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2. Project Title: Photocatalytic Functionalization of Arenes and Alkenes Using Visible Light
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1) Synthesis of Aldehydes by Organocatalytic Formylation Reactions of Boronic Acids with Glyoxylic Acid.

With more than four thousand being commercially available, aryl boronic acids are one of the most versatile building blocks in organic synthesis. Notably, recent significant advance in borylation methods has made aryl boronic acids, particularly those that are heavily functionalized, more readily accessible. The unique reactivity of substances in this family has led to a myriad of carbon-carbon and carbon-heteroatom bond forming processes, which are difficult to carry out or show poor functional group tolerance and/or low efficiency when their halide counterparts are employed as substrates. These reactions, which include the introduction of oxygen, nitrogen, halogen, and alkyl, alkenyl, alkenyl and alkyl moieties, are generally accomplished using transition metal complexes. However, to the best of our knowledge, no examples of catalytic formylation reactions of arylboronic acids exist.

We report a conceptually novel organocatalytic strategy for formylation of boronic acids, in which a new reactivity is engineered into the α-amino acid forming Petasis reaction occurring between aryl boron acids, amines and glyoxylic acid (Scheme 1). The feasibility and preparative power of the protocol was demonstrated by its use to prepare aldehydes from broadly accessible aryl and alkenyl boronic acids, glyoxylic acid, and the cheap N-alkylaniline derivatives, tetrahydroquinoline and indoline, as catalysts. Furthermore, the operational simplicity of the process, which is performed by simply mixing these reagents under ambient conditions, and its ability to generate structurally diverse and valued aryl, heteroaryl and α,β-unsaturated aldehydes containing a wide array of functional groups, demonstrates the practical utility of the newly unveiled synthetic strategy.

Scheme 1. Amine catalyzed formylation reactions of boronic acids with glyoxylic acid.

C-Glycosyl amino acids are a unique class of compounds widely present in nature that have an enormously diverse array of biological properties. In routes developed to date for the synthesis of C-glycosyl amino acids, installation of an amino acid moiety onto a glycosyl framework has relied on the use of well-established α-amino acid synthesis strategies. As part of a recent program to develop radical based cross coupling processes for selective C-C bond formation, we envisaged that an open-shell pathway might be applicable to the concise synthesis of C-glycosyl amino acids under mild conditions. Specifically, we believed that addition of glycosyl radicals, generated from appropriate glycosyl precursors, to readily available α-imino esters would constitute a viable approach to the preparation of these substances. To our knowledge, a strategy of this type has not been documented previously.

In our recent investigation, we developed a direct photochemical process for preparation of C-glycosyl amino acid derivatives that utilizes readily available α-imino esters (Scheme 2). Differing from the role played by imines in typical photoredox catalyzed reactions, α-imino esters in the new process serve as electrophiles in reactions with in situ generated nucleophilic glycosyl radicals. Moreover, in the effort we demonstrated that glycosyl radicals can be generated using redox active esters (RAE) of saccharides, a new class of bench stable and readily prepared C-glycosylation reagents. Moreover, in the effort we demonstrated that glycosyl radicals can be generated using redox active esters (RAE) of saccharides, a new class of bench stable and readily prepared C-glycosylation reagents. As far as we are aware, this study represents the first case of the addition of RAE derived radicals to C=N rather than C=C bond. In addition, we showed that the process does not require use of an often expensive photosensitizer (PS), consistent with Melchiorre’s work. Instead, inexpensive Hantzsch ester (HE, ca. $0.071/mmol) can play the role of both a PS and hydrogen atom transfer donor in the new process. Finally, the preparative power of the new PS and metal free strategy is a consequence of the mildness of the conditions employed and its application to reactions of both armed and disarmed pentoses and hexoses, in which the integrities of preexisting anomeric carbons are preserved.


Selected examples:
3) Organocatalytic transformation of aldehydes to thioesters with visible light.

Thioesters are a class of compounds widely used in chemical and biological synthesis. Transition metals catalyzed processes represent the frontier in their synthesis. Organocatalysis for this process is also developed. However, stoichiometric radical initiators, or oxidants are essential for effective radical generation. Such a large amount of reagents particularly peroxides and the accumulation of in situ produced highly concentrated radicals often induce more side reactions and displays low functional tolerance, which are the main cause of low reaction efficiency in the acyl radical engaged processes.

We questioned whether use of visible light instead of oxidants as radical generation force could afford a milder, and more general and atom economical approach for the synthesis of thioesters. However, it is recognized that the development of photocatalytic thioesterification of aldehydes is particularly difficult because both aldehydes (reactants) and thioesters (products) are often used as acyl radical progenitors in photocatalytic acyl radical formation. The potential cross reactivity could significantly affect the process. The development of a photocatalytic system to selectively control their reactivities is vital. Toward this end, we have developed describe a metal free and oxidant free catalytic method of accessing structurally diverse thioesters from widespread aldehydes (Scheme 3). A strategy of a simple organic 9,10-phenanthrenequinone promoted hydrogen atom transfer (HAT) with visible light is successfully implemented to selectively generate acyl radicals without inducing crossover reactivity of the activation of thioester products. The preparative power of the method is demonstrated by broad substrate scope and wide functional group tolerance, and enables the late-stage modification of complex structures, which are difficult to achieve with the existing protocols.