

# Native chemische Ligation – Staudinger Ligation

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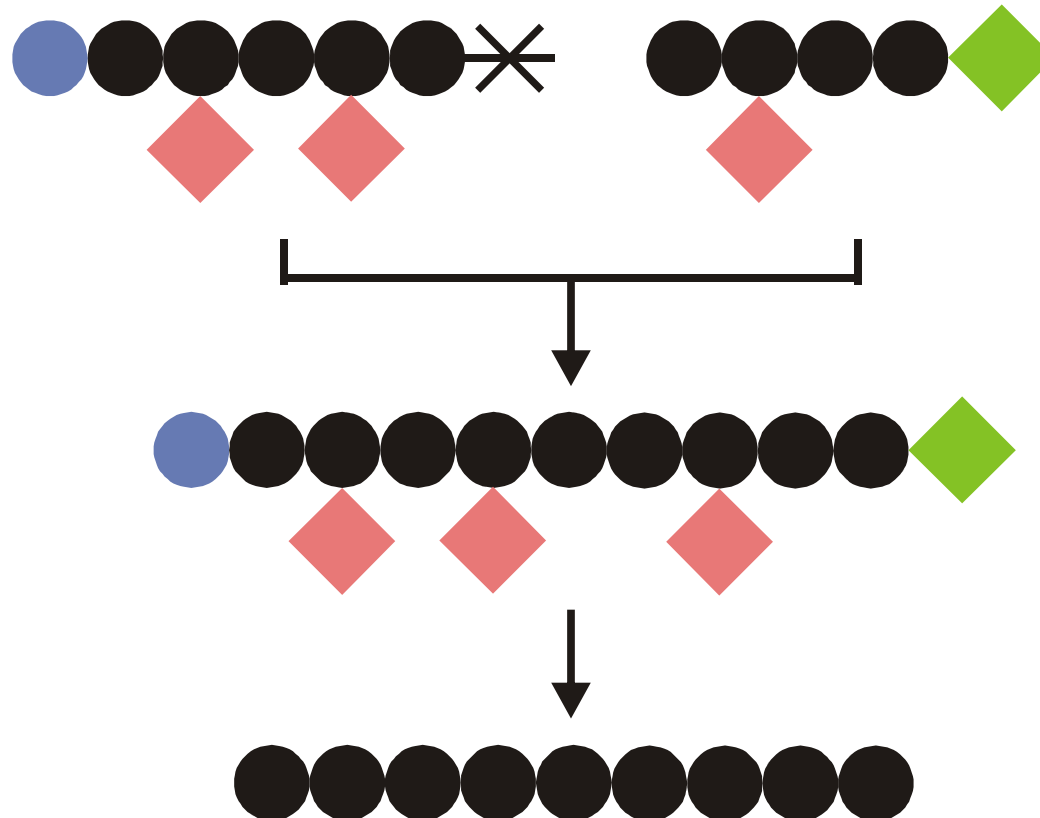


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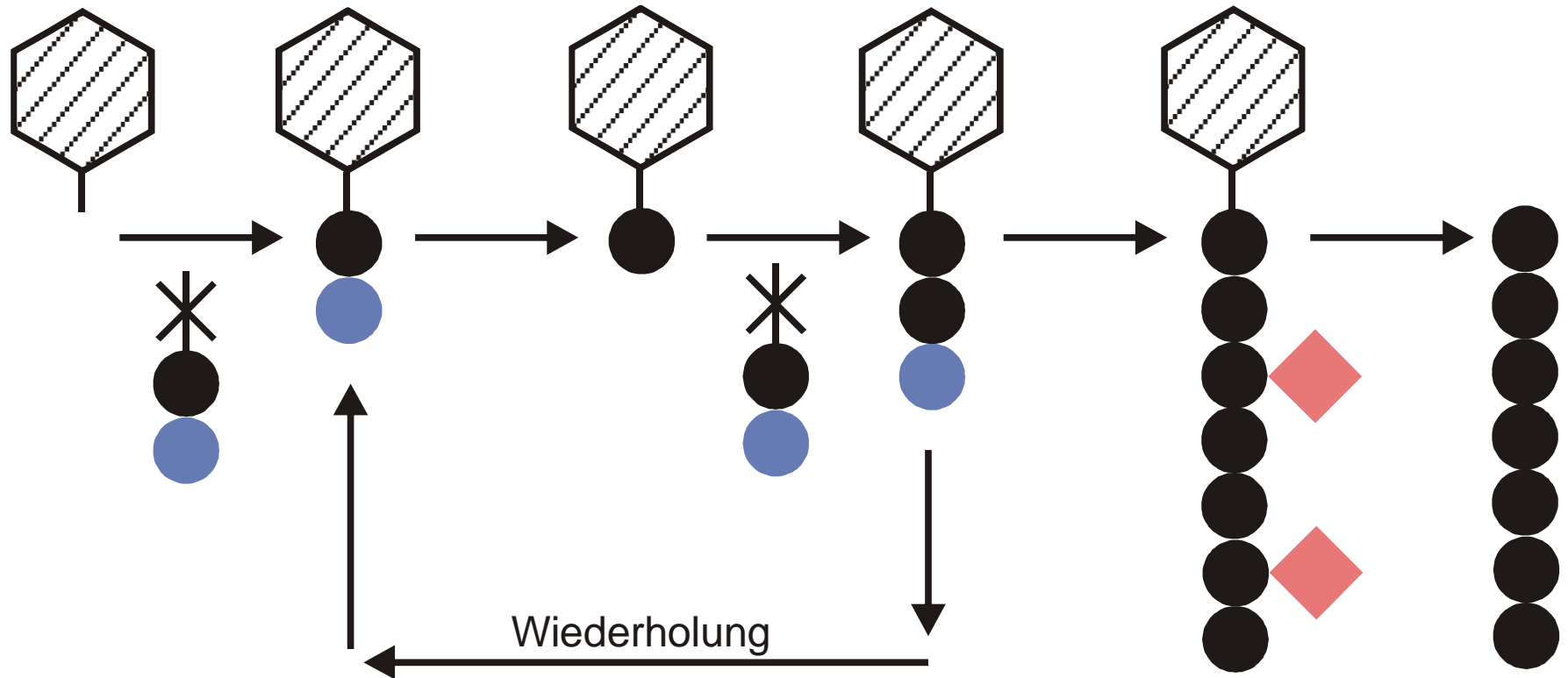
# Polypeptidsynthese – Historie

## ■ „klassische“ Lösung



# Polypeptidsynthese – Historie

## ■ SPPS - Festphasensynthese

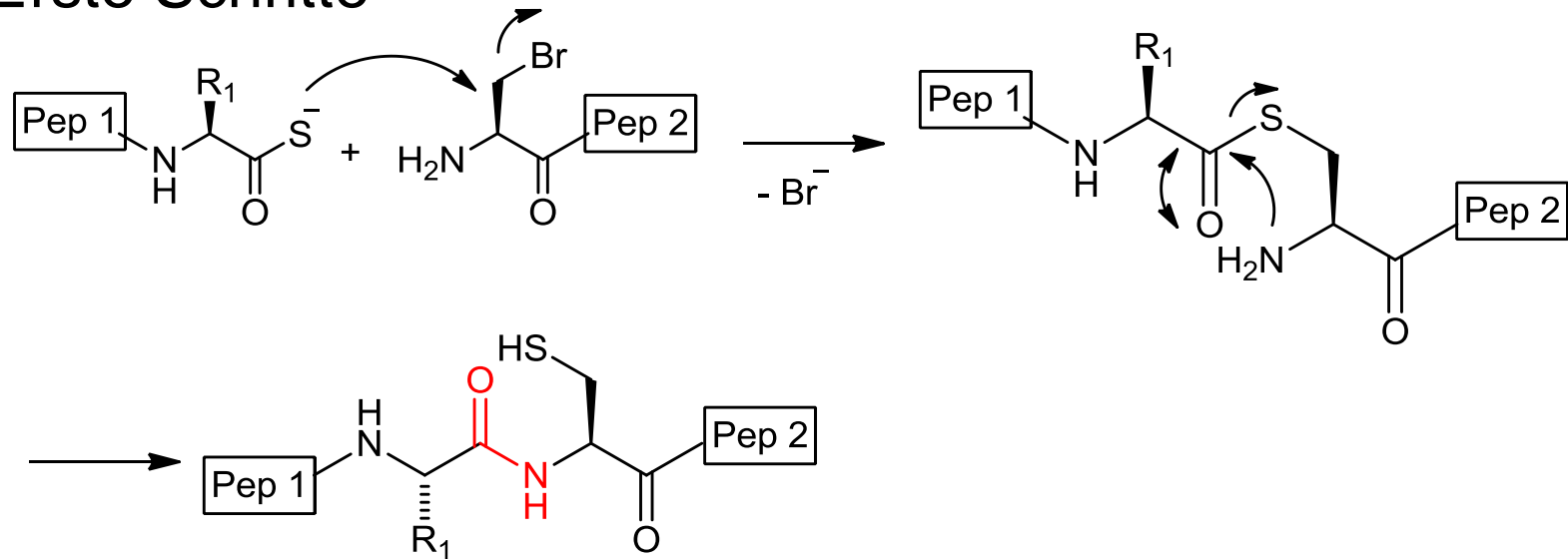


# Anforderungen an neue Synthesemethoden

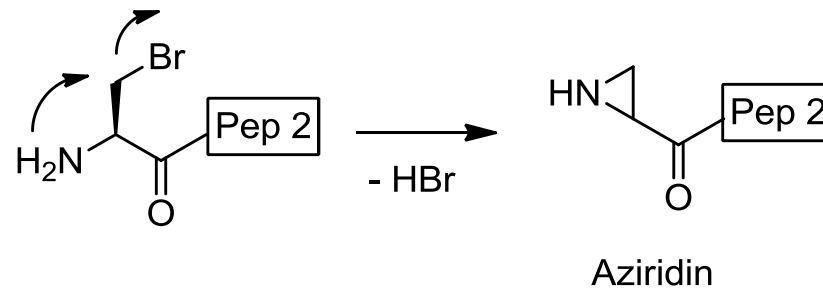
- Motivation
  - völlig konvergent
  - keine Schutzgruppen
  - Reaktion schnell
  - keine Nebenreaktionen
  - Polypeptid direkt darstellbar

# Native chemische Ligation (NCL)

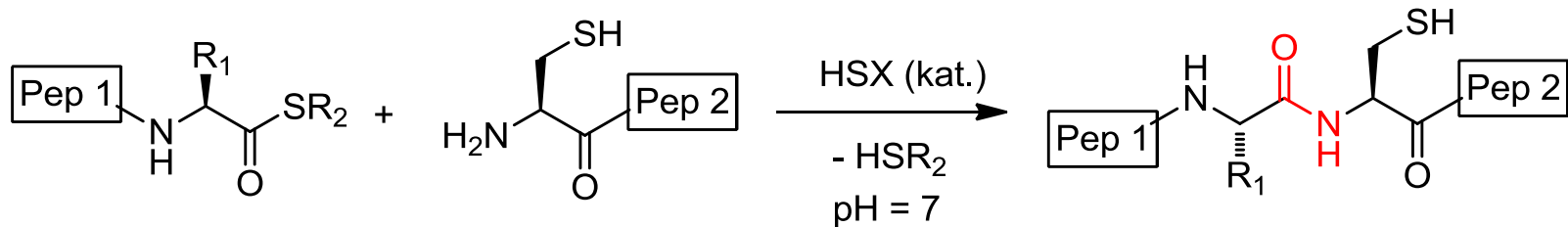
## ■ Erste Schritte



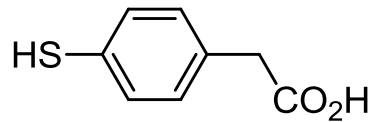
## ■ Nebenreaktion



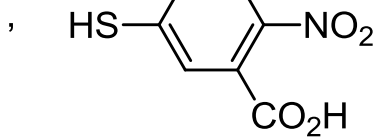
# NCL – Optimierung



HSX:



MPAA



TNB

# NCL – Definition, Wertung

## ■ Definition

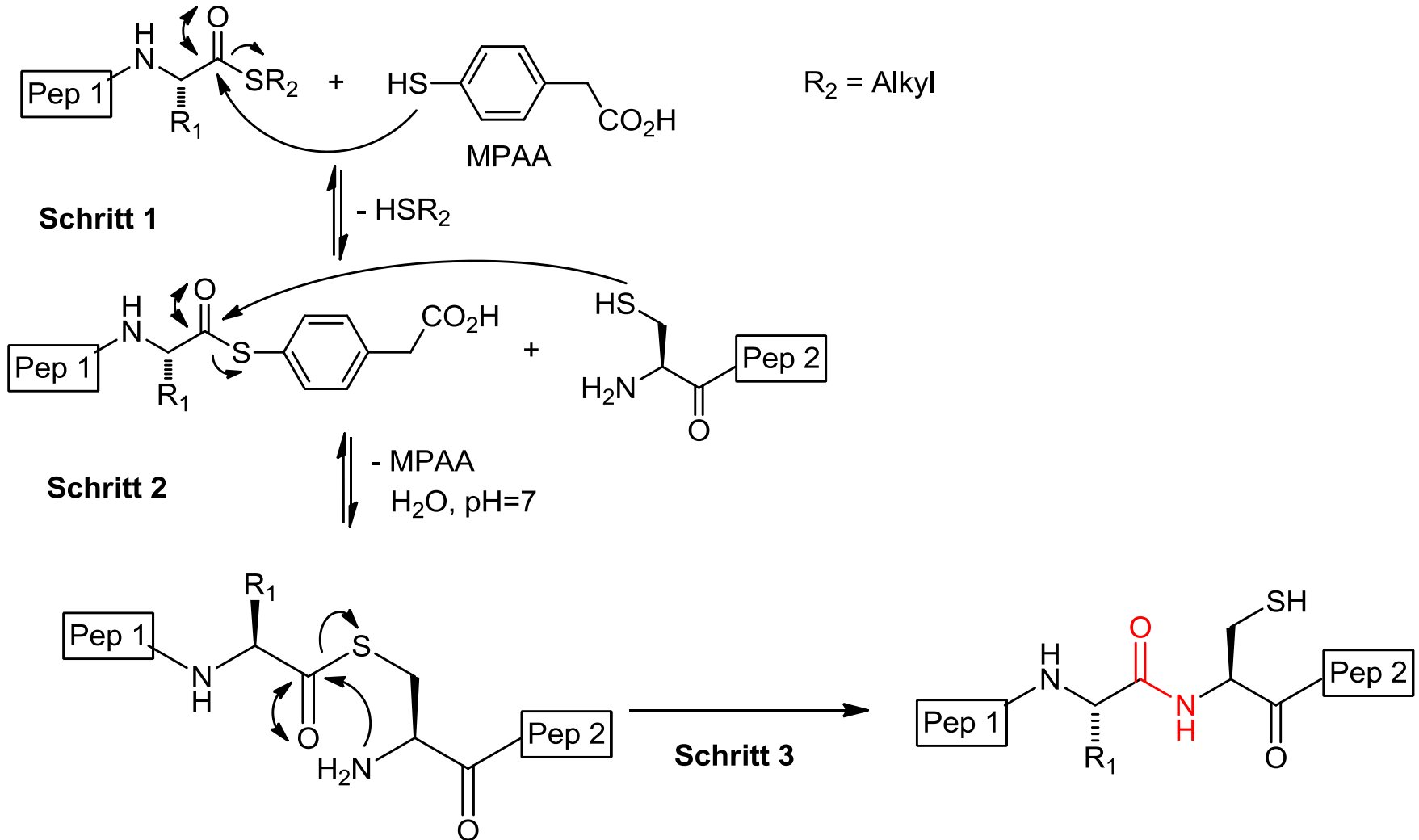
Thioester vermittelte Bildung einer Peptidbindung zwischen zwei ungeschützten Peptidsegmenten mit Hilfe eines Thiol-Thioester Austausches

## ■ Wertung

Vorteile	Nachteile
keine Schutzgruppen	Cys-Abhängigkeit
chemoselektiv	kein Prolin
wässriges Milieu	

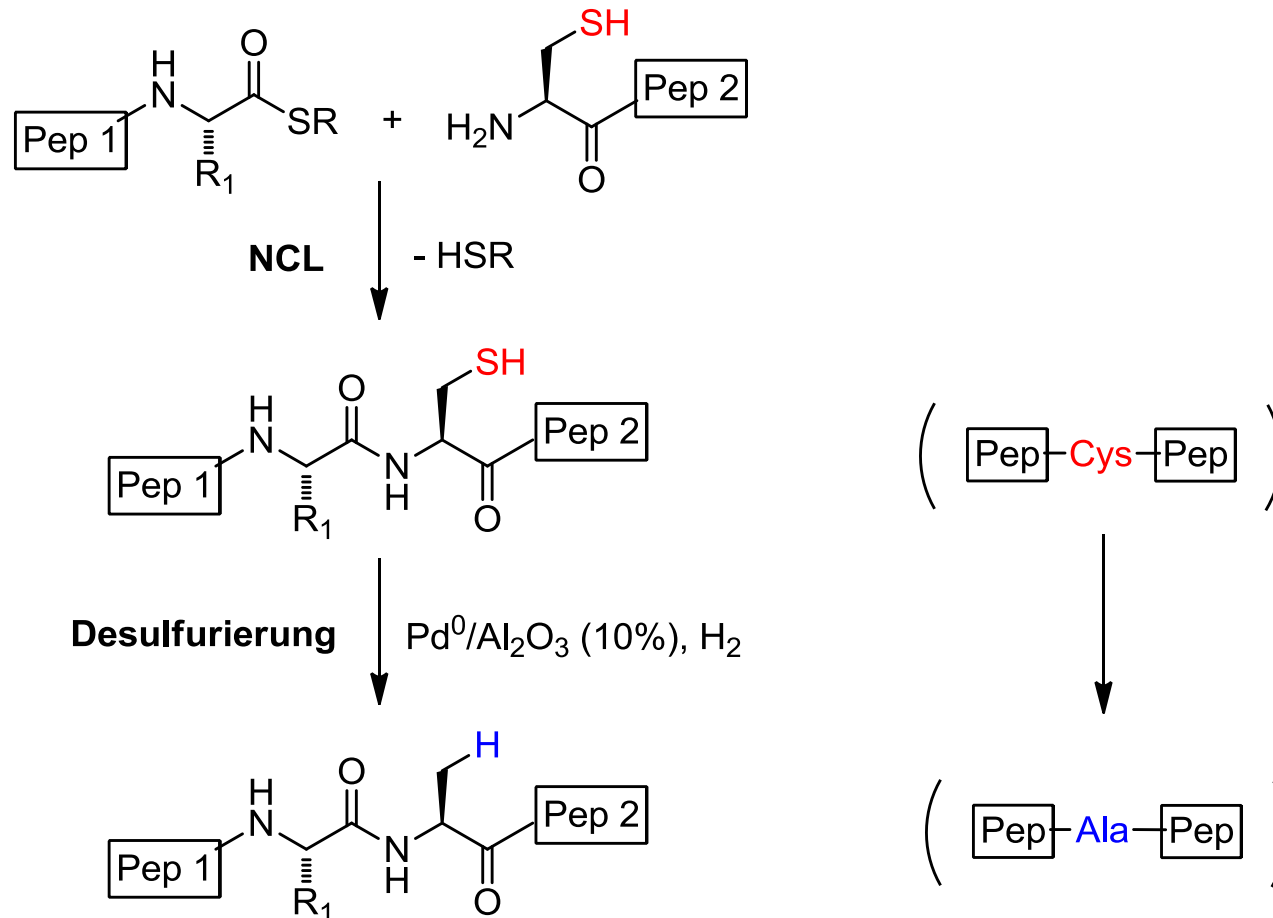


# NCL – Mechanismus



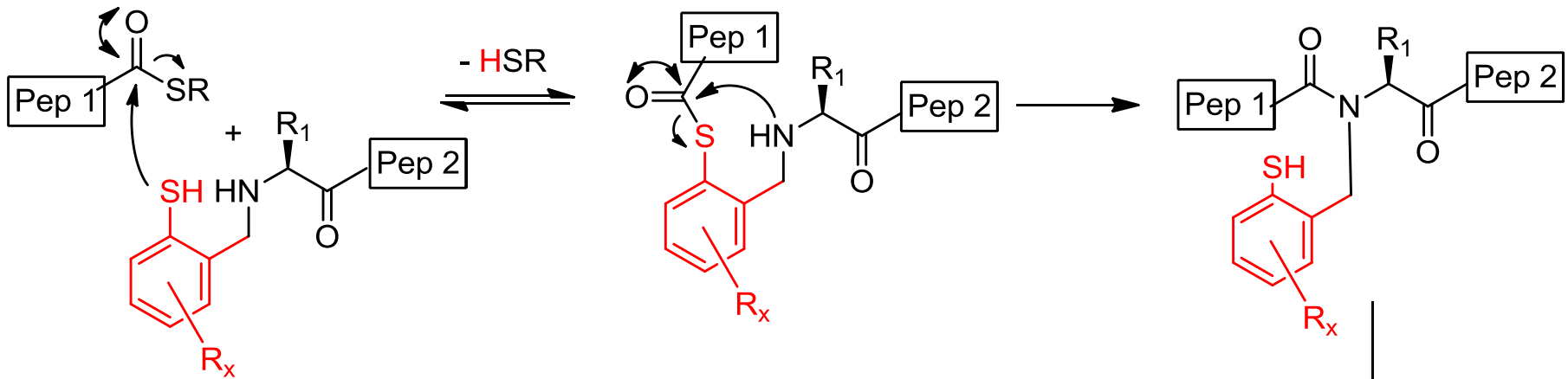
# NCL – Cys Abhängigkeit

## ■ Nachträgliche Desulfurierung



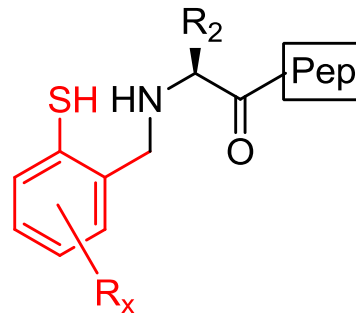
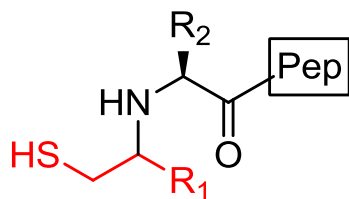
# NCL – Cys Abhängigkeit

## ■ Verwendung von N<sup>α</sup>-Acyl Transfer Auxiliaren



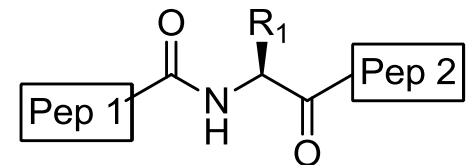
2 Arten von Auxiliaren:

1. N<sup>α</sup>-2-mercaptoethyl-artig
2. N<sup>α</sup>-2-mercaptobenzyl-artig

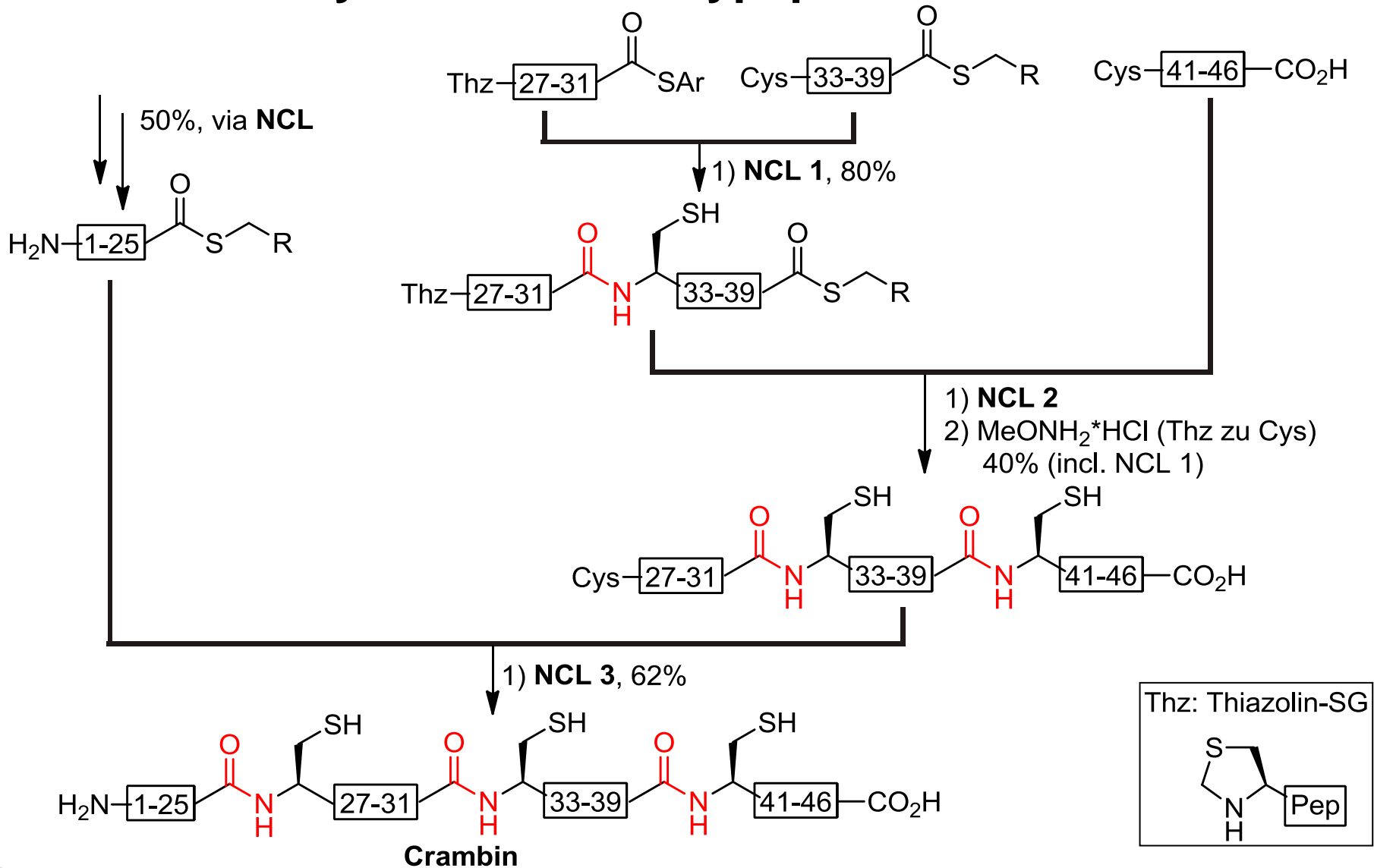


**Abspaltung  
des Auxiliars**

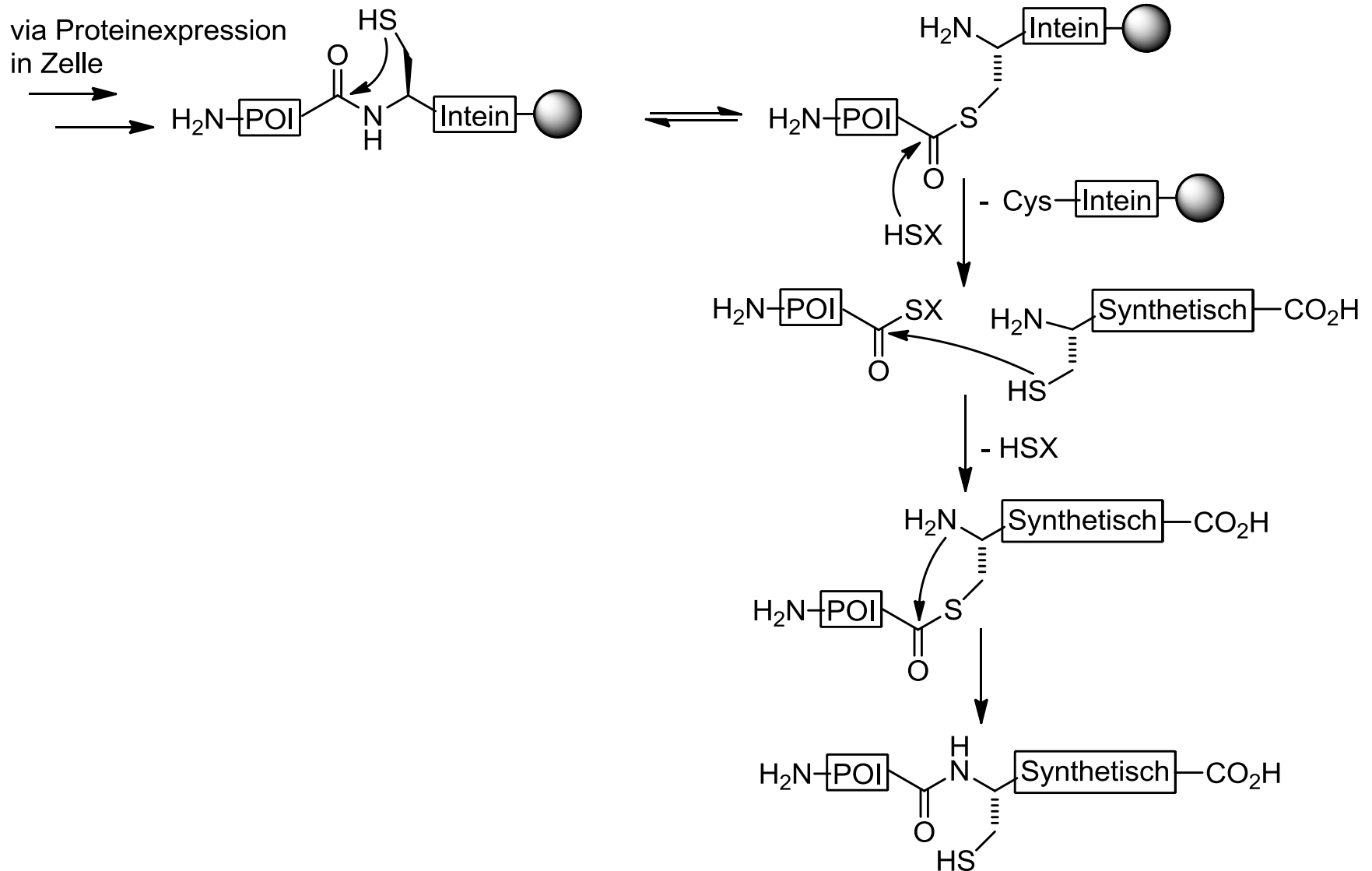
H<sup>+</sup>



# NCL – Totalsynthese von Polypeptiden



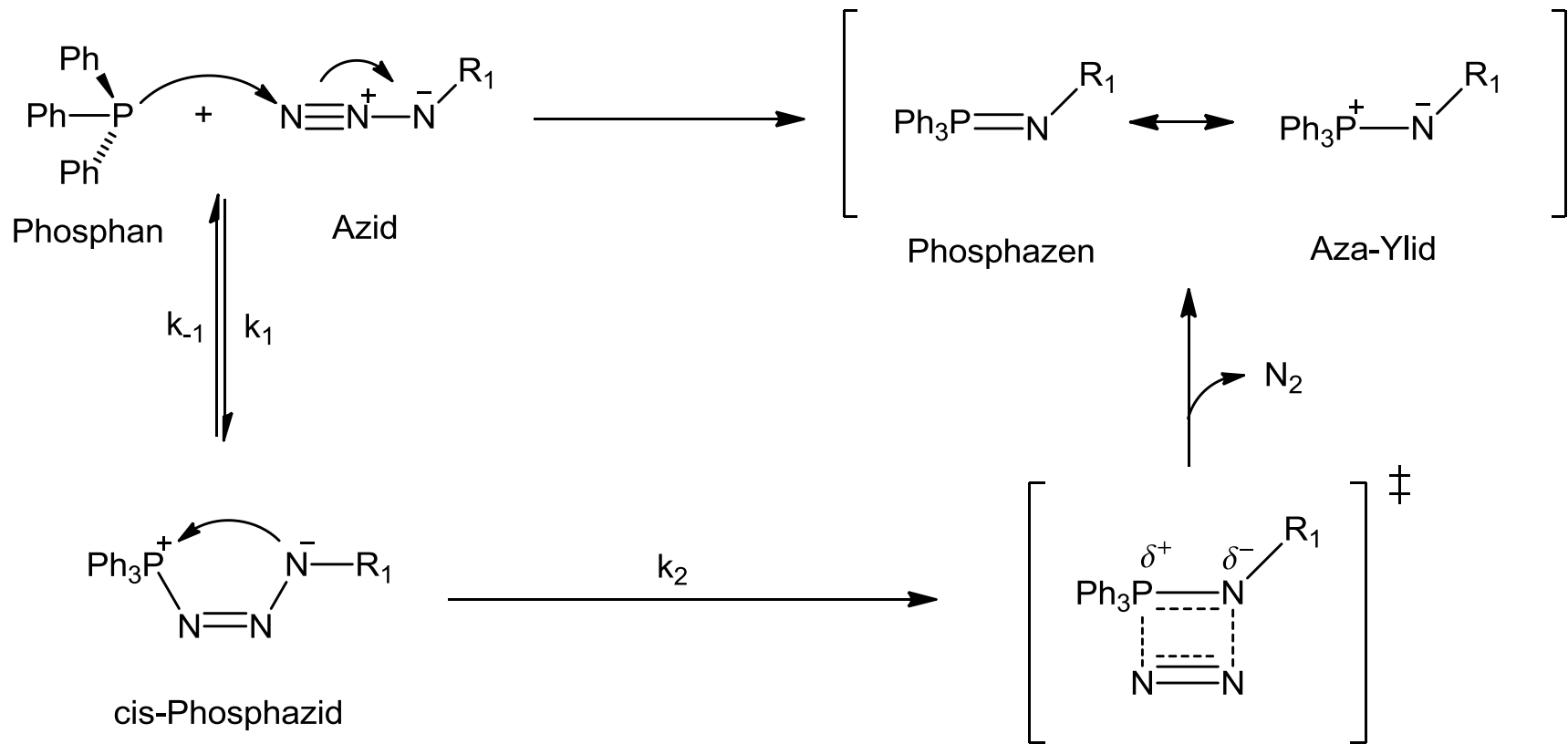
# NCL – Expressed protein ligation (EPL)



# Staudinger Ligation (SL)

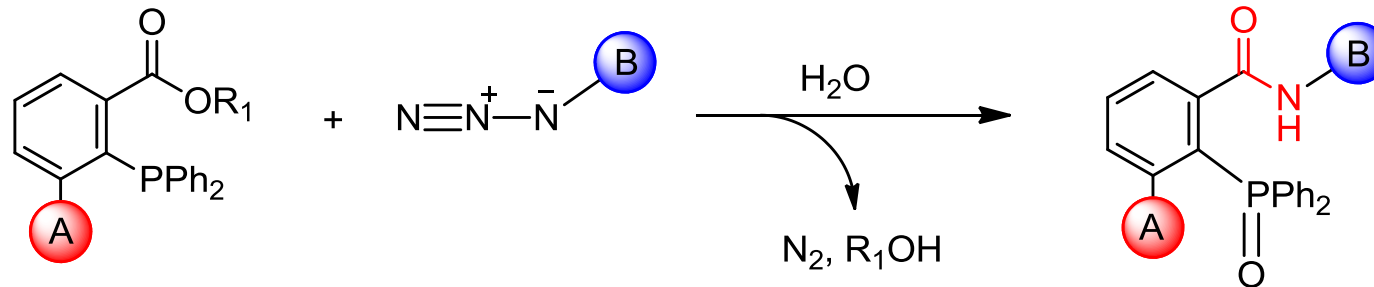
- Motivation
  - chemoselektiv
  - wässriges Milieu
  - keine Schutzgruppen
  
- Merkmale der Azid-Gruppe
  - bioorthogonal
  - reaktiv, trotzdem selektiv
  - kleine Größe

# SL – Rückblick: Staudinger Reaktion



# SL – nontraceless Staudinger Ligation

## ■ Schematisch

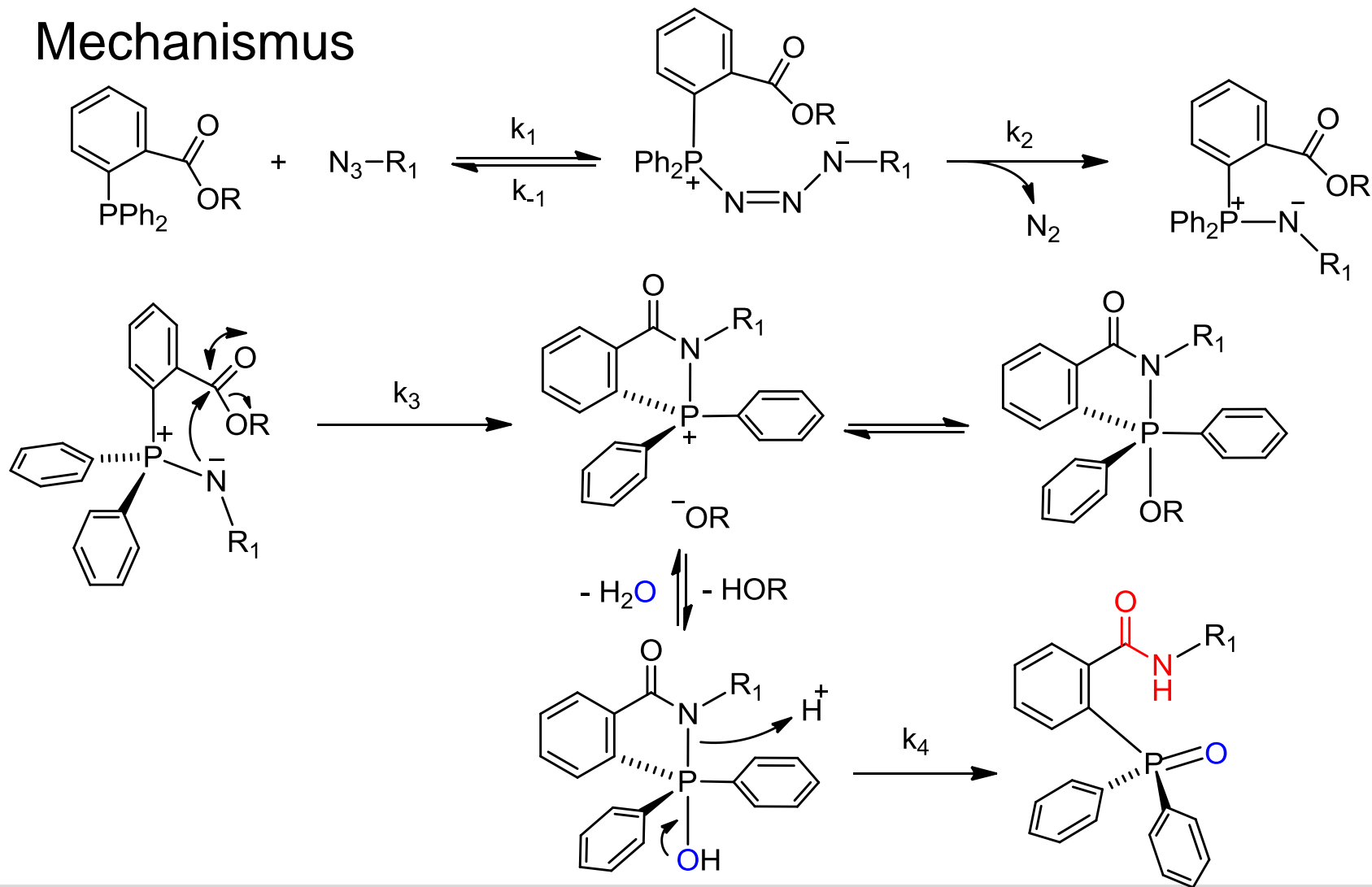


➔ elektrophile Falle verbleibt im Molekül



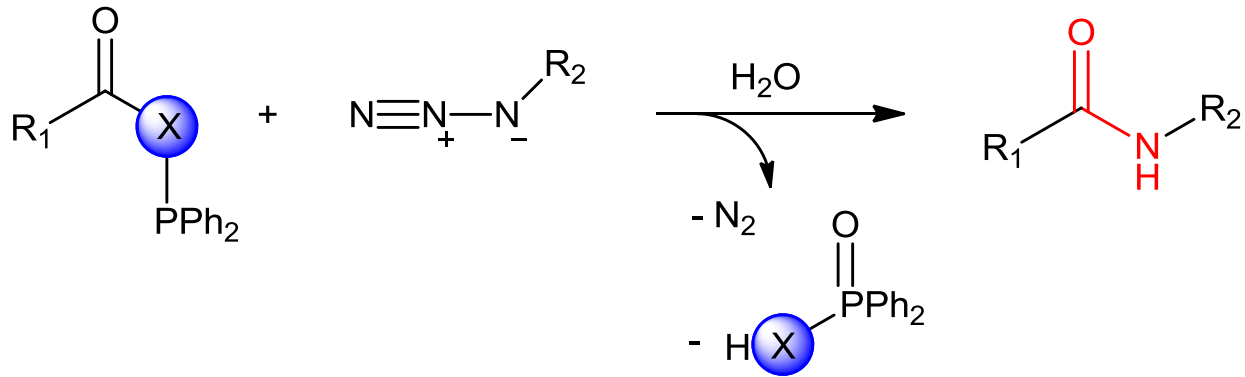
# SL – nontraceless Staudinger Ligation

## Mechanismus

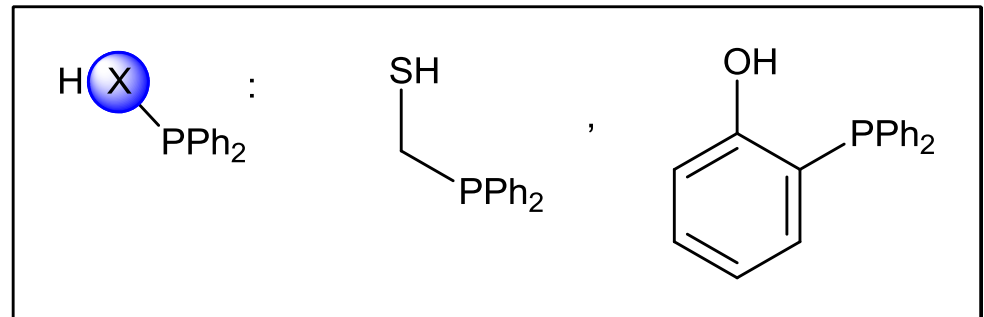


# SL – traceless Staudinger Ligation

## ■ Schematisch

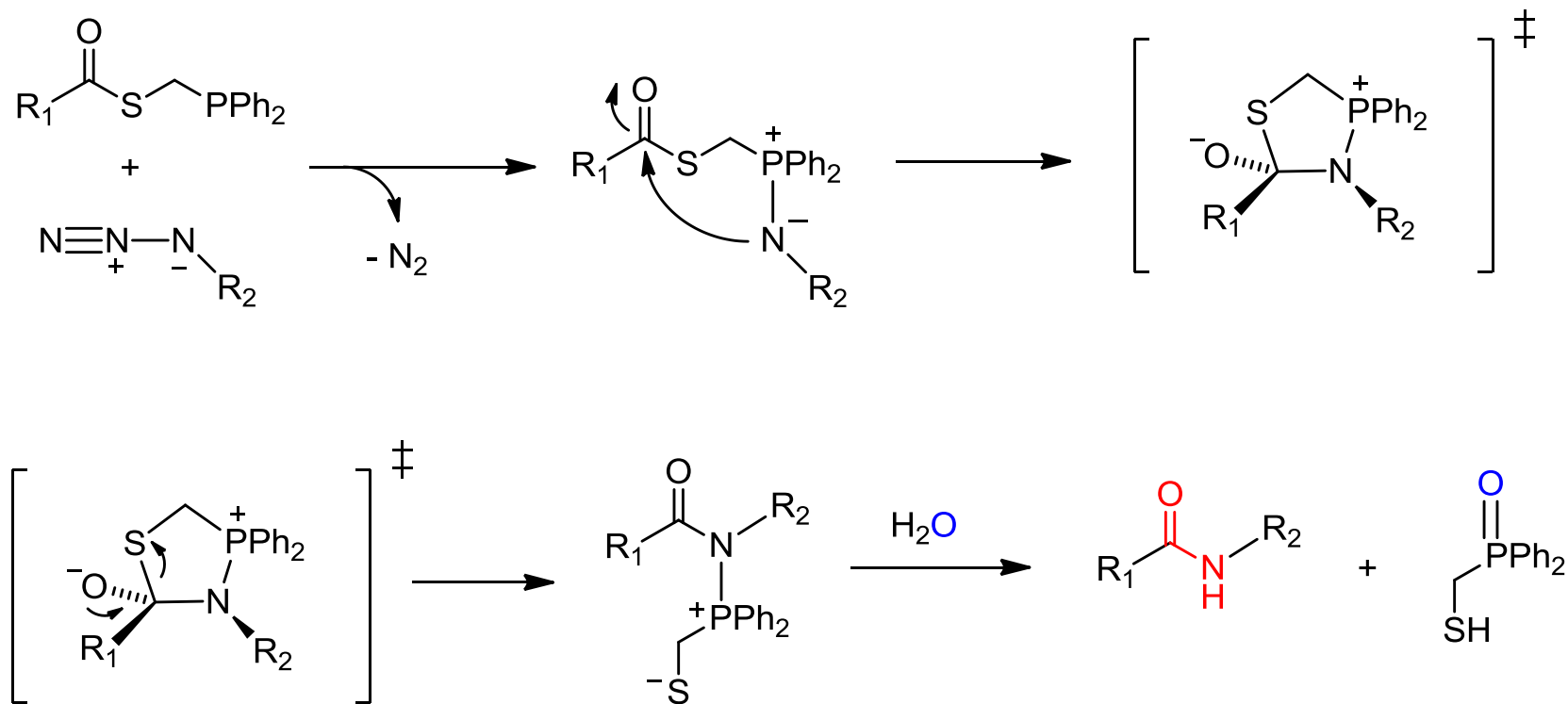


➔ elektrophile Falle verlässt das Molekül



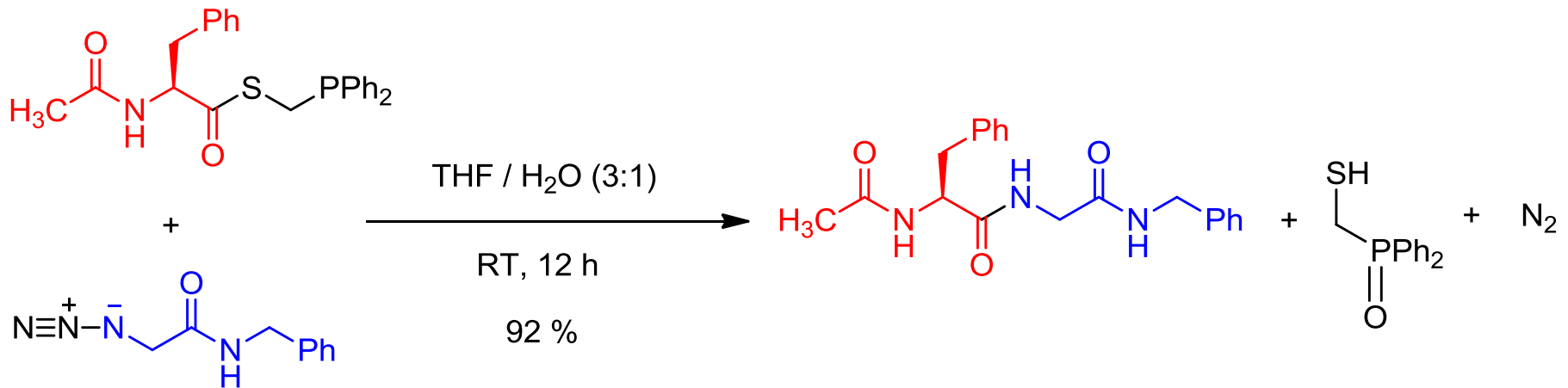
# SL – traceless Staudinger Ligation

## Mechanismus



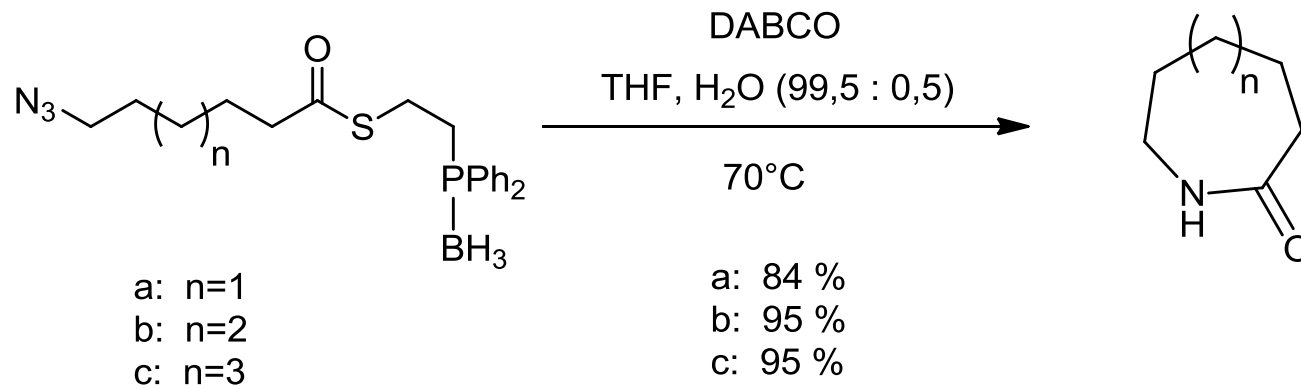
# SL – Anwendung

## ■ Peptid – Ligation

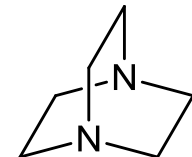


# SL – Anwendung

## ■ Synthese mittelgroßer Lactame



DABCO:



# Zusammenfassung

## ■ Native chemische Ligation

- Thioester + Cystein

- + chemoselektiv
- + keine Schutzgruppen
- + wässriges Milieu

- nur mit Cystein
- kein Prolin kuppelbar

## ■ Staudinger Ligation

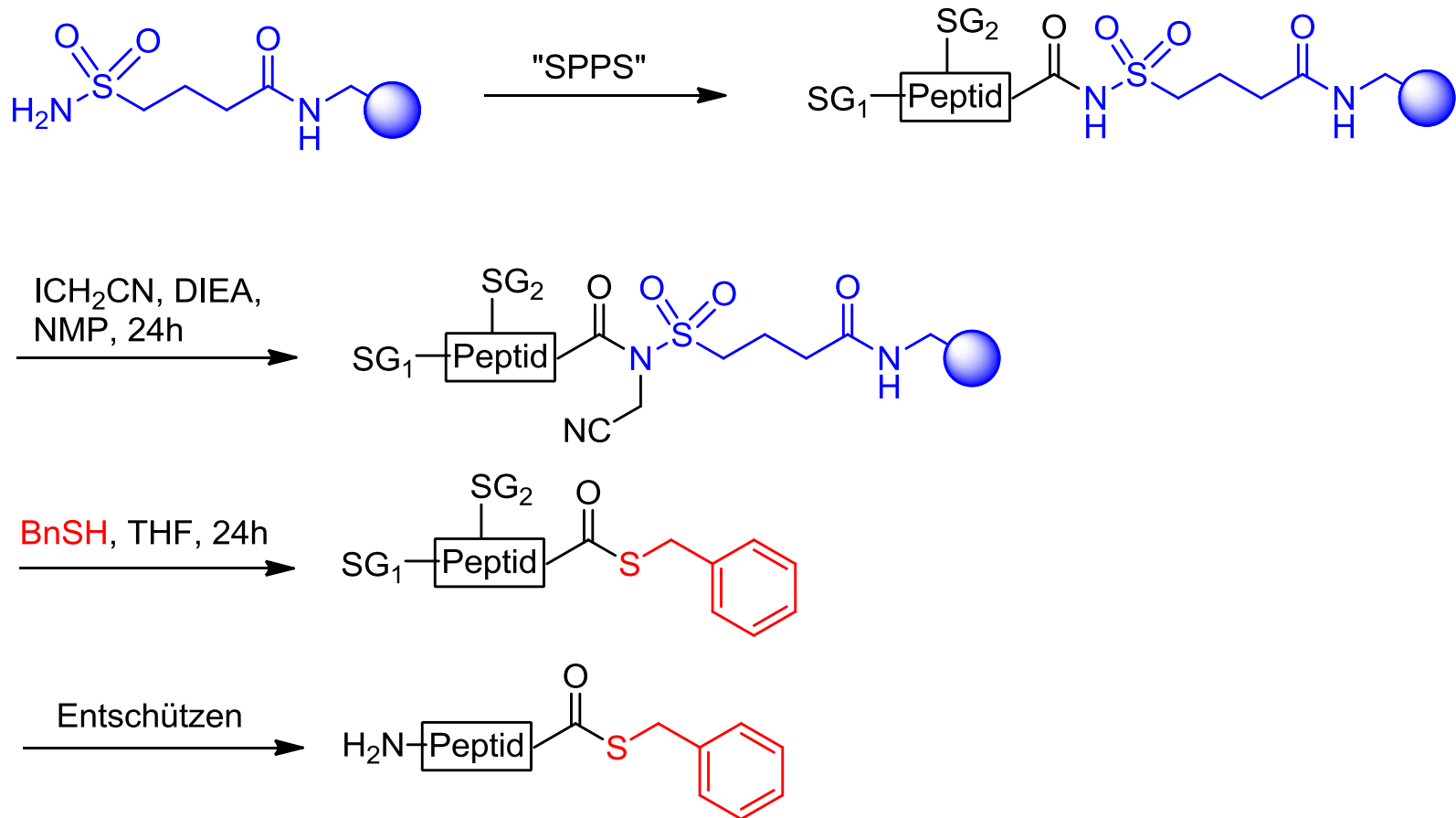
- Azid + Phosphan
- nontraceless / traceless

- + chemoselektiv, bioorthogonal
- + keine Schutzgruppen
- + wässriges Milieu

- mind. 1 Glycin vorteilhaft

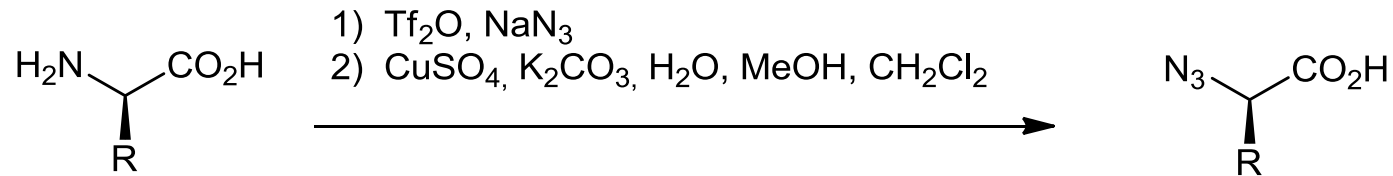
# Darstellung der Thioester-Peptide

## ■ Alkansulfonamid „safety-catch“-Linker Methode



# Darstellung der Azid-Aminosäuren

## ■ Cu(II)-katalysierter Diazo-Transfer nach Wong





# Abspaltung der Thz-Schutzgruppe

