# Synthesis and Evaluation of Removable Acyl Transfer Auxiliaries for Extended Chemical Ligation

Donncha Ó Cearbhaill

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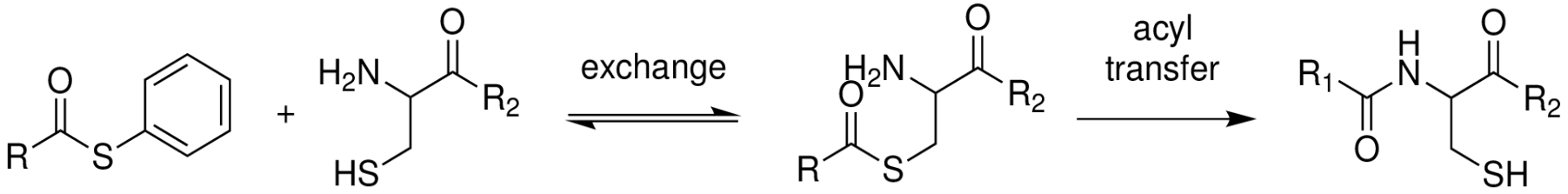
# Native Chemical Ligation

- Excellent method of joining peptide fragments.
- Requirement for a cysteine residue on the N-terminal peptide.

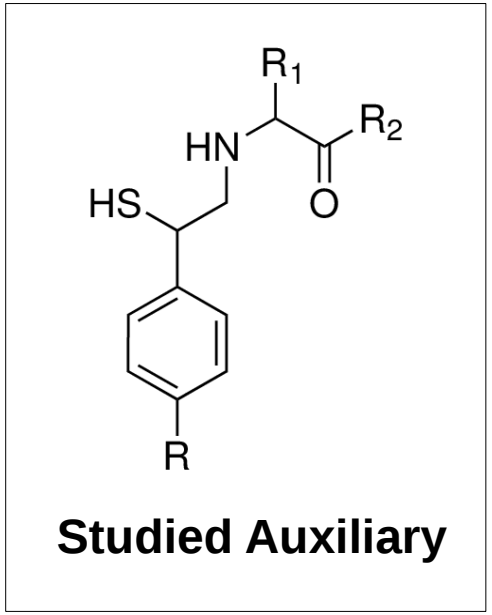


# Auxiliary Mediated Ligation

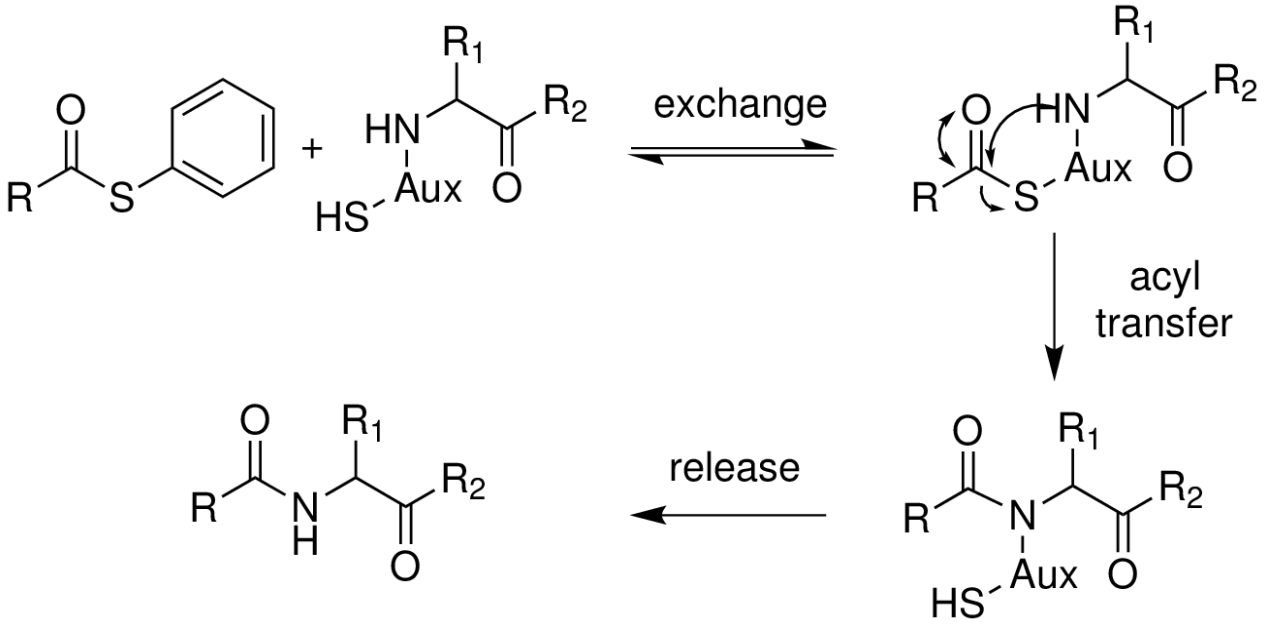
Facilitates ligation at cysteine-free junctions.

Criteria for a synthetically useful ligation auxiliary:

- - **Introducible** to an N-terminal peptide on solid support.
- - **Ligation** facilitated at low peptide concentrations.
- - **Removable** selectively to provide a native peptide

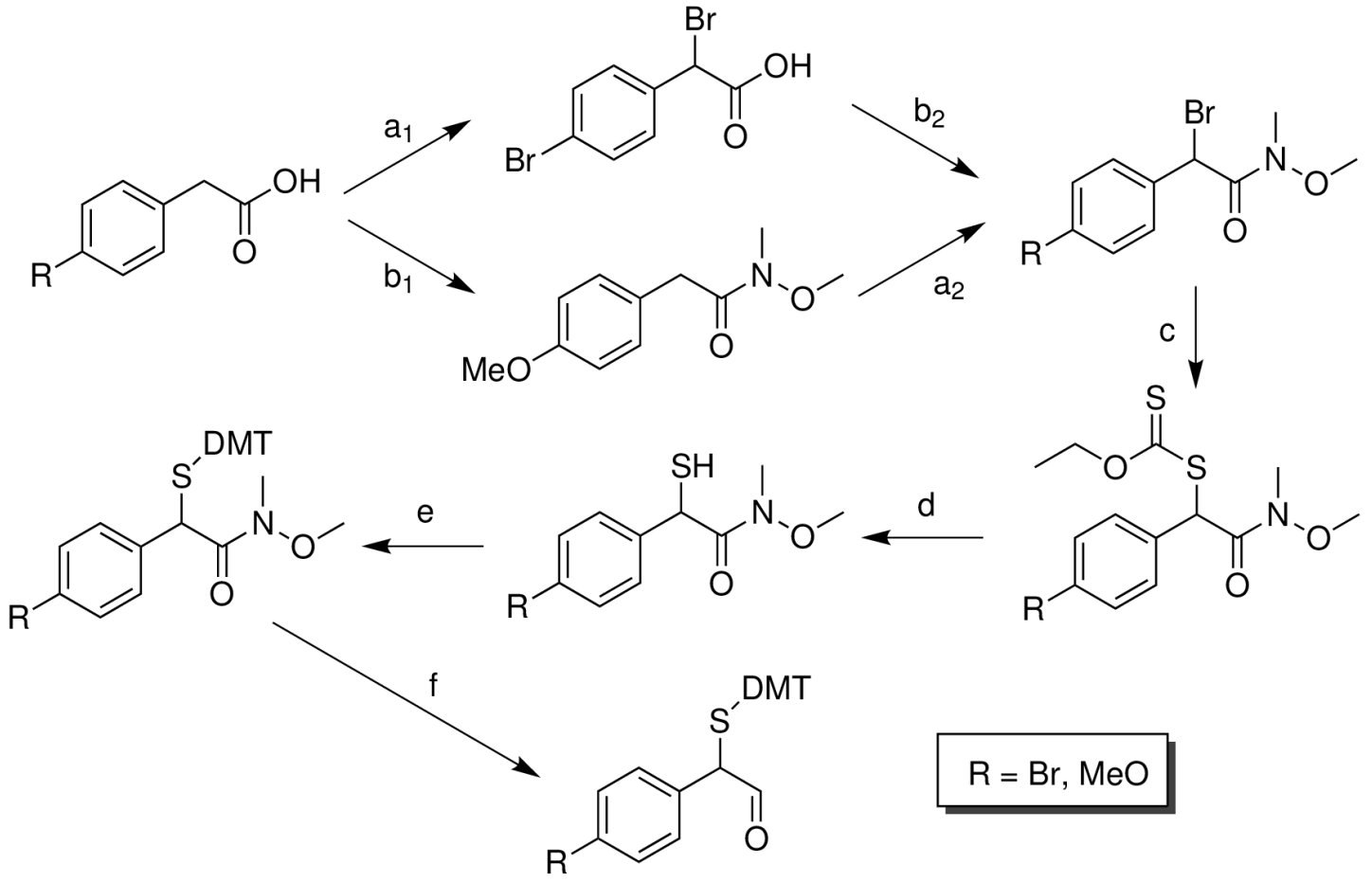



**Studied Auxiliary**



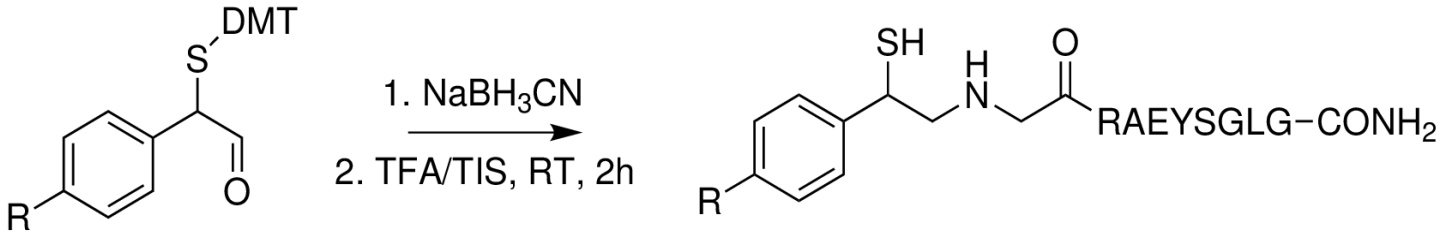
# Auxiliary Synthesis

Two ligation auxiliaries synthesized by a 6 step route with good yields overall (R=Br, 12%; R=MeO, 18%).

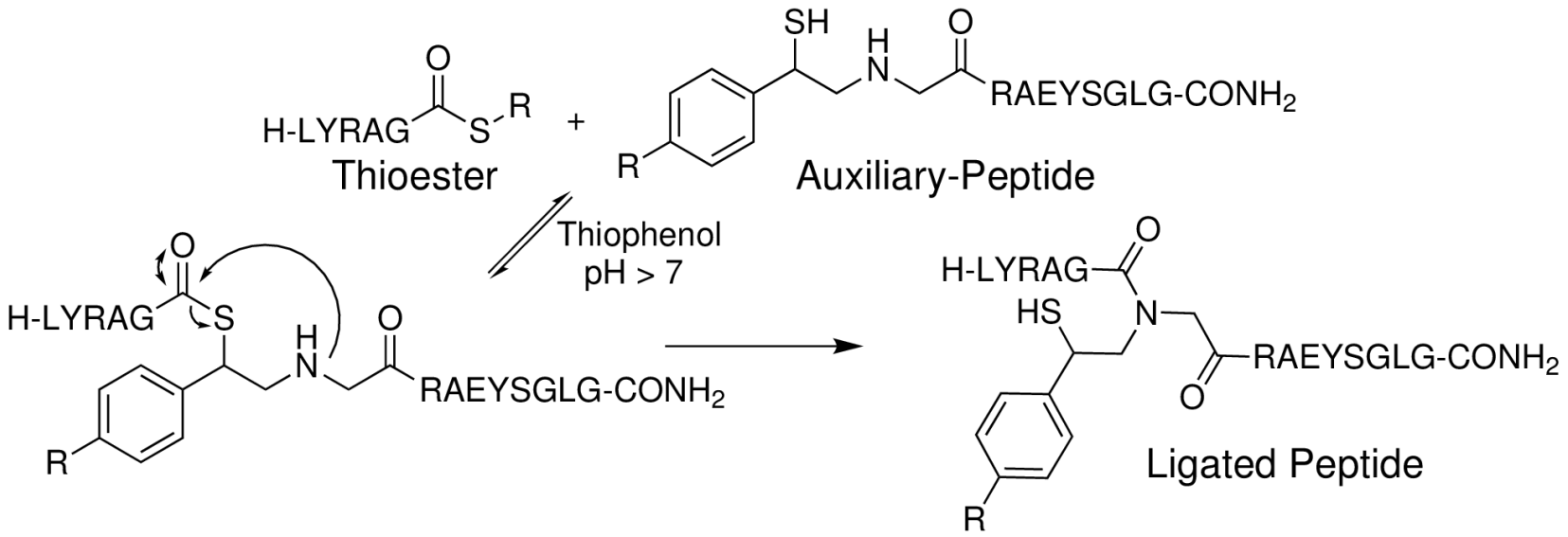


# Auxiliary Introduction and Ligation

- Both auxiliaries **introduced** to a model peptide

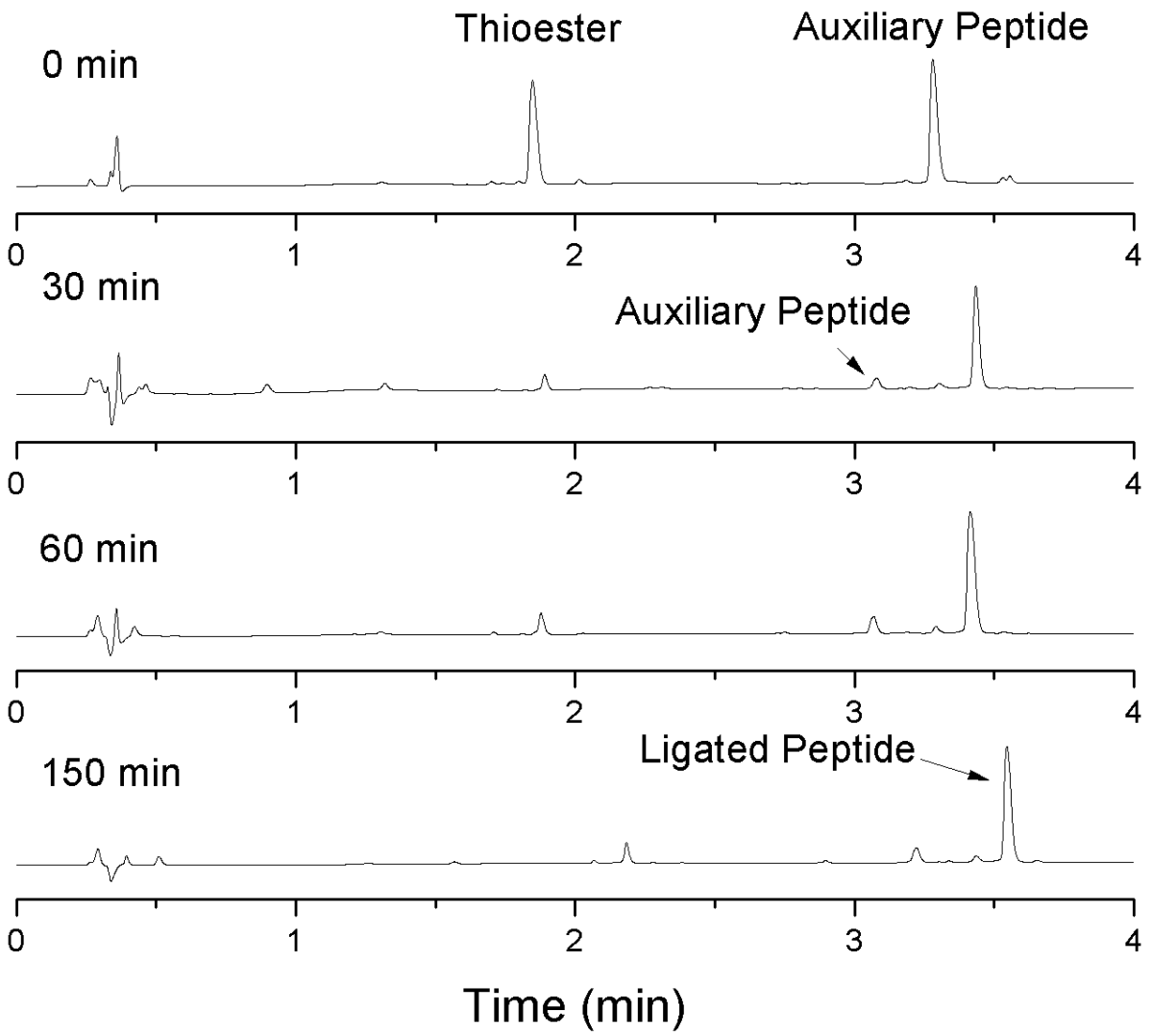



- Auxiliary-peptide **ligated** with peptide thioester

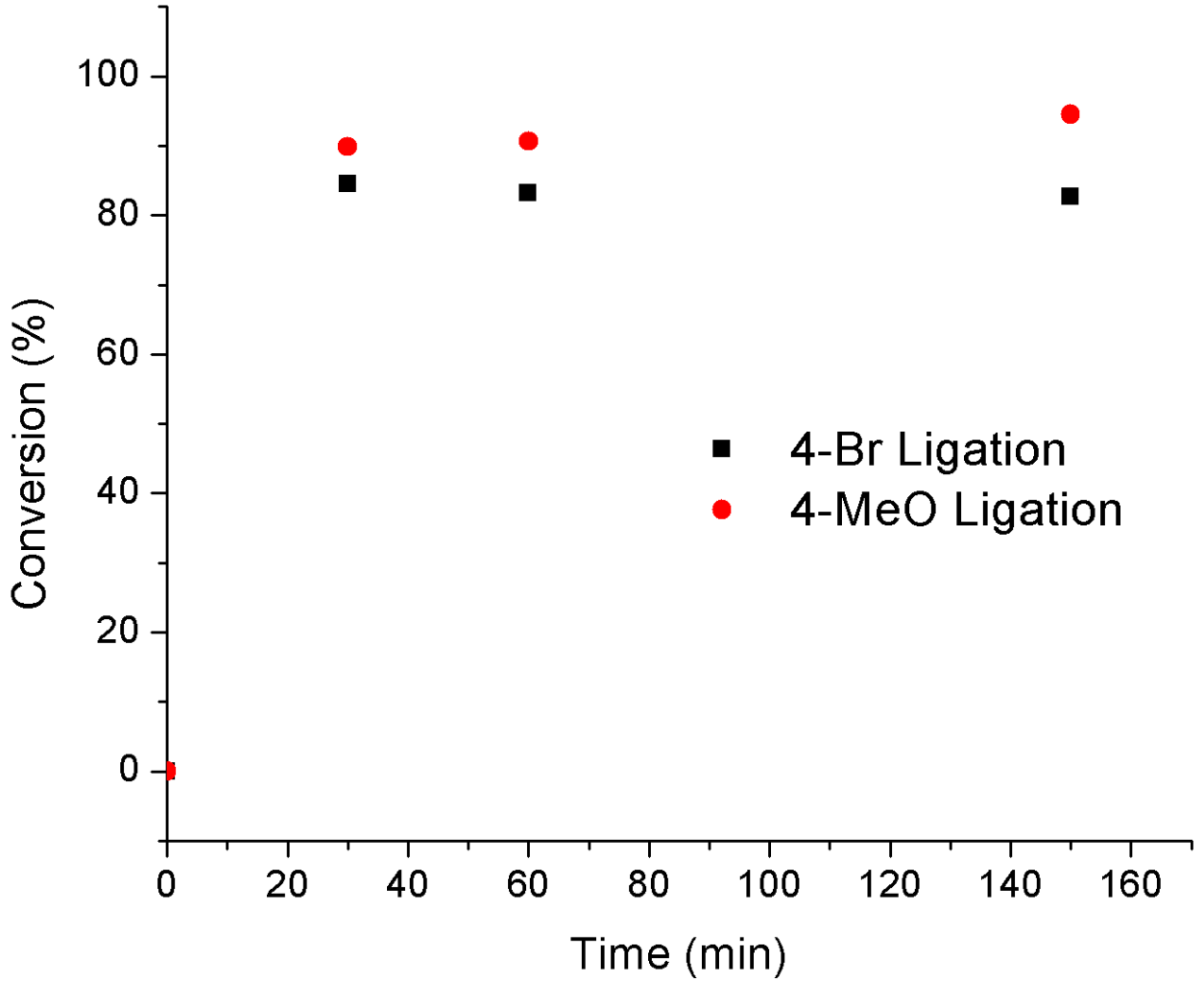


# Ligation

*Br Auxiliary*

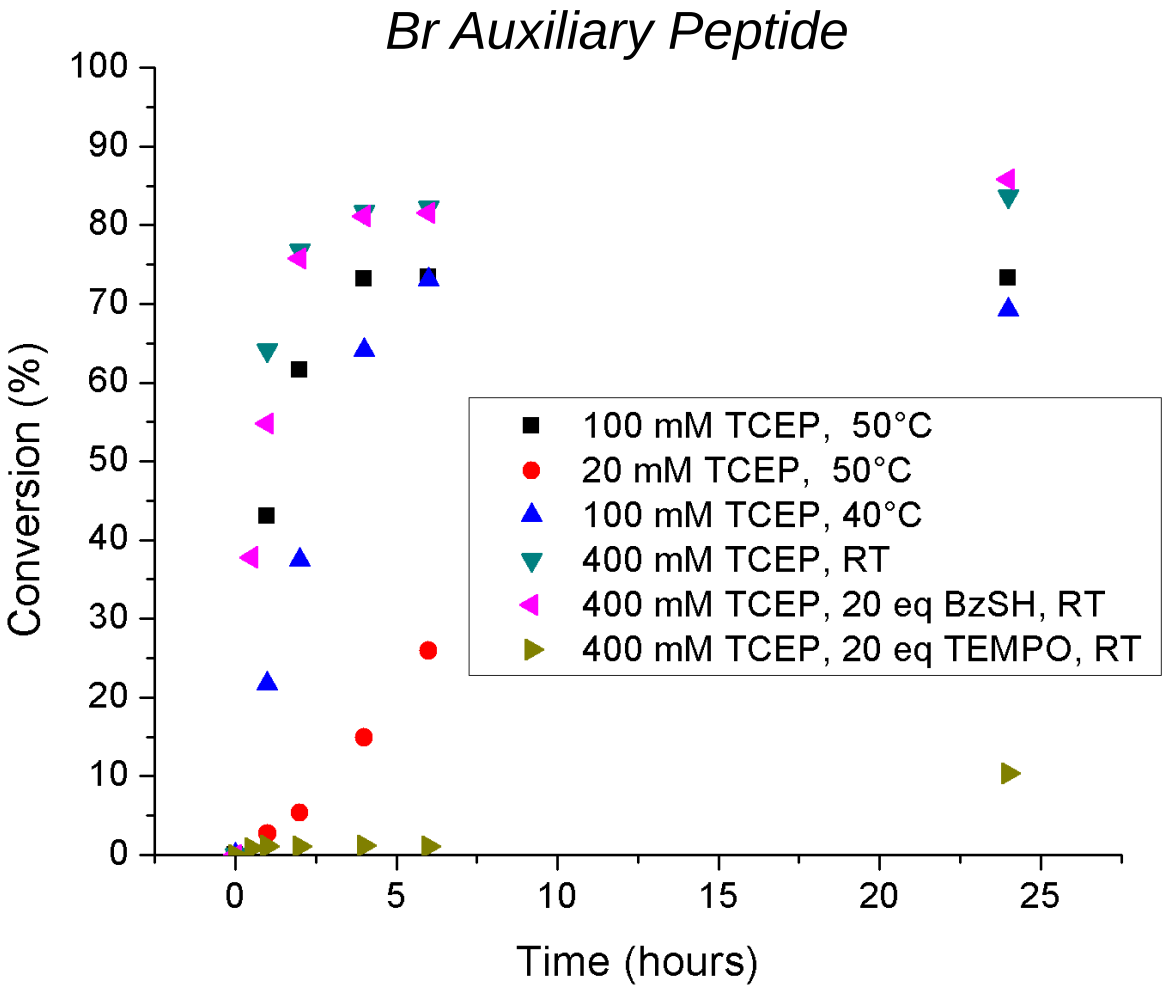


# Ligation


Conversion (%)
100
80
60
40
20
0
0
20
40
60
80
100
120
140
160
Time (min)
4-Br Ligation
4-MeO Ligation

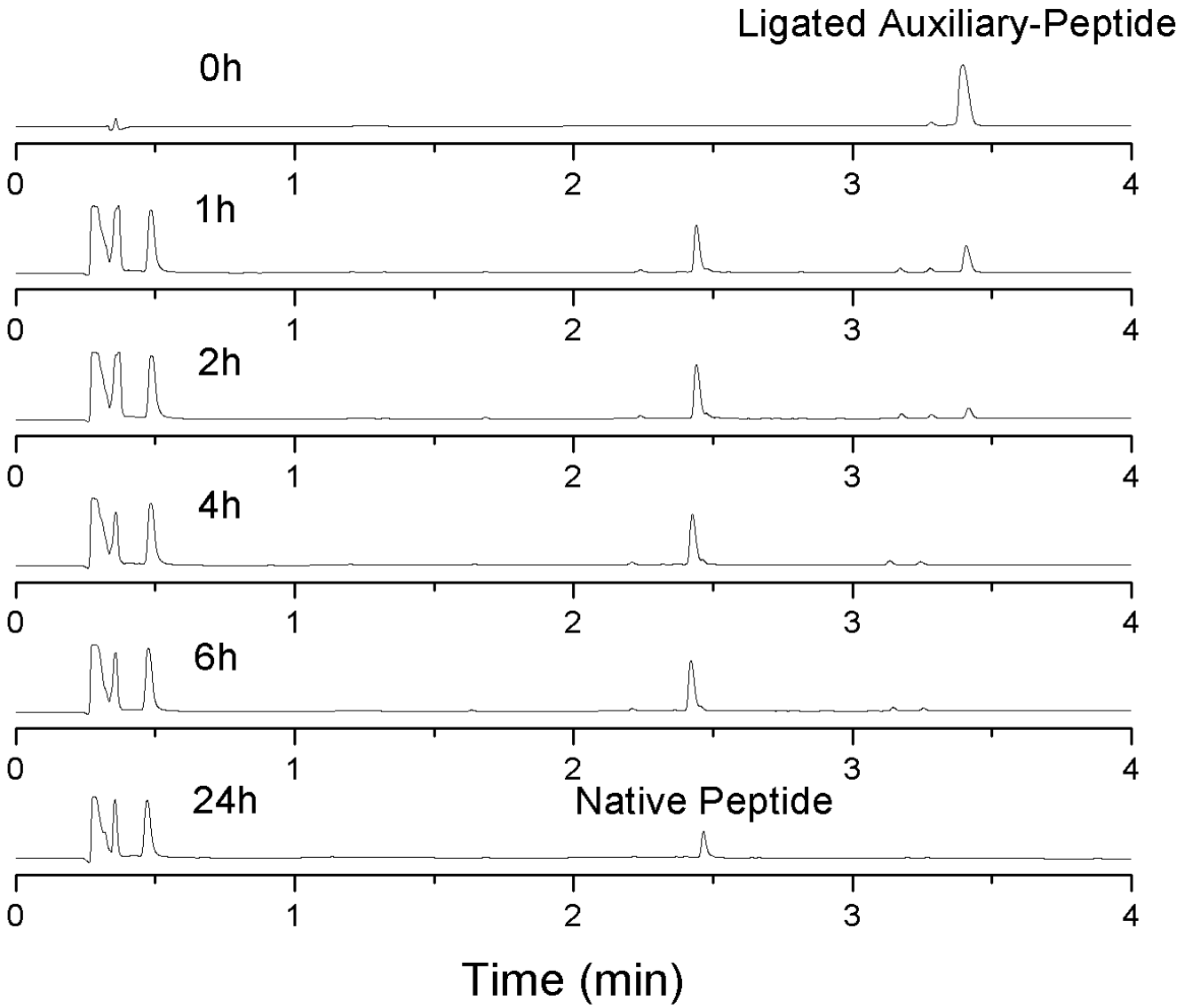
# Cleavage

Cleavage is believed to occur via a TCEP promoted, free-radical mediated process:



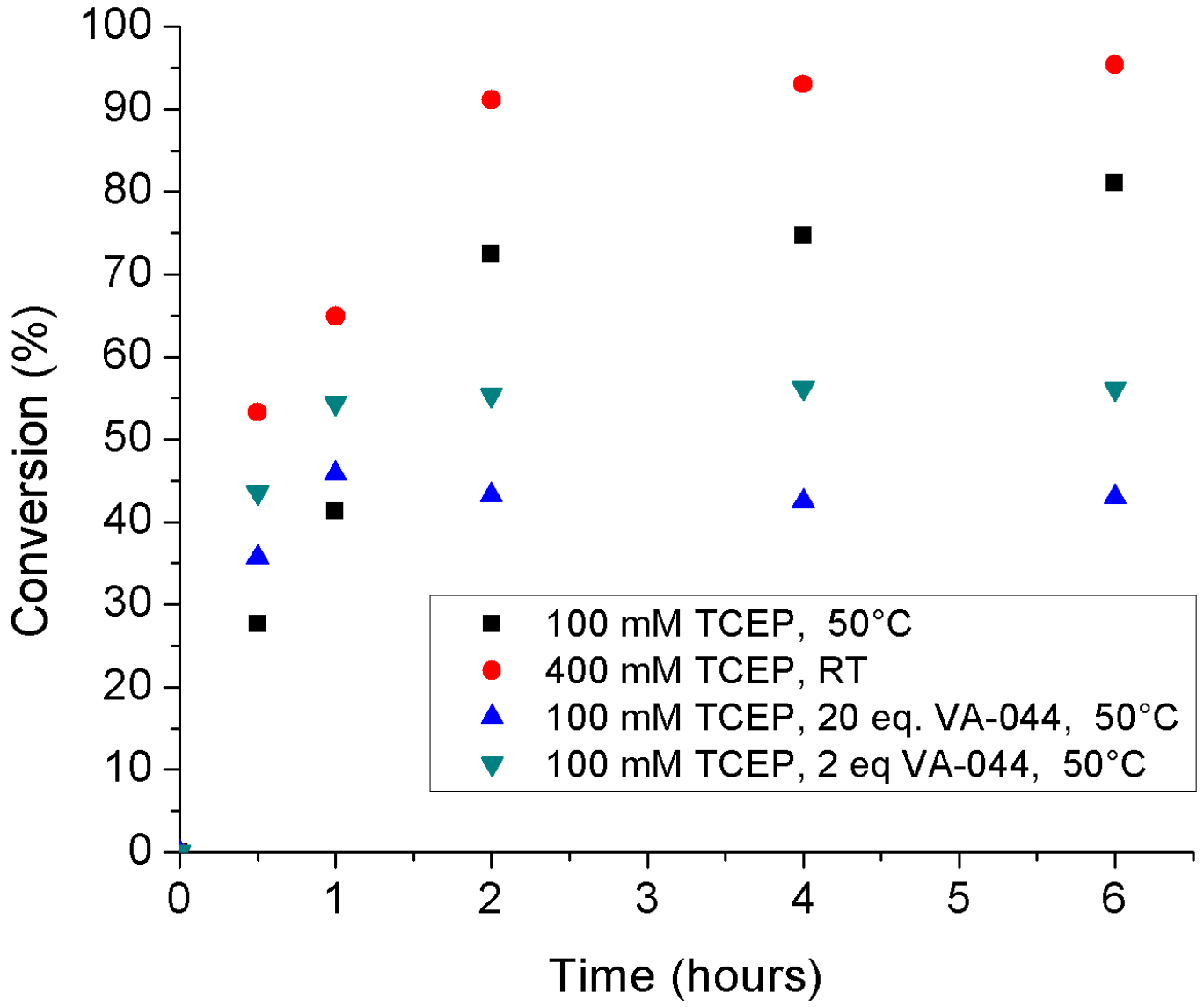
# Cleavage

*Br Auxiliary (400 mM TCEP, R.T.)*



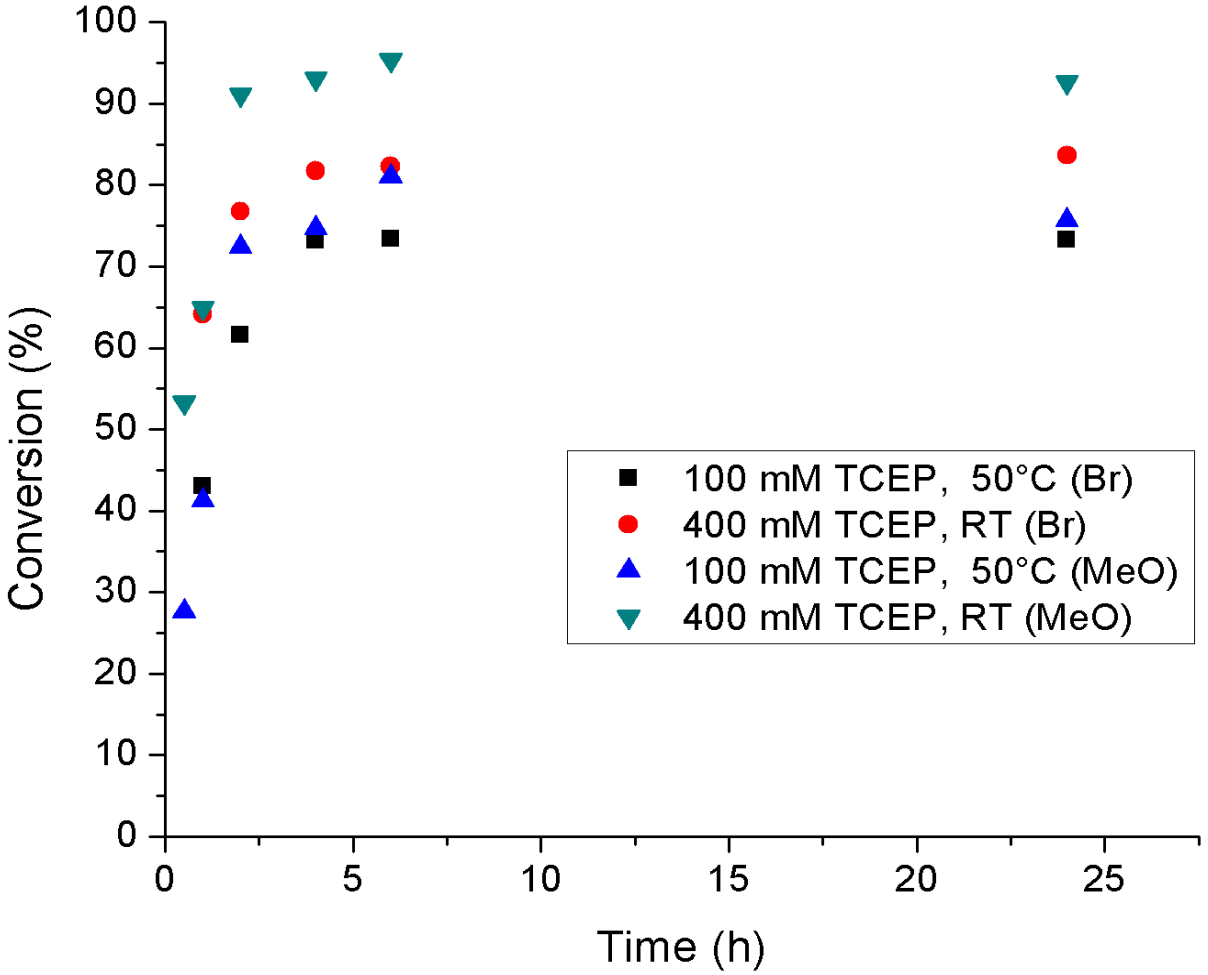
# Cleavage

*MeO Auxiliary*



# Cleavage

**Cleavage** occurs rapidly and selectively under the experimental conditions with both auxiliaries.



# Conclusion

Synthesised two new ligation auxiliaries.

Demonstrated:

- **Introduction** of the auxiliaries to an N-terminal peptide.
- Auxiliary mediated **ligation** with a peptide thioester.
- **Cleavage** of the auxiliaries under novel, mild conditions[1] to yield the desired native peptide.

Successfully achieved the three criteria for a synthetically usefulness ligation auxiliary

Excellent auxiliary for chemical ligation at the studied Gly-Gly site.

[1] Q. Wan, S. Danishefsky, *Angewandte Chemie International Edition,* **2007**, 46, 9248–9252

Thank you for listening