

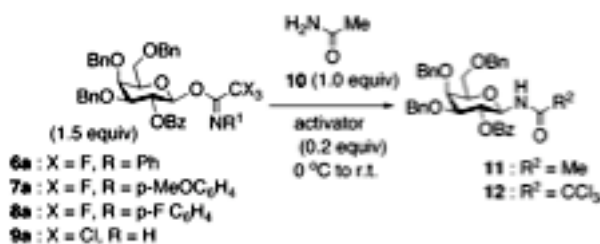
Title: Efficient Stereoselective Synthesis of γ -N-Glycosyl Asparagines by N-Glycosylation of Primary Amide Groups
Authors: H. Tanaka, Y. Iwata, D. Takahashi, M. Adachi, T. Tahahashi*
Affiliation: Tokyo Institute of Technology, Tokyo, JAPAN
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N-glycosyl asparagines are a common and important post-translational modification of proteins. Although a range of enzymes catalyze the attachment of a carbohydrate moiety to a free asparagine, there are no synthetic methods for the direct coupling of an asparagine side chain (an amide) to a glycosyl donor.¹ This lack of an efficient synthetic method stems from the poor nucleophilicity of the amide nitrogen, coupled with the propensity of amide to react with electrophiles via the amide oxygen.

Takahashi et al. offer have developed the first method for the direct N-glycosylation of primary amides, including asparagine containing peptide models. While a combination of trichloroimidates in the presence of TMSOTf as a catalytic activator provide the desired product, the reactions were low yield and complicated by glycosylation of the the trichloroacetamide produced during the reaction. A screen of designed activating groups led to the identification of beta-N-phenyltrifluoroacetimidates as ideal glycosyl donors, providing a model N-glycosyl amide in good yield (Scheme 1). Typical reaction conditions involved treatment of 1.5 equiv of glycosyl b-N-phenyltrifluoroacetimidate with 0.2 equiv TMSOTf and 1.0 equiv of the primary amide in CH₃NO₂ at 0° C, followed by warming to rt. The procedure provided the products in good yield and excellent stereoselectivity at the anomeric position. A variety of protected glycosyl donors were coupled to model mono- and di-asparagines dipeptides in 31–99 % yield. Unfortunately, the use of a tripeptide model negatively impacted the reaction outcome, possibly due to the poor solubility of the tripeptide in organic solvents.

This chemistry has immediate applications for the synthesis of N-glycosyl asparagine monomers for incorporation into larger peptides. Further improvements may allow it to be used to directly glycosylate larger peptide fragments. The resulting glycopeptides will serve as key substrates for ongoing investigations into biological processes, including intracellular protein trafficking.²

Scheme 1



(1) For a review of glycosyl donors, see: Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem. Int. Ed.* **2001**, *46*, 1576–1624.

(2) For reviews of biological activities of N-linked glycoproteins, see: (a) Röhr, J. *Chem. Rev.* **2002**, *102*, 285-303. (b) Bertozzi, C.R.; Kiessling, L. L. *Science* **2001**, *291*, 2357–2364.