

## Narrative Progress Report

1. **PRF#:** 57164-ND1

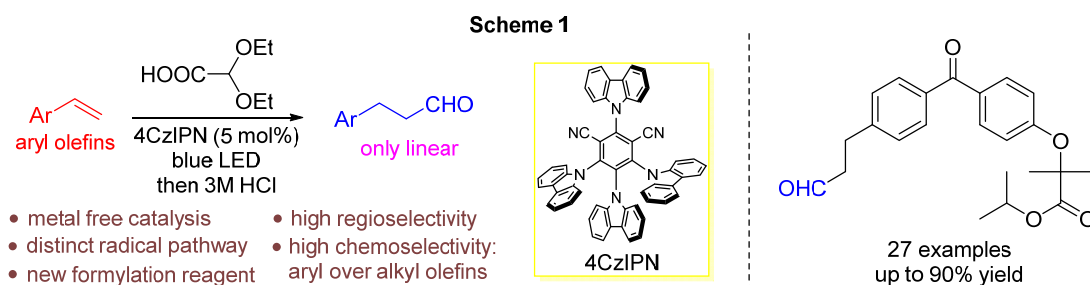
2. **Project Title:** Photocatalytic Functionalization of Arenes and Alkenes Using Visible Light

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### 1) Chemo- and Regio-Selective Organo-Photoredox Catalyzed Hydroformylation of Styrenes via a Radical Pathway.

Hydroformylation is currently the most highly productive homogenous catalyzed process used on an industrial scale to generate more than 10 million tons of oxo products annually. This success is attributable to significant efforts made to develop efficient protocols for aldehyde synthesis. Among these protocols are those that chiefly employ transition metal complexes (e.g., Rh, Co, Ir, Ru and Pd) as catalysts. Unfortunately, these approaches rely on the use of high pressures of toxic syngas (CO/H<sub>2</sub>). In addition, other important issues associated with these protocols include the control of chemoselectivity and regiochemistry when unsymmetrical olefins are substrates. In particular, while the regioselectivity of reactions producing linear aldehydes from alkyl substituted olefins has been addressed, methods for regioselective formylation of aryl olefins remain elusive. In these cases, branched rather than linear formylation products are formed predominantly because CO transfer produces more stable benzylic metal-species as a result of  $\eta^2$  electron donation from the aromatic ring. Although limited in number, a few processes, in which linear formylation of aryl olefins occurs, have been developed by Zhang, Reek and Shi. These approaches require the use of transition metal complexes containing highly functionalized ligands, and/or that special substrates. Furthermore, an intrinsic limitation of transition metal catalyzed processes is associated with the difficulty in controlling chemoselectivity when both alkyl and aryl substituted C=C bonds are present in the substrate. It is clear that a new synthetic paradigm is needed to address the development of a viable olefin hydroformylation process that overcomes shortcomings of the current transition metal catalyzed reactions.

Toward this end, we have developed an unprecedented, chemo- and regio-selective, organo-photoredox catalyzed hydroformylation reaction of aryl olefins with diethoxyacetic acid as the formylation reagent (Scheme 1). In contrast to traditional transition metal promoted ionic hydroformylation reactions, the new process follows a unique photoredox promoted, free radical pathway. In this process, a formyl radical equivalent, produced from diethoxyacetic acid through a dye (4CzIPN) photocatalyzed, sequential oxidation-decarboxylation route, regio- and chemo-selectively adds to a styrene substrate. Importantly, under the optimized reaction conditions the benzylic radical formed in this manner is reduced by SET from the anion radical of 4CzIPN to generate a benzylic anion. Finally, protonation produces the hydroformylation product. By using the new protocol, aldehydes can be generated regioselectively in up to 90% yield. A broad array of functional groups is tolerated in the process, which takes place under mild, metal free conditions.



## 2) Visible Light Promoted Nickel and Organic Co-Catalyzed Formylation Reaction of Aryl Halides and Triflates and Vinyl Bromides Using Diethoxyacetic Acid as a Formyl Equivalent

Arguably, aromatic aldehydes are the most fundamentally important substances used in organic synthesis. Therefore, the availability of predictable and chemoselective methods for formylation of aromatic compounds will continue to have a profound impact on chemical synthesis. Classical methods for the preparation of aromatic aldehydes, such as the Reimer–Tiemann, Vielsmeier–Haack, Gattermann–Koch and Duff reactions, are not atom- and step- economical. Furthermore, the lack of control of the regiochemical course of these reactions makes it difficult to employ them to introduce aldehyde functionality at desired positions. As a result of these limitations, state-of-the-art formylation technologies employing transition metal catalysts have been developed. The pioneering work on palladium catalyzed formylation of aryl halides, using CO and H<sub>2</sub>, by Heck<sup>[3]</sup> triggered significant interests in developing more efficient protocols. Impressive results from studies of this topic have come from the laboratories of Pri-Bar, Stille, Beller, Manabe, Skrydstrup, Kotsuki and Liu. However, the approaches developed by these groups generally require high reaction temperatures, aryl-bromides or -iodides as substrates, and precious palladium complexes as promoters. Moreover, in some cases, toxic CO gas and tin compounds are used. These issues highlight the demand more cost-effective, environmentally friendly and mild protocols for aryl-aldehyde synthesis.

Along this line, we have developed a simple formylation strategy involving the reaction of aryl halides, aryl triflates and vinyl bromides using synergistic nickel and organic dye mediated photoredox catalysis is reported (Scheme 2). Distinct from widely used palladium catalyzed formylation processes, this reaction proceeds by way of a two step mechanistic sequence involving initial *in situ* generation of the diethoxymethyl radical from diethoxyacetic acid by 4CzIPN mediated photoredox reaction. The formyl radical equivalent then undergoes nickel catalyzed substitution reactions with aryl halides and triflate and vinyl bromides to form the corresponding aldehyde products. Significantly, in addition to aryl bromides, less reactive aryl chlorides and triflates and vinyl halides serve as effective substrates for this process. The fact that the mild conditions involved in this reaction tolerate a plethora of functional groups enables the process to be applied to the efficient preparation of diverse aromatic aldehydes.

