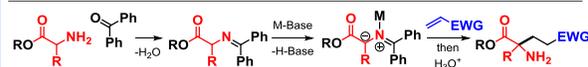


Photocatalytic C-F Functionalization: Transforming Perfluoroarenes from Inert Molecules to Synthetic Linchpins

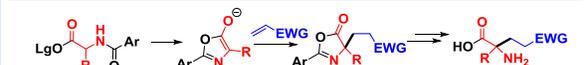
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In the last year, this project has impacted a post-doc and two graduate students. The post-doc worked just a little on the project before unexpectedly taking a permanent research position. He is now working as a process chemist at AMPAC Fine Chemicals. In a previous project, graduate student Kip Teegardin developed a method to access alpha fluoroaryl amino acid derivatives via C–F functionalization with an oxazolone enolate. Upon these products he found that the alpha C–H of the amino esters was rather labile and prone to exchange in protic solvent in the presence of a base. From this, he has recently developed the first example of catalytic Michael addition of N-protected amino acid derivatives. The protecting group can be Boc, Bz, or CBz. He studied the mechanism, which suggested that the reaction was proceeding through kinetic deprotonation of the N followed by tautomerization to the enolate. Importantly, this enolate is a mono-anion. Historically speaking, a similar mechanism was put forth by Tom Hoye to explain his observations in a related alkylation. However, the vast majority of the chemical community has rejected his posited mechanism. Instead believing access to the enolate was only possible if both acidic protons were removed, making a di-anion. Using DFT calculations, and isotope labeling experiments, we were able to conclude that the reaction must really be taking place through the monoanion. Furthermore, we utilized our new understanding to expand the scope to include natural amino esters, making this chemistry incredibly valuable and rich as it provides a massive increase in the number of amino acids that are readily available. The consequence of this project for the student, Kip has been that he recently accepted a job at AMPAC Fine Chemicals and will be starting in December. This is particularly exciting as Kip's success is important. Kip is part Native American, and is also an Army veteran. As a member of the 82 Airborne division he served in both the Iraq and Afghanistan conflicts before returning to the states to start his education.

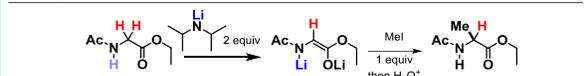
A. α,α -disubstituted amino acids from azomethine ylides



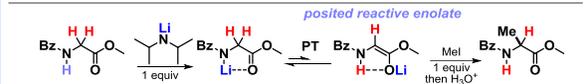
B. α,α -disubstituted amino acids from oxazolone enolate



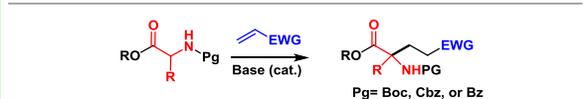
C. Krapcho 1976: Dianion mechanism



D. Hoye 1985: Monoanion mechanism



E. This work: α,α -disubstituted amino acids directly from enolate



Much of our C–F functionalization chemistry has utilized photocatalysis to effect reductive, or mesolytic, fragmentation of fluoride from highly fluorinated arenes. However, in this work we also discovered that some photocatalysts were capable of isomerizing the double bond of styrenoids. Furthermore, in the case of acyclic substituted styrenes it led to enrichment of thermodynamically less favorable alkene. In effect we were accomplishing uphill catalysis, ignoring the energy of the photon. Graduate student Jon Day became curious in what was happening in this reaction and specifically what was causing the change in behavior of the photocatalysts. In hopes that understanding this process more would provide exploitable facets. Indeed, working with another graduate student Kamaljeet Singh (now a post-doc at Novartis) we looked at whether we could capture some of the photochemical energy and harvest in the form of ring strain which ultimately could be used to facilitate synthesis. Specifically, we looked at whether it was possible to use the photoisomerization reaction to make trans-cyclohexene, which we

anticipated would have enormous strain energy. Indeed it is possible to form the trans-cyclohexene, which was evidenced by isotopic labeling. However, at no point do you ever observe any trans-cyclohexene. It is simply too strained to persist long enough to observe it. Yet, we were able to entice it to undergo cyclization reactions. Jon Day studied the mechanism computationally along with a number of other experimental mechanistic studies. The real question is how to utilize a molecule for productive synthesis that is so short-lived. Jon showed that the key was having the electrophile, a proton, already associated with the molecule via a hydrogen bond. This work was recently published in JACS (*JACS*, **2018**, *140*, 9934) and was featured on the cover. Jon's effort has provided great fundamental insight into how the photocatalyst interacts with these molecules, as well as key insights to utilizing ring strain. His more recent work has returned to the efforts of C–F functionalization but is too preliminary to be discussed at this point. He is an outstanding student who is nearing his candidacy exam. Jon's success is important as he is the father to Native American children and is, no doubt, the primary role model for them. Ultimately, these successes will hopefully help make science a more inclusive environment.

