Direct Access to unique C-5'-acyl modified nucleosides through a Pd-catalyzed Cu(I)-mediated thioester-boronic acid coupling

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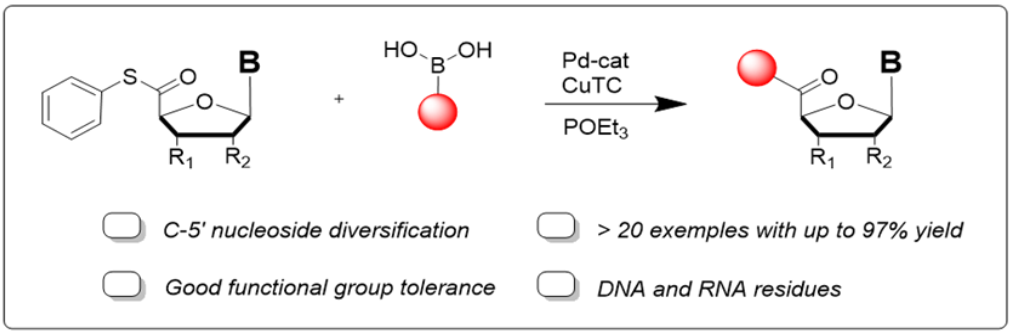
While sugar modifications on C-1', C-2' and C-3' positions in nucleosides have been widely studied and have resulted in several active antiviral,[1] antibacterial[2] and antitumoral[3] compounds, the functionalization of the C-5' position has been neglected and initially avoided due to the importance of the 5'-OH position for nucleoside incorporation[2c] into DNA and RNA. However, the C-5' position offers the potential uncovering of novel biological activities. In the context of the COVID-19 pandemic, the importance and appeal of finding new biologically active nucleosides has grown.

Herein, we describe a straightforward cross-coupling reaction between nucleoside 5'-carbothioates with boronic acids (also known as the Liebeskind-Srogl reaction) for the preparation of C-5' acyl nucleosides.[4] The procedure is rapid, efficient and orthogonal to a wide variety of functional groups due to its mild, baseless, conditions. All of these qualities enable the diversification of the C-5' position which was successfully implemented on pyrimidine nucleosides in both DNA and RNA series, producing a wide-ranging substrate scope containing more than 25 examples with good to excellent isolated yields[5].

This Pd-catalyzed, copper-mediated cross-coupling provides a convenient and direct approach for the preparation of a distinct library of potentially bioactive modified nucleosides. Additional transformation is possible through the conversion of the C-5' ketone, such as reduction to a 5'-alcohol, leading to preparation of corresponding phosphoramidites and their incorporation into oligonucleotides.



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