With Covid-19 mRNA vaccines, the demand on oligonucleotides has never been greater. The challenges faced by the pharmaceutical industry have been numerous. First, there was the development of the vaccine, then came its mass production, and the inherent chemical instability of RNA species. Crucially, the manufacturing of these materials is complex and overly wasteful. Yet, alternative approaches to the preparation of nucleoside and nucleotide building blocks and their incorporation into oligonucleotides can be envisaged, starting with improved methods to generate and activate phosphorous reagents under non-rigorous conditions. This seminar will highlight how a combination of mechanochemistry and ionic liquids can greatly change reaction outcomes and efficacy for the generation of oligonucleotides as long as the right questions are being asked during the method development.