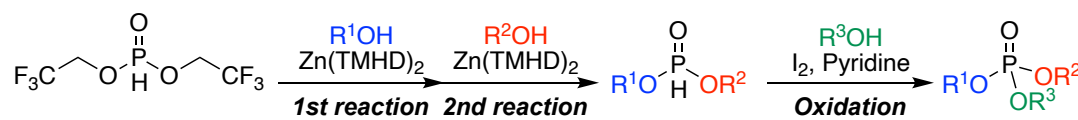


One-pot Catalytic Reactions of Phosphite Diesters toward the Synthesis of Oligonucleotides

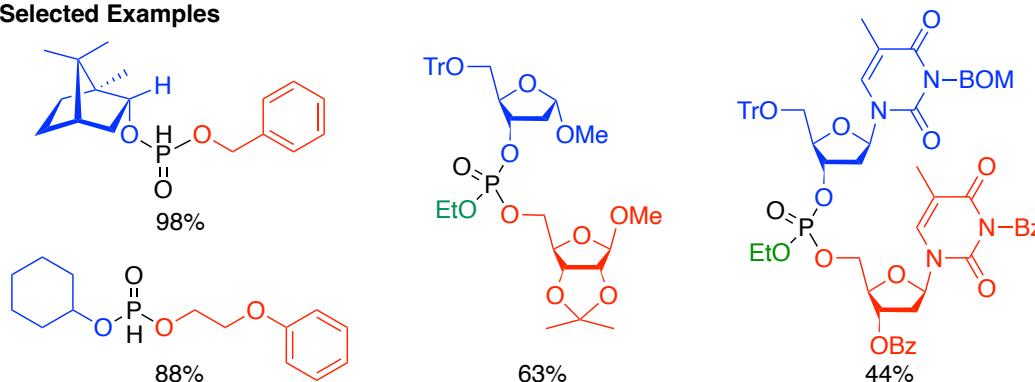
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Keywords: One-pot Synthesis; Phosphite Diester; Zinc Catalyst; Transesterification; Oligonucleotide

Organophosphates play vital roles in various fields, ranging from biology to material science. In particular, oligonucleotide therapeutics have gained a significant attention as promising novel therapeutic modalities due to their high specificity and potential application in treating incurable diseases. Solid-phase phosphoramidite reactions have commonly been the method of choice for oligonucleotide synthesis, offering high reliability.¹ However, this method suffers from requiring excessive amounts of activating reagents. To address this limitation, our laboratory previously reported a zinc-catalyzed synthesis of phosphite diesters under mild conditions.² Despite making significant progress, this approach still possess several limitations; for example, a need for the addition of molecular sieves and a reduction in selectivity for the second phosphorylation step. In this study, we discovered that changing the leaving group from a methoxy group to a 2,2,2-trifluoroethoxy group enabled the desired reaction to proceed with excellent reactivity and selectivity in the absence of molecular sieves. This approach enabled synthesis of asymmetric phosphite diesters in a one-pot manner by using various simple alcohols as nucleophiles. Furthermore, by carefully controlling solvent and temperature, this method proved successful with substrates such as carbohydrates and nucleosides, which possess sterically hindered structures and multiple Lewis basic functional groups. Finally, the obtained phosphite diesters could be readily converted to stable phosphate triesters via oxidative conversion.



Selected Examples



(1) Caruthers, M. H. *Science* **1985**, *230*, 281.

(2) Saito, Y.; Cho, S. M.; Danieli, L. A.; Kobayashi, S. *Org. Lett.* **2020**, *22*, 3171.