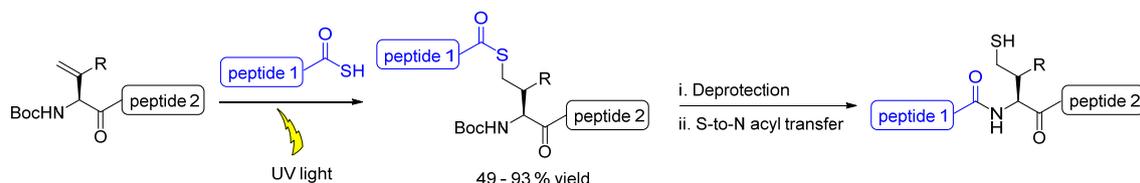


DEVELOPMENT OF NOVEL THIOL-ENE MEDIATED PEPTIDE LIGATION STRATEGIES

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Chemical ligation methodologies provide access to protein targets by ligating shorter peptide fragments in a chemoselective manner. Native Chemical Ligation (NCL) introduced by Kent and co-worker in 1994 offers an efficient ligation methodology.^[1] However, NCL is limited to cysteine containing ligation sites and the crucial thioester forming step can be slow and low yielding, in particular for sterically constrained ligations. This work concerns the development of a novel radical mediated acyl thiol-ene methodology enabling the rapid formation of peptidyl thioesters for peptide ligation. Subsequent desulfurisation/methylation forges the native protein target.



In order to form 6-membered cyclic transition states that undergo rapid acyl transfer^[2], β,γ -unsaturated amino acids β,γ -dehydrovaline and vinylglycine were synthesized and investigated as thiol-ene acceptors. A radical mediated acyl thiol-ene reaction resulted in the fast formation of the corresponding thioesters in good yields.

As a proof of concept, these results highlight the efficiency of the novel acyl thiol-ene reaction in the rapid formation of thioesters. Investigation into larger peptidic examples is ongoing to demonstrate the application of this methodology to peptide ligation.

[1] P. E. Dawson, T. W. Muir, I. Clark-Lewis, S. B. Kent, *Science*. **1994**, 266 (5186), 776.

[2] H. M. Burke, L. McSweeney, E. M. Scanlan, *Nature Communications*. **2017**, 8, 15655.