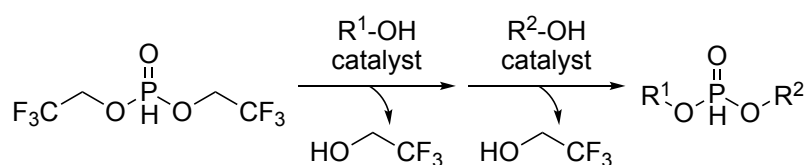


Catalytic Phosphonylation of Alcohols with Bis(2,2,2-trifluoroethyl) Phosphite for the Synthesis of Phosphite Diesters

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Phosphite diesters, a class of organophosphorus compounds, find diverse applications. They serve as key intermediates in the synthesis of organophosphonates, -phosphoramidates and -phosphates, which have garnered attention for their biological activities and medicinal chemistry relevance. Efficient synthesis of phosphite diesters is crucial for advancing the synthesis of P(V) compounds and expanding the scope of phosphorus chemistry. While traditional methods like phosphoramidite and H-phosphonate approaches are well-established, they suffer from drawbacks like excess substrate/reagent usage and dependence on additives. Catalytic and additive-free phosphorylation methods using P(V) reagents often require harsh conditions or are limited to monoesters. Therefore, development of a catalytic approach for additive-free synthesis of organophosphite diesters under mild conditions with minimal waste is a more sustainable alternative. Our group previously reported the use of dimethyl phosphite as a phosphonylating reagent to form phosphite diesters with various alcohols using a Zn catalyst.^[1] Expanding this convenient approach using Zn(II) catalysis to a one-pot synthesis of phosphite diesters utilizing bis(2,2,2-trifluoroethyl) phosphite as the P(III) reagent revealed selectivity issues for challenging substrates. This led us to investigate the metal effect in Lewis acid catalysts, revealing that four metals, Zn(II), Hf(IV), Zr(IV) and Al(III), efficiently catalyzed the phosphonylation of various alcohols and diols. Notably, Hf(IV) and Zr(IV) displayed superior selectivity compared to Zn(II). Further exploration into organocatalysts identified several Lewis base catalysts, particularly imidazole-type ones, with remarkable activity in promoting alcohol phosphonylation.



[1] Y. Saito, S. M. Cho, L. A. Danieli, S. Kobayashi, *Org. Lett.* **2020**, 22, 3171-3175.