

A Bee-Line Approach to Access Organocatalysts; Chemoselective & Time Driven O-functionalisation of Prolinol

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Organocatalysis and Synthesis Laboratory



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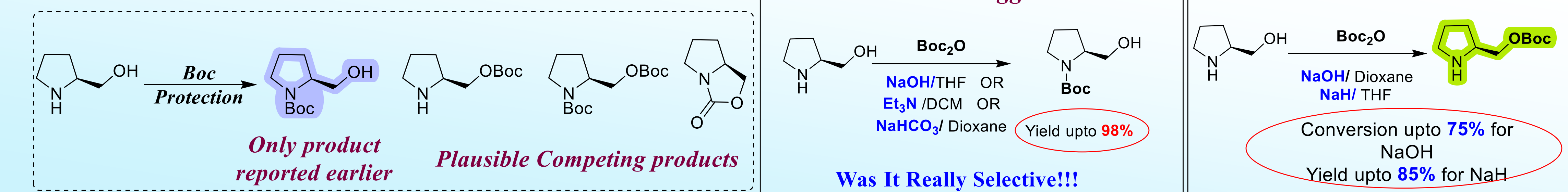
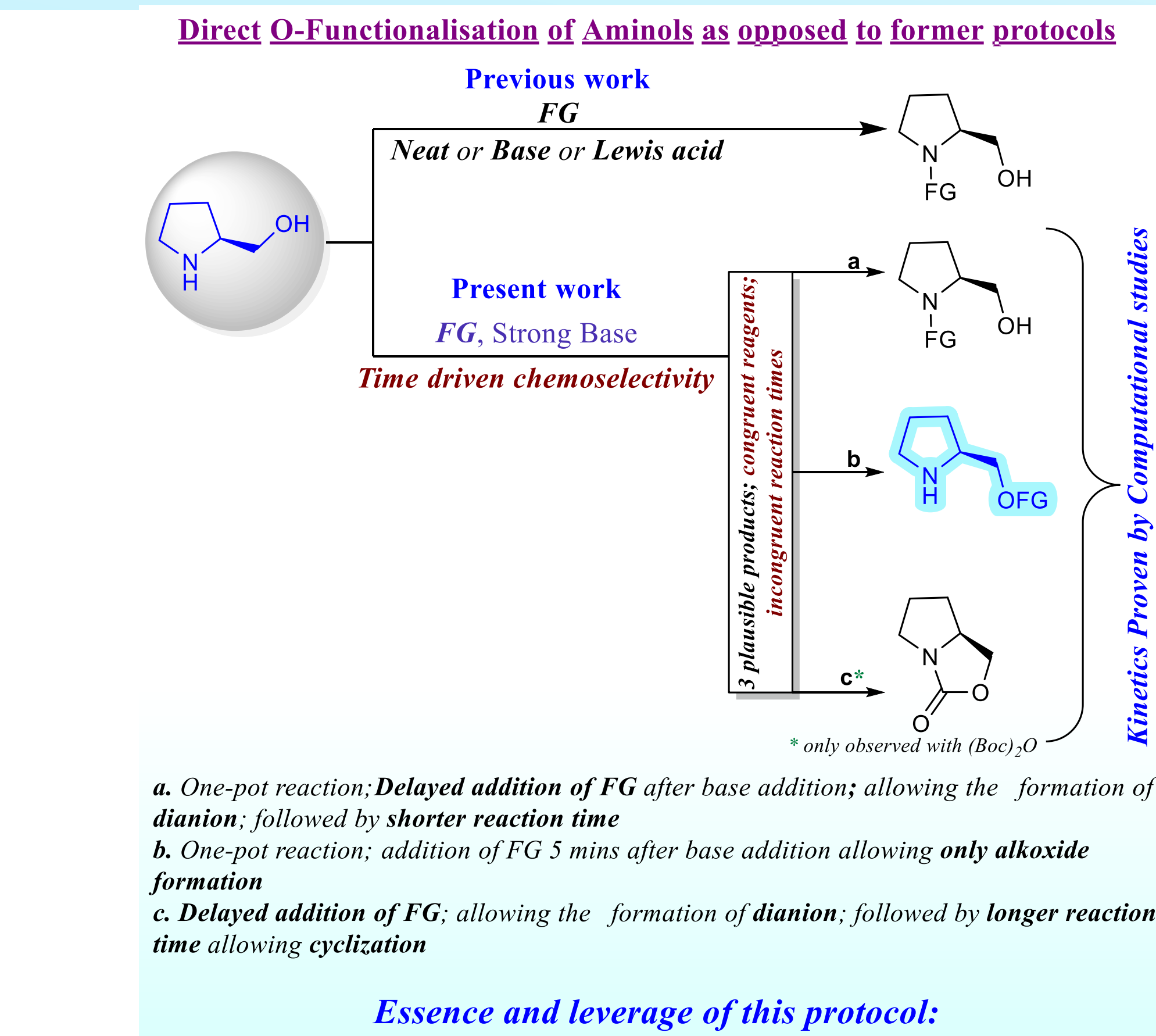
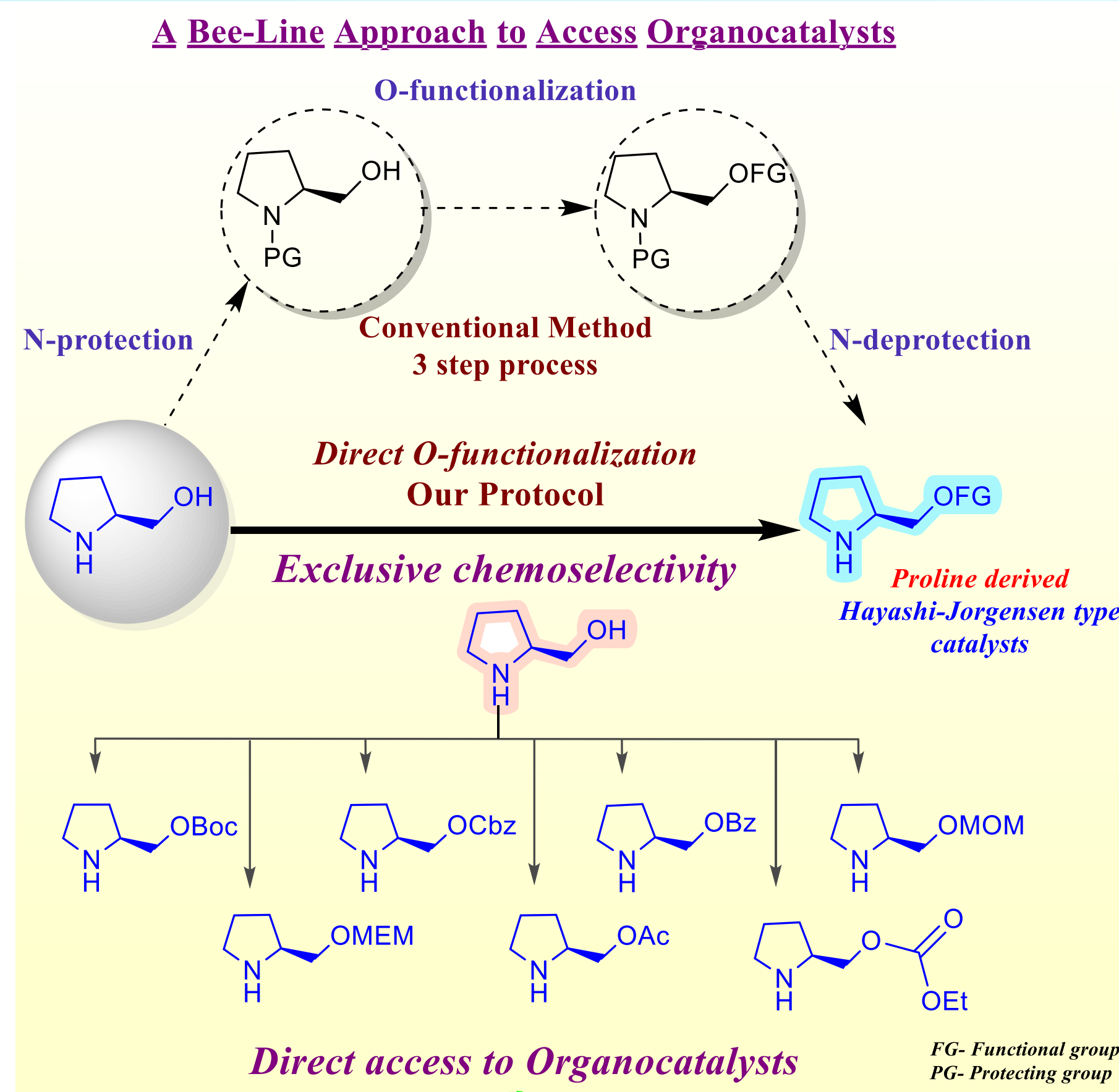
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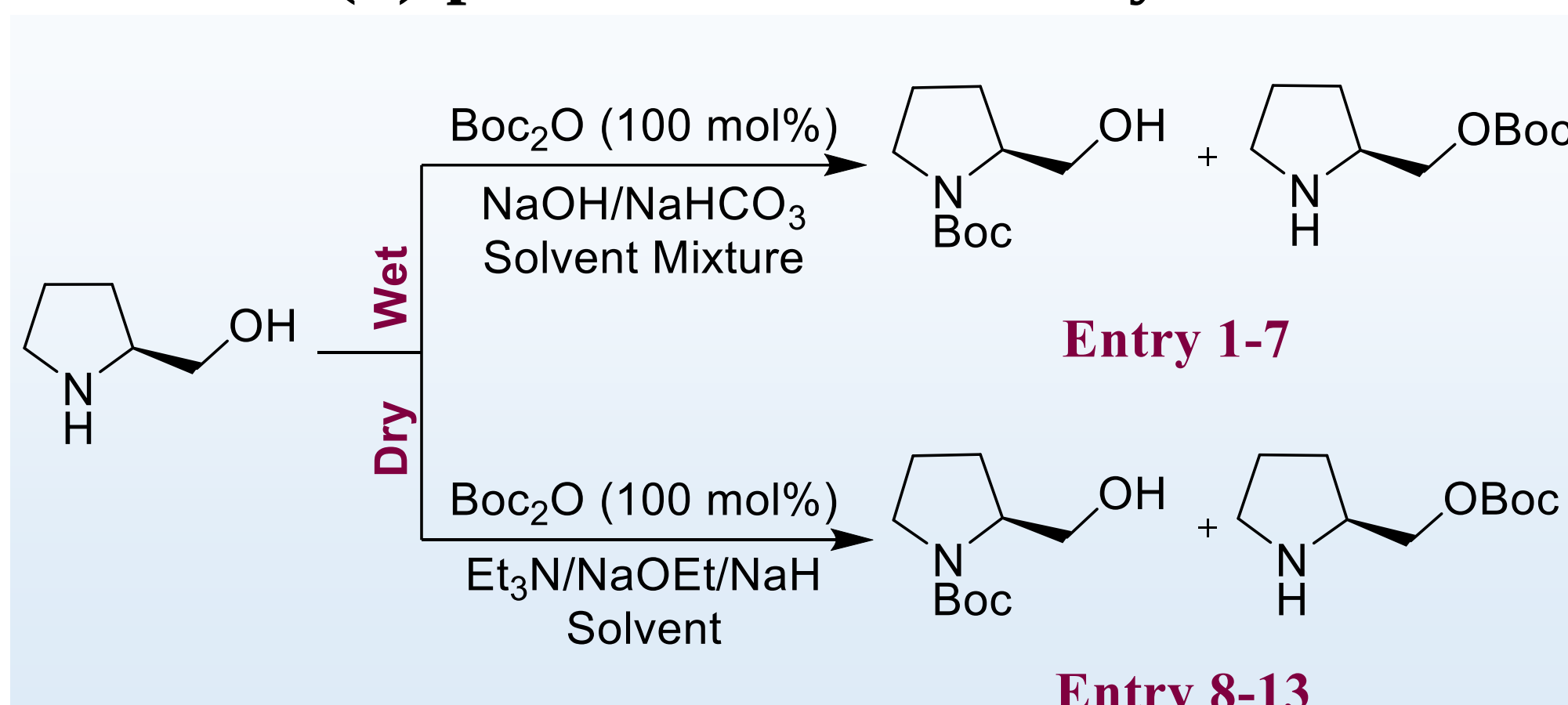
ABSTRACT:

Herein, a successful **chemoselective and time driven** either functionalisation of the nucleophilic sites of prolinol by exploiting the relative acidity difference and inverted nucleophilicity of the corresponding conjugate bases with a suitable base is reported. As an example, mono-Boc functionalisation of prolinol for the exclusive synthesis of either N-Boc/O-Boc/Oxazolidinone derivatives is reported. **Never reported-before O-Boc prolinol has been synthesized in 85% yield** and other known derivatives (N-Boc and oxazolidinone derivatives) have been synthesized in good to excellent yields. Failing to emulate the former protocols, a mechanistic investigation was initiated which revealed that the rudimentary steps can be controlled by: a) A requisite base to distinguish the differently acidic sites (-NH and -OH) for the formation of the conjugate base reacting to the electrophile b) The disparity in nucleophilicity of the completely formed conjugate basic sites. This protocol has been extended to be successful with various other substrates which might prove to be applicatory as suitable catalysts in asymmetric Michael addition reactions.

1. Introduction:

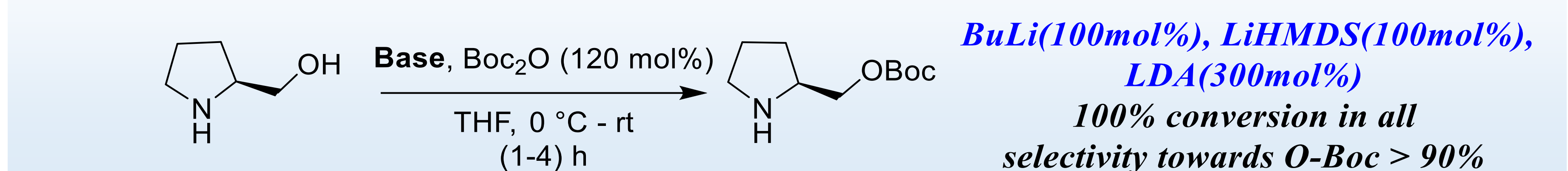


2.2. Optimisation for Chemoselective synthesis of O-Boc-(S)-prolinol in wet and dry solvents:

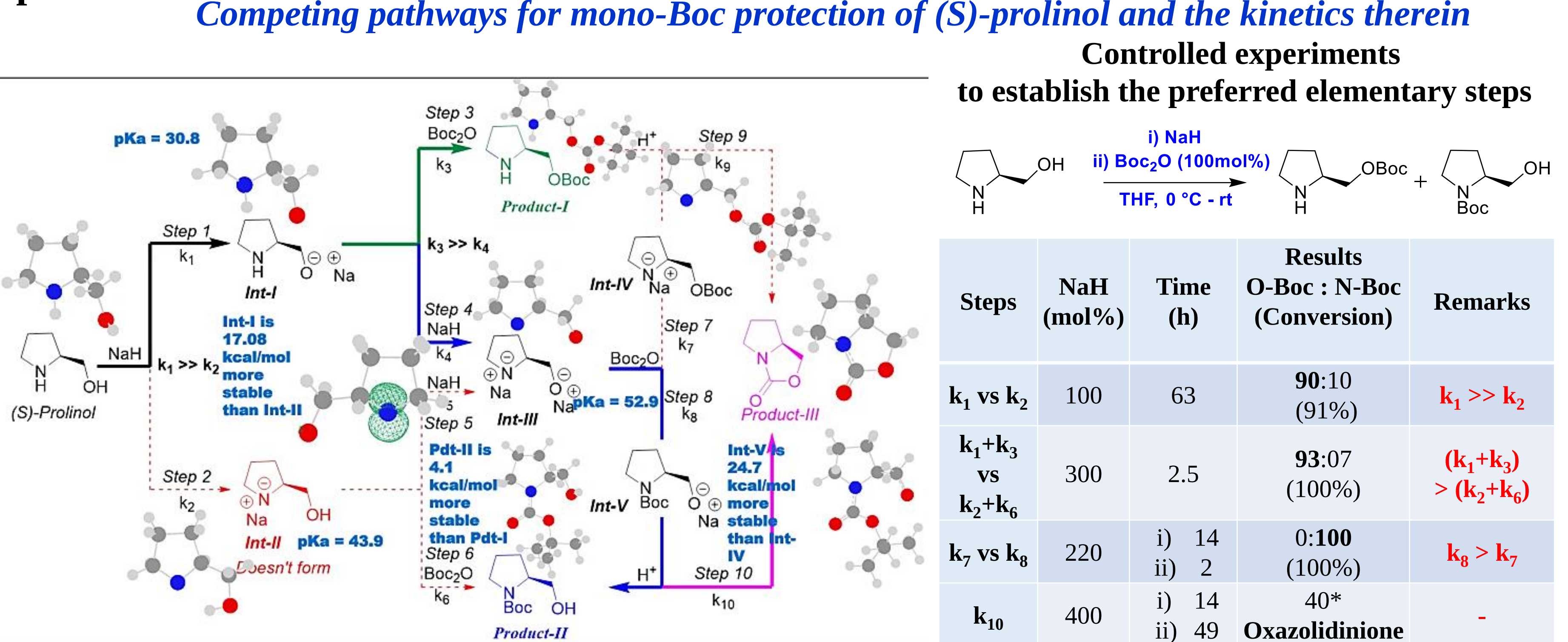


Entry	Base (mol% / M in H ₂ O)	Time (h)	Solvent	(%) Conversion	Product Ratio N-Boc:O-Boc
1	NaOH (100 / 1M)	23	THF	53	40:60
2	NaOH (200 / 1M)	23	THF	52	27:73
3	NaOH (200 / 1M)	23	Dioxane	73	27:73
4	NaOH (300 / 1M)	24	Dioxane	39	23:77
5	NaOH (300 / 3M)	37	Dioxane	87	14:86
6	NaOH (200 / 1M)	23	MeOH	9	100:00
7	NaHCO ₃ 200	24	Dioxane: Water (1:1)	12	100:00
8	Et ₃ N (200)	14	DCM	47	30:70
9	Et ₃ N (200)	21.5	Dioxane	30	100:00
10	Et ₃ N (200)	21.5	Dry THF	24	79:21
11	NaOEt (200)	21	Dry THF	8	100:00
12	NaH (100)	21	Dry THF	80	06:94
13	NaH (300)	2	Dry THF	100	02:98 yield- 85%

2.3. Bases Screened:

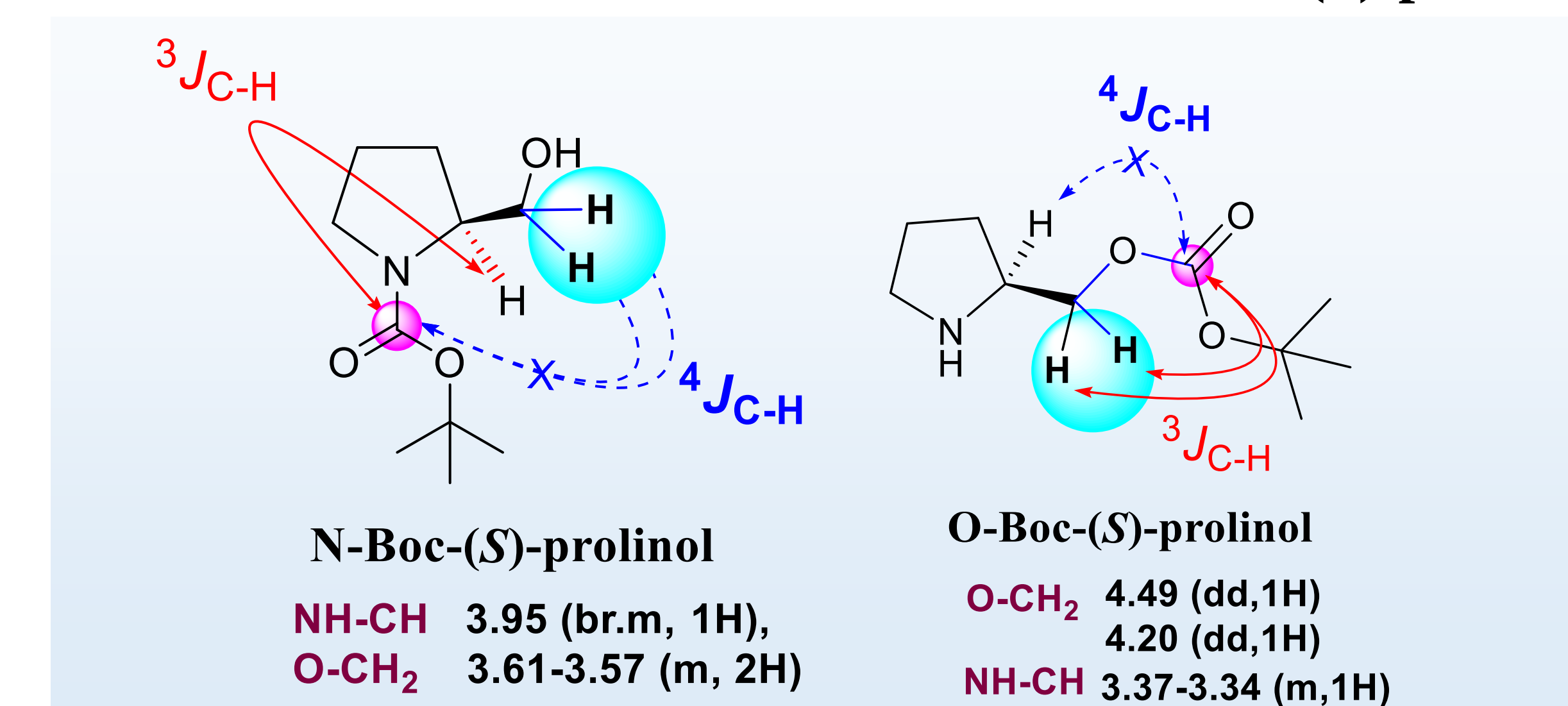
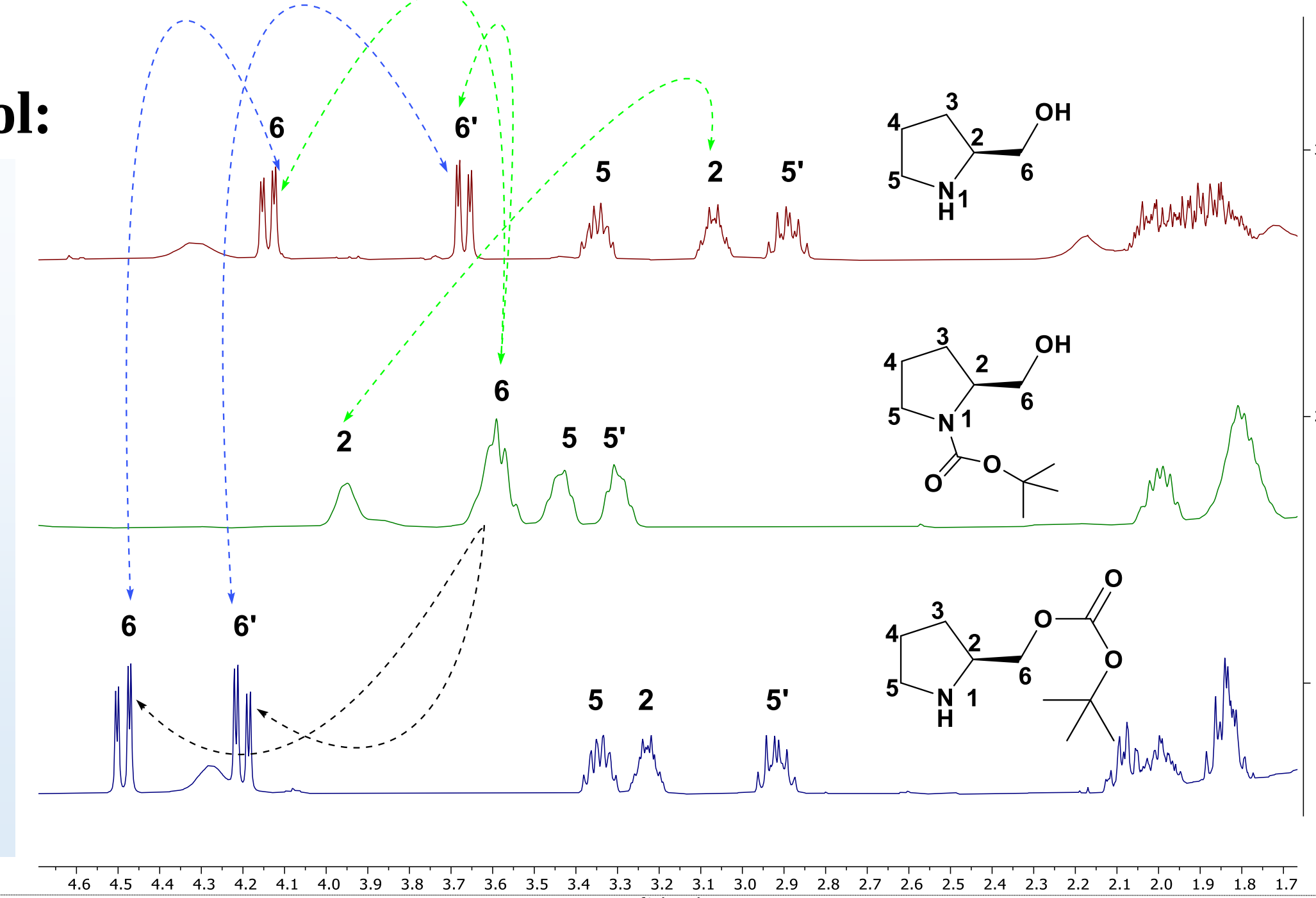


2.4. Mechanistic investigation for the Chemoselective mono-Boc protection of (S)-prolinol:

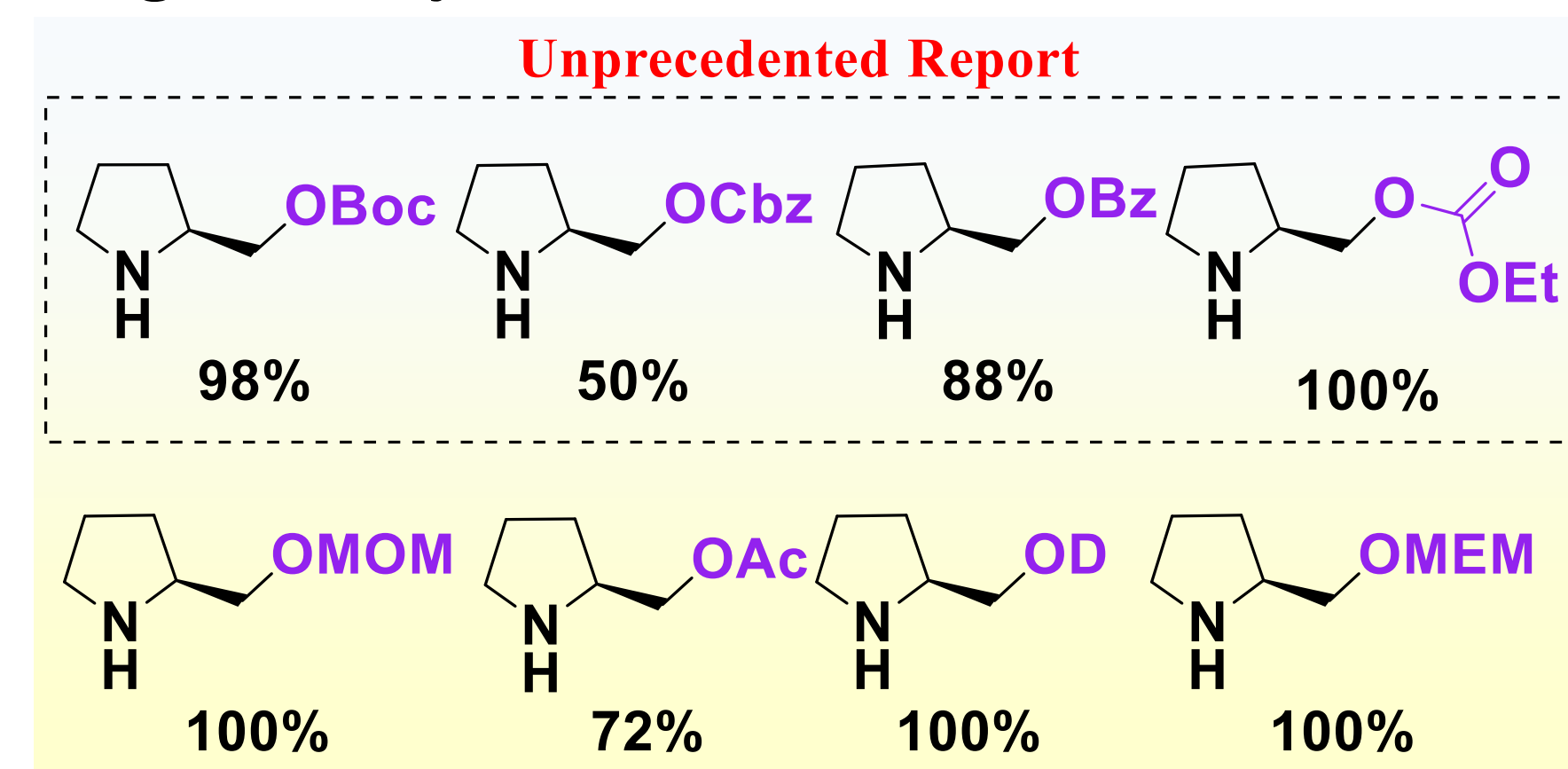


2. Results and discussion:

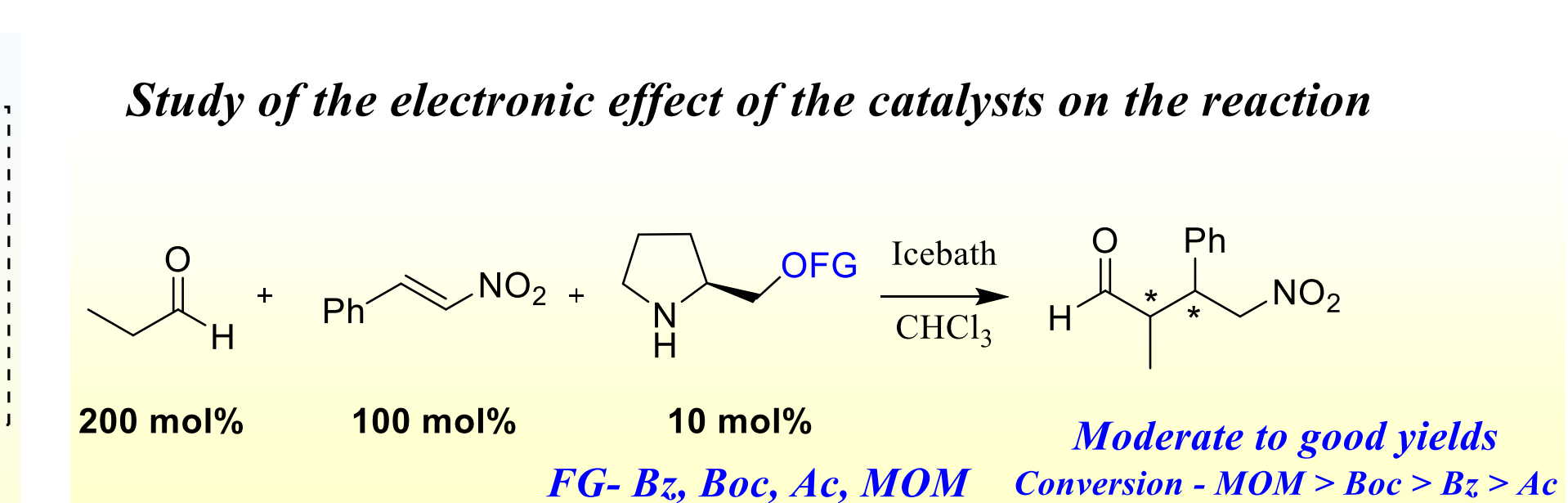
2.1. Characteristic HMBC for N-Boc and O-Boc-(S)-prolinol:



3. Substrate Scope: Direct access to Chiral Organocatalysts:



4. Preliminary study of some catalysts in Michael addition reactions:



5. References:

- Manuscript Communicated
- Computational work was done in collaboration with Dr. Santanab Giri, Haldia Institute of Technology
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