

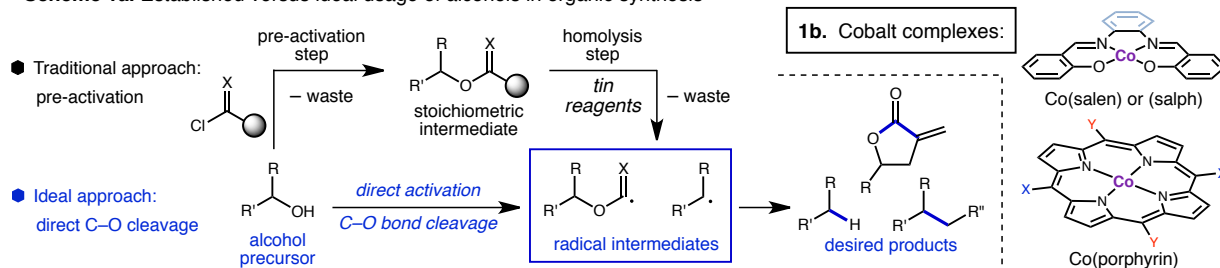
Direct Radical Functionalization of Alcohols Using Cobalt Photocatalysis

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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 B₁₂ (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 β -hydrogen elimination. Over the last 12 months, we have made significant progress in all three areas as described below.

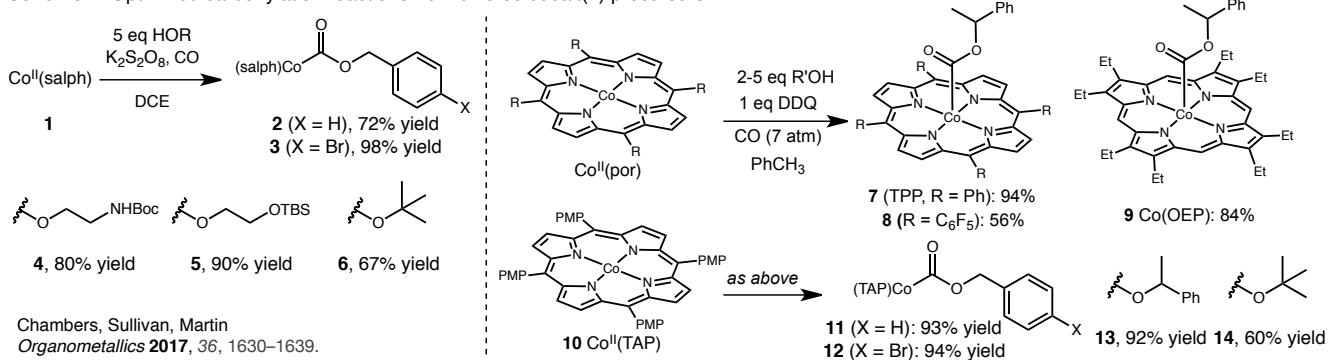
Scheme 1a. Established versus ideal usage of alcohols in organic synthesis



Research Progress

We have developed an optimized synthesis of alkoxy-carbonyl-cobalt species from both Co(III) and Co(II) precursors, guided by an early report by Costa and Mestroni. Previously, we reported a significantly improved method for the synthesis of alkoxy-carbonyl-cobalt products with salen and salph ligands, increasing the functional group tolerance and efficiency of the carbonylation process (Scheme 2, left: *Organometallics* 2017). Guided by follow-up experiments that determined porphyrins were a promising scaffold for subsequent chemistry, we expanded this methodology to provide access to a variety of porphyrin complexes (Scheme 2, right). The mild conditions provide good to excellent yields across a broad range of 1°, 2° and 3° alcohol substrates, tolerating a variety of common functional groups and achieving good yields across electron-rich and electron-deficient porphyrins. We successfully characterized one new porphyrin complex crystallographically (Figure 1, left), securing the structure and bond metrics of these key intermediates.

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



The C–Co bond dissociation energies (BDE) of a variety of *alkyl* cobalt complexes have been measured experimentally through the extensive studies of Halpern and others, and more recently DFT calculations have provided estimates for many more complexes. The C–Co BDEs for *alkoxy-carbonyl* complexes, on the other hand, have not been reported to the best of our knowledge. Working with our collaborator Prof. Mathieu Frenette at the Université du Québec à Montréal (UQAM), we performed DFT calculations to provide a predicted structure of complex **13**, which showed excellent overlap with the crystal structure (Figure 1, right) with a calculated C–Co bond length of 1.892 Å vs 1.906 Å in the crystal structure. We calculated complex **13**'s C–Co BDE using the BP86 functional that was found to correctly predict BDEs for alkyl C–Co BDEs, providing an estimate of 39.8 kcal/mol. This value is somewhat higher than earlier values for alkyl complexes. The details of these studies have been submitted for publication and are currently in revision.

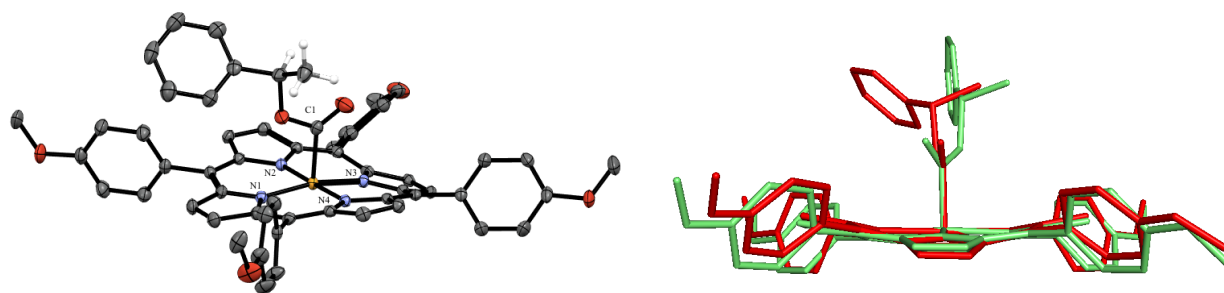
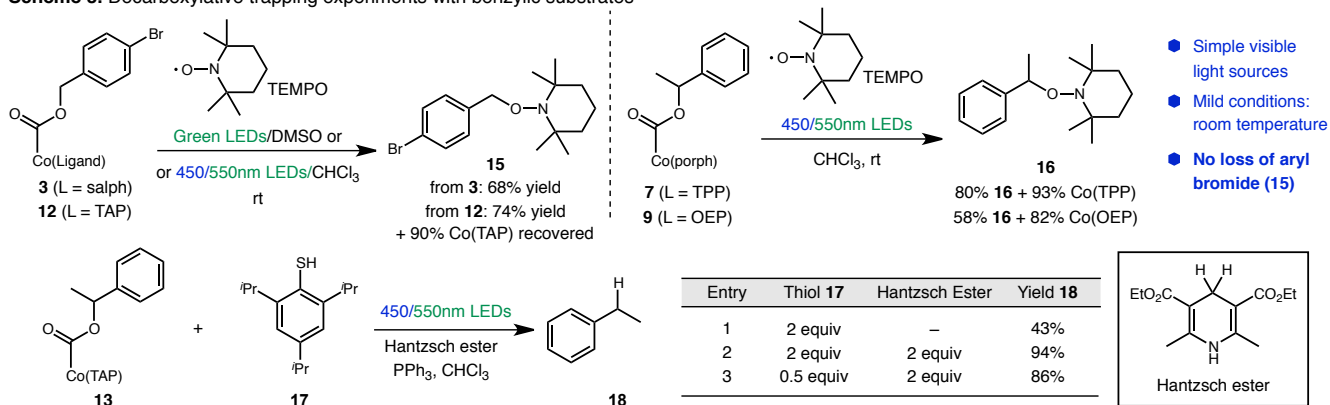


Figure 1. Left: X-ray crystal structure of **13** with thermal ellipsoids at the 50% probability level. The compound crystallizes as a racemate; only one enantiomer is shown for clarity. Co–C1 bond length = 1.906(2) Å. Right: Overlay of the optimized structure at the BP86/LanL2DZ level of theory (green) and X-ray crystal structure of compound **13** (red).

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, salph and porphyrin complexes, varying reaction solvent, temperature and light source. Compared to the salen and salph complexes previously explored, the porphyrin complexes provided superior yields of the TEMPO-trapped products (Scheme 3, top). Porphyrin derivative **12** undergoes conversion to product **15** 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. Furthermore, we were able to isolate the Co(II) porphyrin product in substantial yield (82–93% recovery), paving the way for reoxidation in a tandem or catalytic reaction manifold.

Scheme 3. Decarboxylative trapping experiments with benzylic substrates



Finally, irradiation of porphyrin complex **13** in the presence of H-atom donors led to deoxygenated product **18** in a variety of solvents (Scheme 3, bottom). Choosing an appropriate, hindered thiol increased the yield of ethyl benzene (Entry 1, 43% yield). Even with an excess of hindered thiol **17**, only moderate yields were achieved despite full consumption of thiol. We explored Hantzsch ester as a stoichiometric reducing agent to regenerate the thiol from the presumed thiyl radical. Gratifyingly, inclusion of Hantzsch ester increased the yield of ethyl benzene to 94% (Entry 2). Although Hantzsch ester was not effective in the absence of thiol (<5% yield), it allowed the H-atom donor to be reduced to sub-stoichiometric quantities, providing ethyl benzene in 86% yield (Entry 3). The success of these reactions 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 one graduate student and one post-doctoral researcher, as well as to supply researchers 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 two graduate students and one post-doctoral scholar, including supporting research presented at local conferences in the area of organometallics and organic synthesis. The first PhD graduate from the Martin lab carried out research supported by the PRF and completed her PhD in August 2019. Her most recent publication is in revisions and she has secured a post-doctoral research position. The PRF has also supported travel for the PI to the 2019 Pacific Symposium on Radical Chemistry to present the research results of this work. The support of the PRF greatly increased our ability to focus on generating new knowledge and key preliminary results to secure federal funding to support this project going forward. Overall, the impact of the PRF has been significant in the pursuit of our research objectives and will have a lasting impact on our success.