Ultra-Rapid Electrophilic Cysteine Arylation

PhD Seminar

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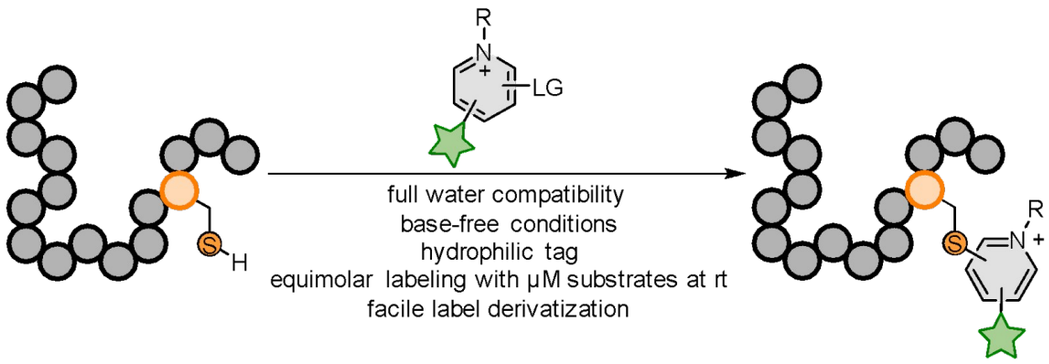
Friday, March 29, 2024
2:00 – 3:00 p.m.
Beaupre Room 105

Small molecule-based bioconjugation enables *in vitro* and *in vivo* functionalization of proteins and peptides, significantly expanding the chemical space of biomacromolecules. Among these transformations, nucleophilic aromatic substitution (S_NAr) of cysteine residues is a widely employed strategy for protein bioconjugation.

Although many reagents facilitate cysteine arylation, they are disadvantageous in two crucial aspects–limited synthetic modularity and undesired hydrophobicity. First, conventional cysteine arylating reagents are frequently activated by multiple electron-withdrawing groups (EWGs) on a single aromatic ring, leaving few synthetic handles to derivatize the reagents for advanced applications. Second, these labeling reagents are generally hydrophobic in nature and scarcely soluble in water, thus necessitating the use of organic cosolvents incompatible with certain biomolecules. Overall, these challenges highlight the current limitations of cysteine arylation chemistry and reflect the increasing need for rapid reactions allowing for bioconjugation at low micromolar concentrations within hours.

In this talk, I will present a series of cationic reagents that enable rapid cysteine arylation under mild conditions compatible with proteins and peptides. The highly polarized carbon–leaving group bond and attractive nucleophile-electrophile Coulombic interactions substantially accelerate the reaction, leading to unusually high-rate constants. The synthetic modularity of this approach allows for the direct coupling of structurally diverse functional motifs to cysteine residues of biomacromolecules with high efficiency. This simple, user-friendly chemistry enables fast bond formation between commonly used bioconjugation partners, thus greatly streamlining the workflow, and can be easily developed as convenient kits for chemical biology and medicinal chemistry applications.



References:
Lipka, B. M.; Betti, V. M.; Honeycutt, D. S.; Zelmanovich, D. L.; Adamczyk, M.; Wu, R.; Blume, H. S.; Mendina, C. A.; Goldberg, J. M.; Wang, F., Rapid Electrophilic Cysteine Arylation with Pyridinium Salts. *Bioconjugate Chem.* **2022,** *33*, 2189-2196.

Lipka, B. M.; Honeycutt, D. S.; Bassett G. M.; Kowal T. N.; Adamczyk, M.; Cartnick Z. C.; Betti, V. M.; Goldberg, J. M.; Wang, F., Ultra-Rapid Electrophilic Cysteine Arylation. *J. Am. Chem. Soc.* **2023,** *145*, 23427–23432.