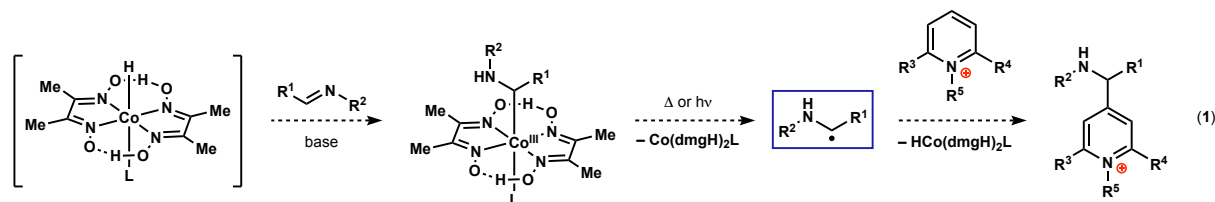


## Development of Cobalt(I)-Catalyzed Radical-Polar Crossover Reactions

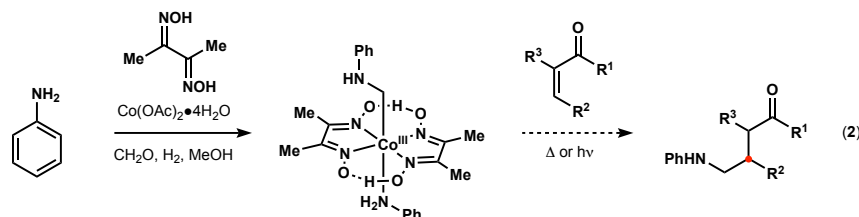
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The long-term goal of our research is to develop new chemical methods and approaches that allow for direct and selective access to useful structural motifs and valuable synthetic intermediates. Alkyl radicals are versatile reactive intermediates that participate in a variety of useful chemical reactions. Recent renaissance in the development of new radical transformations resulted from the advent of new catalytic methods, including those based on the Mukaiyama-type hydrogen atom transfer (HAT) to alkenes. The success of these methodologies is attributed in part to the facile and selective generation of alkyl radicals from readily available precursors. However, the regioselectivity of HAT is typically dictated by the stability of the resulting alkyl radicals, limiting the accessible functionalization patterns, and carbon-heteroatom double bonds have yet to be engaged in similar transformations. Overcoming these limitations is expected to yield new chemical methods that complement current toolkit of catalytic radical transformations. We proposed the development of new methods for catalytic radical ( $\alpha$ -amino)alkylation and ( $\gamma$ -oxo)alkylation reactions. To investigate the utility of the proposed transformations, we also planned to apply these methods to alkylation of heteroaromatic compounds in a Minisci-type process.

In the first proposed transformation, we sought to generate ( $\alpha$ -amino)alkyl radicals from the corresponding ( $\alpha$ -amino)alkylcobalt intermediates. The latter would in turn be obtained via a nucleophilic addition of cobalt(I) complexes to the corresponding imines (equation 1). The ( $\alpha$ -amino)alkyl radicals would then be captured by Michael

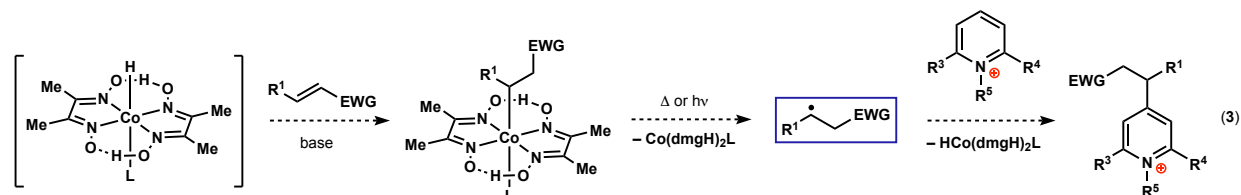


acceptors, such as  $\alpha,\beta$ -unsaturated carbonyl compounds and electron-deficient heteroarenes. In our initial investigations, we decided to evaluate the stoichiometric variant of this reaction. Relying on the early precedent from Schrauzer and Windgassen, we successfully prepared an aminomethylcobalt complex possessing an aniline fragment (equation 2). We then attempted to generate the corresponding aminomethyl radicals and capture with Michael

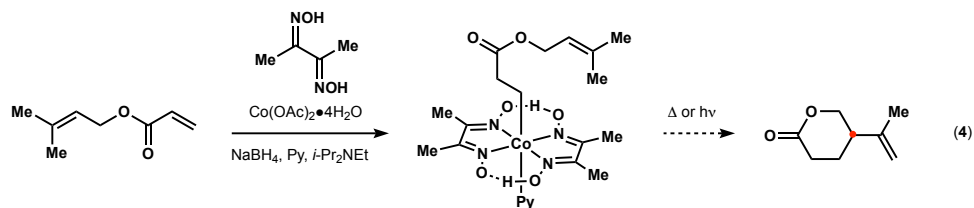


acceptors. We evaluated numerous reaction conditions and various unsaturated ketone partners, but observed only trace amounts of the desired ( $\gamma$ -amino)carbonyl compounds. In our future studies, we plan to evaluate a broader scope of Michael acceptors and substitution patterns in the aminomethyl fragment and assess the effect of Lewis acid additives, which can be expected to facilitate the conjugate addition. We will then seek to translate our findings to the corresponding catalytic processes.

In the second proposed transformation, we sought to generate ( $\gamma$ -oxo)alkyl radicals from the corresponding ( $\gamma$ -oxo)alkylcobalt intermediates. The latter would in turn be obtained via a nucleophilic addition of cobalt(I) complexes to the corresponding  $\alpha,\beta$ -unsaturated carbonyl compounds (equation 3). The ( $\gamma$ -oxo)alkyl radicals would then be captured by Michael acceptors, such as  $\alpha,\beta$ -unsaturated carbonyl compounds and electron-deficient heteroarenes. We began with evaluation of the stoichiometric variant of the process. In these early stages, we sought to capture the



( $\gamma$ -oxo)alkyl radicals in an intramolecular fashion with a pendant alkene. Taking advantage of the early example from Schrauzer and Windgassen, we prepared ( $\gamma$ -oxo)alkylcobalt complex from the corresponding acrylate ester (equation 4). Attempted homolysis of the C-Co bond under various conditions lead to small amounts of the desired



lactone (<5%). We also attempted preparation of the corresponding  $\alpha,\beta$ -unsaturated ketone, but encountered competitive reduction of the substrates. In our future studies, we plan to develop conditions for preparation of ( $\gamma$ -oxo)alkylcobalt complexes from the corresponding  $\alpha,\beta$ -unsaturated ketones. We will also investigate the potential of the intermolecular capture of the ( $\gamma$ -oxo)alkyl radicals derived from the corresponding acrylate esters. We will then seek to translate our findings to the corresponding catalytic processes.

Funding from the ACS PRF has had a transformative effect on the research in our laboratory as it has allowed us to pursue new directions in the catalytic organic synthesis. While the intended catalytic transformations have yet to be realized, studies performed under the auspices of this grant have led to training of new synthetic chemists and have inspired investigations of new catalytic processes in the realm of other ongoing projects.