

# Computational Analysis of Reaction Mechanism for Trifluoromethylation of Organic Compounds



Dr. Henk Eshuis, Montclair State University

Olivia Schmidt, Plainview Old-Bethpage John F. Kennedy High School, oliviaschmidt623@gmail.com



## Introduction

- *Trifluoromethyl* is a functional group consisting of one carbon atom and three fluorine atoms
- The trifluoromethylation of organic compounds to create a C-CF<sub>3</sub> bond is significant due to its uses in pharmaceuticals and agrochemicals
- The Swarts Reaction is the traditional method for creating this bond, but in order for it to occur extreme conditions, such as high temperatures, must be achieved and volatile reagents must be used
- New mechanisms have been suggested in which *visible-light photocatalysis* and transition-metal catalysis are combined to create the desired bond with *copper-catalyzed* trifluoromethylation<sup>1</sup>
  - Photocatalysis relies on the utilization of light energy to accelerate reactions, often via the use of semiconductor photocatalysts<sup>2</sup>
  - Transition metal catalysis is involved in organic synthesis, where carbon is bonded to another element<sup>3</sup>
- *Yingda Ye and Melanie S. Sanford* of the University of Michigan designed this method in order to be able to produce a good yield under *mild* conditions
  - Within the first part of the mechanism, the Ru(bpy)<sub>3</sub> complex forms CF<sub>3</sub> radicals, which are then used in the second step for trifluoromethylation

Why Computational Analysis?

- Allows for the study and identification of transition states, intermediates, pathways, and overall reaction mechanisms
- This methodology makes the study of complex kinetics more feasible

## Hypothesized Mechanism

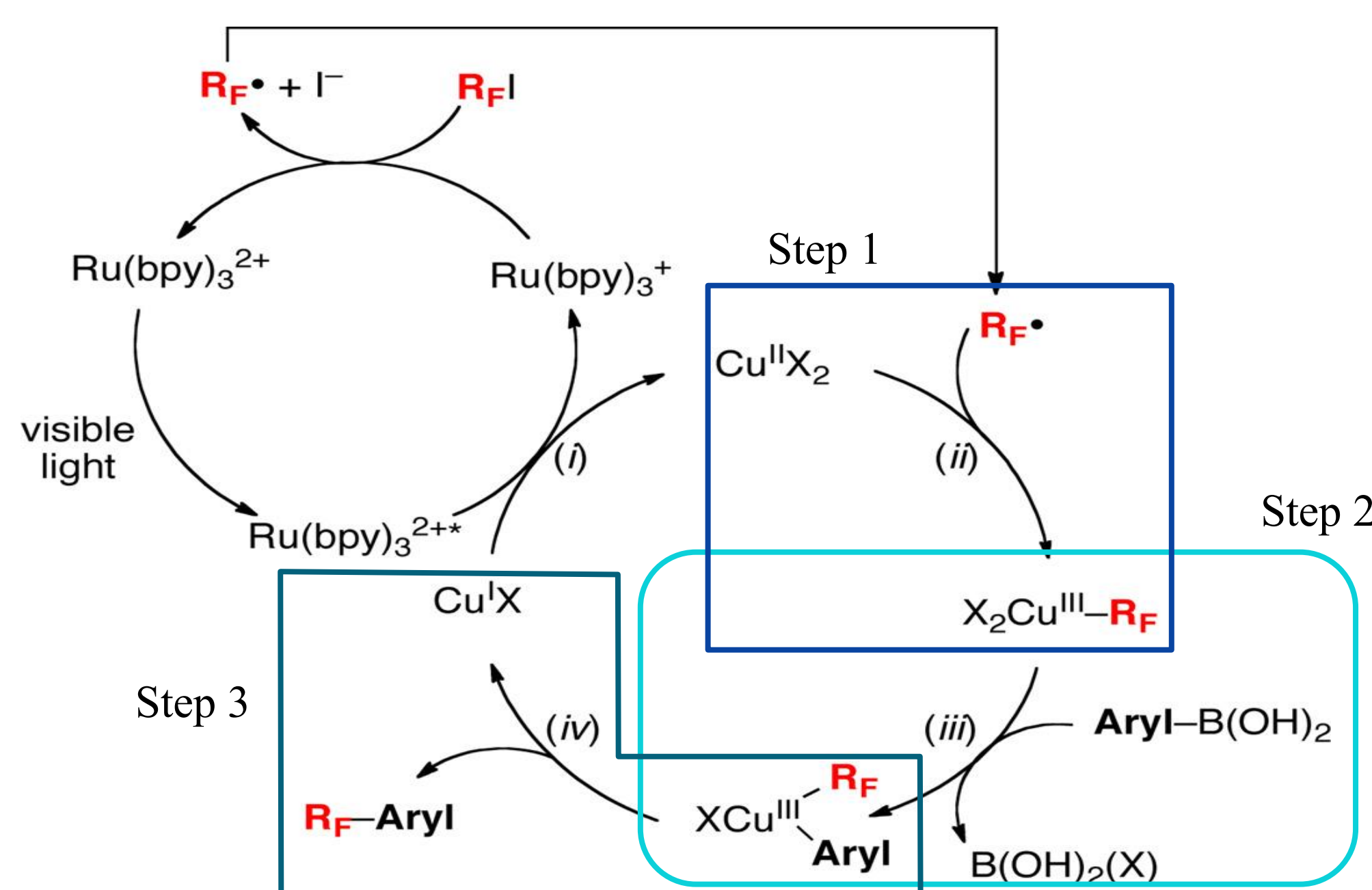


Figure 2: Potential Mechanism for Trifluoromethylation of Boronic Acid  
Ye, Y., & Sanford, M. S. (2012)

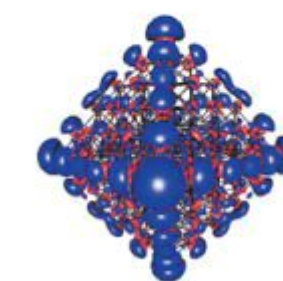
**Mechanism Processes Studied:**

1.  $\text{Cu}(\text{OAc})_2 + \text{CF}_3 \rightarrow \text{Cu}(\text{OAc})_2 \text{CF}_3$
2.  $\text{Cu}(\text{OAc})_2 \text{CF}_3 + \text{B}(\text{OH})_2\text{C}_6\text{H}_4\text{F} \rightarrow \text{B}(\text{OH})_2(\text{OAc}) + \text{Cu}(\text{OAc})\text{CF}_3(\text{C}_6\text{H}_4\text{F})$
3.  $\text{Cu}(\text{OAc})\text{CF}_3\text{C}_6\text{H}_4\text{F} \rightarrow \text{CF}_3(\text{C}_6\text{H}_4\text{F}) + \text{CuOAc}$

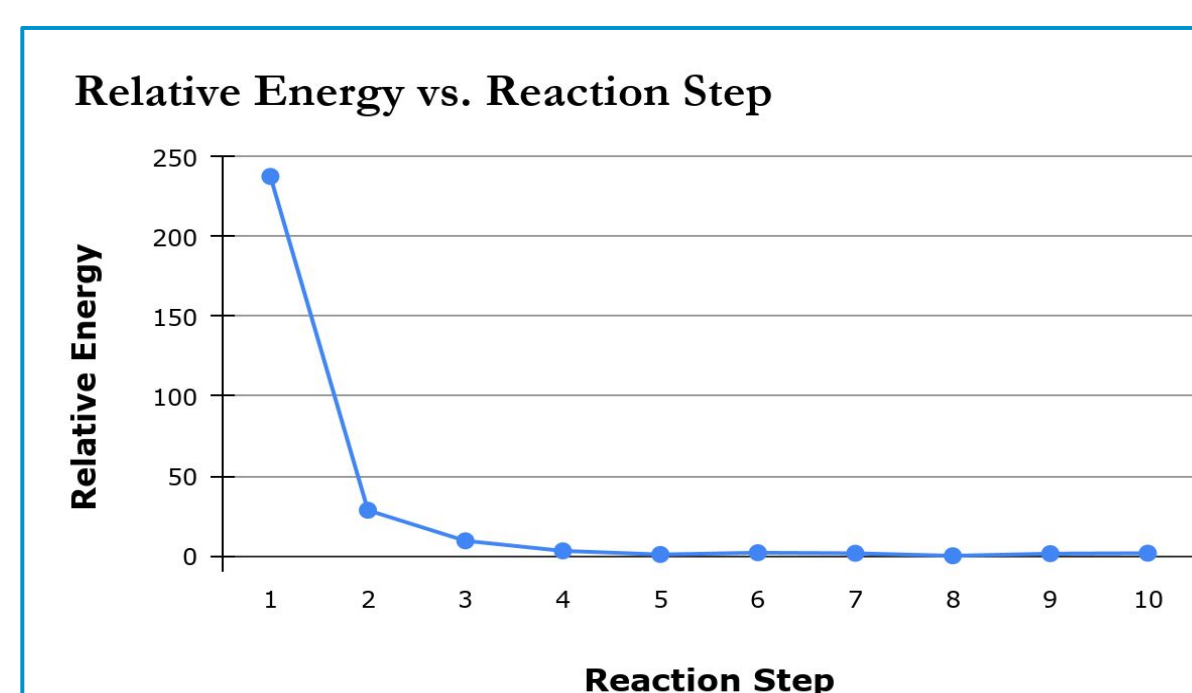
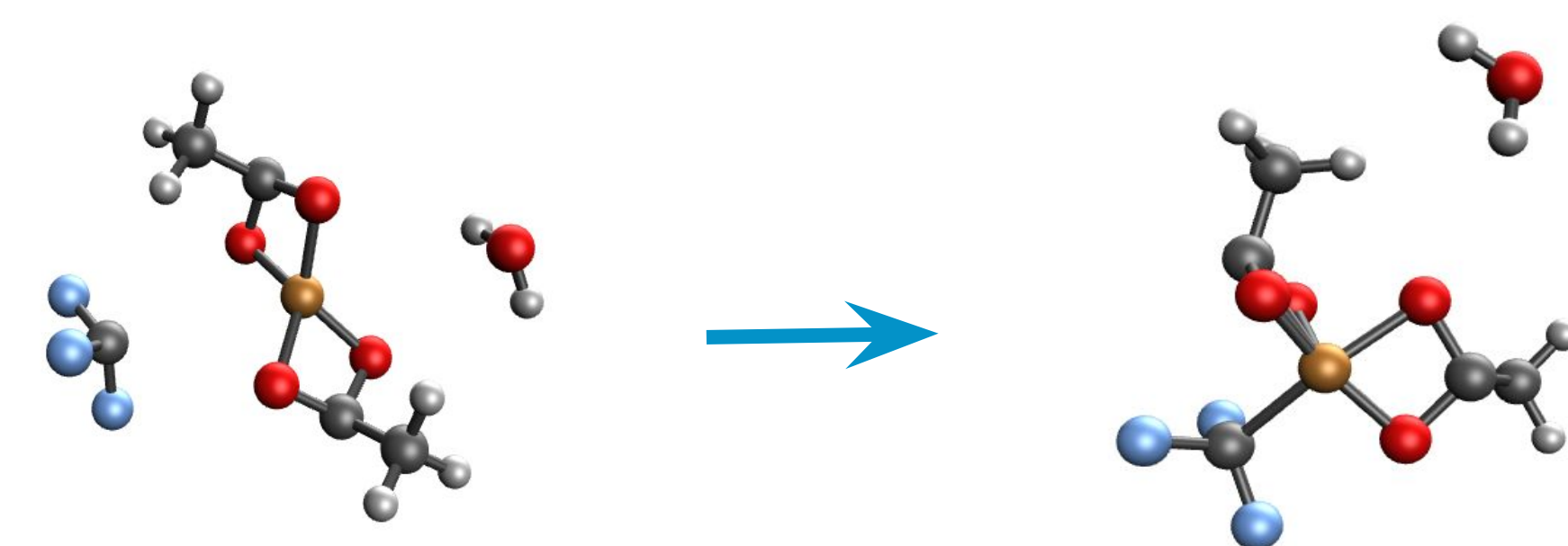
## Computational Methods

Building Structures	Geometry Optimization	Woelfling Calculation
All structures built using IQMOL program	- Turbomole calculation with pbe0 functional and def2-TZVP basis set - Solves quantum mechanical equations to find best geometry for molecules	Creates path from reactant geometry to product geometry and optimizes path to one of lowest energy

TURBOMOLE



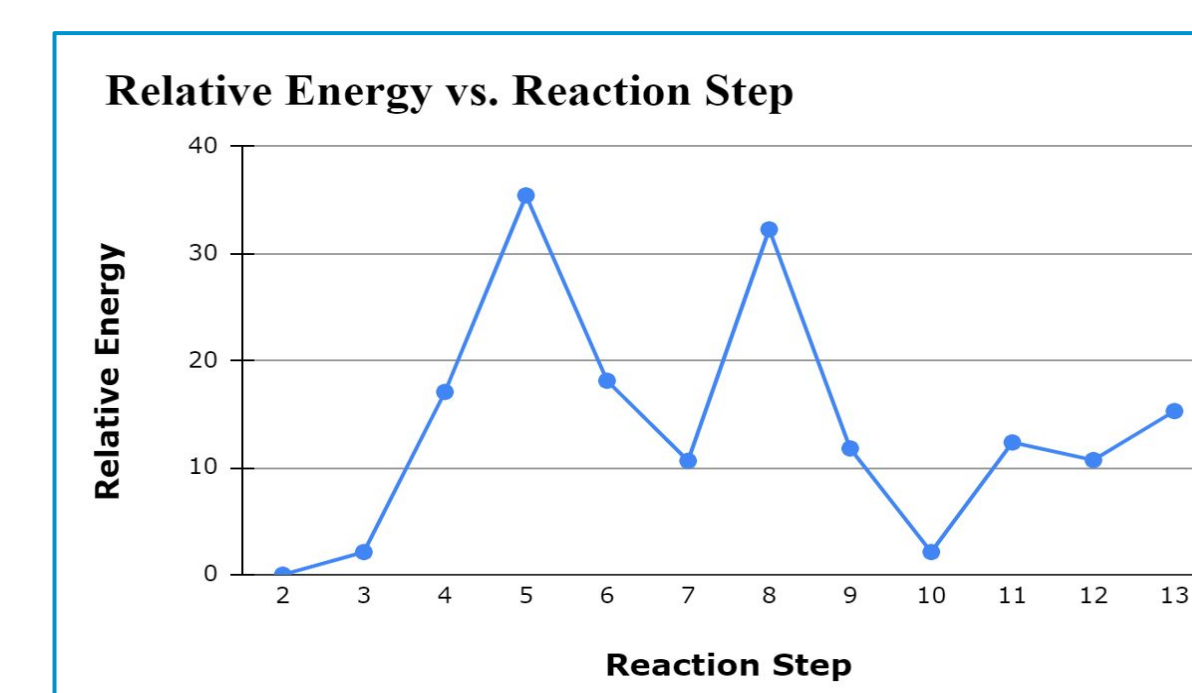
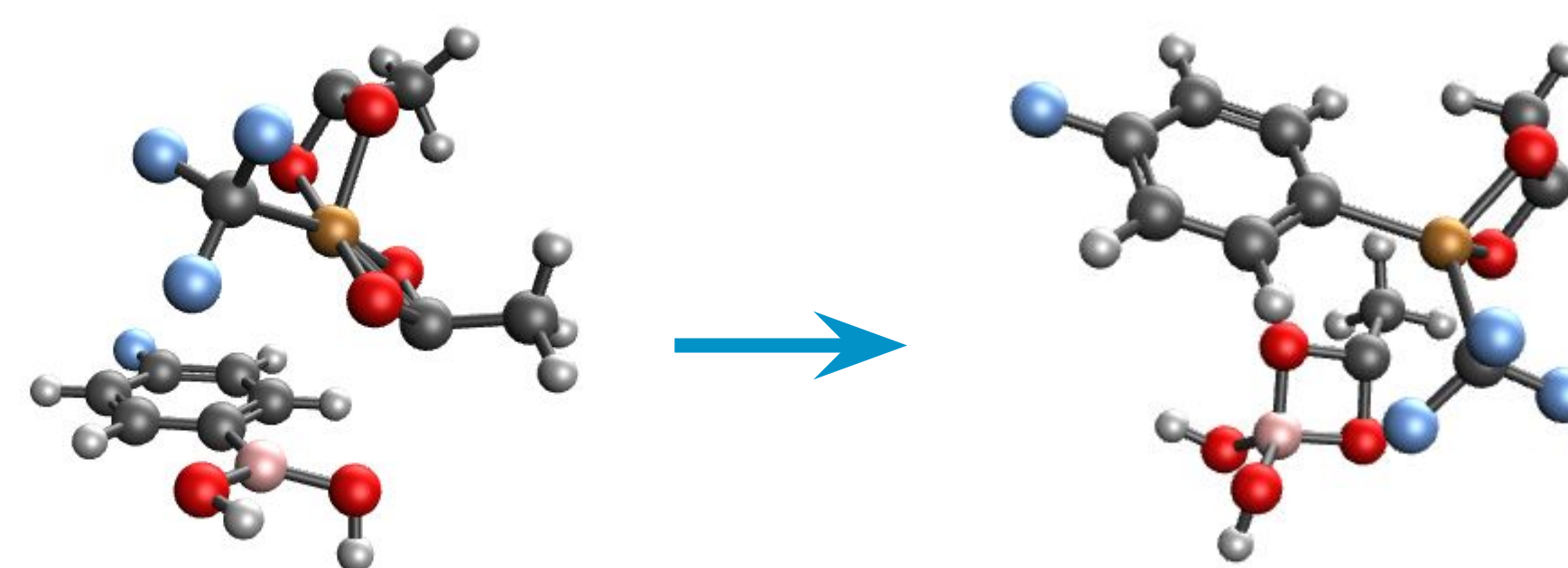
## Step 1



Figures show optimized structures with a central copper, Cu, atom surrounded by two acetate molecules

Central atom, Cu, is then bonded to the central carbon atom of CF<sub>3</sub>

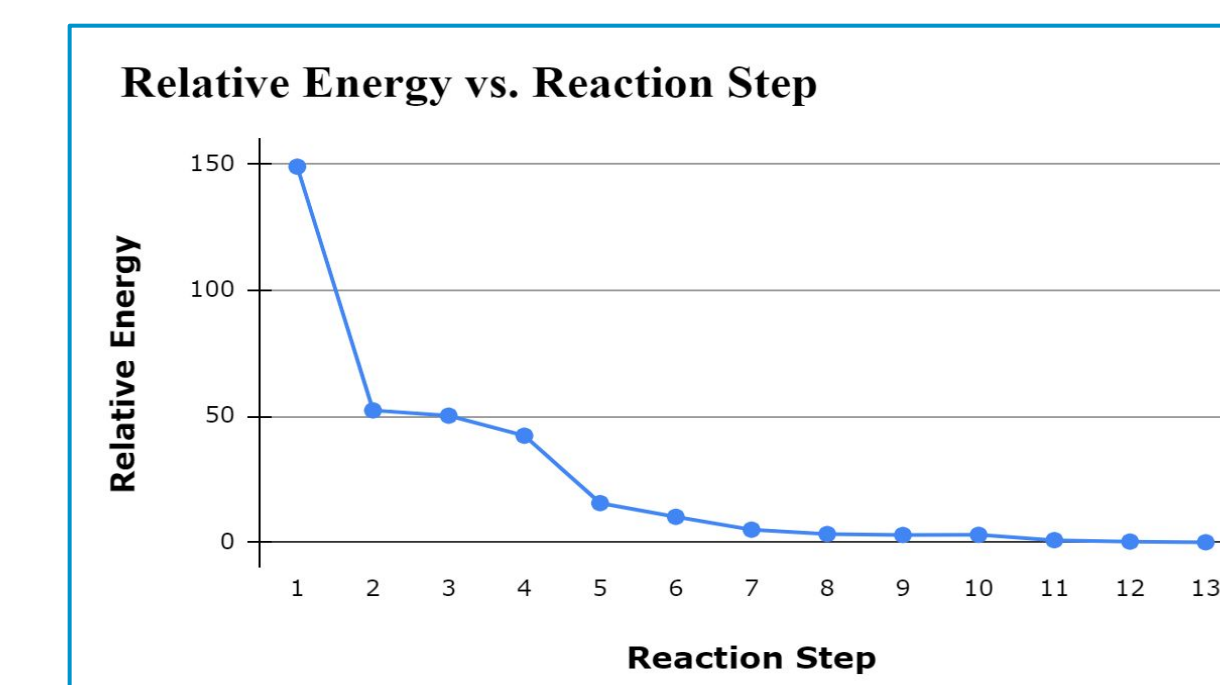
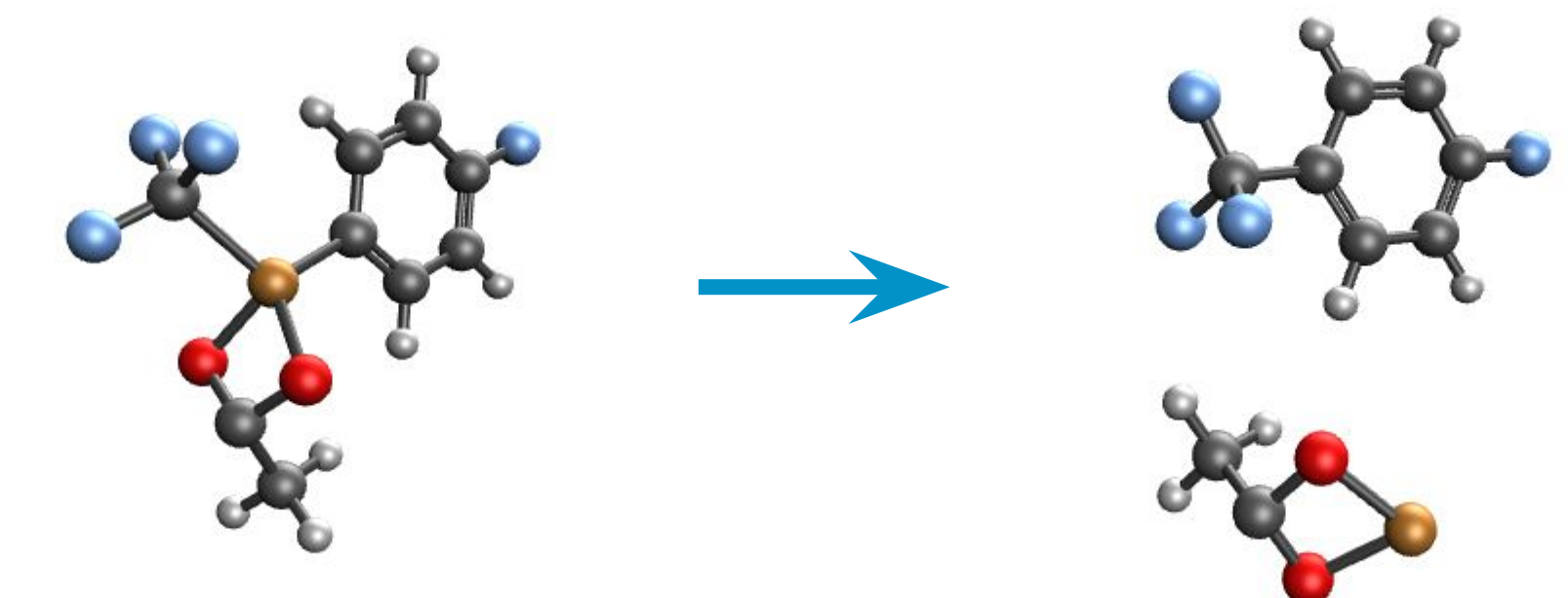
## Step 2



Figures show optimized structures with organic carbon ring bonded to boronic acid facing the product from Step 1, Cu(OAc)<sub>2</sub>CF<sub>3</sub>

Boronic acid then bonds with one acetate molecule, and the carbon ring bonds to the Cu central atom that is attached to one acetate and CF<sub>3</sub>

## Step 3



Figures show optimized structure of product from Step 2 - central atom Cu surrounded by CF<sub>3</sub>, acetate, and the carbon ring.

CuOAc molecule breaks away and CF<sub>3</sub> forms desired bond with the carbon ring

## Conclusions

Analysis of 3 individual steps of the proposed reaction mechanism for trifluoromethylation suggest possible thermodynamic favorability. Steps 1 and 3 display little to no barrier, thus making them energetically favorable. Step 2, however, appears to be the limiting step due to its significant energy barriers and fluctuations. While there is still much analysis and investigation to be done for this mechanism, these initial results suggest that the energy barriers within this process are reasonable, making this specific pathway a feasible possibility. This analysis did incur some limitations, though. The data displayed and discussed does not consider the effects of the solvent involved in the reaction. Additionally, these pathways are rather rudimentary, and need refinement to determine more definite answers.

## Future Work

These calculations and analyzes explored the copper-catalyzed aspect of this mechanism solely, yet this aspect must occur in conjunction with visible-light photocatalysis. Thus, future work should focus on the first piece of the mechanism to determine if it is thermodynamically favorable. It is necessary to investigate both halves of the mechanism in order to truly be able to acknowledge this process as a valuable avenue for trifluoromethylation reactions. Furthermore, the mechanism explored is only one possible path, and as such variations on this process must be researched so that an ultimate pathway can be determined.

## Acknowledgments

1. Ye, Y., & Sanford, M. S. (2012). Merging visible-light photocatalysis and transition-metal catalysis in the copper-catalyzed trifluoromethylation of boronic acids with CF<sub>3</sub>I. *Journal of the American Chemical Society*, 134(22), 9034–9037. <https://doi.org/10.1021/ja301553c>
2. Xiaogang Yang and Dunwei Wang (2018). Photocatalysis: From Fundamental Principles to Materials and Applications. *ACS Applied Energy Materials*, 1 (12), 6657-6693. <https://doi.org/10.1021/acs.aem.8b01345>
3. C. He, A. Lei (2013). 6.17 - Application of Nontoxic Iron Salts in Oxidative CC Coupling Reactions. *Comprehensive Inorganic Chemistry II* (Second Edition), Elsevier, 521-547, <https://doi.org/10.1016/B978-0-08-097774-4.00619-7>