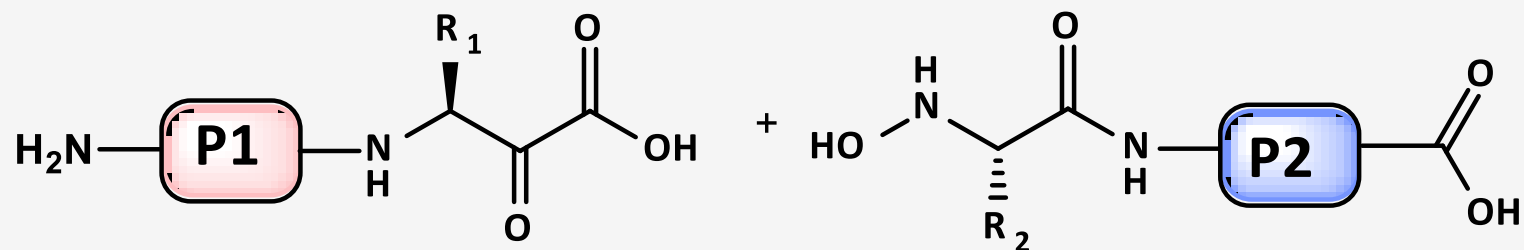


REACTION OF THE DAY

KAHA LIGATION



Lori Digal
May 29th 2018
Synthesis Club

An introduction to KAHA ligation

KAHA ligation is used in peptide chemistry to prepare both peptides and proteins

Strategy proposed by Jeffrey Bode and group members (ETH Zürich)

Development consisted of a 12 year long process

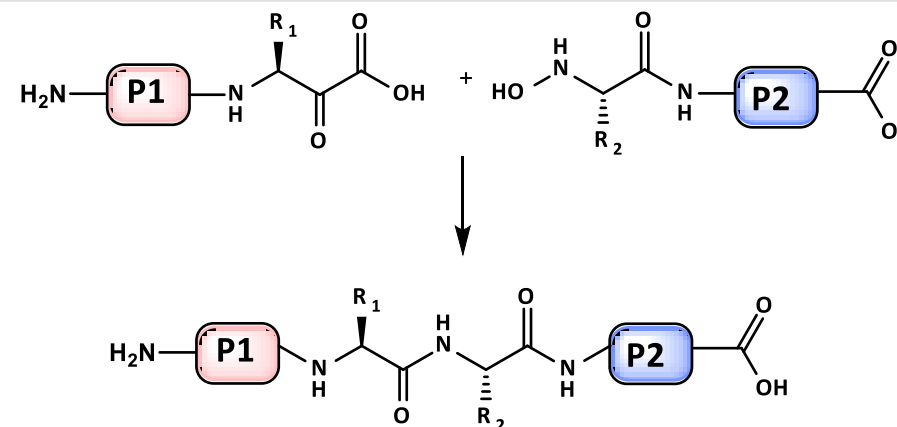
The strategy used to prepare peptides and proteins requires both an α -ketoacid (**KA**) and a hydroxylamine(**HA**)



Bode



The Bode group

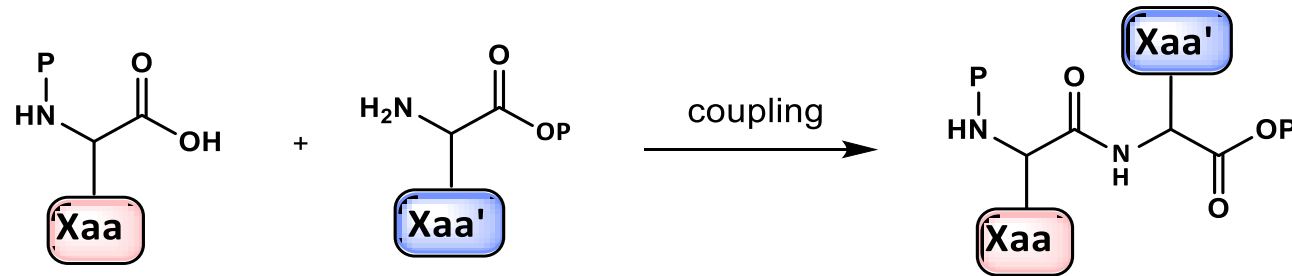


General scheme of KAHA

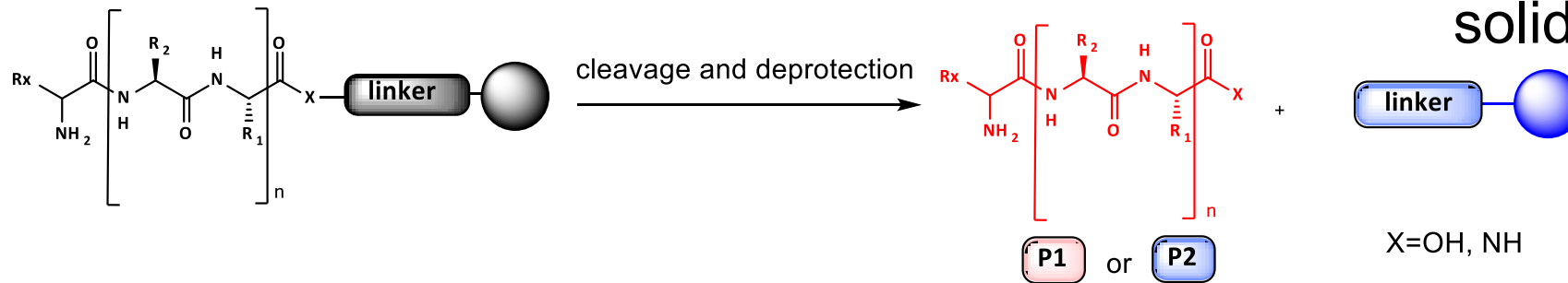
How does KAHA ligation compare to other strategies in the field of peptide chemistry?

Peptide preparation

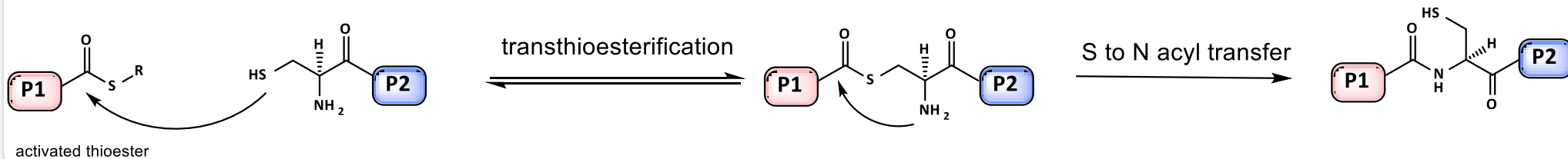
Methods to prepare peptides synthetically include:



solution phase



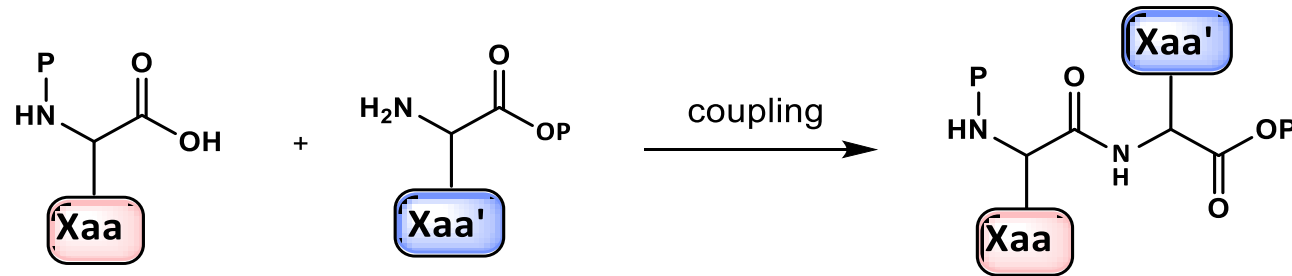
solid phase



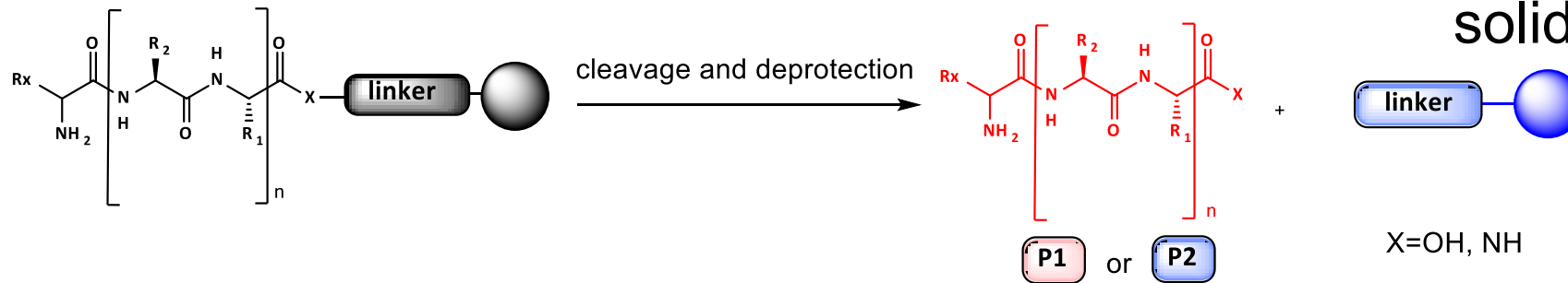
chemoselective coupling

Peptide preparation

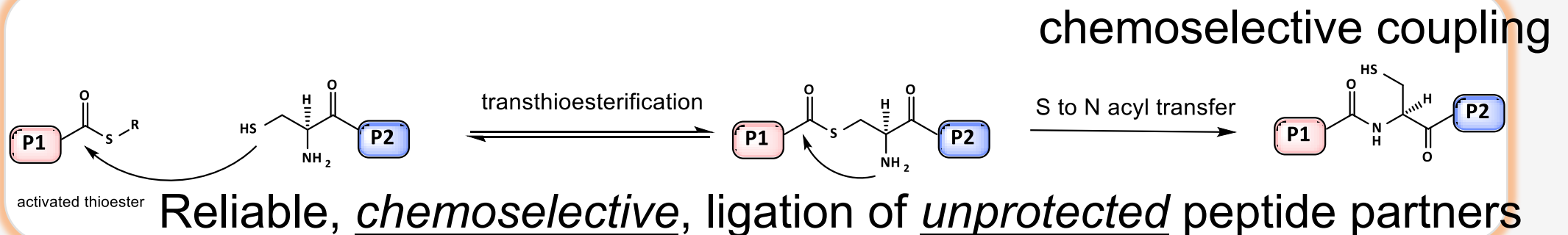
Methods to prepare peptides synthetically include:



solution phase



solid phase



chemoselective coupling

Peptide preparation

Solution Phase

Solid Phase
Peptide
Synthesis

Chemoselective
coupling

Peptide preparation

Solution Phase

Solid Phase
Peptide
Synthesis

Chemoselective
coupling

Peptide preparation

Solution Phase

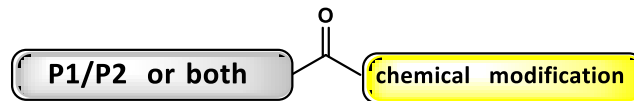
Solid Phase
Peptide
Synthesis

Chemoselective
coupling

Pre-
modified

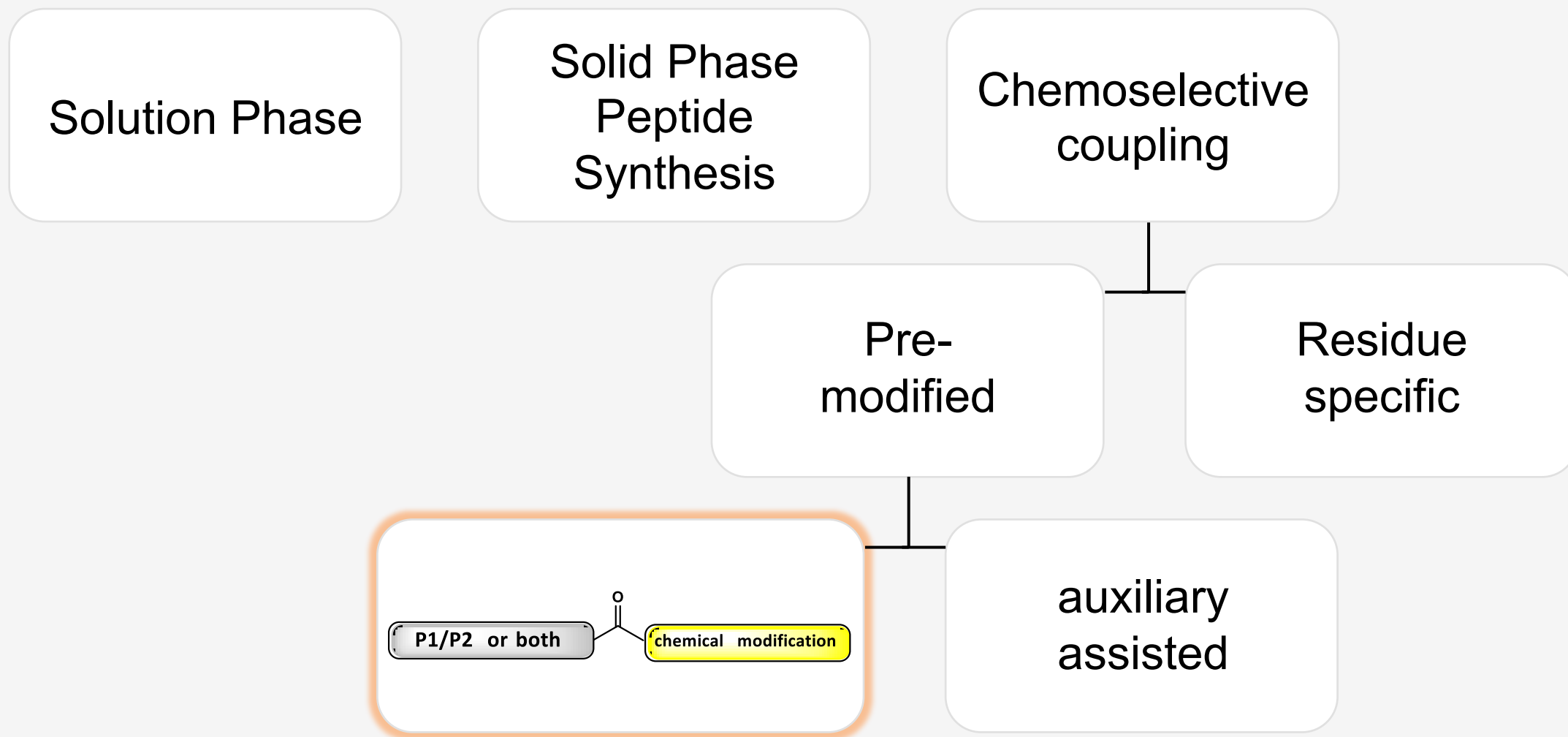
Residue
specific

auxiliary
assisted

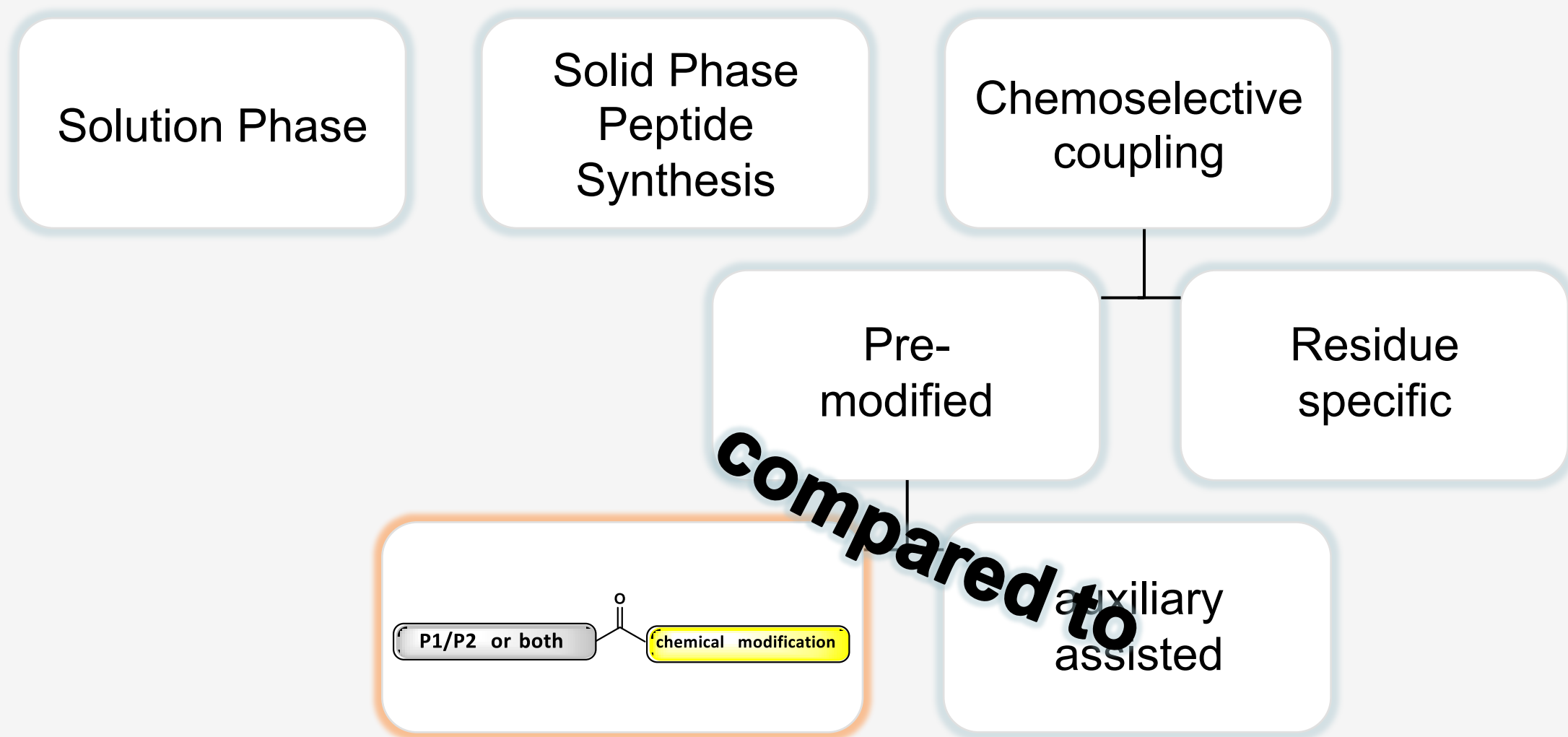


KAHA ligation falls
underneath the class of pre-
modified chemical ligation
strategies

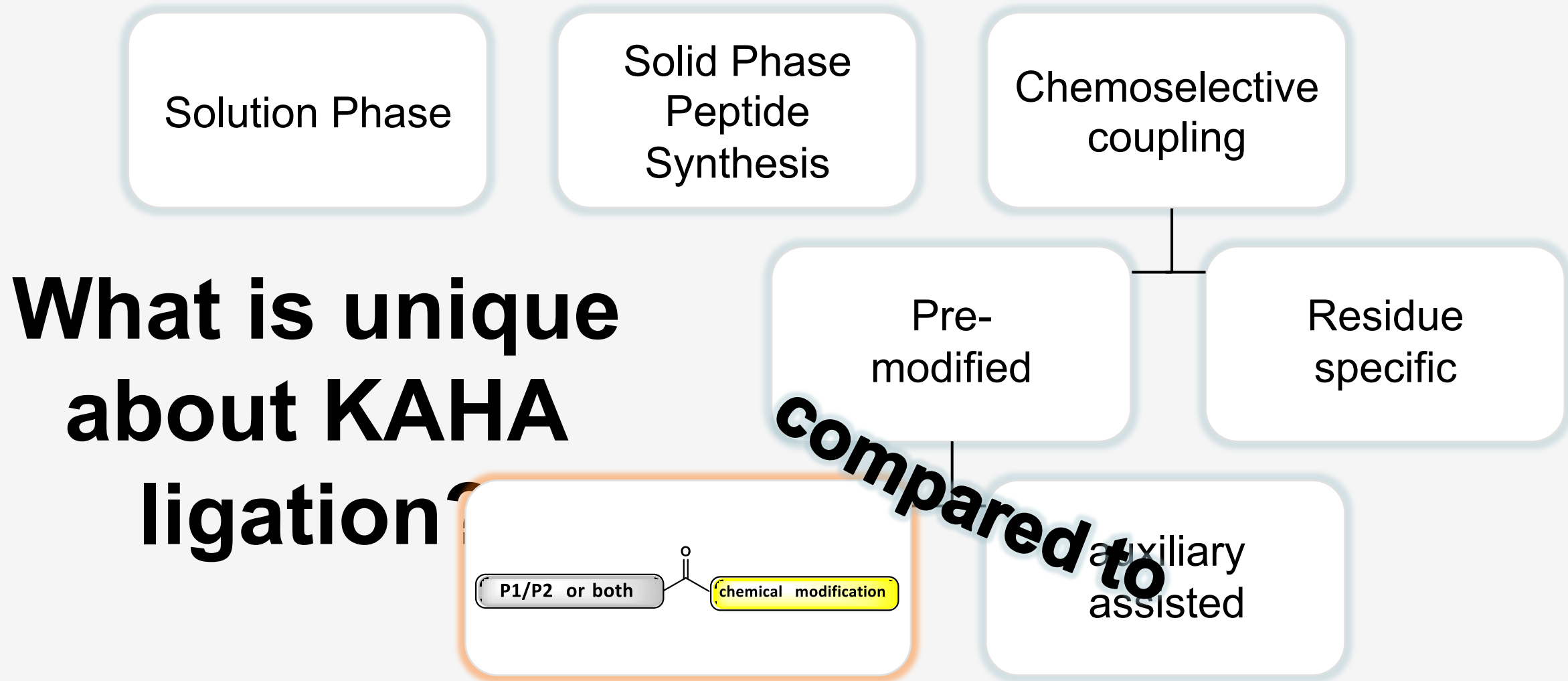
Peptide preparation



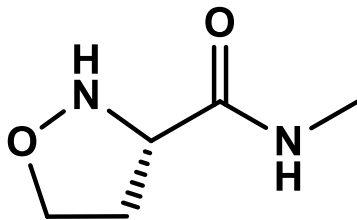
Peptide preparation



Peptide preparation



About the reaction



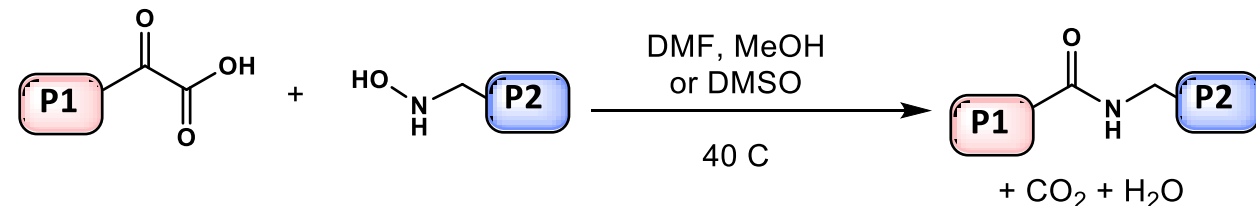
(S)-5 oxaproline is so far is the most compatible hydroxylamine in KAHA

Stable towards standard methods and practices with solid-phase synthesis

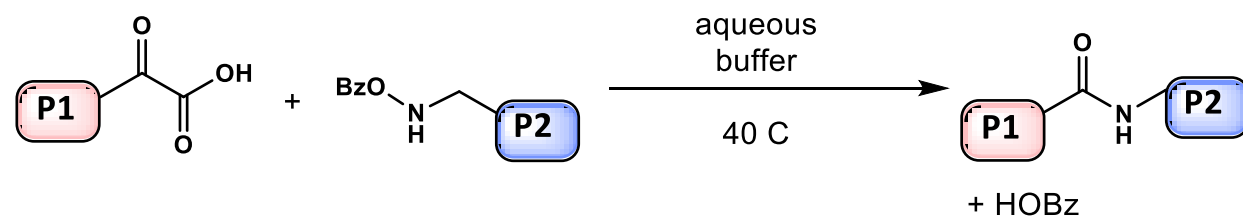
Compatible with NCL, making possible one-pot ligations of

multiple segments

type I KAHA ligations (O-unsubstituted species)

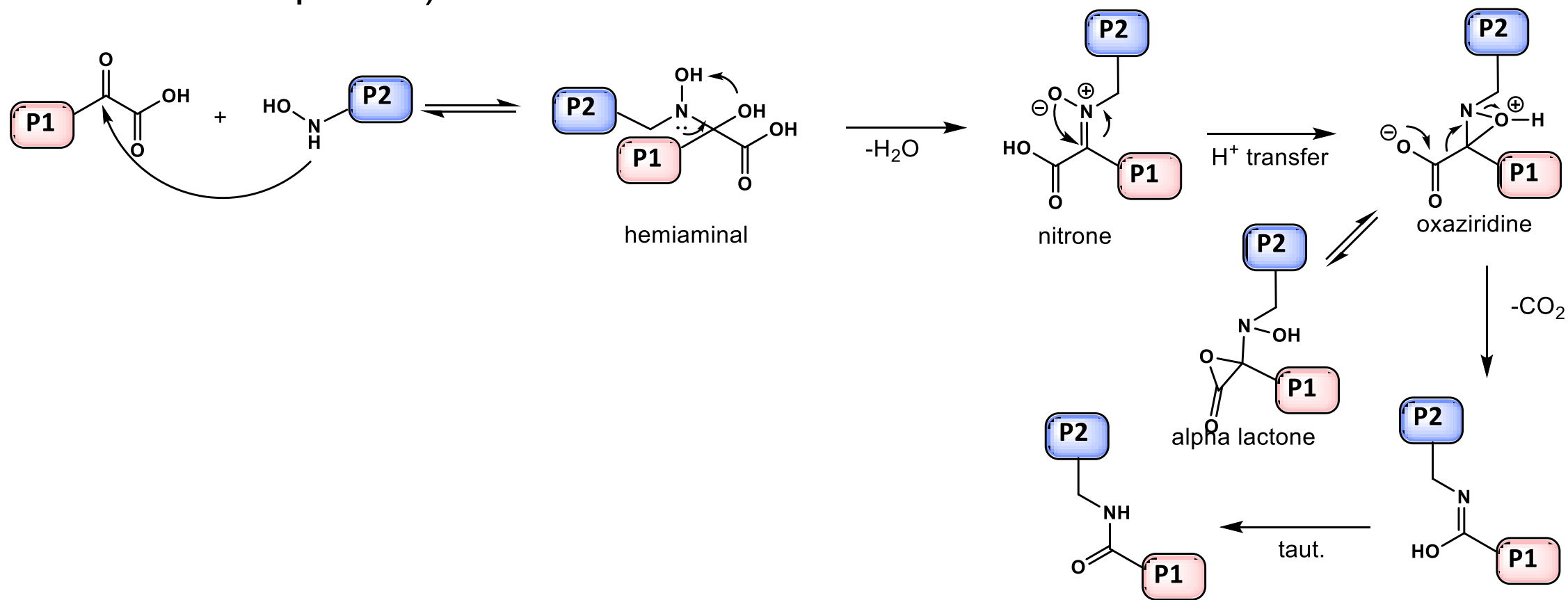


type II KAHA ligations (O-substituted hydroxylamines)



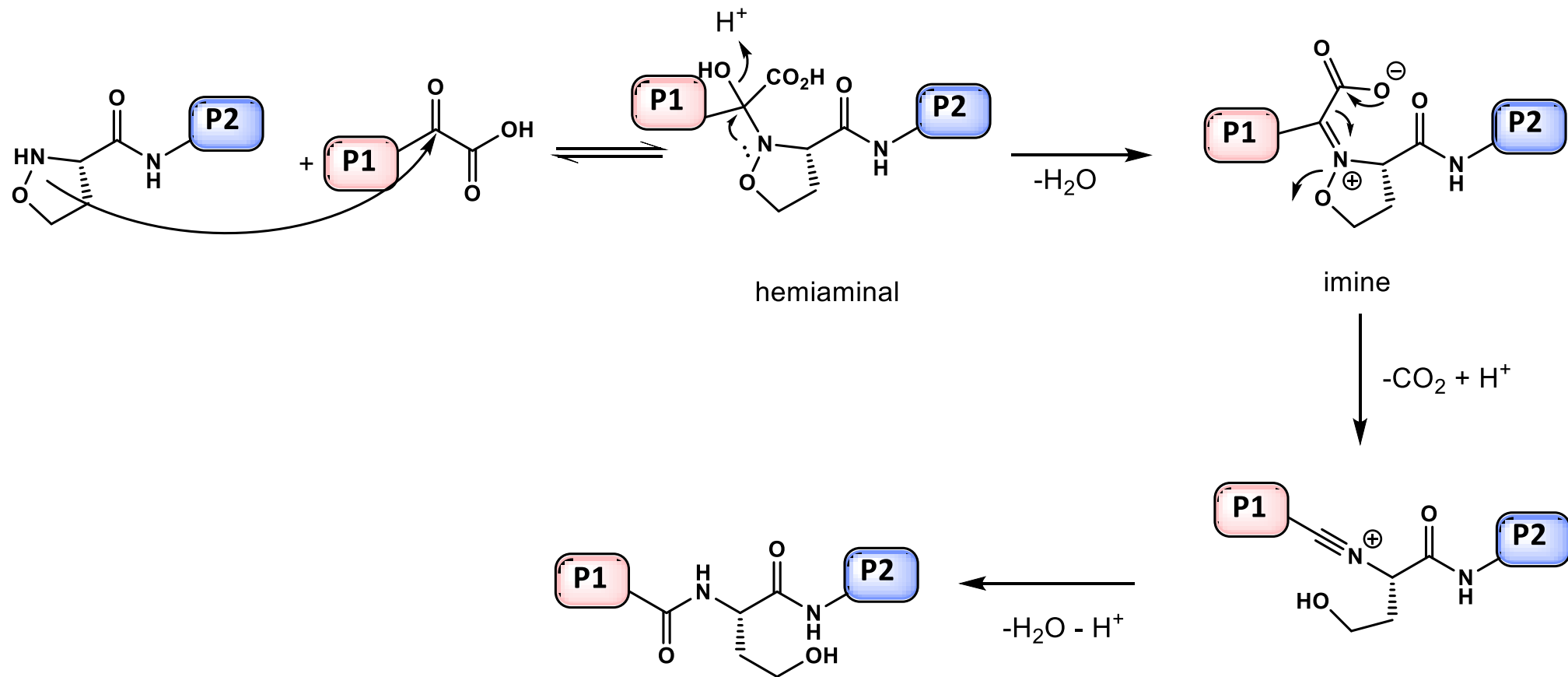
Mechanism

type I KAHA ligations (O-unsubstituted species)



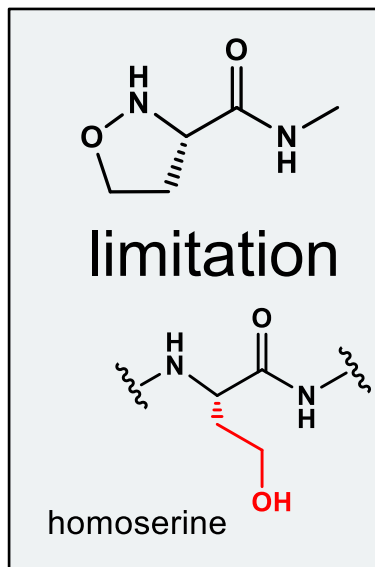
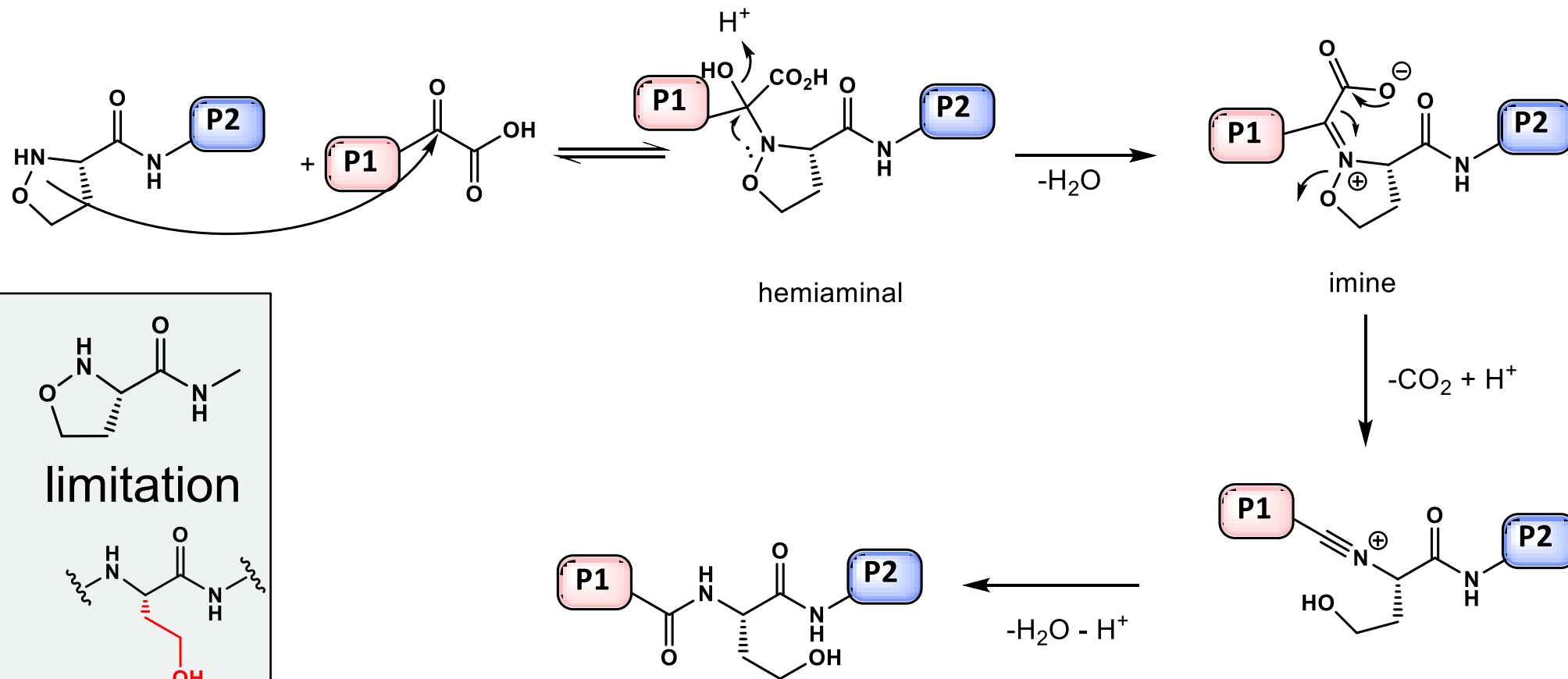
Mechanism

type II KAHA ligations (O-substituted hydroxylamines)



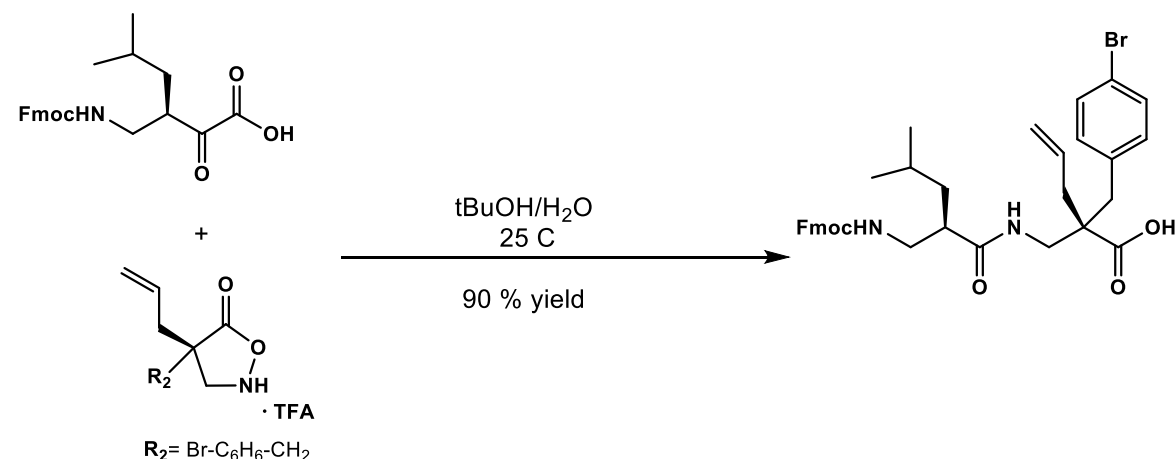
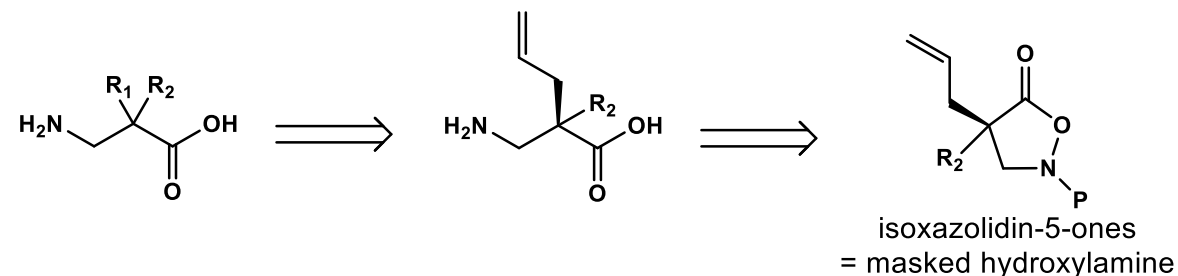
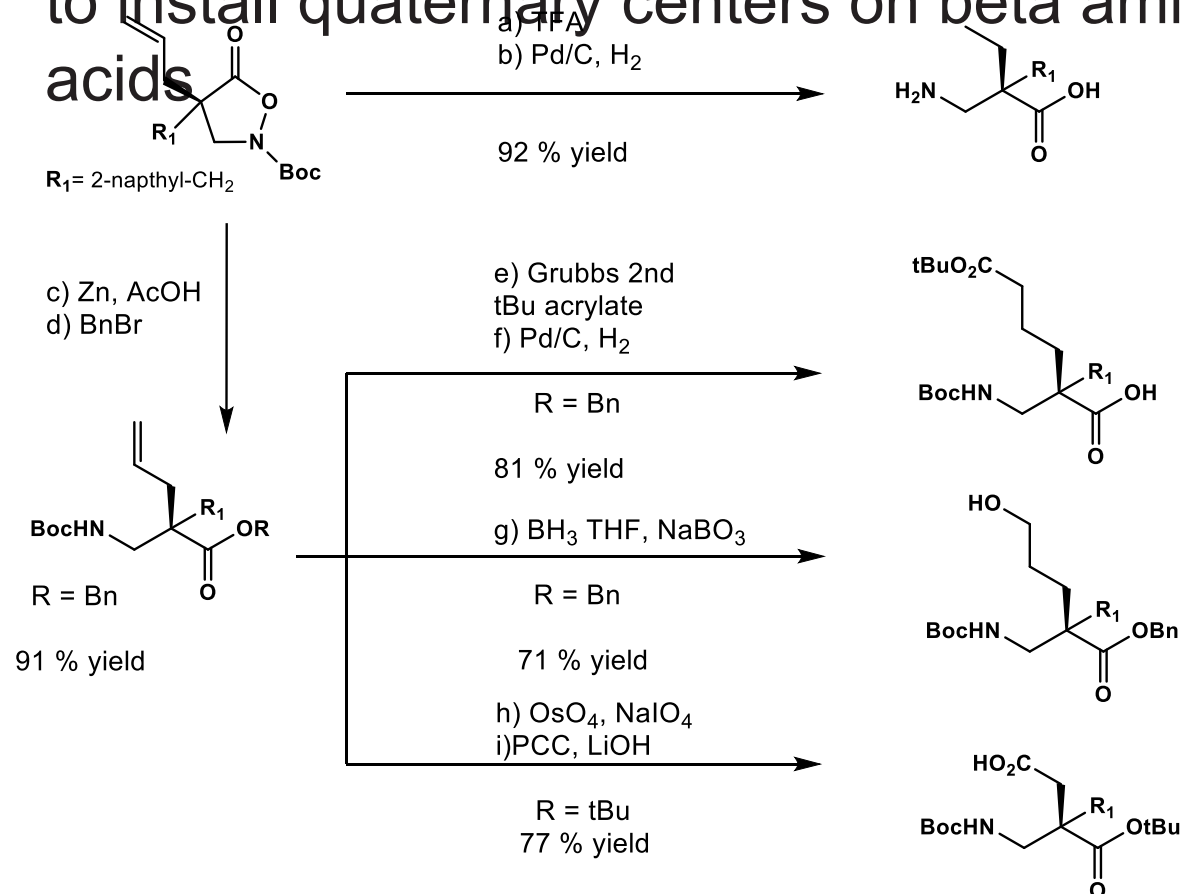
Mechanism

type II KAHA ligations (O-substituted hydroxylamines)



Where synthesis and peptide chemistry converge

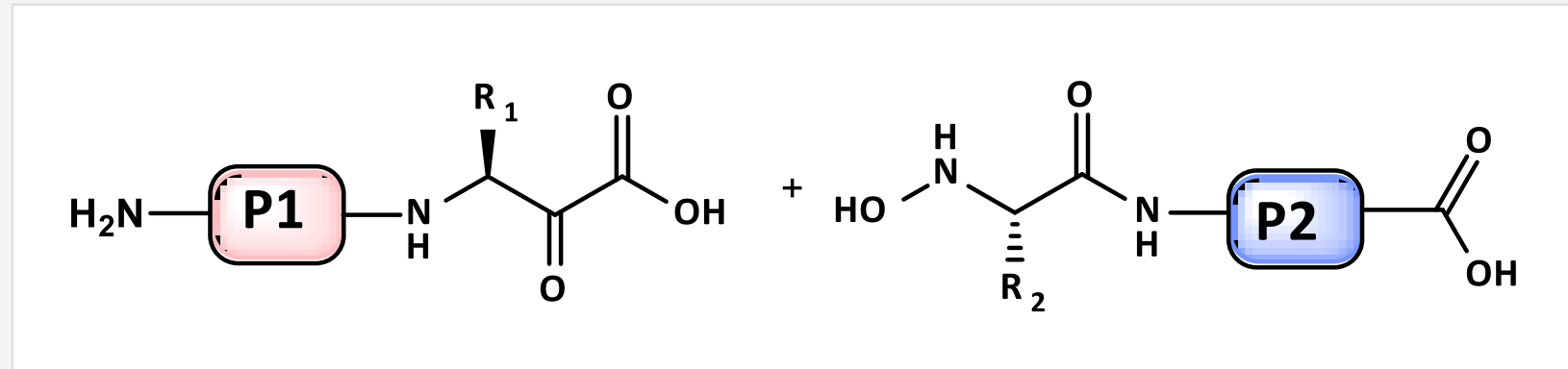
Using methods developed by Stoltz, Tunge, Trost, and others, the Shibasaki group were able to install quaternary centers on beta amino acids



The isoxazolidin-5-ones can be used to prepare more peptide derivatives using KAHA ligation!

Concluding Remarks

Using the KAHA ligation strategy, it can be used as a convenient tool to prepare both peptides and proteins using alpha-ketoacids and hydroxyl amines



Thank You