

New Alkene Hydrofunctionalization Reactions: Approaches to Aldehyde Activation Using Base Metal Catalysis

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Introduction

The intent of this funded research program was to develop efficient alkene hydrofunctionalization catalysts using readily available and nontoxic first-row transition metals such as Fe, Co, and Ni. Synthetic routes which feature catalytic hydrofunctionalization reactions typically benefit from good step efficiency and inherently high atom economy because they minimize prefunctionalization and derivatization processes. Employing catalytic hydrofunctionalization reactions therefore facilitates the practical synthesis of chemical commodities with high utility. Furthermore, catalysts derived from first-row transition metals provide cost and safety benefits when compared to the second- and third row transition elements. We believe that Co-catalyzed aldehyde activation provides an excellent manifold for new reaction development along those lines.

Our initial investigations focused heavily on alkene and alkyne hydroacylation with Co catalysts. One significant drawback to transition-metal-catalyzed hydroacylation reactions has been the necessary incorporation of a chelating directing group within the aldehyde substrate. These directing groups have historically been used to accelerate oxidative addition into the aldehyde C–H bond, and perhaps more importantly, to limit the extent of decarbonylation observed when a catalytic metal acyl-species occurs. These chelating directing groups typically take the form of polar functionalities such as alcohols, ethers, thiolates, and amines. While chelating directing groups have provided efficient reactivity in chemical terms, they restrict the substrate scope considerably and practical applications for these reactions have been limited. Our group hypothesized that common reactive functional groups such as the halogens may indeed behave as coordinating directing groups in order to facilitate hydroacylation reactions (**Figure 1**). While these hypothetical reactions would still technically require a coordinating directing group, that directing group could potentially serve as a versatile handle for subsequent chemical manipulation.

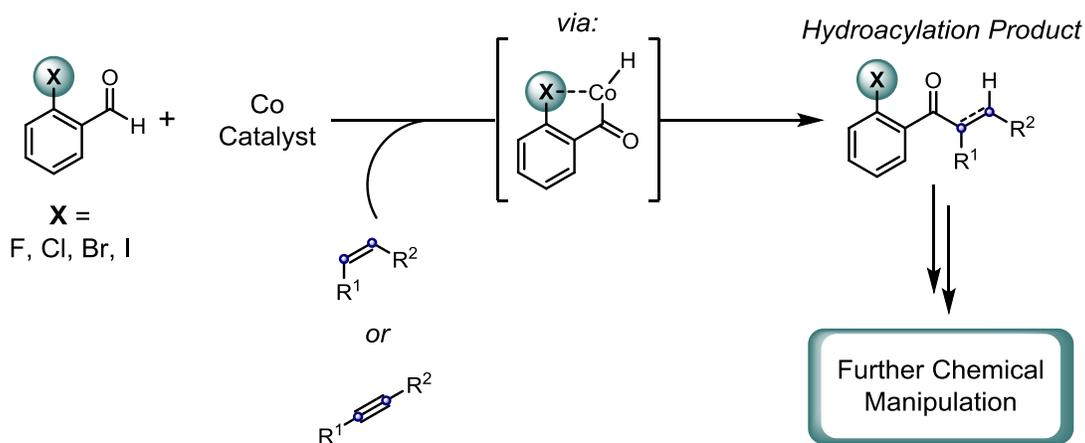


Figure 1. Undergraduate research students tested the hypothesis that halogen atoms could serve as coordinating directing groups for alkene and alkyne hydroacylation. Initial investigations focused on Co-catalyzed reactions with common classes of alkenes and alkynes. While our initial attempts brought little success, our observations did lead us to the creation of several useful Ni-catalyzed annulation reactions.

Undergraduate research students in my lab synthesized and tested a wide variety of Co catalysts with different amine, phosphine, and bis(imino)pyridine ligands. A wide variety of conditions were screened with both alkenes and alkynes. Unfortunately, only trace quantities of the desired hydroacylation products could ever be observed, typically only when alkynes were used as the reactive π component. Even though group 9 metals such as Co and Rh are known to

selectively react with C–H bonds in the presence of weaker C–X bonds, we frequently observed byproducts consistent with oxidative addition into the C–Br bond in 2-bromobenzaldehyde. Because a similar reactive motif is present in certain Pd-catalyzed annulation reactions (such as the Larock indenone synthesis), we felt an approach using 2-bromobenzaldehyde as a bifunctional reagent might prove more successful. After extensive investigations with Co, we began to consider Ni catalysts since this first-row transition metal is known to actively engage both C–H and C–Br bonds under similar reaction conditions. We were pleased to find that Ni-based catalysts with certain phosphine ligands can indeed effect the desired reactivity. Using the developed conditions 2-bromobenzaldehyde can participate in efficient annulation reactions with a variety of unsaturated compounds including alkyl-substituted alkynes (e.g. 51% with 4-octyne). This is noteworthy since Pd is known to catalyze a variety of useful annulation reactions, but reactions with alkyl-substituted alkynes have remained challenging. These initial results are already comparable to some of the most efficient Pd catalysts. Yields for the desired indenone can reach 80% depending on the identity of the reactants used. While this reaction does not fall within the broader definition of hydrofunctionalization (because the reactive H is not incorporated within the product), it does accomplish the original intent of the proposal in that an aldehyde C–H bond is formally converted into a new C–C bond and the only other functional group required in the reactant also participates in useful chemical reactivity.

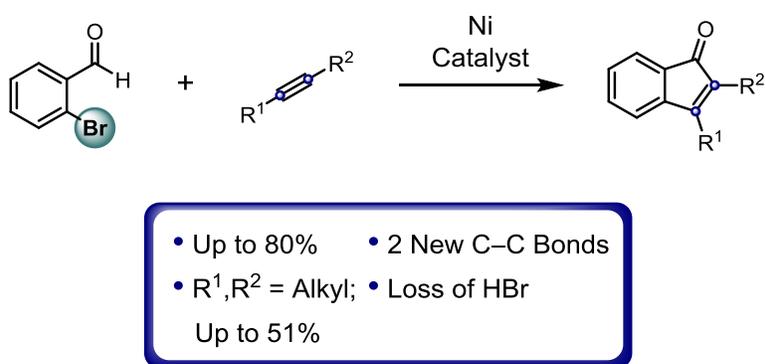


Figure 2. Undergraduate research students within my laboratory have developed several Ni-catalyzed annulation reactions. Reactions between 2-bromobenzaldehyde and alkyl-substituted alkynes can provide indenone products with isolated yields above 50%. These results are promising because these conditions appear to provide useful reactivity with substrates which have historically proven recalcitrant with Pd catalysts.

Future work within my undergraduate research group will focus on further developing the scope of this chemical reaction and publishing our results in a peer-reviewed journal. The indenone annulation reactions with alkyl alkynes should be impactful if the yields can be improved slightly. Reactions with other halogenated aldehydes and alkenes will also be investigated since these reactants are also problematic for Pd.

Impact

This ACS-PRF UNI award has greatly benefitted several different undergraduate students at Samford University. Three different students were supported during the second year of this award. This ACS-PRF UNI award provided stipends for these students' living expenses for a summer research program, and it also covered materials and supplies for their research. These students' research would not be possible without these ASC-PRF funds. The students received training in organic and inorganic synthesis, and in a variety of analytical techniques including mass spectrometry (MS), nuclear magnetic resonance (NMR) spectroscopy, and infrared (IR) spectroscopy. One of these undergraduate students has applied to dental school, and the other two students are planning on applying to medical school and graduate school in chemistry. These students' educational paths have improved substantially due to these ACS-PRF funds. In March 2018 one of my former undergraduate research students (supported under the previous budget period) attended the national ACS meeting in New Orleans. This student participated in professional career development activities and had the opportunity to speak with numerous job recruiters about their undergraduate research experience. This ACS-PRF UNI award has also benefitted my personal professional career. This funding provided our group critical momentum in order to develop several new projects. I anticipate being able to publish our results within a peer-reviewed journal within the next couple months.