INTRODUCTION

Initially envisioned by Brenner and Lerner,\textsuperscript{1} the use of DNA encoded libraries (DEL) is a powerful technology enabling the screening of small molecules on an unprecedented scale. Upon construction of vast chemical libraries using split and pool synthesis, millions or even billions of compounds can be evaluated in a single test tube against protein targets.\textsuperscript{2} Previously, DNA-templated synthesis sought to deconvolute combinatorial chemistry efforts,\textsuperscript{3} but recent advances in DEL have enabled researchers to identify single molecules out of a mixture of billions.\textsuperscript{2} This advance is made possible by unique DNA tags that record which building blocks are pieced together. Hits are identified by amplifying and sequencing the DNA tags. Hit compounds are then resynthesized using traditional methods to verify target affinity and are then used as lead compounds in medicinal chemistry campaigns. Generating compounds for DEL comes with a different set of challenges from traditional organic synthesis. Reactions such as amide bond formation, Suzuki coupling, and aldol additions are commonly utilized in DEL,\textsuperscript{4,5} but many organic reactions are not usable owing to harsh reaction conditions or incompatibility with aqueous environments. Thus, the development of DEL-compatible, or “on-DNA”, reactions is important for increasing library diversity, which will generate higher quality lead compounds for drug discovery efforts.

ON-DNA RADICAL ALKYATION OF ACRYLATES

Although radical intermediates participate in a wide variety of organic transformations, radical chemistry is generally avoided in DEL due to its perceived incompatibility with DNA. In a 2018 study, however, Baran and coworkers report the first radical-based synthesis in DEL, enabling the construction of highly important C(sp\textsuperscript{3})-C(sp\textsuperscript{3}) linkages on DNA.\textsuperscript{4} The authors apply Reaction Progress Kinetic Analysis to determine concentration driving forces and optimize the reaction for DEL conditions, presenting 22 examples with good yield (Scheme 1). The reported method requires careful control of oxygen to avoid hydroxylated side products.

**Scheme 1. On-DNA Decarboxylative Giese Reaction**

![Scheme 1. On-DNA Decarboxylative Giese Reaction](image)

ON-DNA PHOTOREDOX CATALYZED RADICAL ALKYATIONS

In 2019, Molander and coworkers further developed on-DNA radical reactions, reporting a Ni/photoredox C(sp\textsuperscript{2})-C(sp\textsuperscript{3}) cross coupling and the first on-DNA photoredox radical/polar crossover alkylation.
Both reactions are operationally simple and do not require air-free conditions. Both reactions do produce byproducts. Also, in the reported substrate scope, reaction conditions are modified for substrates, which may be unrealistic in split pool synthesis in which hundreds of substrates may react at once.

**Scheme 2. On-DNA Ni/Photoredox Cross Coupling and Radical/Polar Crossover**

**NEAR-ANHYDROUS ON-DNA REACTIONS**

In 2019, Baran, Dawson, and coworkers use the Reversible Adsorption to Solid Support approach to bind DEL compounds to an inert quaternary ammonium resin, enabling on-DNA reactions to take place in near anhydrous organic solvent, eliminating the need for time-consuming and tedious translation of organic reactions to DEL-type aqueous conditions. Using this method, the authors expand on Molander’s Ni/photoredox reaction by utilizing unstabilized radical intermediates. Additionally, the method enables an unprecedented on-DNA electrochemical amination and an improved reductive amination.

**REFERENCES**


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