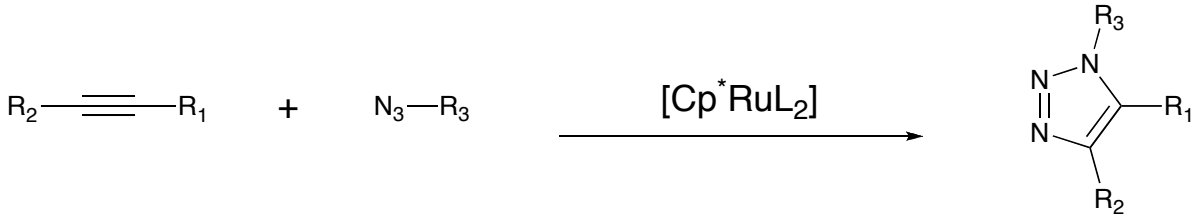
# Ruthenium-Catalyzed Azide-Alkyne Cycloaddation: Scope and Mechnism



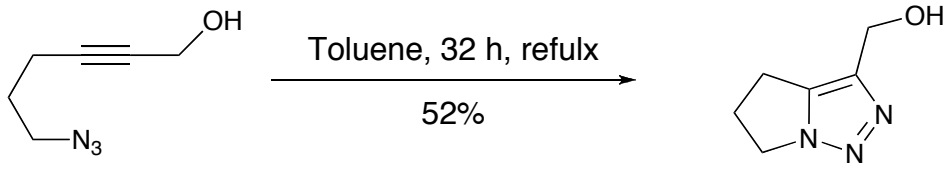
1,2,3-triazoles

Boren, B. C.; Narayan, S.; Rasmussen, L.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V.
*J. Am. Chem. Soc*, **2008**, ASAP

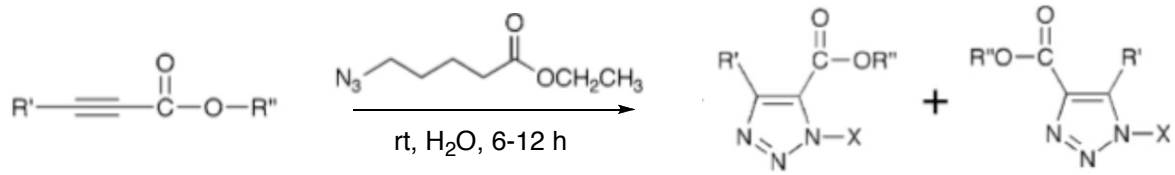
Wipf Group Current Literature
Tingting Mo
June, 28, 2008

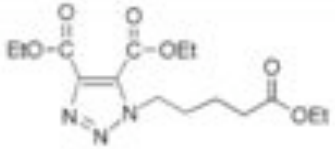
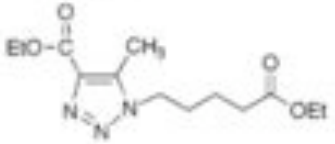
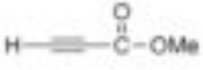
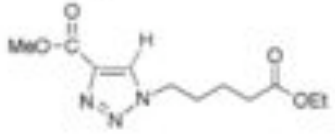
# Huisgen 1,3-Dipolar Cycloaddation to Make 1,2,3-triazoles

Long reacton times
High temperatures
Formation of regioisomeric mixtures



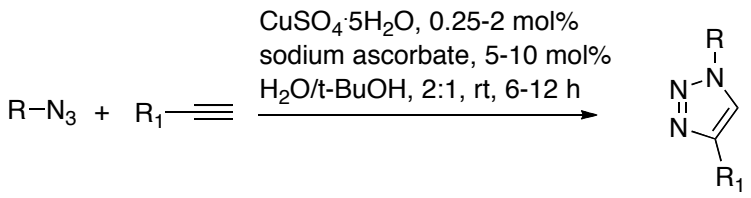

W. H. Pearson, S. C. Bergmeier and J. A. Chytra, *Sythesis*, **1990,** 156

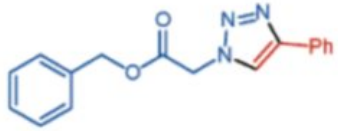
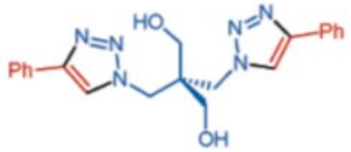
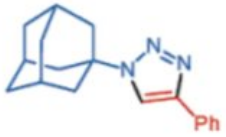



| Entry[a] | Alkyne | Product | Yield (%) |
|---|---|---|---|
| 1 |  |  | 81 |
| 2 |  |  | 94 |
| 3 |  |  | 82 |

Li, Z.; Seo, T. S.; Ju, J. *Tetrahedron Let*. **2004**, *45*, 3143

# Cu(I) Catalyzed 1,3-Dipolar Cycloaddation to Make 1,4 substituted 1,2,3-triazoles

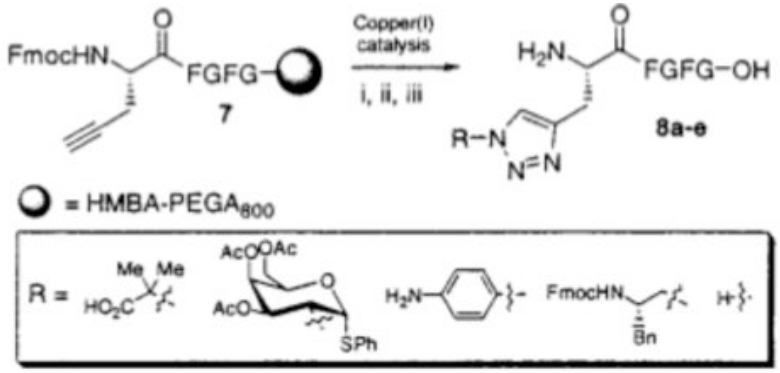



| Entry | Product | Yield, % |
|---|---|---|
| 1 |  | 92[a] |
| 2 |  | 98[b] |
| 3 |  | 84[a] |

Aqueous systems
Broad temperature range 0-160°C
Insensitive to pH (range from 4 to 12)
Fuctional group tolerence
Proceeds well in human plasma

Rostovtsev, V.; Green, L.; Fokin, V.; Sharpless, B. K. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596
Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. *J. Am. Chem. Soc.* **2005**, *127*, 210

## Affording Peptidotriazoles of N-Substituted Histidine Analogs

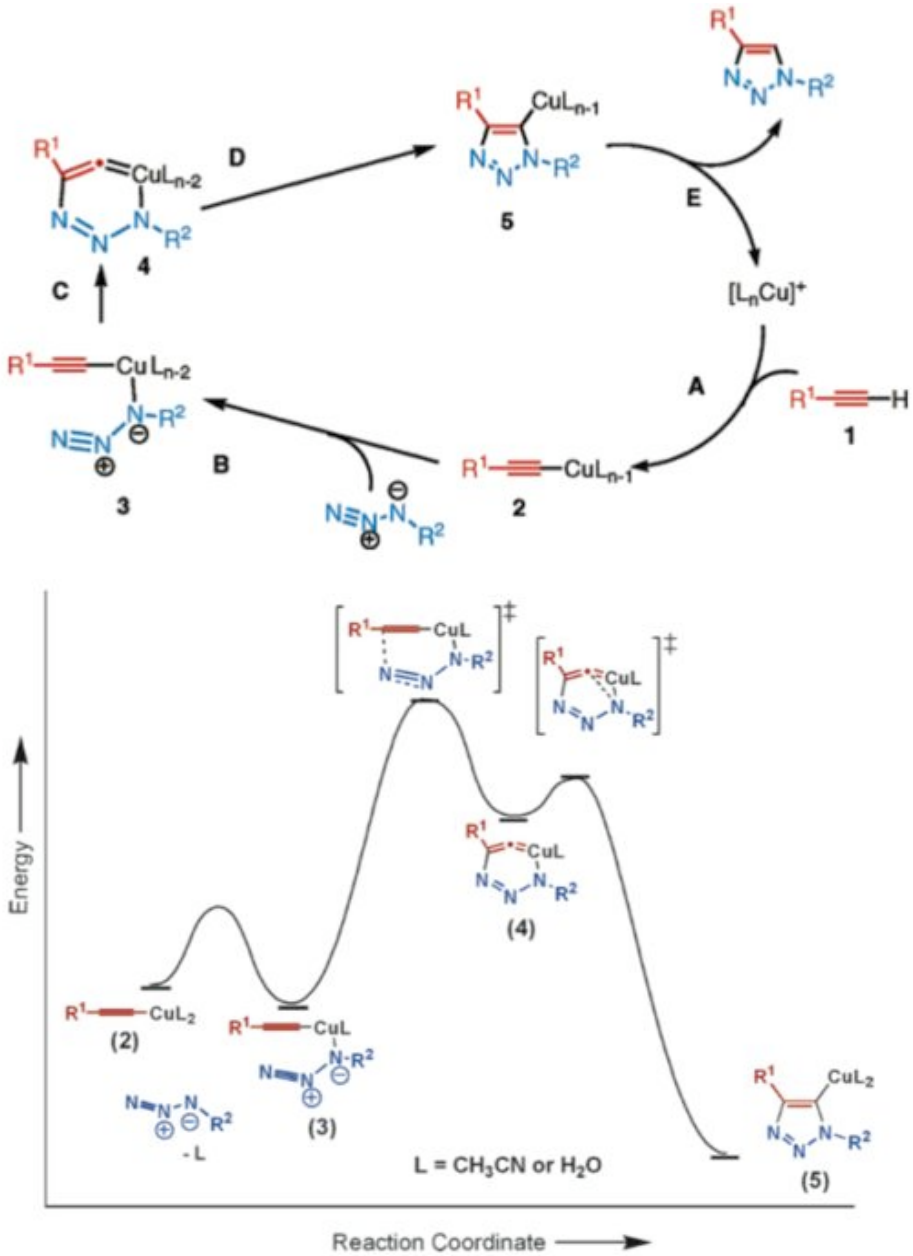



[a] (i) R–$N_3$, DIPEA, CuI; (ii) 20% piperidine/DMF; (iii) 0.1 M NaOH (aq).

Tornoe, C.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057

1,4-regioselectivity
Only for terminal alkyne

# Mechanism of Copper(I)-Catalyzed cycloaddtion of 1,4-Substituted 1,2,3-Triazoles

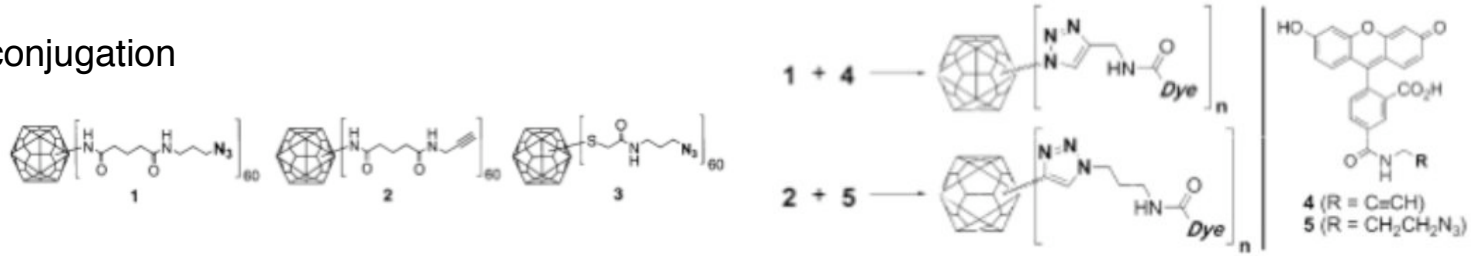



Proposed according to DFT calculation
Formation of copper(I) acetylide **2**
Azide replacement to coordinate
Formation of copper(III) metallacycle **4**
Reductive elimiation
Proteolysis

Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. *J. Am. Chem. Soc.* **2005**, *127*, 210

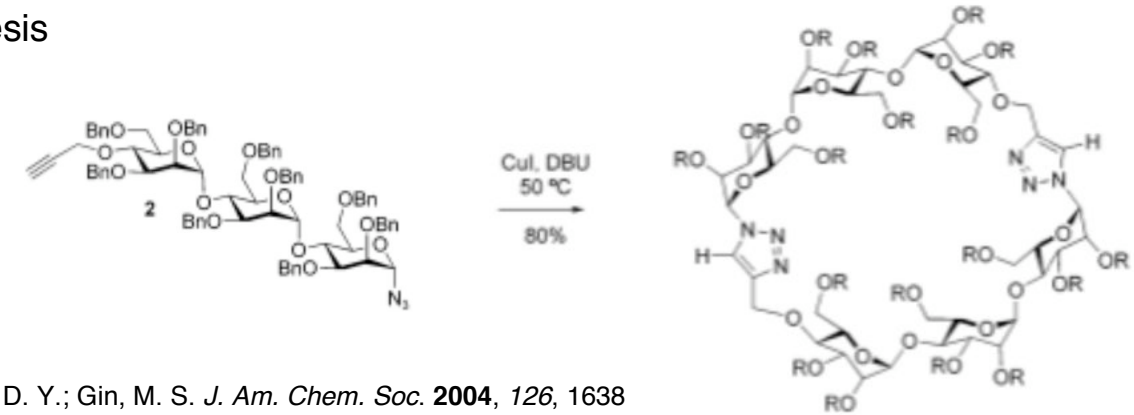
# Applications of Copper(I)-Catalyzed cycloaddtion of 1,4-Substituted 1,2,3-Triazoles

## Bioconjugation



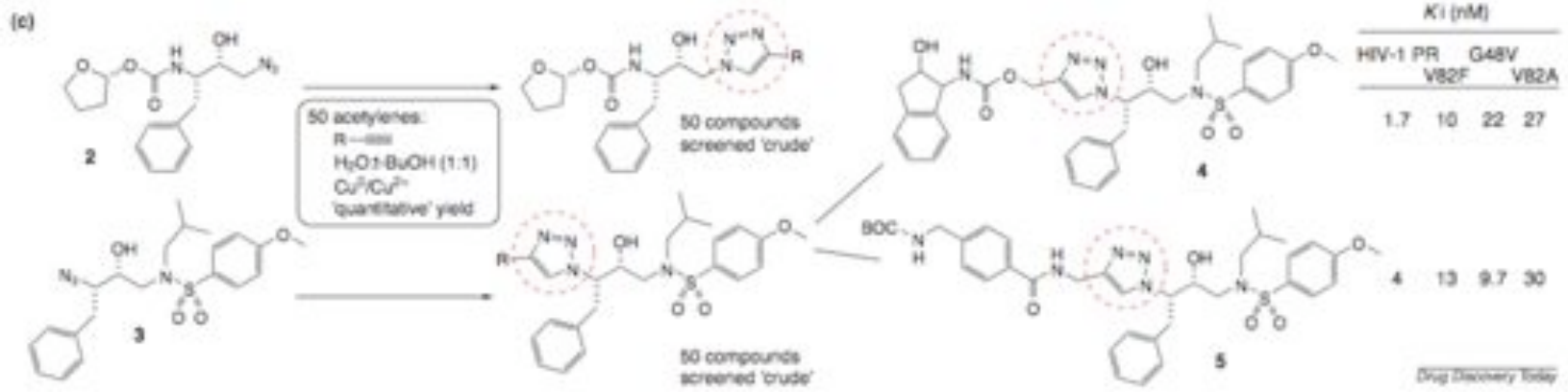

Wang, Q.; Chan, T.; Hilgraf, R.; Fokin, V.; Sharpless, K. B.; Finn, M. G. *J. Am. Chem. Soc.* **2003**, *125*, 3192

## Organic synthesis



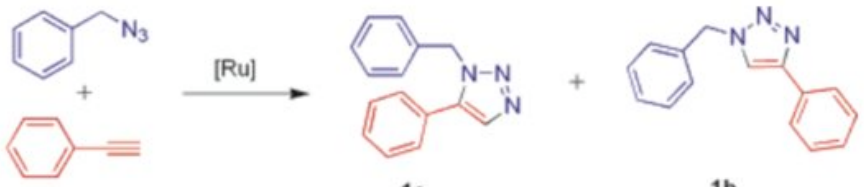

Bodine, K. D.; Gin, D. Y.; Gin, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 1638

## Click Chemistry on Drug Discovery

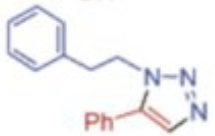
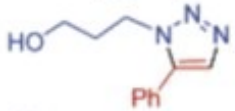
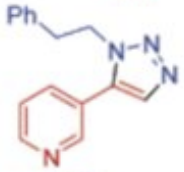
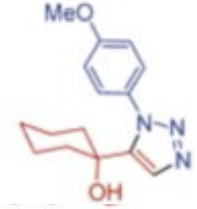



Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8,* 1128

# Ru-catalyzed Cycloaddition to make 1,5-substituted triazoles




| | 1a | 1b |
|---|---|---|
| $Ru(OAc)_2(PPh_3)_2$ | – | 100% |
| $CpRuCl(PPh_3)_2$ | 85% | 15% |
| $Cp^*RuCl(PPh_3)_2$ | 100% | – |
| $Cp^*RuCl(NBD)$ | 100% | – |

| entry | product | | reaction time, h | yield, % |
|---|---|---|---|---|
| 8 |  | **8a** | 2 | 89[b] |
| 9 |  | **9a** | 2 | 82[b] |
| 10 |  | **10a** | 6 | 80[c] |
| 11 |  | **11a** | 12 | 94[c] |

[$Cp^*RuCl$] most effective catalyst

Aprotic Solvents: THF, PhH, Toluene

Temp range from ambient to 110°C

Not very sensitive to water and oxygen

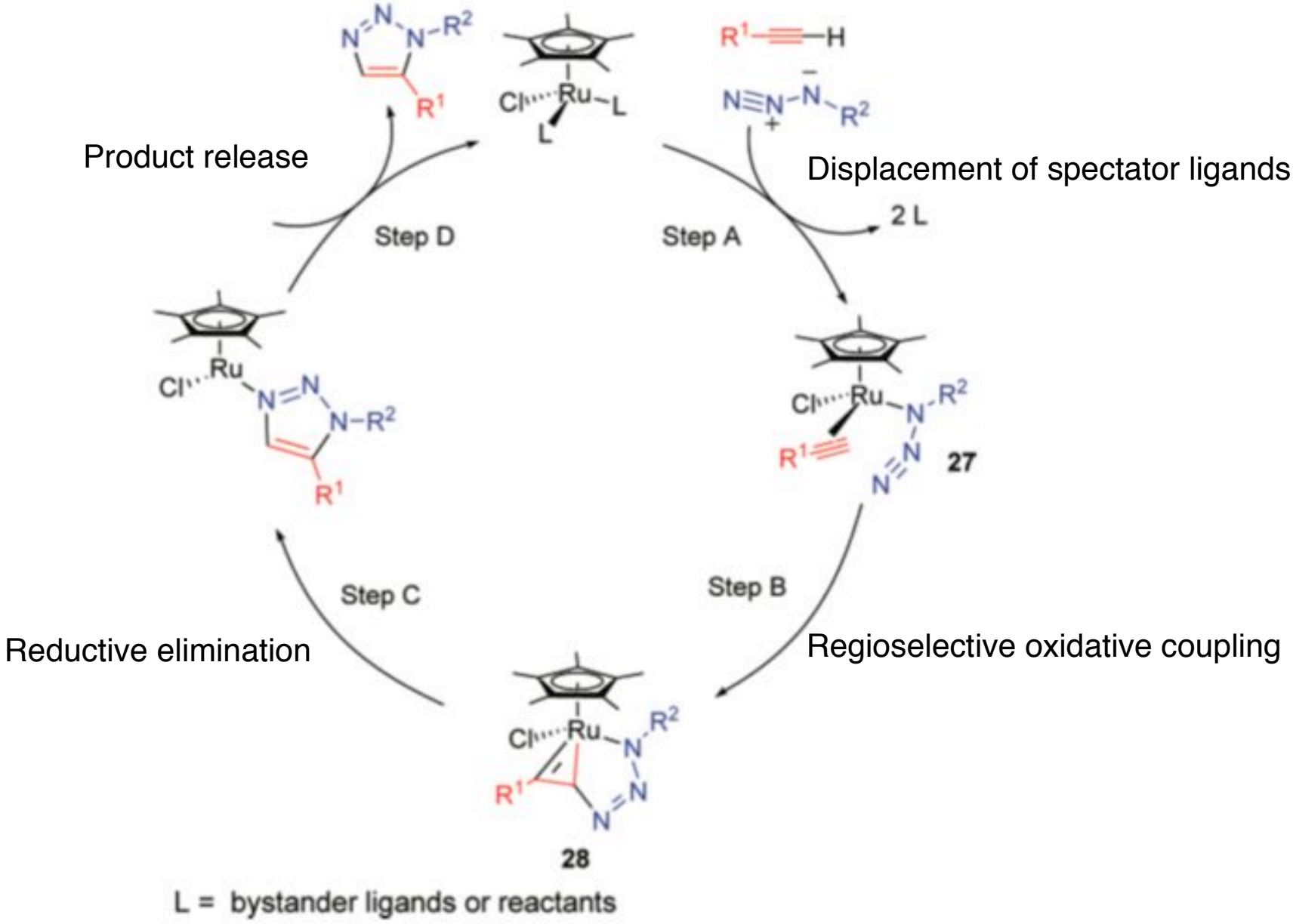
Primary, secondary and aryl azides

Terminal and Internal alkynes

Good functional group tolerence


Zhang, L.; Chen, X.; Xue, P.; Sun, H.; Williams, I. D.; Sharpless, K. B.; Folin, V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998
Boren, B.; Narayan, S.; Rasmussen, L,; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. *J. Am. Chem. Soc.* **2008**, ASAP

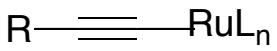
# Mechanism of the Ru-Catalyzed Azide-Alkyne Cycloaddition




Boren, B.; Narayan, S.; Rasmussen, L,; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. *J. Am. Chem. Soc.* **2008**, ASAP

# Michanistic Consideration

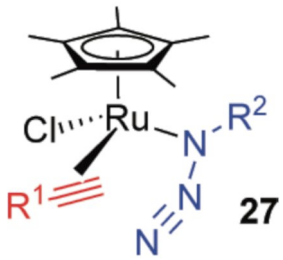
Participation of both terminal and internal alkynes in catalysis: ruthenium acetylides not involed



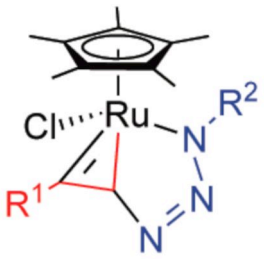

$Cp^*RuCl(PPh_3)_2$, $Cp^*RuCl(COD)$, $Cp^*RuCl(NBD)$ and $[Cp^*RuCl]_4$ are competent catalysts, neutral $[Cp^*RuCl]$ is the catalytically active species

$[Cp^*RuBr]$ and $[Cp^*RuI]$ complexes are significantly less active
the removal of the chloride with $Ag^+$ are devoid of the catalytic activity
chelating diphosphines deactivate the catalyst

The higher activity of $Cp^*$ complex than Cp complex can be attributed to the lability of the spectator ligans in such system (facilitates ligand replacement to form **27**), the more sterically demanding natrue of the $Cp^*$ ligand (facilitaes the reductive elimination)



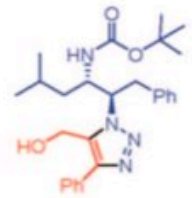
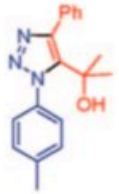
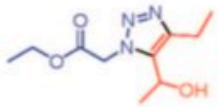

**27**



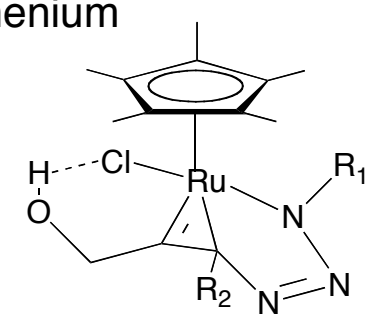

**28**

Boren, B.; Narayan, S.; Rasmussen, L,; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. *J. Am. Chem. Soc.* **2008**, ASAP

# Regioselectivity of Addition with Internal Alknye: Directing Effect

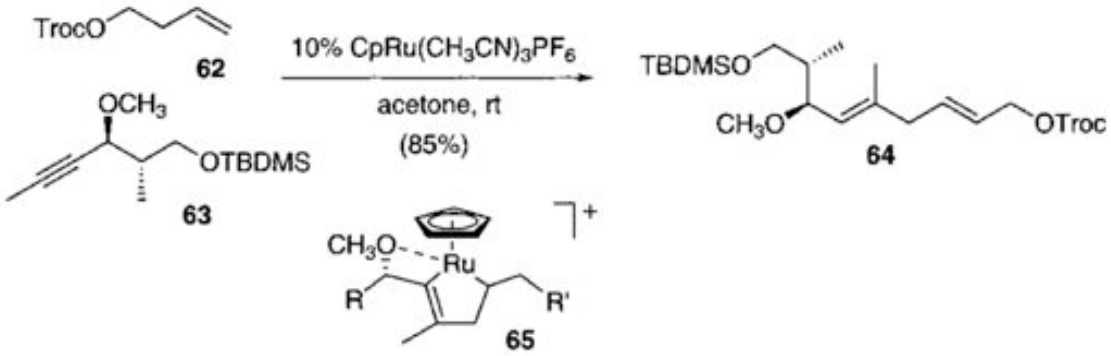
| entry | product | procedure | yield, % | m.p., °C |
|---|---|---|---|---|
| 1 |  **13** | B | 69 | 205.0-207.0 |
| 2 |  **14** | B | 93 | 161.8-163.3 |
| 3 |  **15** | B | 71 | oil |

Formation of a strong H-bond between the alcohol or amine and the chloride ligand on the ruthenium



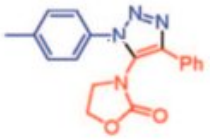
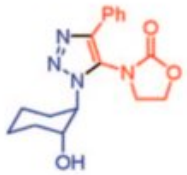
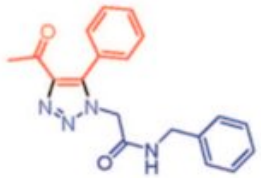

Boren, B.; Narayan, S.; Rasmussen, L,; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. *J. Am. Chem. Soc.* **2008**, ASAP

Hydroxy group, amino group and ether influence the regioselectivity through coordination to Ruthenium

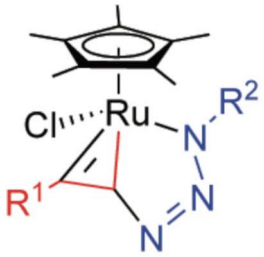



Trost, B. M.; Toste, D.; Pinkerton, A. B. *Chem. Rev*. **2001**, *101*, 2067

# Regioselectivity of Addition with Internal Alknye: Electronic Effect

| entry | product | procedure | yield, % | m.p., °C |
|---|---|---|---|---|
| 4 |  **16** | B | 97 | 181.3-182.5 |
| 5 |  **17** | B | 95 | 144 -145 |
| 6 |  **18** | B | 79 | 155.5-156.5 |

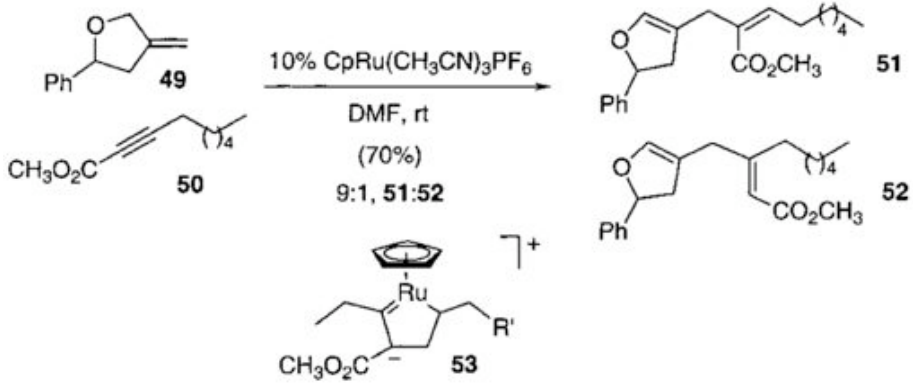
The new bond in the intermediate **28** is formed between the more nucleophilic carbon of the alkyne



**28**

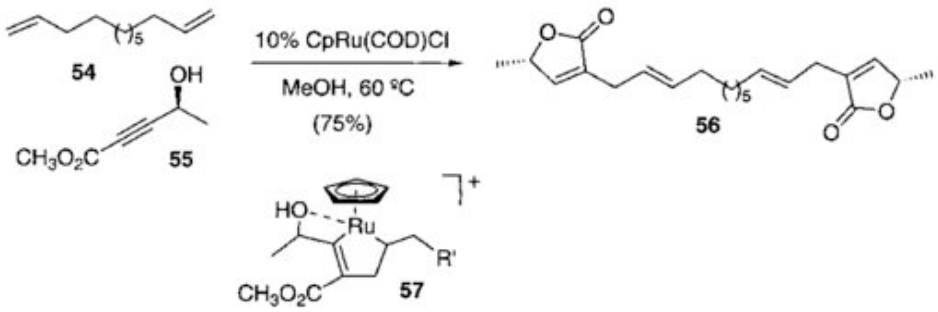
Boren, B.; Narayan, S.; Rasmussen, L,; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. *J. Am. Chem. Soc.* **2008**, ASAP

Polarization of the ruthenacycle **53** has been postulated as one of the factors which favors the placement of an EWG at the β-carbon of the rughenacycle



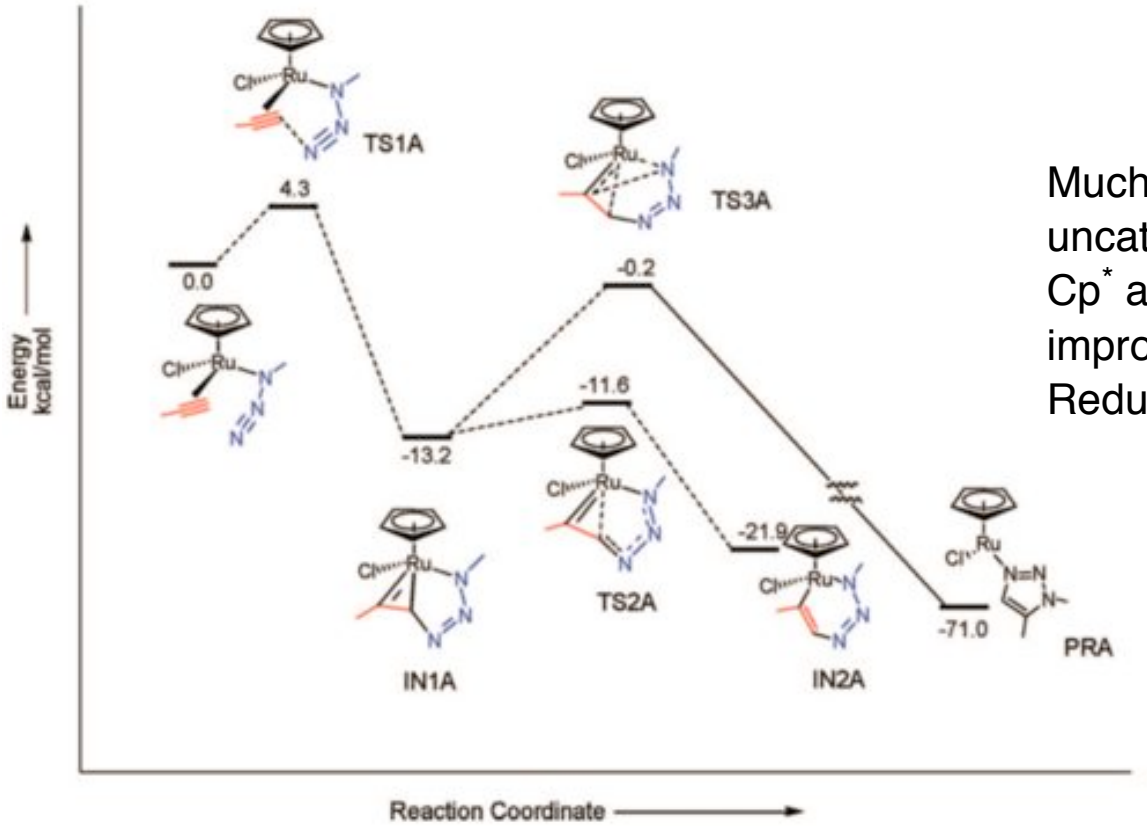

Trost, B. M.; Toste, F. D. *Tetrahedron Lett.* **1999,** *40*, 7739

Combination of these two factors profuces the product with excellent control of regioselectivity




Trost, B. M.; Calkins, T. L.; Bochet, C. G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 6021

# DFT calculation



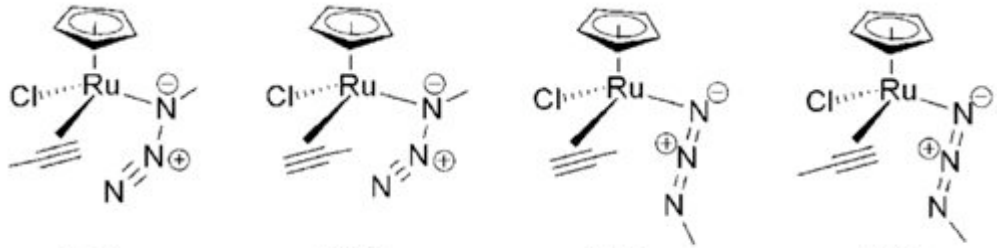

Much lower activation energy than uncatalyzed reaction

$Cp^*$ amplify the steric interaction to improve catalysis

Reductive elimination is the RDS

Azide coordinates via the nitrogen proximal to carbon (PCA vs PCD)

1,5-disubstituted over 1,4 (PCA vs PCB)




Boren, B.; Narayan, S.; Rasmussen, L,; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. *J. Am. Chem. Soc.* **2008**, ASAP

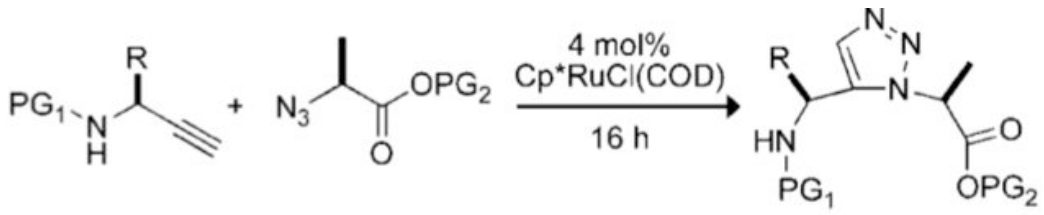
# Summary

The first general method for generation of 1,5-disubstituted 1,2,3-triazoles through catalyzed 1,3-dipolar cycloaddition between azides and terminal alkynes

This ruthenium catalyzed process engages internal alkynes in catalysis, providing access to fully substituted 1,2,3-triazoles

Exploration of mechanism provides the basis and impetus by which new reactions may be discovered: other dipoles like nitrile oxides with alkynes?

Applications: Protein Prosthesis: 1,5-Disubstituted[1,2,3]triazoles as cis-Peptide Bond Surrogates




Tam, A.; Arnold, U.; Soellner, M. B.; Raines, R. T. *J. Am. Chem. Soc.* **2007**, *129*, 12670