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New Directions in Photoredox Catalysis
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The goal of our proposed research program is the discovery of novel strategies for the catalytic generation of carbon–carbon bonds from simple, inexpensive, and abundant components of petrochemical feedstock. Our research strategy is guided by the hypothesis that new carbon–carbon bonds can be formed between two sp^3 carbons with the aid of two modes of catalysis: (1) visible light mediated activation in the presence of a photocatalyst, (2) and transition metal catalysis.

In Aim 1 of the grant, we proposed to develop a remote sp^3 – sp^3 C–H allylation of amides with allyl halides. The allylation of amines and amides is a useful chemical transformation, because the resulting allylic amines are synthetically versatile building blocks that can be converted into a broad range of products (Figure 1).¹ Classically, the treatment of amides with allylic electrophiles under basic conditions leads to an *N*-allylated product. The selectivity for *N*–H functionalization in this transformation is derived primarily from the lower pK_a of *N*–H bonds compared to C–H bonds (25 vs. 50), which leads to the preferential formation of a nitrogen-based anion.

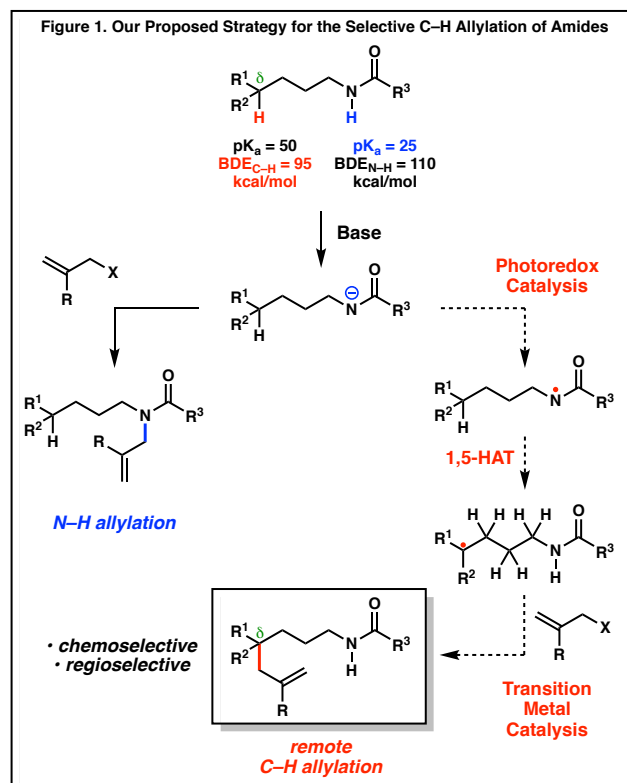
To expand the synthetic utility of the allylation of nitrogen containing molecules, we were interested in developing a novel reaction with amides that would result in selective C–H allylation. Two selectivity issues required attention. First, the inherent preference for *N*–H allylation over C–H allylation (chemoselectivity) needed to be overcome. Second, the selective functionalization of a single type of C–H bond in a molecule with multiple C–H bonds (regioselectivity) needed to be addressed.

To tackle the issue of *chemoselectivity*, we hypothesized that a radical based mechanism would provide the enthalpic driving force to favor C–H allylation over *N*–H allylation based on a comparison of bond dissociation energies for an sp^3 C–H bond and an amide *N*–H bond (95 kcal/mol vs. 110 kcal/mol). Moreover, we hypothesized that a *regioselective* sp^3 C–H allylation of amides could be developed by leveraging the entropically-driven regioselectivity of intramolecular 1,5-hydrogen-atom-transfer processes, which results in δ -functionalization of amide substrates.²

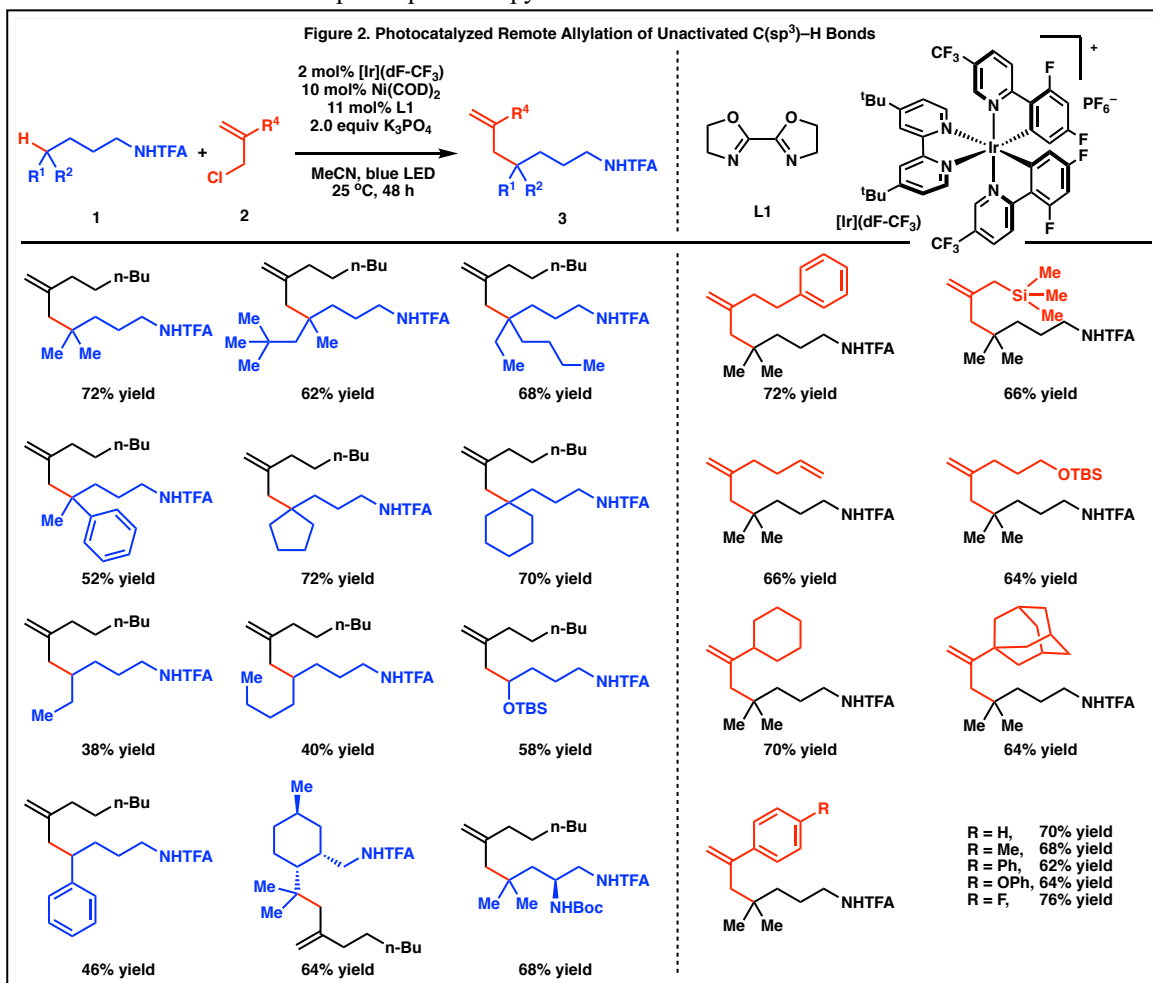
With this strategy, we have developed the first example of remote sp^3 C–H allylation of amides by a dual catalyst system comprised of an iridium-based photoredox catalyst and a nickel complex (Figure 2).^{3,4} Our approach to selective C–H allylation overrides the traditional chemoselectivity observed in *N*–H allylation of amides, and it generates products with high δ -selectivity. Various allyl substituted amides (**3**) are obtained with good yields, high δ -selectivity, and high functional group tolerance. The reaction is compatible with a broad range of amides (**1**) as well as allyl chlorides (**2**). We recently published these studies in *ACS Catalysis*.⁵

The impact of this research on my career and that of the researcher who participated in the project has been tremendous. For me, this was my first direct experience with photocatalysis. I had to learn a new area of chemistry, which exposed me to primary literature and reviews outside my traditional areas of expertise. My involvement with this project was the motivation for adding lectures on photochemistry and radical reactivity to the graduate course I teach on Chemical Structure & Reactivity.

For the researcher who participated in the project, this was also his first direct experience with photocatalysis. He had to learn the theory of photocatalysis as well as the experimental setup required for performing reactions with blue LED. The project exposed him to new techniques for studying the mechanisms of photocatalyzed reactions. For example, we established a collaboration with Dr. Ludovic Troian-Gautier (formally a postdoc at University of North Carolina, Chapel Hill and now a Chargé de Recherches at Université Libre de Bruxelles). While Dr. Troian-Gautier



was still at UNC, the researcher from my laboratory visited UNC and spent several days with Dr. Troian-Gautier to gain first-hand experience in conducting steady-state and time-resolved photoluminescence quenching experiments as well as nanosecond transient absorption spectroscopy.



References

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