Copper(I) Catalyzed [3+2] Cycloaddition Reaction with Mechanistic Disparity: A DFT Study

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http://youtu.be/OAXBKoUjbG8

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Introducing myself

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Presentation overview

1. Huisgen [3+2] cycloaddition reaction
2. Limitations of uncatalyzed [3+2] cycloaddition reaction
3. Catalytic [3+2] cycloaddition reaction
4. Interplay between experiment and theory
5. Transition metal catalyzed [3+2] cycloaddition reaction
6. Copper(I) catalyzed [3+2] cycloaddition reaction
7. Conclusions
8. Acknowledgements

1. Huisgen [3+2] cycloaddition reaction

[3+2] Cycloaddition (32CA) reaction:

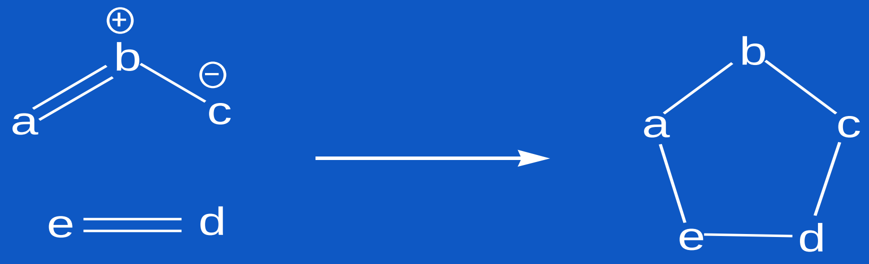
- Union of a dipole and a dipolarophile to yield a five membered cyclic compound.
- Formation of two new σ-bonds at the expense of two π-bonds. [1]

In the 1960's, Prof Rolf Huisgen established the general application of 32CA reactions in organic chemistry. [2]

1,3 dipole

+

dipolarophile



Scheme 1.

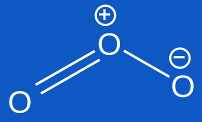
[1] Huisgen, R. *Angew. Chem. Int. Ed.* **1963**, *2*, 565-632. [2] Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, 98, 863-909.

1. Huisgen [3+2] cycloaddition reaction

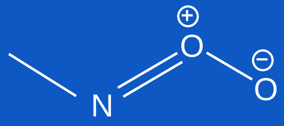
1,3 dipole [2]

(a-b-c)

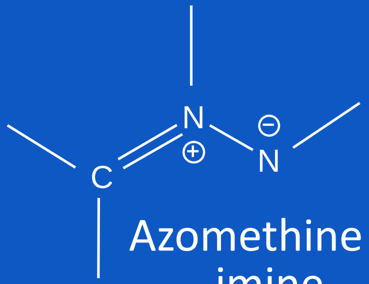
Allyl anion type (bent shape)



Ozone

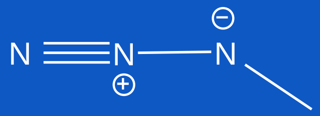


Nitrous oxide



Azomethine imine

Propargyl/allenyl anion type (linear shape + central atom *b* limited to nitrogen)



Azides

"1,3 dipoles range from the familiar atmospheric components such as ozone and nitrous oxides to the synthetically valuable azides of click chemistry fame. [3]*"*

[3] Ess, D. H.; Houk, K. N. *J. Am. Chem. Soc.* **2007**, 129, 10646-10647 (and references therein).

2. Limitations of the uncatalyzed [3+2] cycloaddition reaction

Thermal unactivated 32CA : *methyl azide + propyne*

Limitations:

- Slow 32CA reaction , even at elevated temperatures (80-120°C for 12-24h).
- High activation barrier (ca. 25-26 kcal/mol) with respect to the activated 32CA reaction.
- Mixture of regioisomers (as illustrated in Scheme 2) due to the presence of unsymmetrical substituted alkyne. [4]

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[4] Liu, P. N.; Li, J.; Su, F. H.; Ju, K. D.; Zhang, L.; Shi, C.; Sung, H. H. Y.; Williams, I. D.; Fokin, V. V.; Lin, Z.; Jia, G. *Organometallics* **2012**, 31, 4904-4915 (and references therein).

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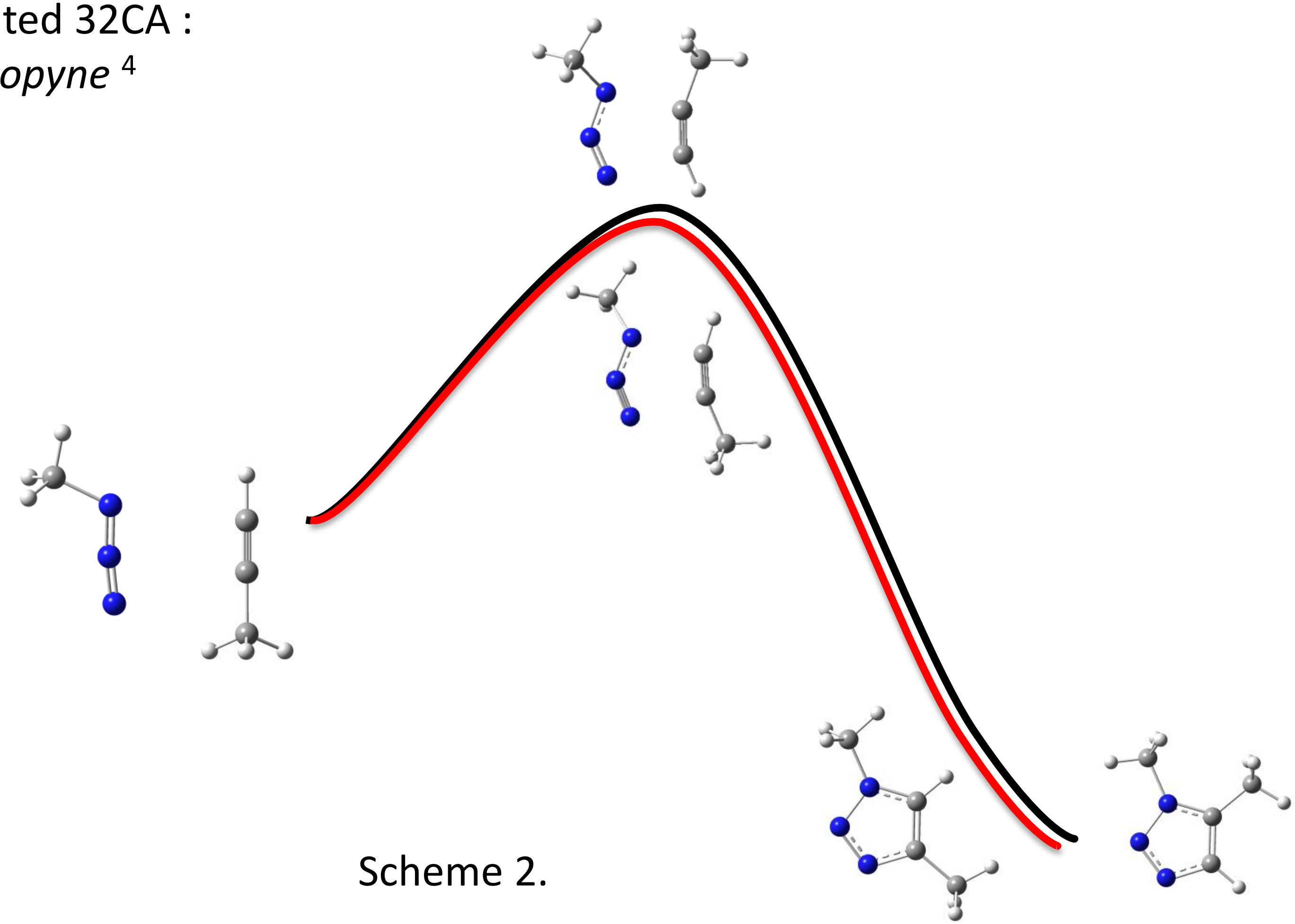

Scheme 2.

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[4] Liu, P. N.; Li, J.; Su, F. H.; Ju, K. D.; Zhang, L.; Shi, C.; Sung, H. H. Y.; Williams, I. D.; Fokin, V. V.; Lin, Z.; Jia, G. *Organometallics* **2012**, 31, 4904-4915 (and references therein).

2. Limitations of the uncatalyzed [3+2] cycloaddition reaction

Without activators/catalyst:

1,3 dipole + dipolarophile → NO CYCLOADDUCT/S [5]

Example: Reaction of an azomethine imine + a phenylacetylene (see scheme 3) [6]

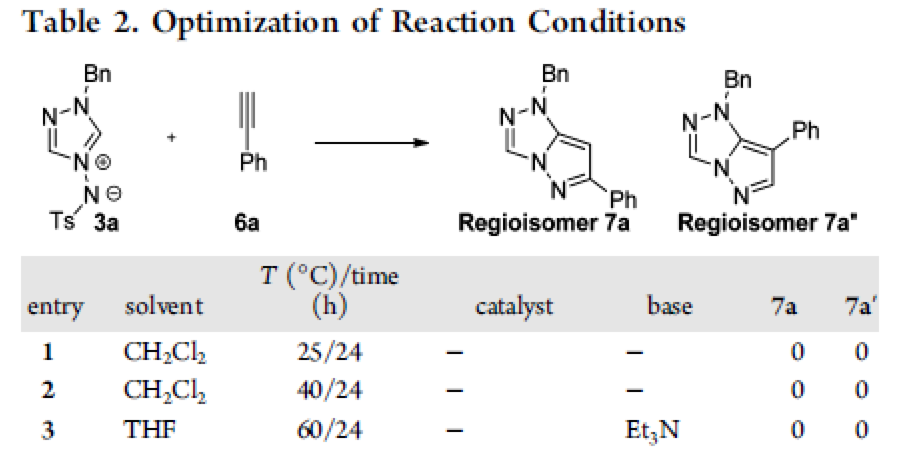

Table 2. Optimization of Reaction Conditions

entry	solvent	T (°C)/time (h)	catalyst	base	7a	7a′
1	CH_2Cl_2	25/24	–	–	0	0
2	CH_2Cl_2	40/24	–	–	0	0
3	THF	60/24	–	Et_3N	0	0

Scheme 3.

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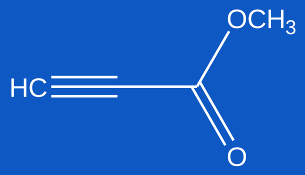
[5] Qi, X.; Ready, J. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 3242-3244 (and references therein). [6] Jishkariani, D.; Hall, C. D.; Oliferenko, A. A.; Leino, D.; Katritzky, A. R. *J. Org. Chem.* **2012**, 77, 5813-5818.

3. Catalytic [3+2] cycloaddition reaction

32CA reactions can be activated via various strategies:

- Conjugation of the dipolarophile unit with electron-withdrawing ester groups. [7]
  (e.g. Propiolates derivatives, ethynyl ketones and ethynyl aldehydes)



Methyl propiolate

- Use of transition metal catalyst. [8]
  (e.g. Gold, silver, palladium, copper, cobalt, ruthenium, nickel)

- Use of organocatalyst. [9]

[7] Kislukhin, A. A.; Hong, V. P.; Breitenkamp, K. E.; Finn, M. G. *Bioconjugate Chem.* **2013**, *24*, 684-689. [8] Gulevich, A. V.; Dudnik, Alexander S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev.* **2013**, *113*, 3084-3213. [9] Moyano, A.; Rios, R. *Chem. Rev.* **2011**, *111*, 4703-4832.

3. Catalytic [3+2] cycloaddition reaction

Catalysis of 32CA reactions displays unique

(1) ***Reactivity*** + (2) ***Selectivities***[10]

The enhanced rate of the concerted/stepwise reaction (1) and the distinct stereoelectronic effect on the reaction pathways (2)

have initiated extensive studies on **catalytic 32CA reaction mechanisms**.

[10] Imaizumi, T.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2012**, *134*, 20049-20052.

3. Catalytic [3+2] cycloaddition reaction

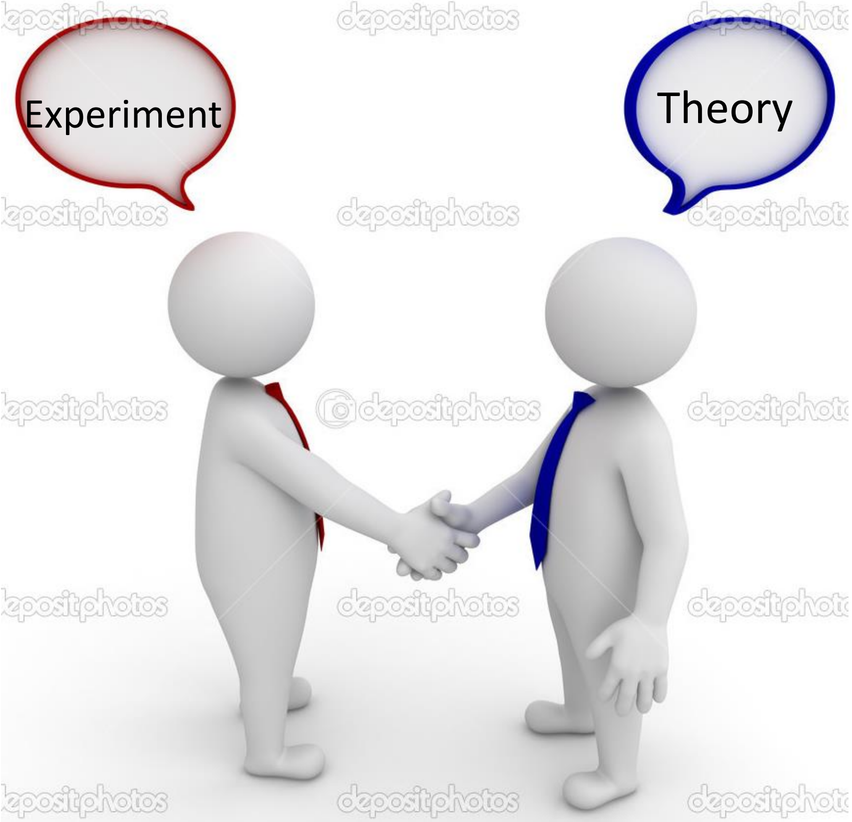
Studies on ***catalytic mechanisms of 32CA reactions*** are of utmost importance: [11]

- to optimize reaction parameters,
- to develop novel catalytic processes,
- to locate and characterize competitive catalytic pathways, and
- to enhance the understanding of fundamental reactivity.

[11] Worrell, B. T.; Malik, J. A.; Fokin, V. V. *Science* **2013**, *340*, 457-460.

4. Interplay between experiment and theory

- The catalytic 32CA reaction mechanisms are dictated by the subtle interplay between the electronic and steric factors.
- Thus, difficult to explain observed reactivities.
- ***Quantum chemical computations*** comes to the rescue. [12]
- Provides detailed insights into the transition states, intermediates and competing pathways.

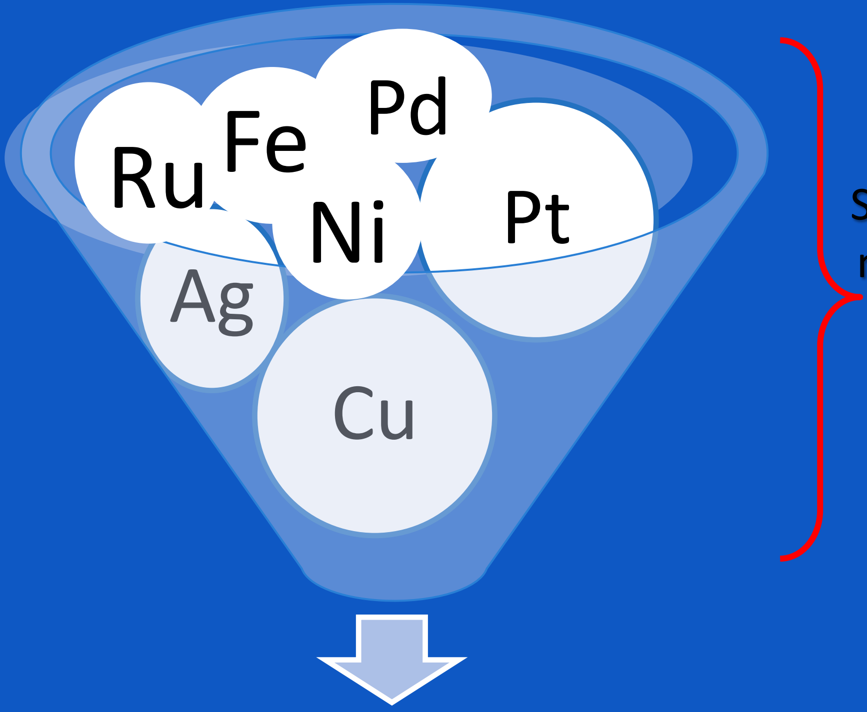


http://depositphotos.com/12629970/stock-photo-3d-businessmen-shaking-hands-concept.html

[12] Mörschel, P.; Janikowski, J.; Hilt, G.; Frenking, G. *J. Am. Chem. Soc.* **2008**, *130*, 8952-8966.

5. Transition metal catalyzed [3+2] cycloaddition reaction

To-date, transition metal catalyzed 32CA reaction have received numerous attention from both a synthetic and theoretical point of view.



Some transition metals that are involved in catalysis of 32CAs.

Cu

Yet, a changing trend from the rare and expensive metal catalyst (Pd, Rh, Ru) to the more abundant and cost-effective (Cu, Fe, Ni) ones is being observed . [10,11, 13]

[10] Imaizumi, T.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2012**, *134*, 20049-20052. [11] Worrell, B. T.; Malik, J. A.; Fokin, V. V. *Science* **2013**, *340*, 457-460. [13] Smith, C. D.; Greaney, M. F. *Org. Lett.*, **2013**, *15*, 4826-4829.

6. Copper(I) catalyzed [3+2] cycloaddition reaction

Undeniably, several theoretical and experimental studies have been devoted to copper(I) catalyzed 32CA reactions. [7,14, 15]

So far, several copper(I) catalyzed 32CA mechanisms have been postulated. [6, 10, 16]

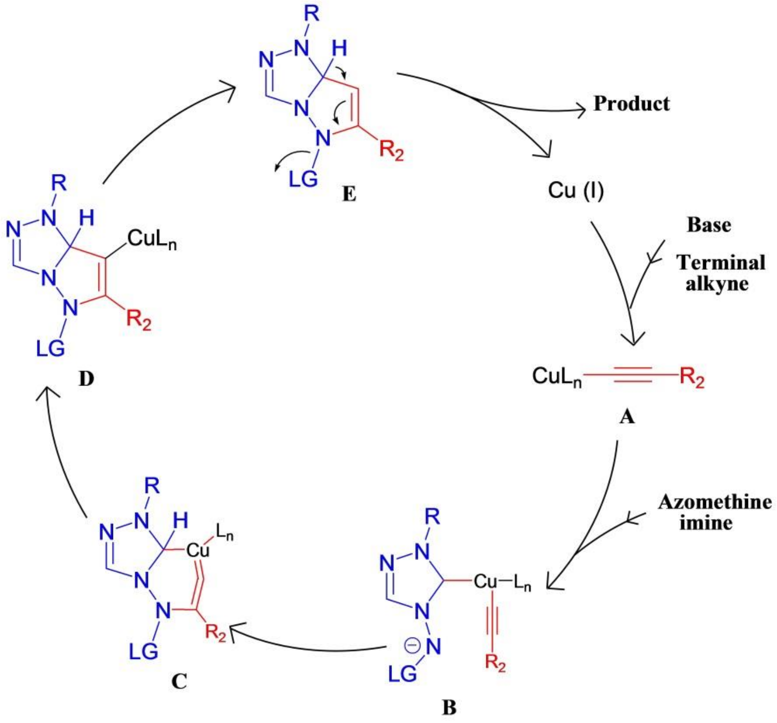
Among the various postulates present , the mechanism related to the famous copper(I) catalyzed alkyne-azide 32CA click reaction has received widespread attention. [16]

[6] Jishkariani, D.; Hall, C. D.; Oliferenko, A. A.; Leino, D.; Katritzky, A. R. *J. Org. Chem.* **2012**, 77, 5813-5818. [7] Kislukhin, A. A.; Hong, V. P.; Breitenkamp, K. E.; Finn, M. G. *Bioconjugate Chem.* **2013**, *24*, 684-689. [14] Struthers, H.; Mindt, T. L.; Schibli, R. *Dalton Trans.* **2010**, *39*, 675-696. [15] Cantillo, D.; Ávalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. *Org. Biomol. Chem.* **2011**, *9*, 2952-2958. [16] Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210-216.

6. Copper(I) catalyzed [3+2] cycloaddition reaction

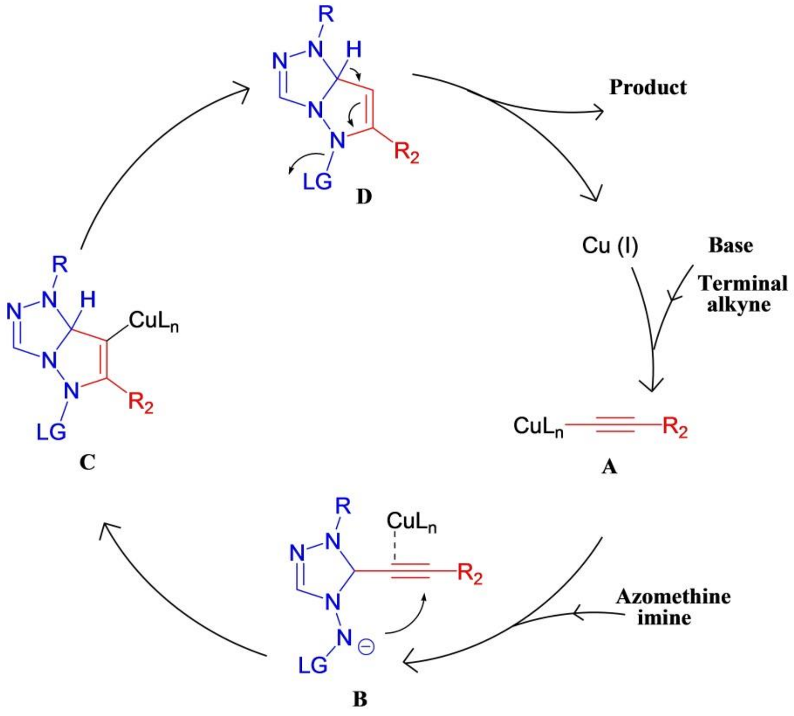
Objective:

Compare the click mechanism [16] (Scheme 4) with the recently postulated novel copper(I) catalyzed 32CA mechanism [6] (Scheme 5).



R = Bn, R_2 = Ph, LG = Ts, L_n = Br

Scheme 4.



R = Bn, R_2 = Ph, LG = Ts, L_n = Br

Scheme 5.

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[6] Jishkariani, D.; Hall, C. D.; Oliferenko, A. A.; Leino, D.; Katritzky, A. R. *J. Org. Chem.* **2012**, 77, 5813-5818. [16] Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210-216.

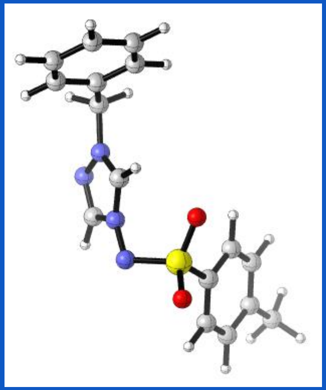
6. Copper(I) catalyzed [3+2] cycloaddition reaction

Methodology

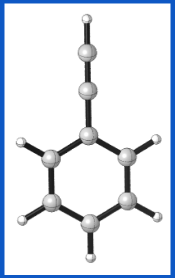
- B3LYP/6-31G(d) level of theory
- In solvent, DCM: To mimic reaction condition
- IRC computations: To locate all stationary points

Representative 32CA substrates

- 1,3 dipole: azomethine imine (a)
- Dipolarophile: terminal alkyne (b)



(a)



(b)

6. Copper(I) catalyzed [3+2] cycloaddition reaction

Results

- All the TSs connect the minima (reactant, intermediates and product) on the potential energy surface.
- The novel copper(I) catalyzed 32CA reaction has a lower energy barrier than the click mechanism for the reaction of azomethine imine and terminal alkyne considered herein.
- The energy barrier of the click mechanism is higher than that of the uncatalyzed reaction.

7. Conclusions

- It can be deduced that the click mechanism is not appropriate for the 32CA reaction of azomethine imine and terminal alkyne.

- The novel copper(I) catalyzed mechanistic postulate is well versed for the reaction of azomethine imine and terminal alkyne.

- This study can further incite experimentalists to isolate and characterize the intermediates.

- ***Future work****: Study the substitution effect on the 32CA reaction of azomethine imines and terminal alkynes.*

8. Acknowledgments

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- Dr. Lydia Rhyman
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- Prof. Alan R. Katritzky
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