

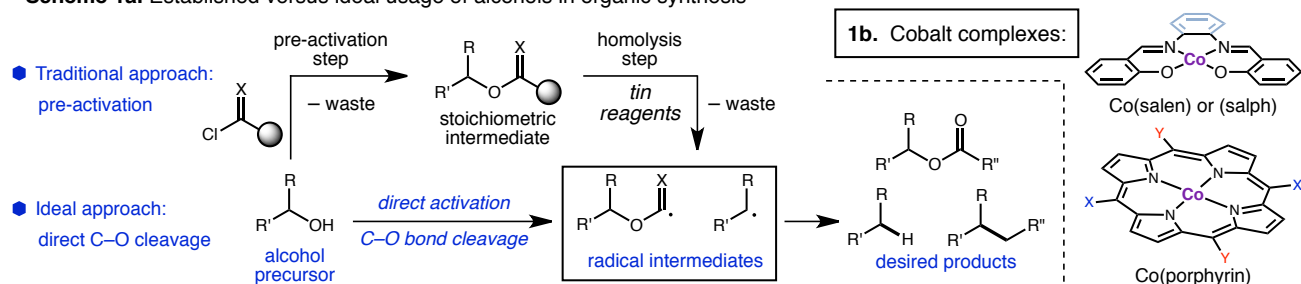
## Direct Radical Functionalization of Alcohols Using Cobalt Photocatalysis

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### Background

Alcohols are very important intermediates for the deployment of radical methods, from the Barton–McCombie deoxygenation reaction to complexity generating C–C bond forming reactions. The availability of cheap, abundant alcohol feedstocks suggests these methods should be a powerful solution for a variety of important chemical challenges. Unfortunately, radical methods nearly all rely on the pre-activation of the alcohol substrate, for example as an acyl selenide or thiocarbonyl derivative (e.g. xanthate), generating stoichiometric waste in both the activation step and the radical process (Scheme 1a). Acknowledging the tremendous power of these cornerstone strategies, a major goal of our research is to develop a general cobalt catalysis platform to generate carbon-centered radical intermediates directly from aliphatic alcohols. Cobalt complexes inspired by vitamin B<sub>12</sub> (Scheme 1b) are being explored for their ability to promote three key steps of this process: carbonylation, Co–C bond homolysis and turnover via redox chemistry or  $\beta$ -hydrogen elimination. Over the last 15 months, we have made significant progress in all three areas as described below.

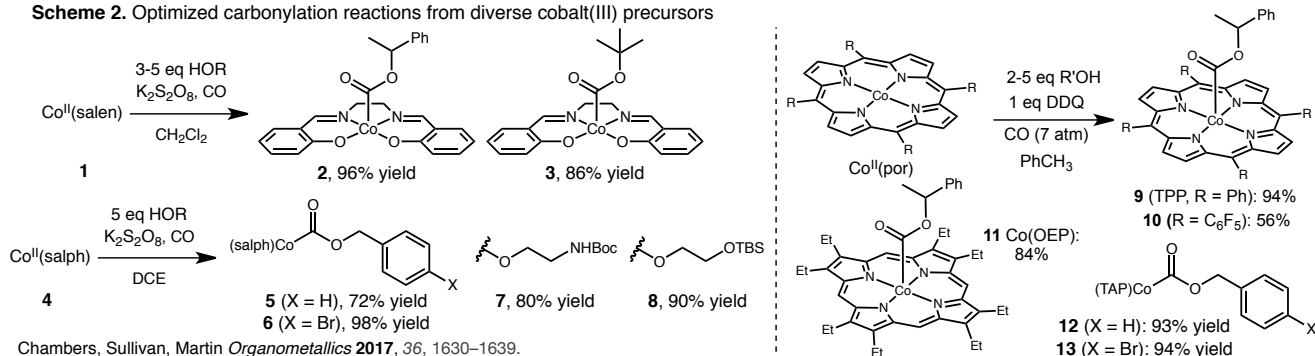
**Scheme 1a.** Established versus ideal usage of alcohols in organic synthesis



### Research Progress

We have developed an optimized synthesis of alkoxyacetyl-cobalt species from both Co(III) and Co(II) precursors, guided by an early report by Costa and Mestroni. Using salen and salph complexes, we could reduce the stoichiometry of the alcohol to 3–5 equivalents while maintaining the synthetic efficiency (Scheme 2, 80–98% yield). The mild conditions provide good to excellent yields across a broad range of 1°, 2° and 3° alcohol substrates and tolerate most common functional groups including alkenes, alkynes, arenes, halides, protected alcohols and protected amines. This functional group tolerance will be important for future catalytic methods with complex substrates. We have also incorporated <sup>13</sup>C-enriched CO and characterized three complexes crystallographically, securing the structure and bond metrics of these key intermediates. Recent follow-up studies with Co-porphyrin complexes have been similarly successful, tolerating diverse functional groups and achieving good yields across electron-rich and electron-deficient porphyrins.

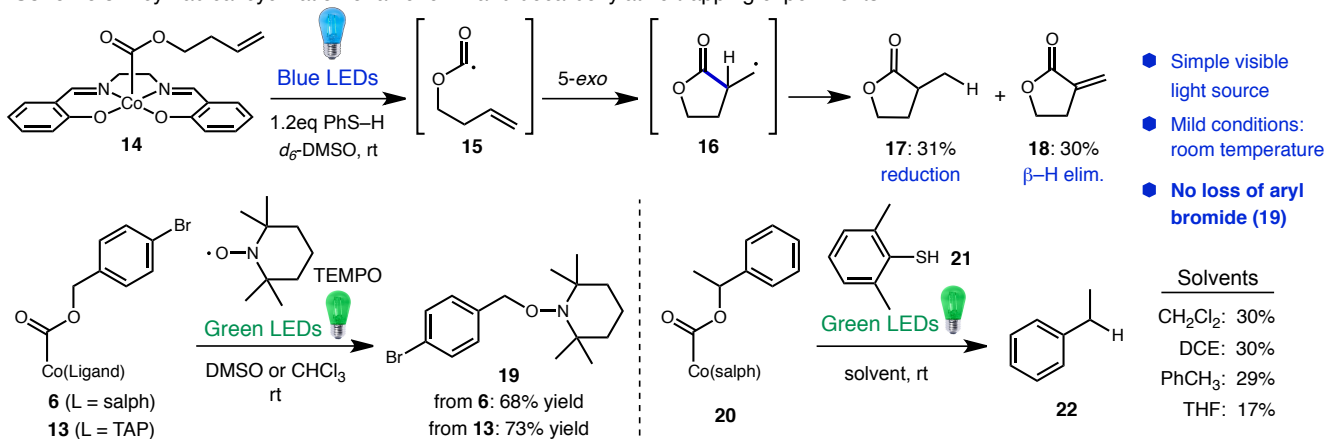
**Scheme 2.** Optimized carbonylation reactions from diverse cobalt(III) precursors



After carbonylation, the next key step of the proposed mechanistic pathway is photoexcitation and homolysis of the Co–C bond. We have performed irradiation experiments of several cobalt-salen and salph complexes, varying reaction solvent, temperature and light source (Scheme 3, top). Using blue LEDs as the light source ( $\lambda_{\text{max}} = 455 \text{ nm}$ ), irradiation of butenyloxyacetyl complex **14** (as well as the corresponding salph complex) in the presence of stoichiometric thiol results in saturated lactone **17** and substantial  $\alpha,\beta$ -unsaturated lactone **18**. Mechanistically speaking, homolysis should lead to acyl radical **15**, which undergoes 5-*exo*-trig cyclization to form primary radical **16**. Reduction of this radical by the thiol leads to

saturated lactone **17** while cobalt-mediated  $\beta$ -hydrogen elimination leads to unsaturated lactone **18** and a cobalt hydride. We are continuing to investigate the selectivity for these two pathways, both of which provide useful motifs found in a number of natural products.

**Scheme 3.** Acyl radical cyclization of alkene **14** and decarboxylative trapping experiments



We have also performed the irradiation of benzyloxycarbonyl complexes **6** and **13**, which readily undergo homolysis and decarboxylation with various light sources, including blue or green LEDs (Scheme 3, bottom). We have trapped the resulting radical with TEMPO to product *p*-bromobenzyl-TEMPO adduct **19** under mild conditions. Porphyrin derivative **13** also undergoes conversion to product **19** with no observable loss of the bromide. The compatibility with halides shows that cobalt-mediated radical chemistry will be orthogonal to traditional radical initiation methods and potentially complementary to other transition metal-catalyzed processes. Finally, irradiation of salph complex **20** in the presence of thiol **21** led to deoxygenated product **22** in a variety of solvents. While the yield of this reaction is low, it demonstrates most of the key steps of our proposed deoxygenation and paves the way for additional investigations of the critical turnover step.

### Impact:

The PRF DNI award has had a tremendously positive impact on Dr. Martin's career and the research and training of members of his research group. The resources provided by the PRF have been used to support graduate students and supply the lab with the necessary equipment and chemicals to perform the research studies described here. During the grant period, the funds have supported the professional development of graduate students and one post-doctoral scholar, including travel to local conferences in the area of organometallics and organic synthesis. The PRF has also supported travel for the PI to a Gordon Research Conference (2018 Organic Reactions and Processes) to present the research results of this work. The ongoing support of the PRF will enable the continued pursuit of our research objectives, the publication of important project outcomes and travel to conferences and workshops for students and the PI.