consistent over a variety of conditions

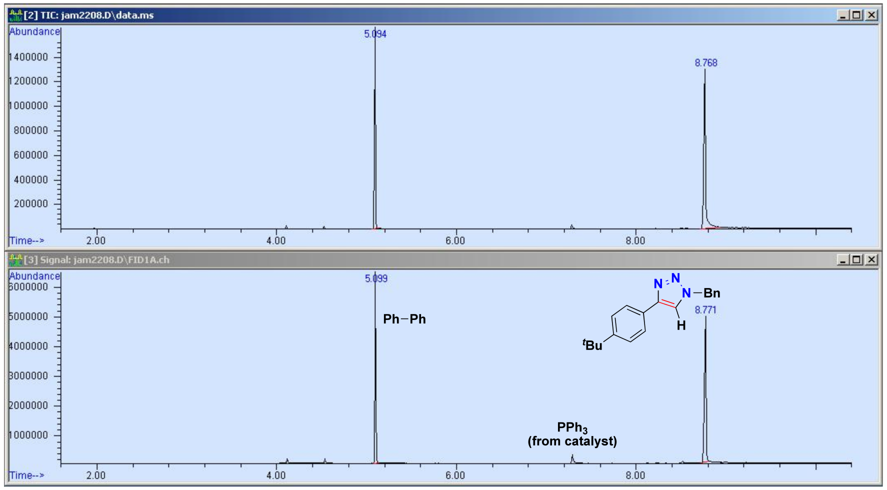
- Lowering catalyst concentration resulted in a corresponding decrease in maximum rate (i.e. positive order dependence on the exogenous copper)
- Multiple exogenous copper sources exhibit similar catalytic efficacy
- Organic azides bearing sterically hindered or aliphatic functional groups show comparable rate acceleration in the presence of added copper
- Similar rate differences were observed in other solvents including chloroform and DMF



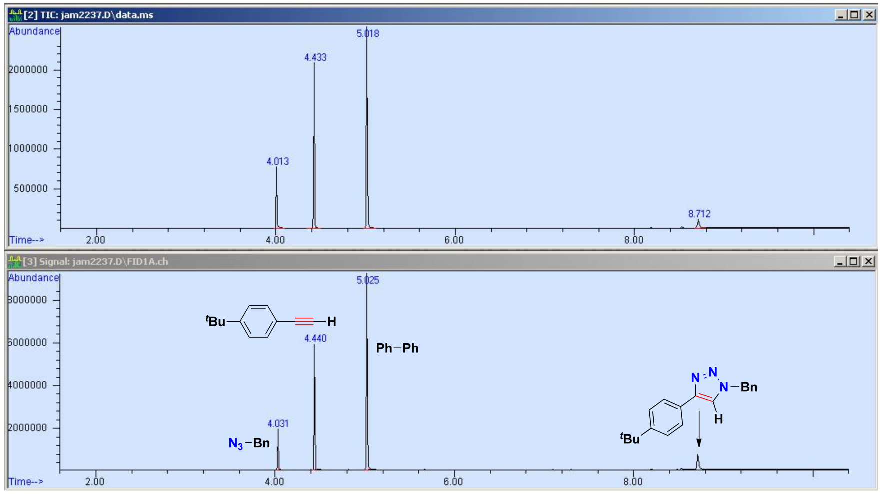


- Agreement in conversion measured by GC-MS and heat flow validates the use of reaction calorimetry.

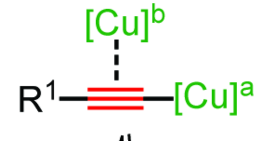
*Catalyzed reaction of azide **1** and acetylide **2** monitored by GC-MS (reaction aliquoted at 1 hour):*

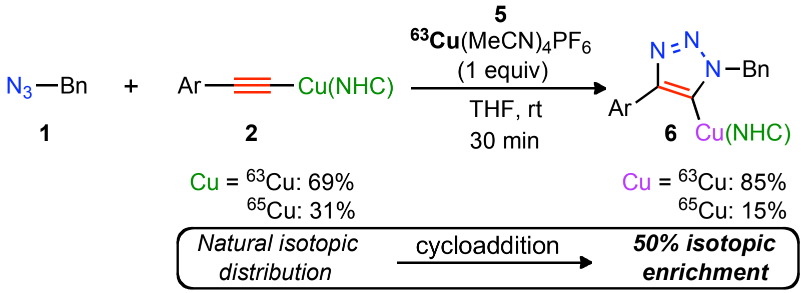


*Uncatalyzed reaction of azide **1** and acetylide **2** monitored by GC-MS (reaction aliquoted at 1 hour):*



Investigating the Role of Each Copper Species in the Catalytic Cycle





- A stoichiometric crossover study using an istopically pure exogenous ^{63}Cu catalyst was carried out to test the discrete bonding hypothesis
- The ratio of triazolide[^{63}Cu]: triazole[^{65}Cu] peaks is 85:15 showing a 50% enrichment of ^{63}Cu, disproving the discrete bonding hypothesis
- The observed statistical enrichment could occur in one of three steps

1. Via the acetylide intermediate **2**
2. Via the triazolide
3. Within the cycloaddition step

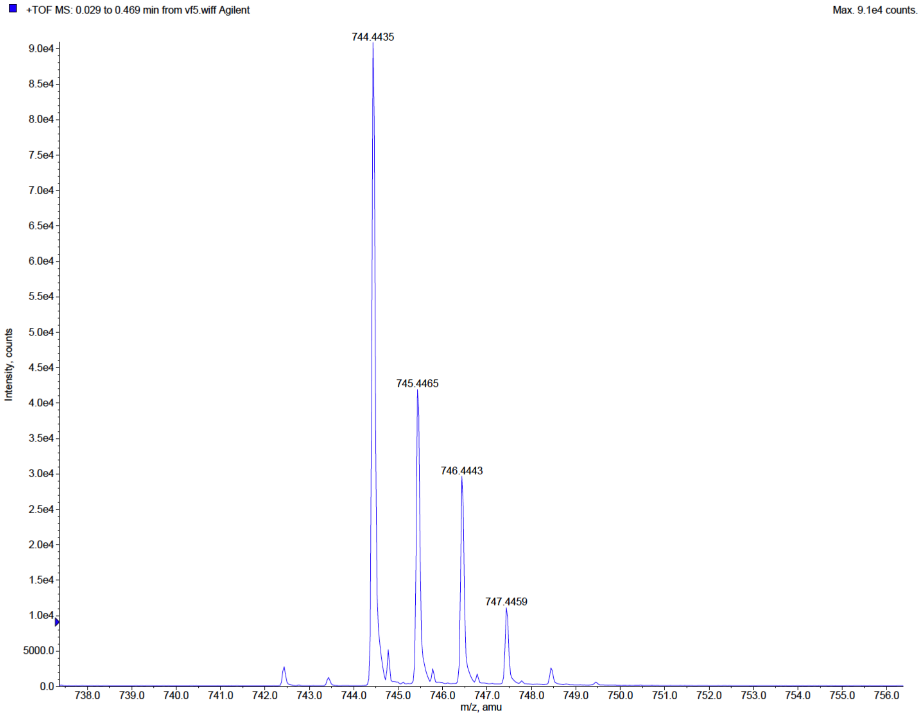


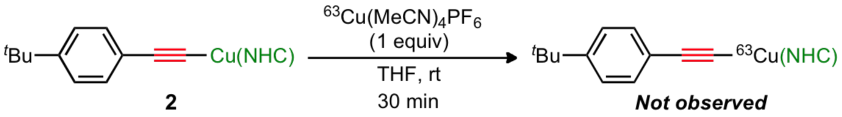
Figure S9. TOF-MS spectrum of enriched triazolide **6**.

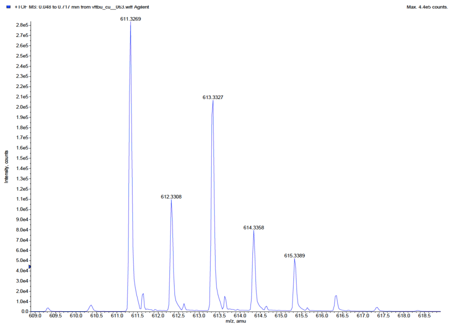
744.4435 = M+1 of enriched triazolide **6** – ^{63}Cu isotope
746.4443 = M+1 of enriched triazolide **6** – ^{65}Cu isotope

The relative intensity of the above peaks corresponds to the 85:15 ^{63}Cu:^{65}Cu content (or 50% enrichment with ^{63}Cu).

Mechanistic Explanation for the Statistical Enrichment of the Triazolide

1. Via the acetylide intermediate **2**

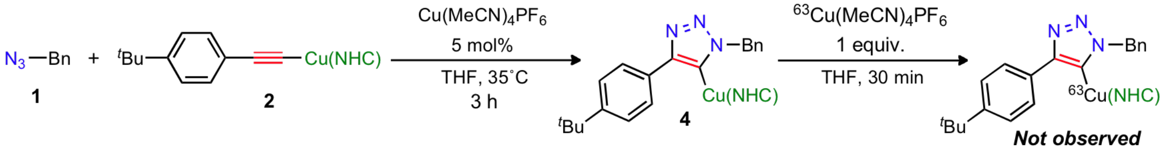


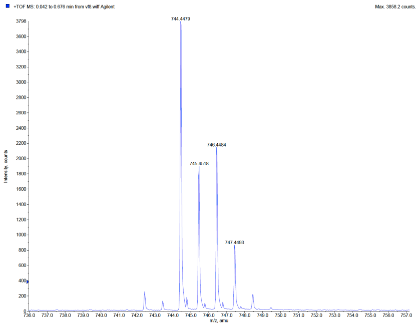


No enrichment in TOF mass spectrum

** no enrichment with added azide

2. Via the triazolide intermediate **4**

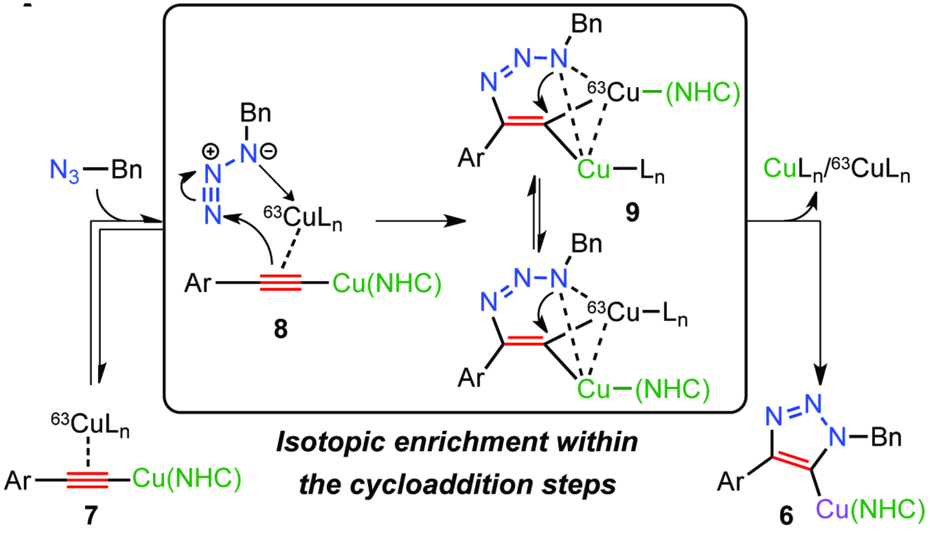




No enrichment in TOF mass spectrum

3. Thus, the observed 50% isotopic enrichment must occur within the cycloaddition step

Enrichment in the Cycloaddition Step via Rapid Ligand Exchange



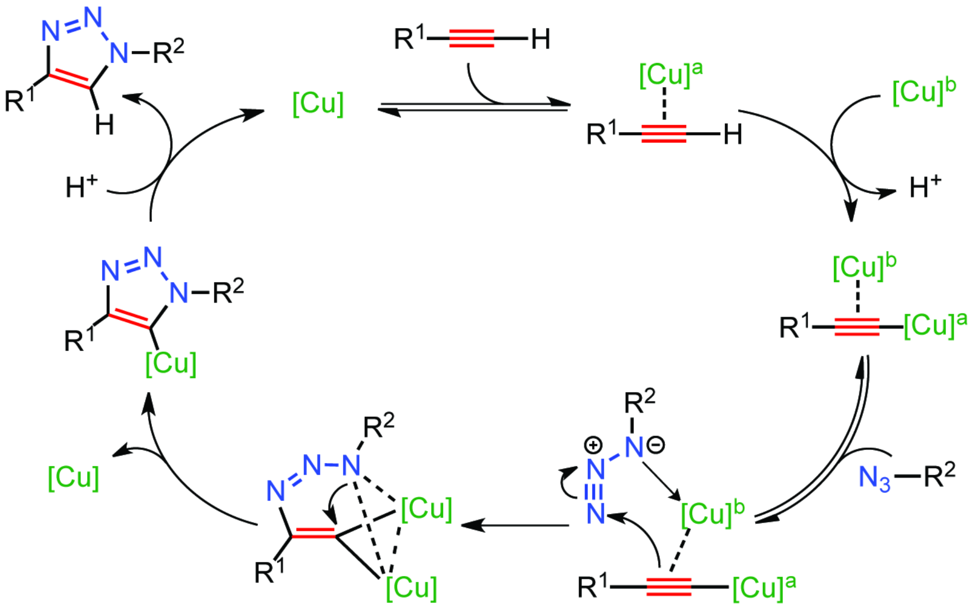
Isotopic enrichment within the cycloaddition steps

Cu = ^{63}Cu: 69%
^{65}Cu: 31%

L$_n$= MeCN, THF, N$_3$Bn or **2**

Cu = ^{63}Cu: 85%
^{65}Cu: 15%

Summary of Mechanistic Studies, Why is this Work Significant



- The study deduces the existence and role of two non-isolatable copper species in the catalytic cycle of the CuAAC reaction which have eluded more conventional mechanistic studies

- The proposal of a plausible mechanism allows the rationalisation of experimental results and the design of new and improved systems

- Broad Implications beyond the CuAAC reaction include:
  – New insight into the interaction of metals with carbon-carbon multiple bonds (a mechanism for all electron rich σ-acetylides)
  – potential for new reactions which exploit of the weak interaction of copper catalysts with triple bonds

- The copper isotope analysis employed in this study could be used to track the metal in biological systems where its function is important but not well understood