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CRSI RSC-15  
March 24, 2022



## Unprecedented Chemoselective O-functionalization of Prolinol: An Unmediated Approach to Access Organocatalysts

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Under the supervision of

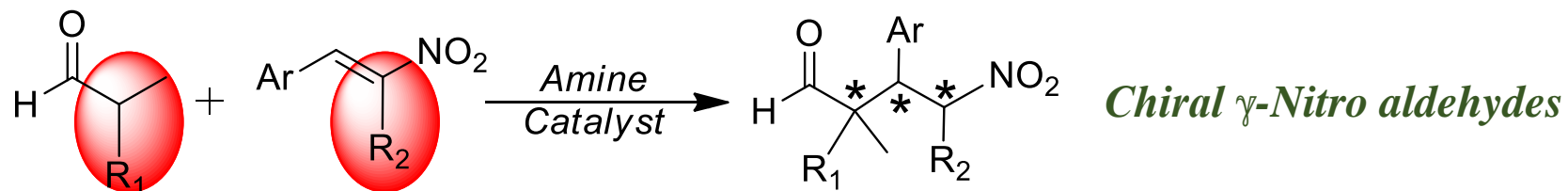
*Dr. Gokarneswar Sahoo*

**Organocatalysis and Synthesis Laboratory**

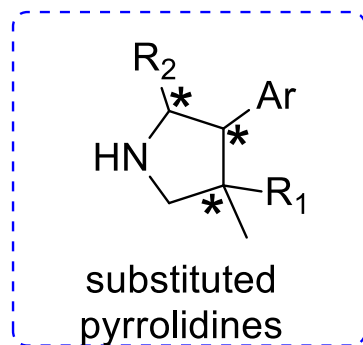
*National Institute of Technology Rourkela*

Odisha, 769008

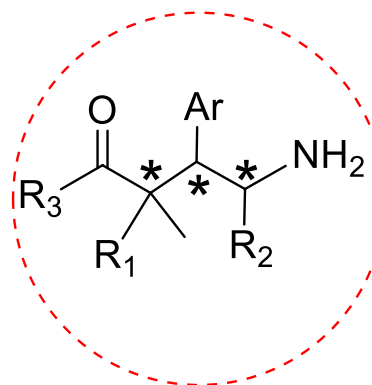
# *Our aim and motivation for work: Asymmetric Michael addition reaction*



Known Organic Transformations

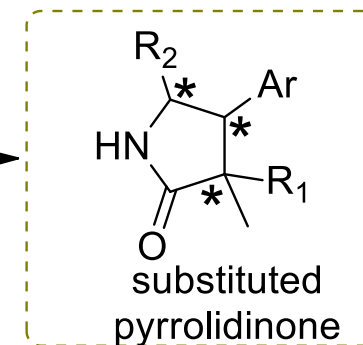


*Present in structural frameworks of various natural products*

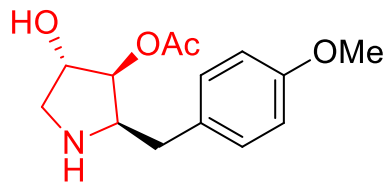


GABA: R<sub>3</sub> = OH

*GABA analogues- Inhibitory Neurotransmitters*

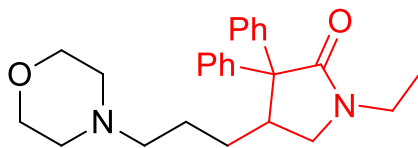


*Present in structural frameworks of various natural products*



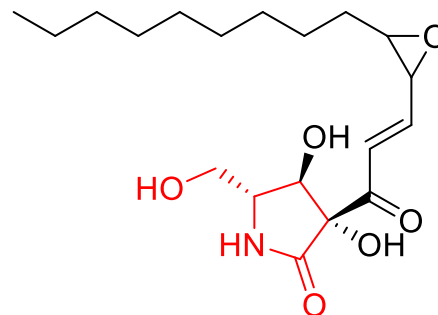
**Anisomycin**

As an inhibitor in eukaryotic protein synthesis.



**Doxapram**

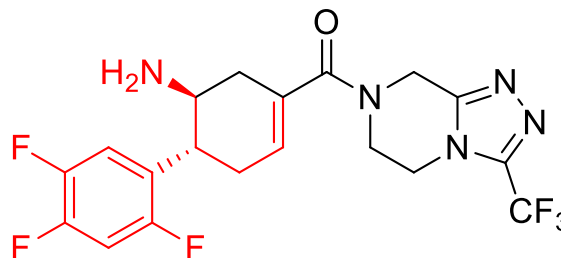
used to stimulate breathing  
Also used during recovery period of anesthesia



**Pramixinic**

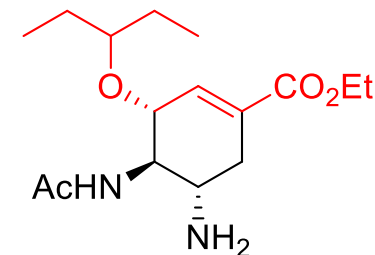
antimicrobial and antibacterial activity.

*Functionalized  $\gamma$ -lactams/pyrrolidines are of high interest and have great potential in medicinal chemistry.*



**ABT-341**

DPP4-selective inhibitor  
used in therapy for type 2 diabetes



**Oseltamivir**

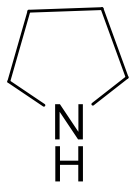
prevention of influenza A and influenza B  
**SWINE FLU**

*Michael additions of aldehydes with nitroalkenes catalysed by diphenylprolinol silyl ether proved to be a powerful method for the synthesis of the above*

## ***Our Assumption Towards an Optimum Catalyst***

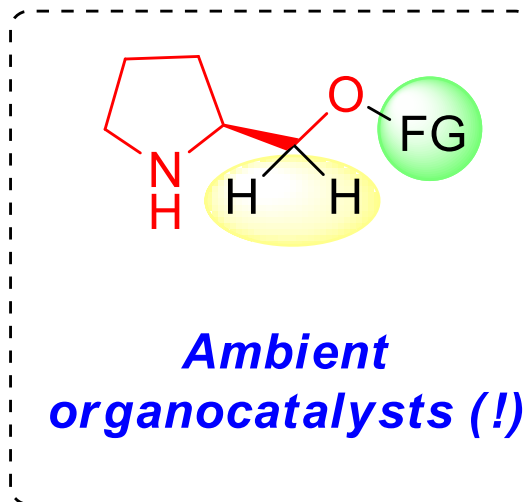
- ❖ *As a first attempt it was assumed that an **intermediate prolinol** derived catalyst with **suitable steric** in the ring might be needed for the transformation*
- ❖ *Where there would not be any compromise towards the **yield and selectivity***

# ***Steric tuning of prolinol based organocatalysts***



**Pyrrolidine**

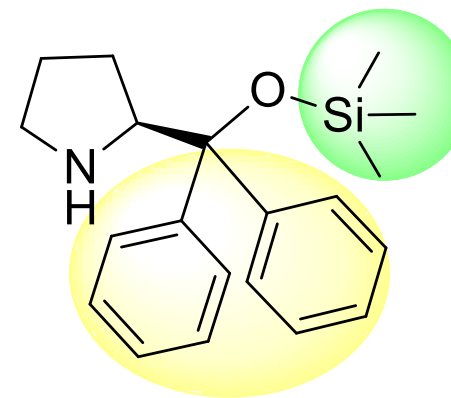
- \* **Successful catalyst**
- \* **Racemic adduct**
- \* **Less bulky**



**Ambient  
organocatalysts (!)**

*Steric enough to give  
selectivity*

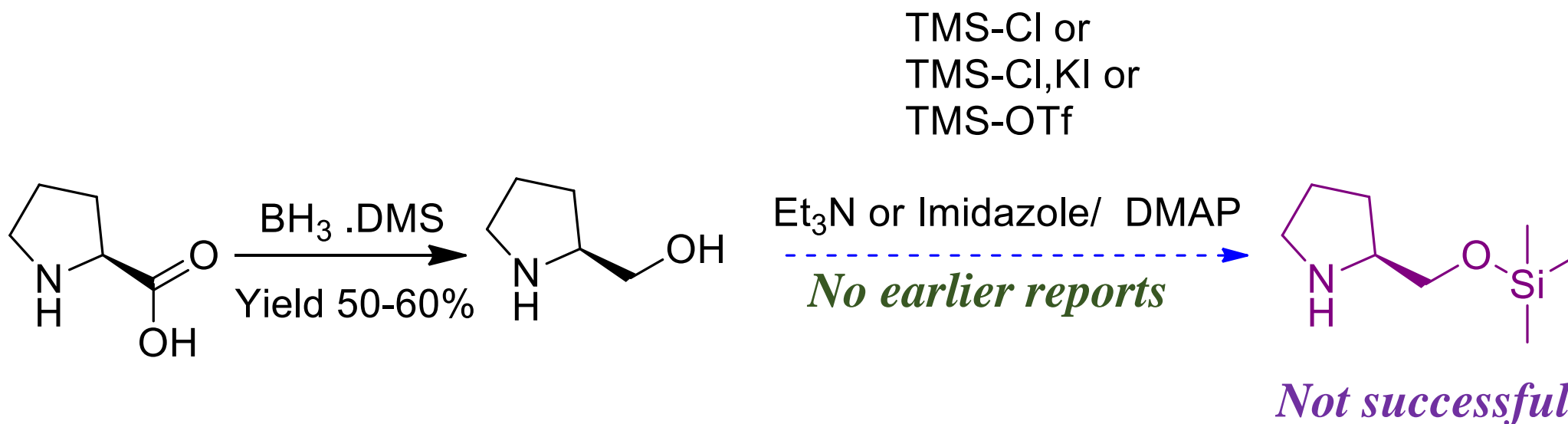
*Not steric enough to give  
reactivity*



**Hayashi-Jorgensen catalyst**

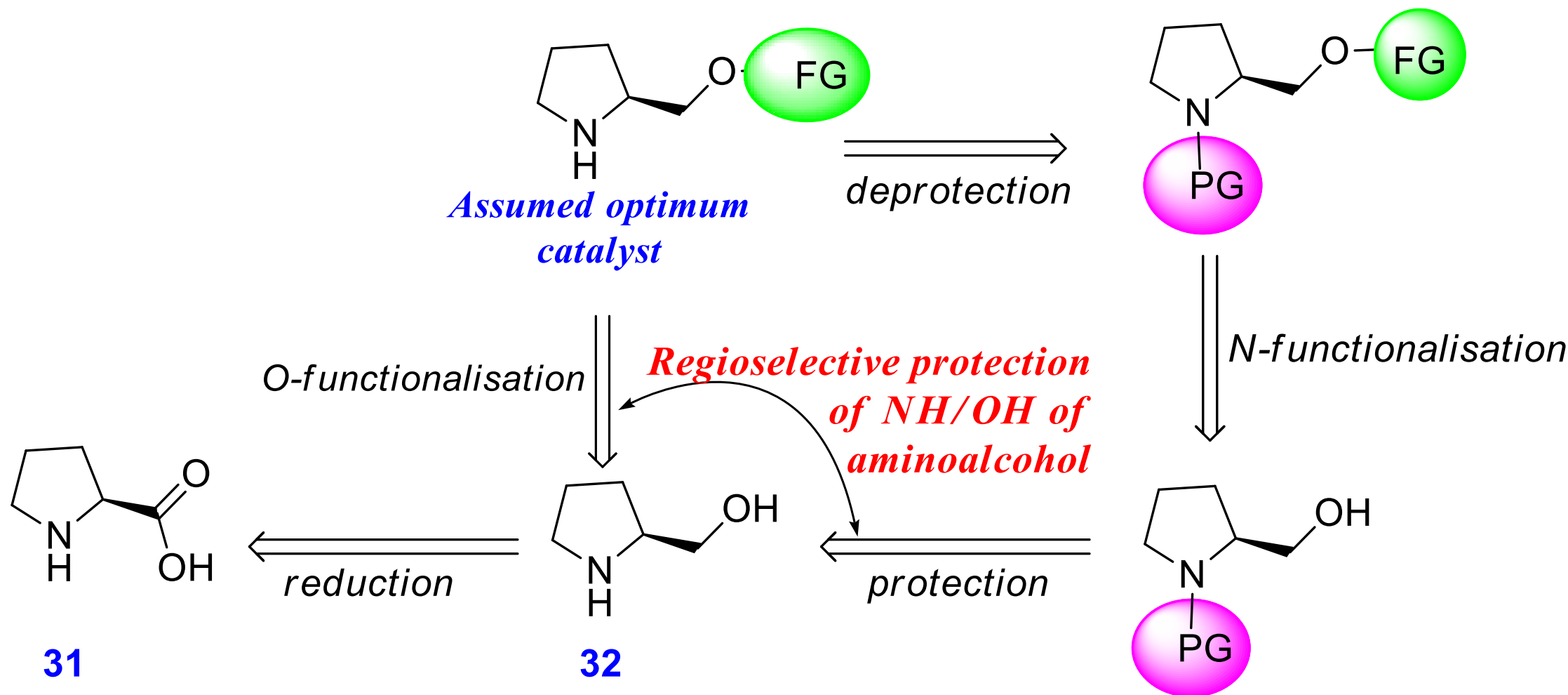
- \* **Failed catalyst (very bulky)**
- \* **Selective for less hindered substrates**

## *First attempt towards an ambient organocatalyst*

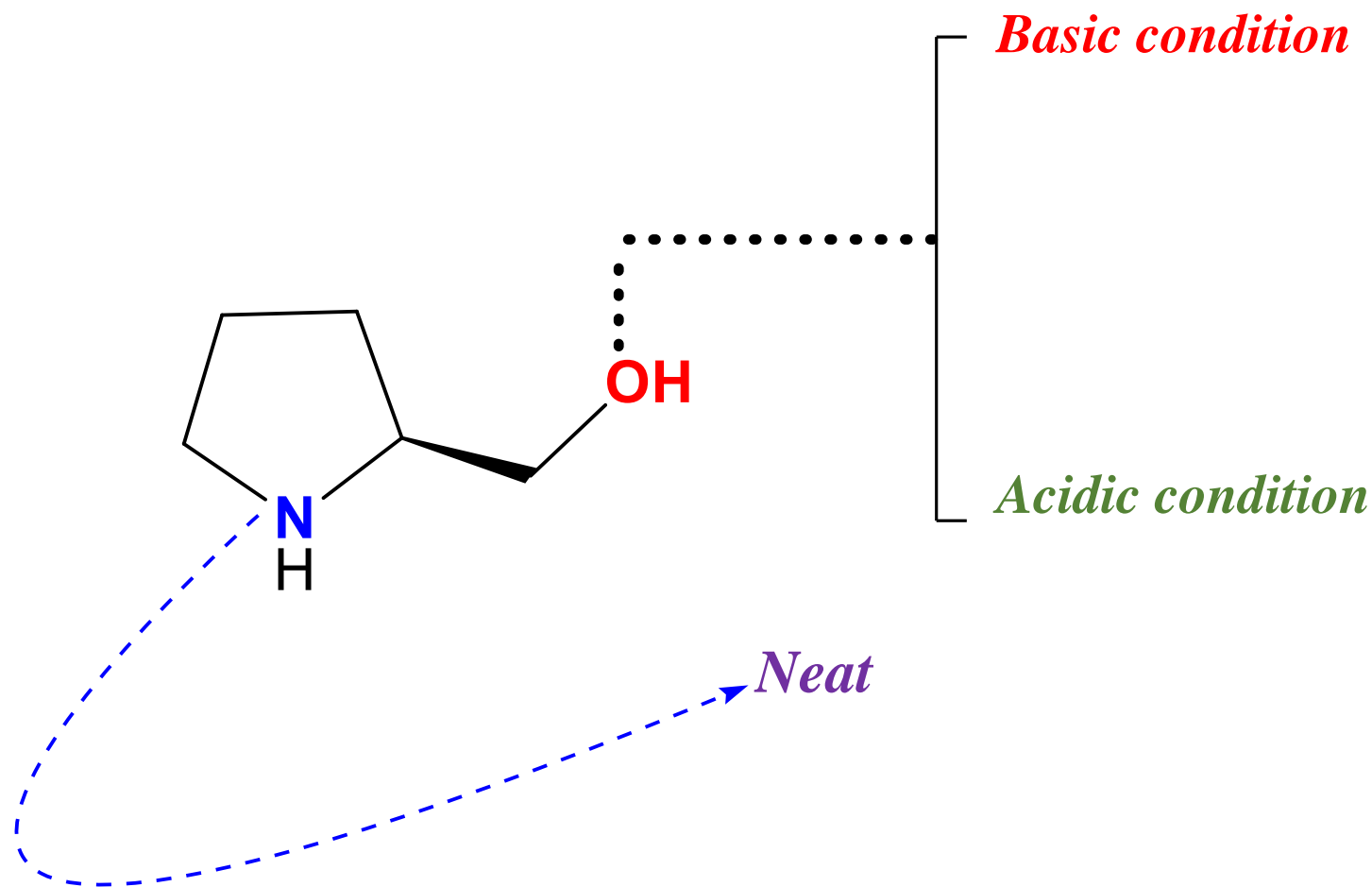


- *Assuming the issue of regioselectivity and the formation of hydrophilic salt, a lengthier yet simpler procedure was adapted*

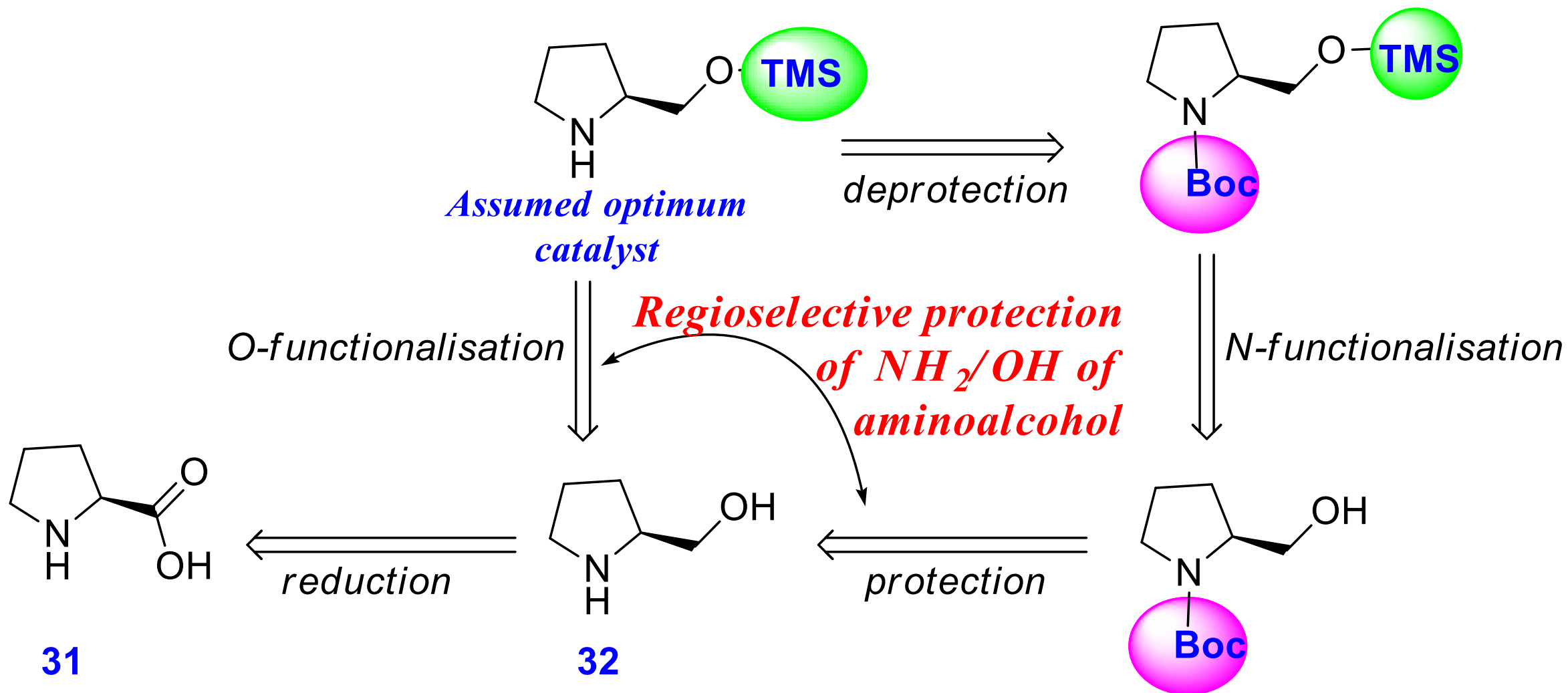
# Retrosynthetic route for catalyst synthesis



➤ *The functional reactivity between an amine group and alcohol group towards an electrophile is quite close*

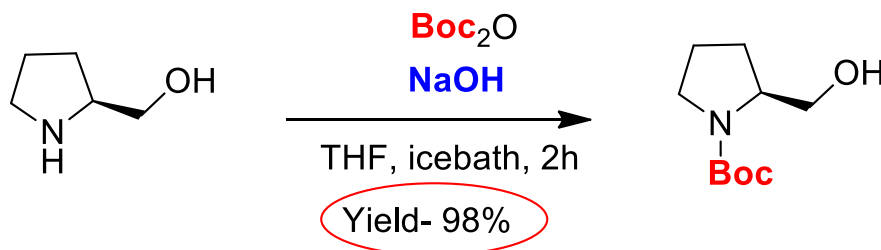




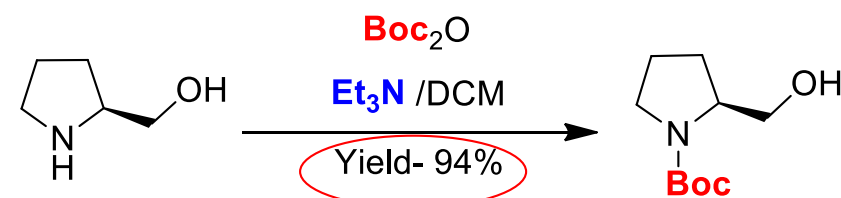


# Literature precedence for Boc-protection of aminols:

## Base catalysed amine protection of prolinol:

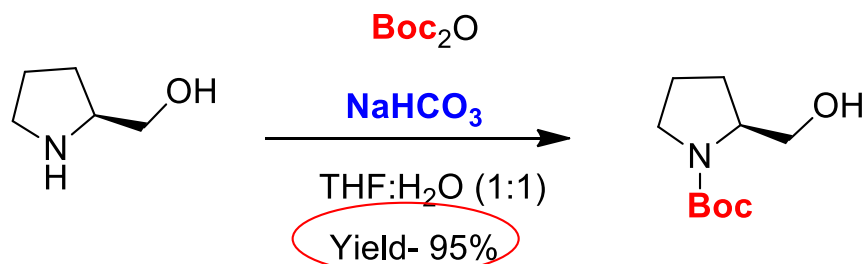


Lentini, G. *ChemMedChem* **2010**, 5, 696

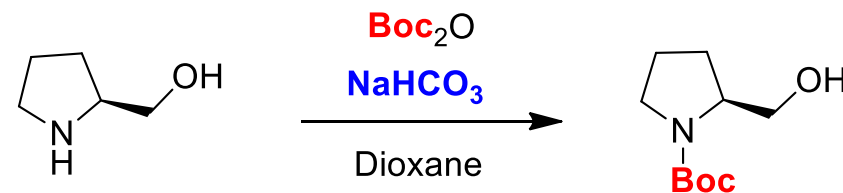


Molander G. A. *Tetrahedron*. **2005**, 61, 2631

Chuan, F. L. *Tetrahedron Lett.* **2013**, 54, 3777

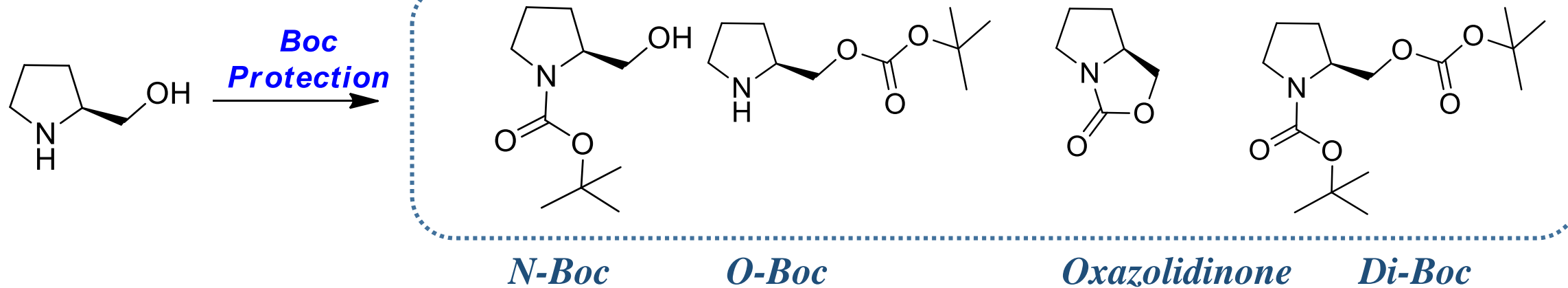


Llop, J. *Tetrahedron Lett.* **2011**, 52, 615

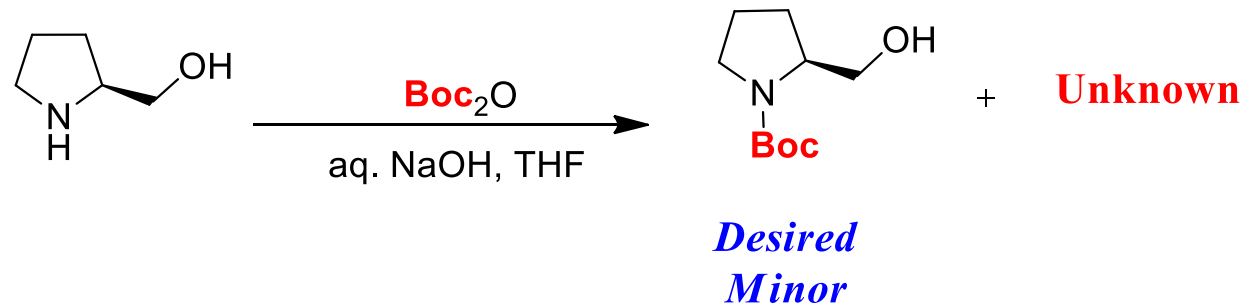


Wu, A. *Eur. J. Org. Chem.* **2014**, 7823

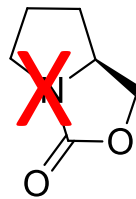
# *Possible competing products during Boc protection of aminols*



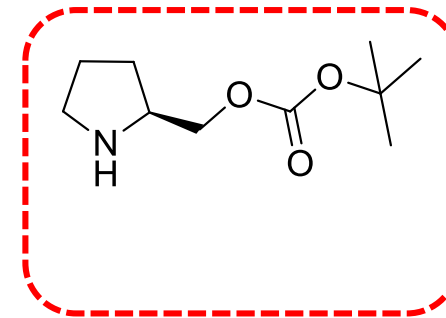
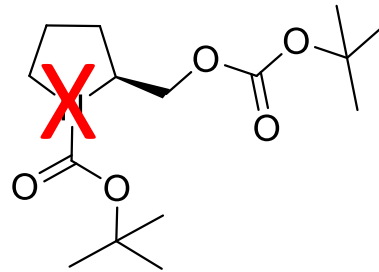
## *Base Catalysed Boc protection of aminols:*



## *Conclusions from NMR analysis*

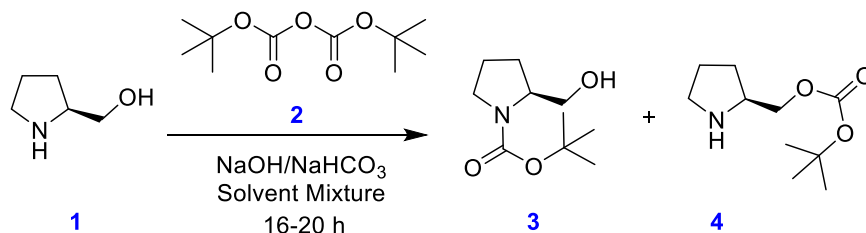


*Not a match with  
previously reported  
NMR data*



*Characterised by  
1D and 2D NMR  
data*

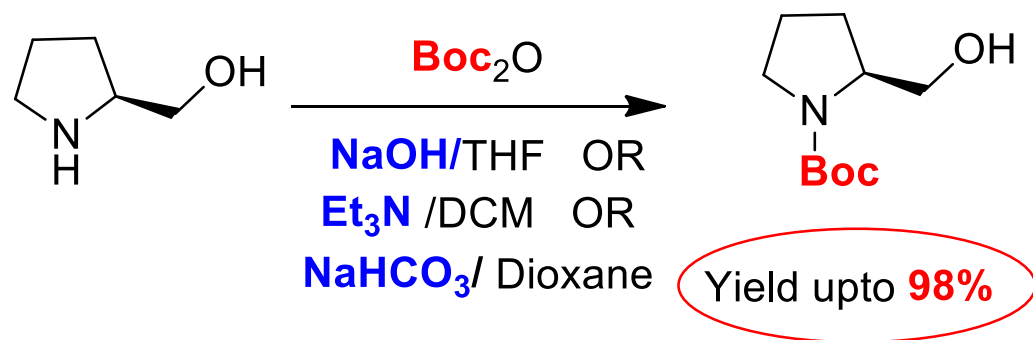
## Optimisation for regioselective synthesis of *O*-Boc-(*S*)-prolinol in *wet solvent*



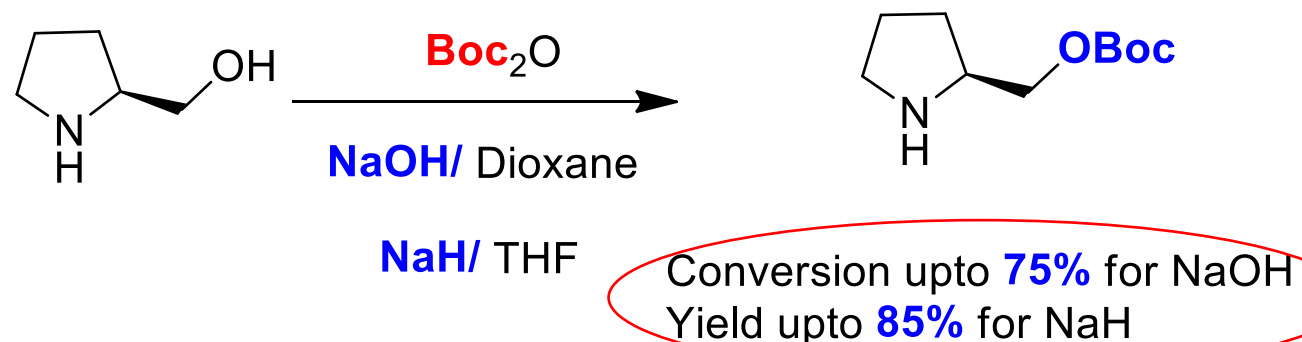
| Entry | Boc <sub>2</sub> O (mol%) | Base (mol%/M in H <sub>2</sub> O) | Solvent             | Ratio of compounds 1:3:4 |
|-------|---------------------------|-----------------------------------|---------------------|--------------------------|
| 1     | 120                       | NaOH (100 / 1M)                   | THF                 | 47:21:32                 |
| 2     | 100                       | NaOH (120 / 1M)                   |                     | 50:07:42                 |
| 3     |                           | NaOH (200 / 1M)                   |                     | 49:14:37                 |
| 4     |                           | NaOH (120 / 1M)                   | Dioxane             | 62:15:23                 |
| 5     |                           | NaOH (200 / 1M)                   |                     | 27:20:53                 |
| 6     |                           | NaOH (300 / 1M)                   |                     | 61:09:30                 |
| 7     |                           | <b>NaOH (300 / 3M)</b>            |                     | <b>13:12:75</b>          |
| 8     |                           | NaOH (200 / 1M)                   | MeOH                | 91:09:00                 |
| 9     |                           | NaHCO <sub>3</sub> 100            | Dioxane:Water (1:1) | 88:12:00                 |

- *Poor conversion in THF and MeOH*
- *Dioxane-soluble both in organic and water layer*
- *The conversion and regioselectivity was moderate*

*Literature suggests*



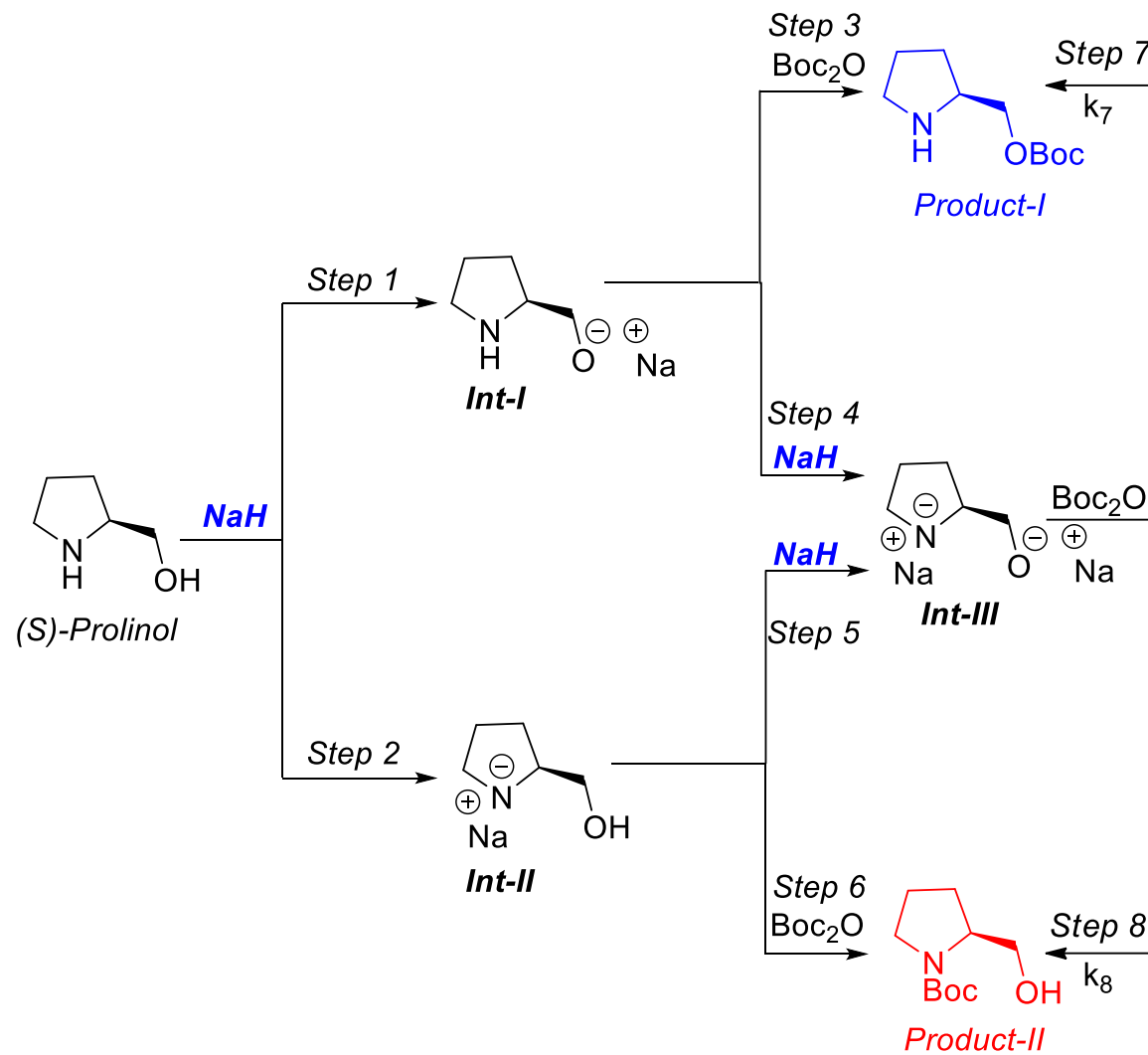
*Our Protocol Contradicts It*



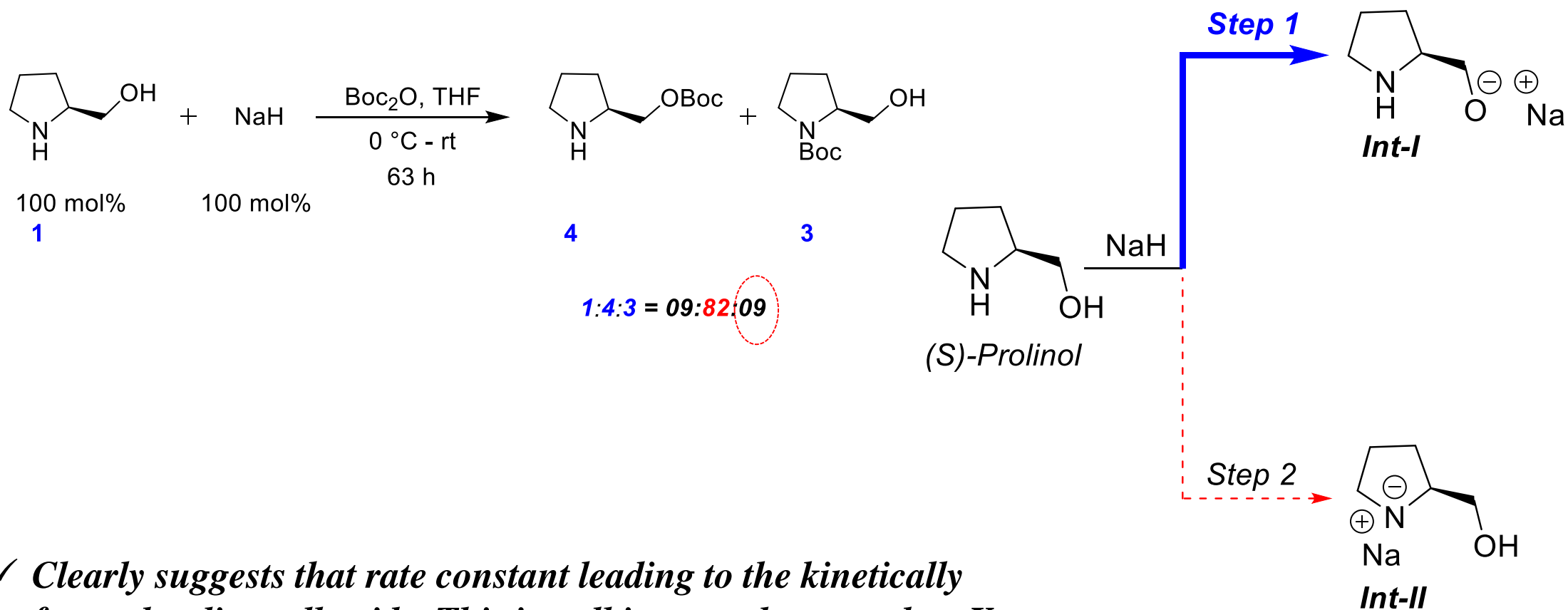
# Mechanistic investigation for the regioselective mono-Boc protection of (S)-prolinol

## Competing pathways for the mono-Boc protection of (S)-prolinol and the kinetics therein

- i) Abstraction of H from OH/NH
  - ii) Nucleophilic attack of N/O<sup>-</sup> to the Boc<sub>2</sub>O
- The initial competition of “H-abstraction by NaH (Step 1 vs step 2)” followed by “the second H abstraction in case of **excess base** or the nucleophilic attack of the anion to Boc<sub>2</sub>O (step 4 vs step 3/step 5 vs step 6 respectively)” would decide any kind of regioselectivity
- Also if the dianion (Int-III) forms, then the regioselectivity would depend on the preferential attack of the N/O<sup>-</sup> to the Boc<sub>2</sub>O (step 7 vs step 8).



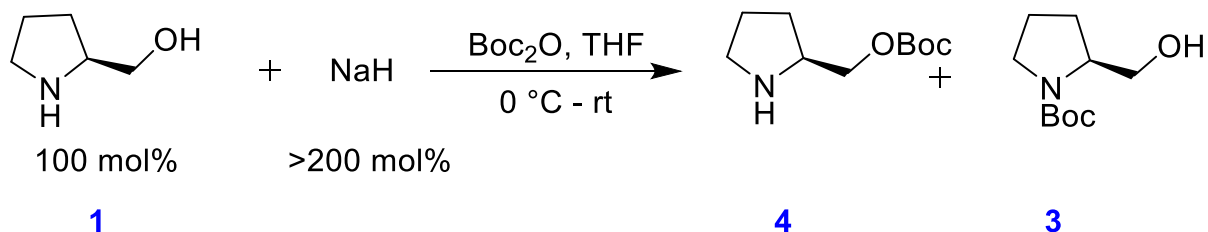
*Controlled experiments to establish the preferred elementary steps:*



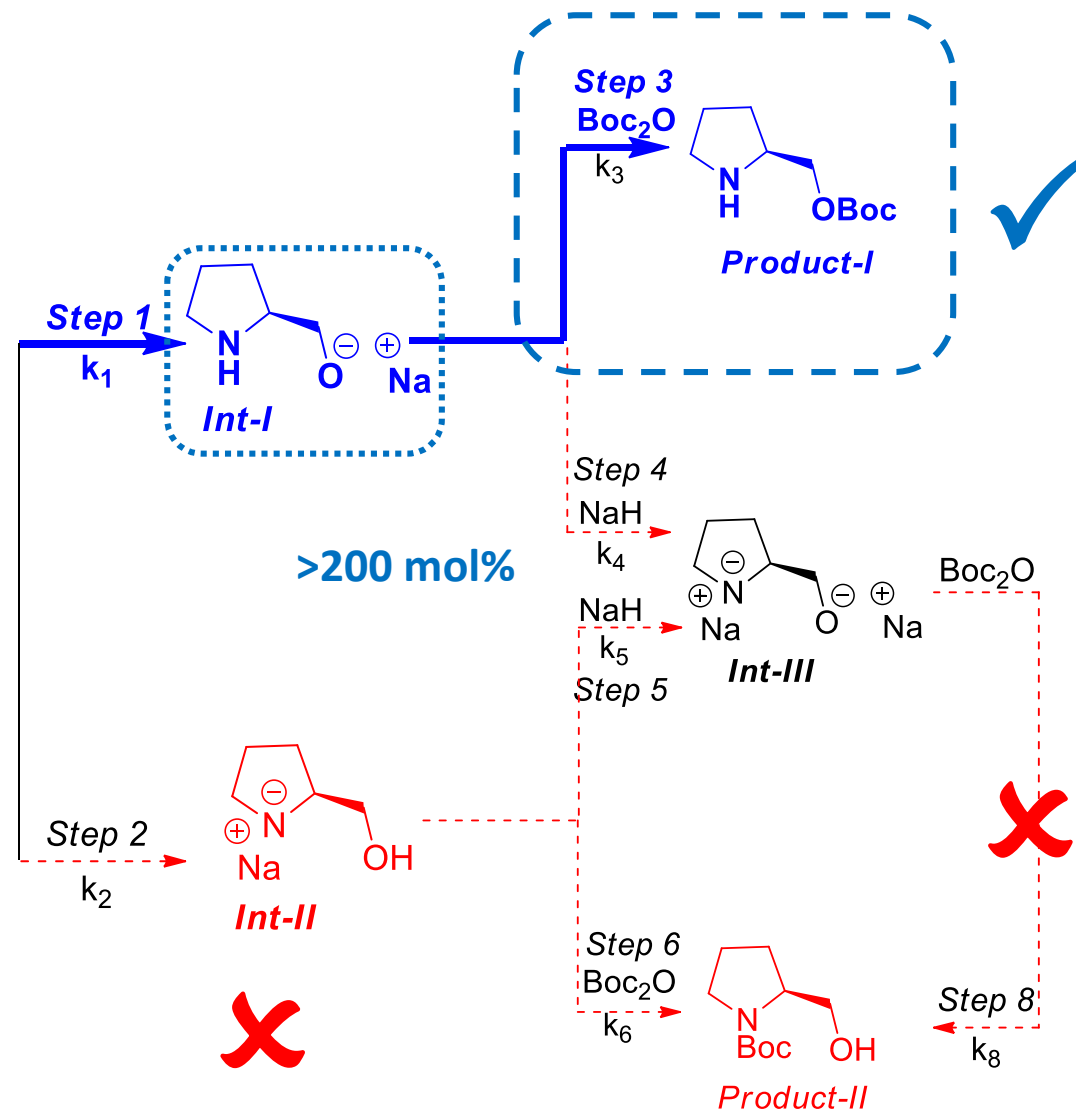
✓ *Clearly suggests that rate constant leading to the kinetically favored sodium alkoxide. This is well in accordance to the pKa of alcohol (pKa for EtOH in DMSO = 29.8) and amine (pKa for pyrrolidine in DMSO = 44.0).*



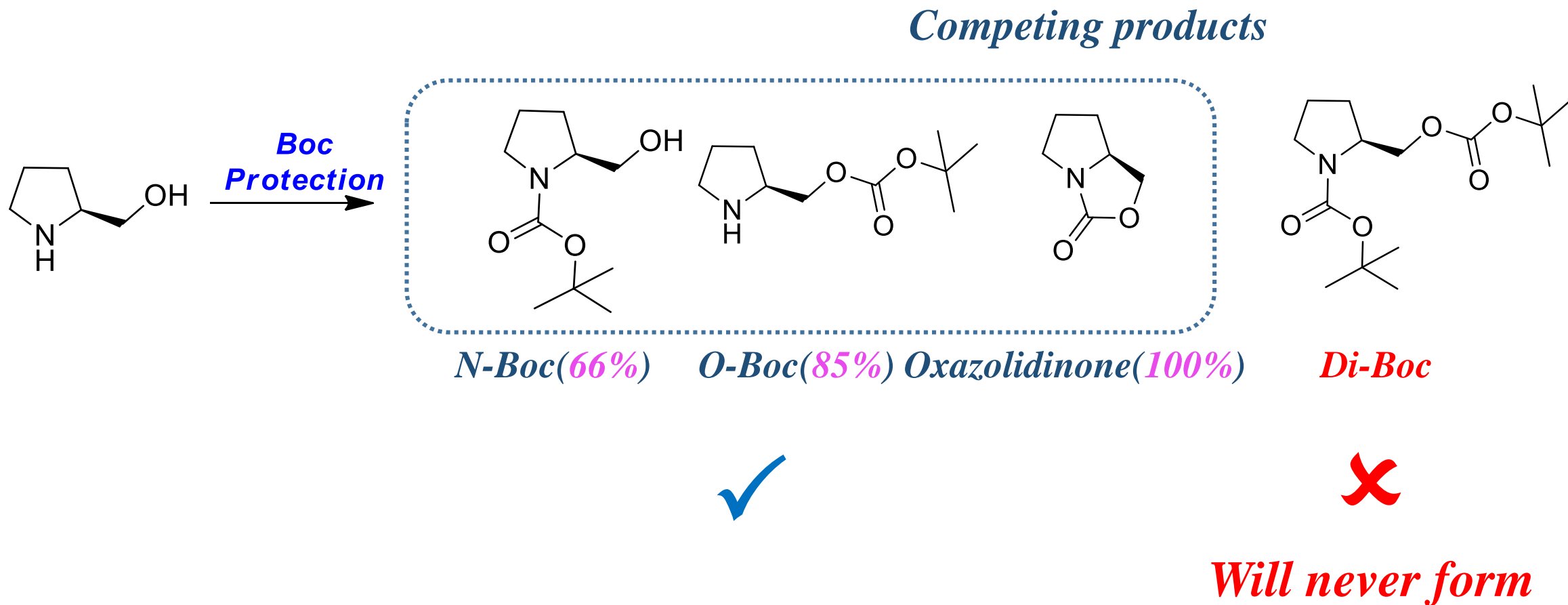
## Reaction with excess (> 200 mol%) NaH



| Entry | NaH mol% | Time       | (Boc) <sub>2</sub> O mol% | 1:3:4                    |
|-------|----------|------------|---------------------------|--------------------------|
| 1     | 300      | 2 h 30 min | 100                       | 00:07:93 ( <b>85%*</b> ) |
| 2     | 220      | 4 h 20 min |                           | 00:07: <b>93</b>         |



*Successfully synthesized all the Possible competing products*



# *Summary*

- Contrary to the earlier reports never-reported-before O-Boc-(S)-prolinol was noticed in the Boc protection of (S)-prolinol in base-mediated reactions . Furthermore, the synthesis of O-Boc-(S)-prolinol has been optimised to 85% and characterized thoroughly through 1D and 2D NMR spectroscopic data.
- The understanding of the elementary steps led us to find the optimised condition for the exclusive N-Boc protection of (S)-prolinol by delaying the addition of  $\text{Boc}_2\text{O}$ . N-Boc-(S)-prolinol could be synthesized in 66% yield.
- Base-catalysed deprotection of O-Boc functionality was successful, whereas N-Boc functionality led to the formation of oxazolidinone, confirming the slower abstraction of NH proton than the deprotection of the O-Boc compound.
- The other competing product Oxazolidinone could also be synthesized exclusively starting from (S)-prolinol, which again proved the superior elementary steps

## ***References :***

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2. Bujok, R.; Cmoch, P.; Wróbel, Z.; Wojciechowski, K. *Org. Biomol. Chem.* **2017**, 15, 2397.
3. Yang, R.; Qi, L.; Liu, Y.; Ding, Y.; Kwek, M. S. Y.; Chuan, F. L. *Tetrahedron Lett.* **2013**, 54, 3777.
4. Khong, S. N.; Kwon, O. *Molecules* **2012**, 17, 5626
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