Protecting-group-free phosphate cross-coupling enables efficient synthesis of ADP-ribose molecules

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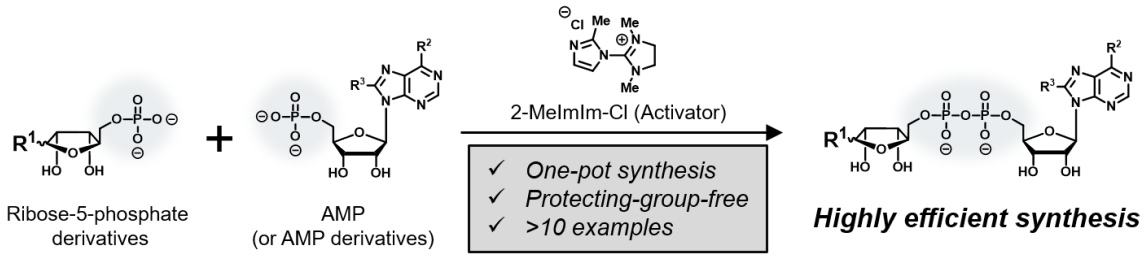
ADP-ribosylation, one of post-translational modifications (PTMs), is a reaction that transfers ADP-ribose moiety from NAD^+ to specific amino acid residues. This PTM plays an important role in a variety of cellular processes including DNA repair, signal transduction, transcriptional regulation, cell differentiation and apoptosis [1]. Its biological importance has widely been investigated but detailed functions of ADP-ribosylation remain poorly understood. The main difficulty in the molecular level research is to obtain homogeneous ADP-ribosylated samples from nature. Therefore, chemical synthesis is highly demanded.

In this study, we present an efficient method for chemical synthesis of diverse ADP-ribose derivatives through pyrophosphate formation by protecting-group-free phosphate cross-coupling reaction. We used 2-MeImIm-Cl, a hydroylsis stabilized ImIm-Cl [2], to activate a phosphate group by introducing an 2-methylimidazole leaving group for the phosphate cross-coupling reaction.

After chemoselective activation of the phosphate group of AMP (or derivatives) with 2-MeImIm-Cl, protecting-group-free phosphate cross-coupling reaction with various ribose-5-phosphate derivatives allowed for highly efficient synthesis of various ADP-ribose derivatives. Furthermore, we developed a method for the synthesis of ADP-ribose *N*-glycoside using stereoselective amidation reaction by traceless Staudinger ligation [3] with an azido analog of ADP-ribose.



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