

# Development of methodology for late-stage acylation of threonine residue enabled by chemoselective acyl transfer followed by desulfurization

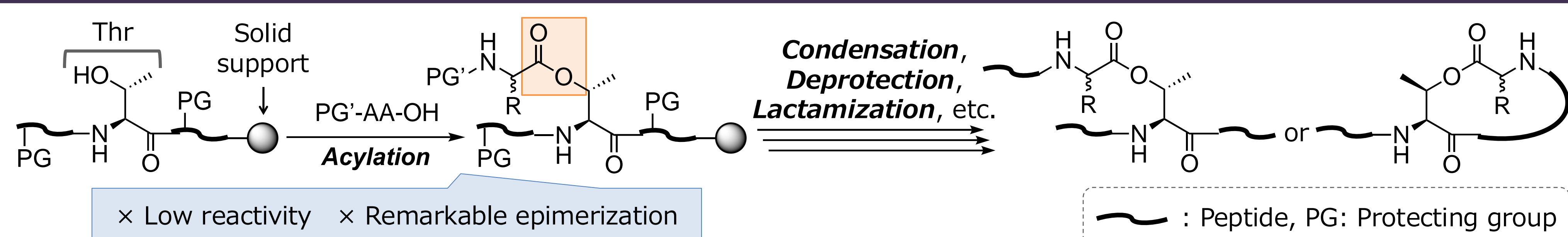
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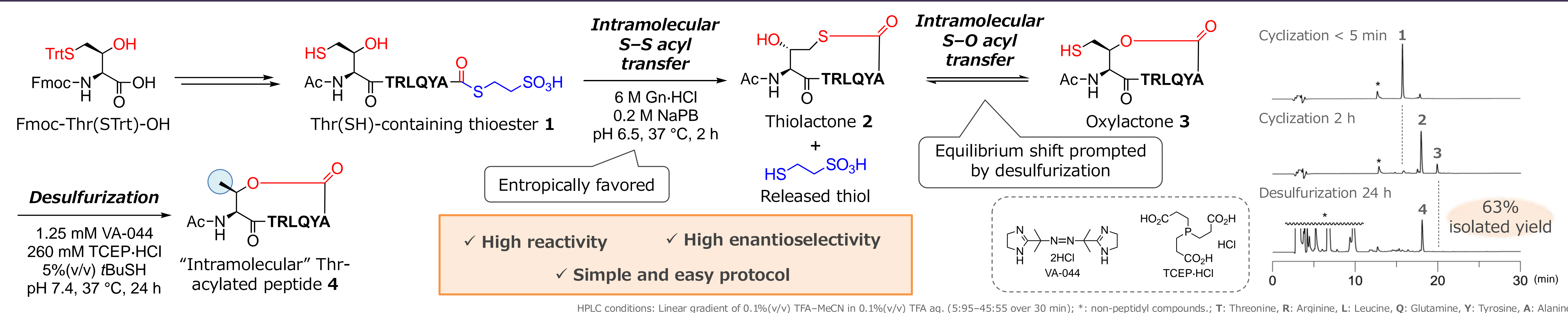
## 1. Background

Construction of ester linkage between threonine (Thr) hydroxyl side chain and carboxylic acid has been a synthetic challenge and would be useful for syntheses of both druggable peptides and function-unknown proteins. However, the low nucleophilicity of Thr hydroxy group has prevented a development of efficient acylation protocol.

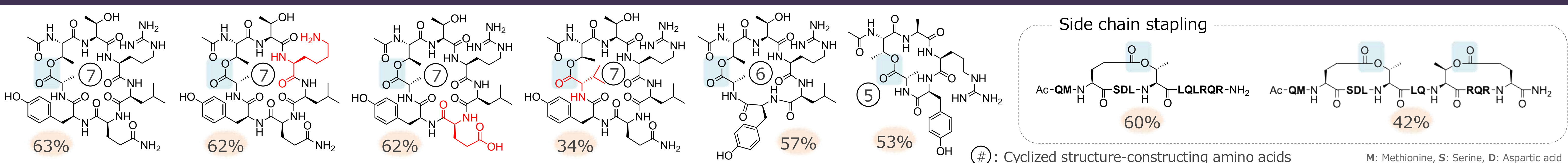
## 2. Conventional acylation method<sup>[2]</sup>



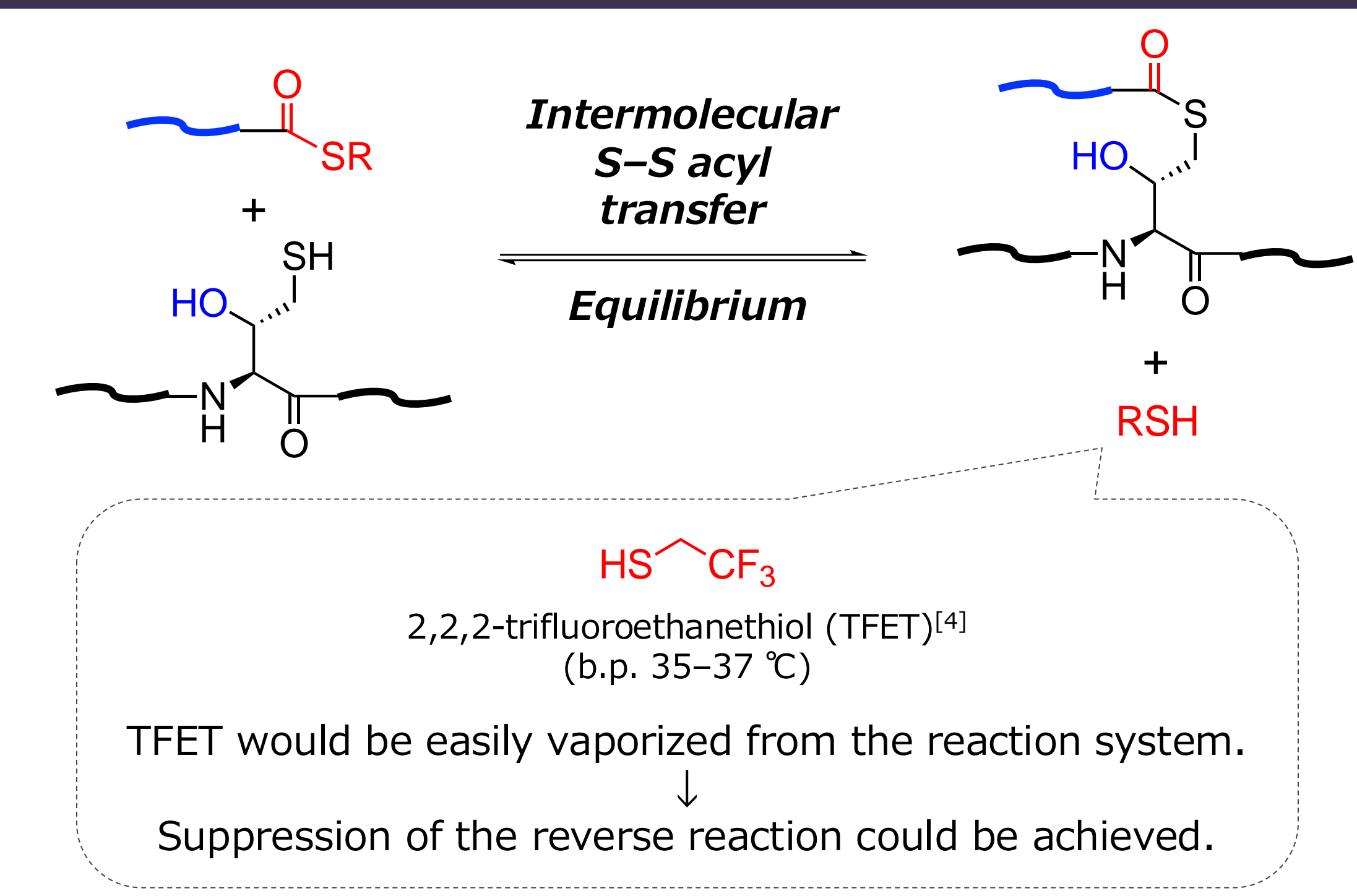
## 3. "Intramolecular" acylation of Thr using thiol-incorporated threonine derivative (Thr(SH))<sup>[3]</sup>



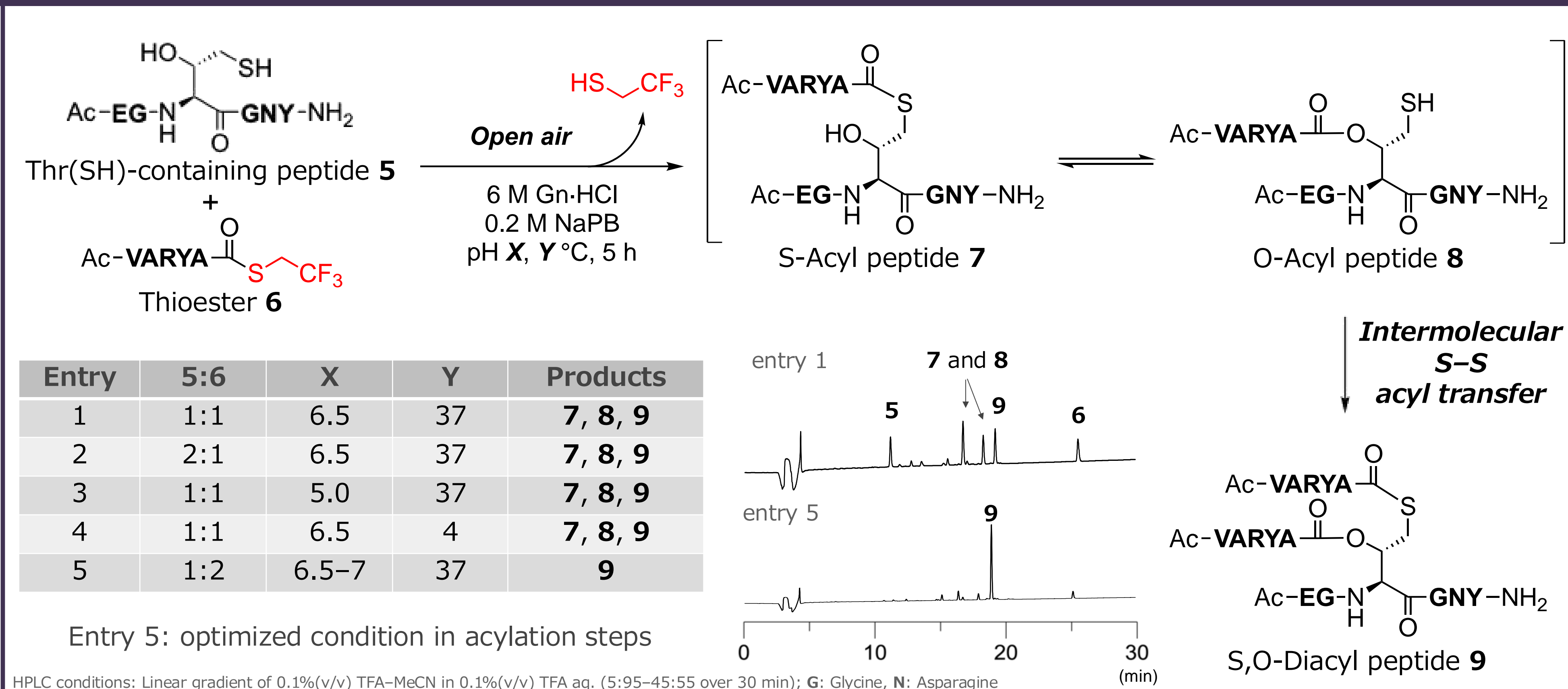
## 4. Scope of the developed intramolecular acylation



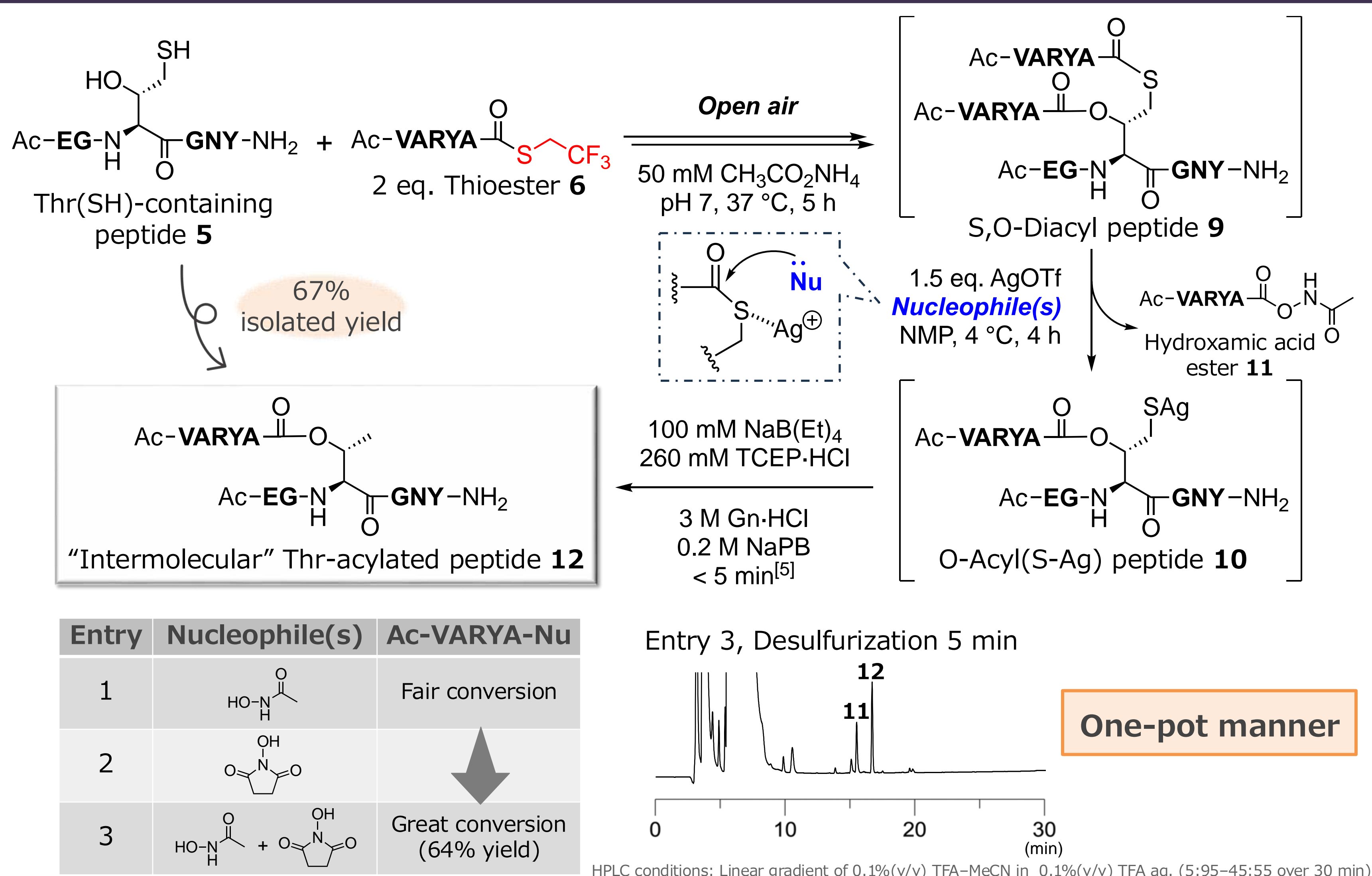
## 5. Strategy for accelerating entropically disfavored intermolecular S-S acyl transfer



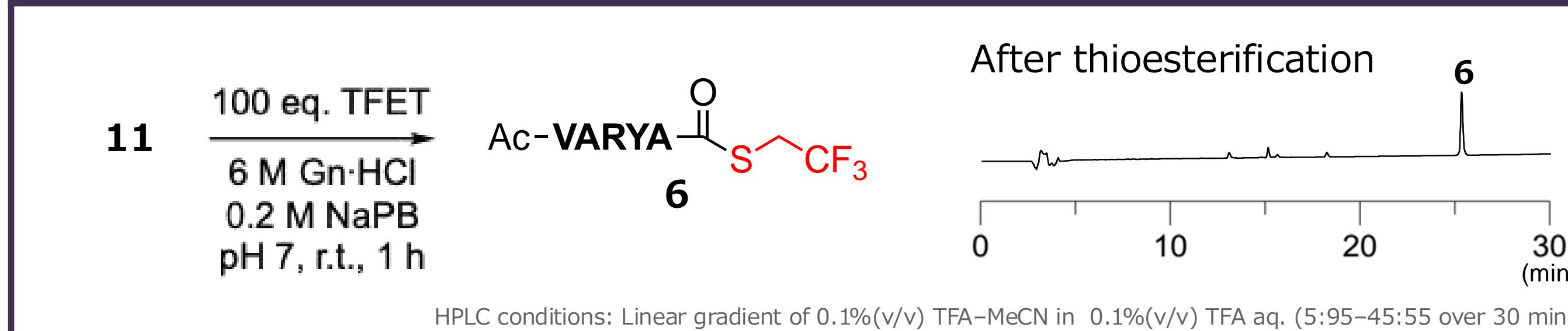
## 6. Optimization of reaction conditions (acylation steps)



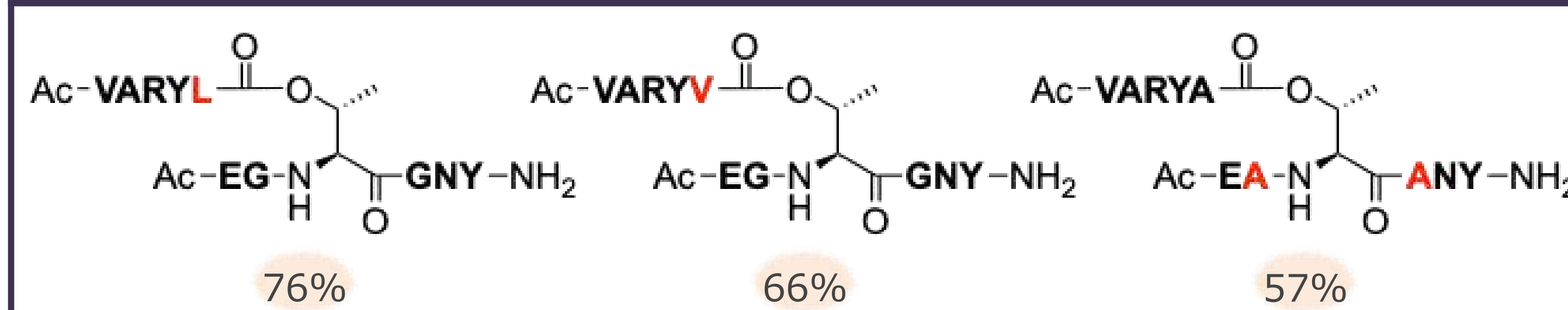
## 7. Optimization of reaction conditions (deacylation-desulfurization steps)



## 8. Recover of the substrate



## 9. Scope of the intermolecular Thr acylation



## 10. Conclusion

We developed an unprecedented late-stage Thr O-acylation protocol using sequential acyl transfers-desulfurization. The thiol unit on the Thr derivative allows for the facile derivatization of an acyl moiety on the low nucleophilic neighboring hydroxy group. Developed protocol features high acylation efficiency and enantioselectivity. We next plan to synthesize ubiquitinated protein using developed protocol.

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