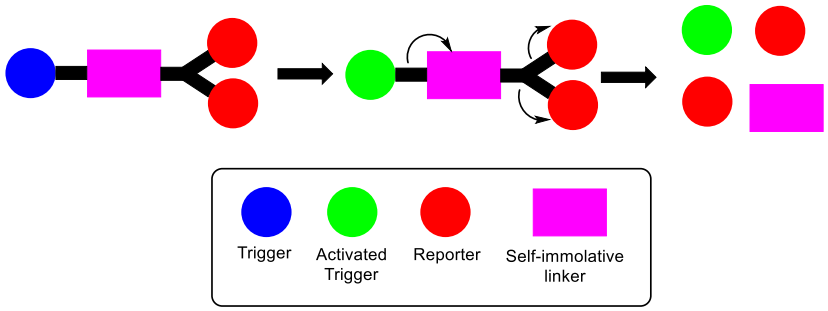
Self-immolative and traceless linker for amino acids

Maël Djaïd, Christian G. Bochet*

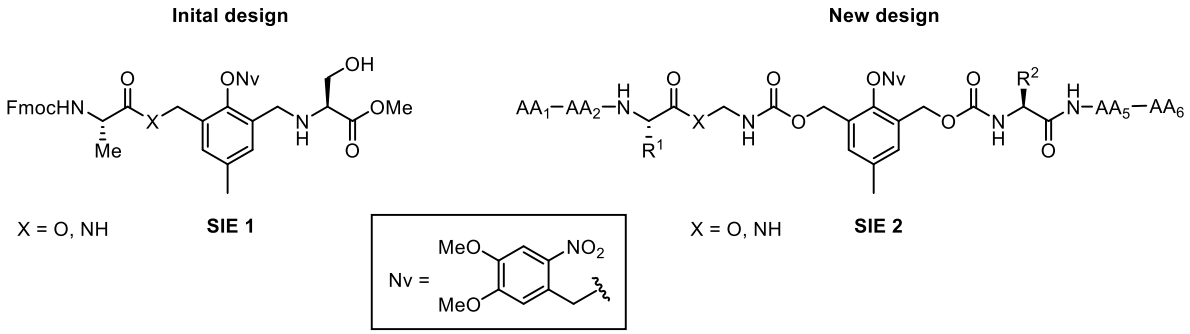
Department of Chemistry, University of Fribourg, Chemin du Musée 9, Fribourg, Switzerland
mael.djaid@unifr.ch

Self-immolative entities (SIE) are covalent assemblies (small molecule, polymer, dendrimer) designed to correlate the cleavage of two bonds between a protecting group (trigger) and a compound of interest (reporter) in response to a specific stimulus (pH, temperature, redox, light…) (Scheme 1). They have found plenty of applications especially for drug delivery systems and polymer chemistry.[1]



Scheme 1: General structure of self-immolative entity (SIE) with two reporters.

The goal of this project is to design a traceless photoremovable self-immolative linker for amino acids (Scheme 2). The designed linker should be capable to bind two peptide fragments and then release them upon activation with a specific stimulus (although photochemistry will be mainly used this could be, in principle, any reaction able to uncover a phenol). To be useful in real biological applications, the two fragments need to be liberated from complementary termini (*N* and *C*) and the introduction of the linker needs to be compatible with automated solid-phase peptide synthesis (SPPS). Starting from *p*-Cresol, the initial target **SIE 1** was synthetized and irradiated at 365 nm. Irradiation was followed by ESI-MS to seek for the expected mass peaks but unfortunately the release of the attached amino acids was inefficient. The most intense peak was the one from unprotected **SIE 1**. The mass peak of serine methyl ester (*N*-terminus) could be observed along with the corresponding moiety suggesting that some release was done but possibly via a side reaction of the photodeprotection of nitroveratryl rather than self-immolation of unprotected phenol. This hypothesis is currently under investigation. A new SIE based on the self-immolation of carbamates and amino/alkoxy methyl carbamate to release amine (*N*-terminus) and carboxylic acid or amide (*C*-terminus) respectively was designed **SIE 2**.



Scheme 2: Initial and new targeted self-immolative entites.

[1] R. V. Gonzaga, L. A. do Nascimento, S. S. Santos, B. A. Machado Sanches, J. Giarolla, E. I. Ferreira, *J. Pharm. Sci*., **2020**, *109*, 3262−3281.