Preparation of a clickable monomer compatible with automated PNA synthesis

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SRS SPRING 2021 - TCU

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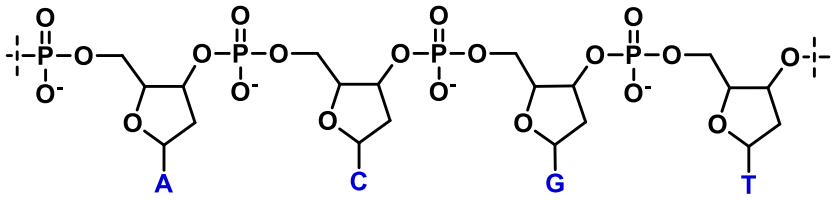
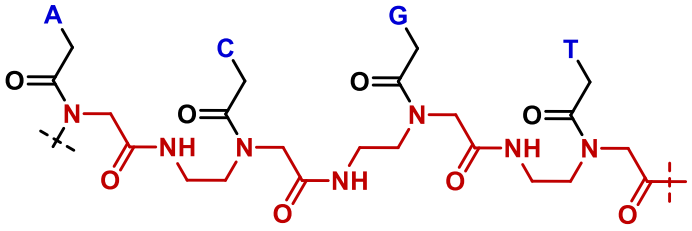
Peptide Nucleic Acids (PNAs)
WHAT ARE THEY?

- General structure of DNA:

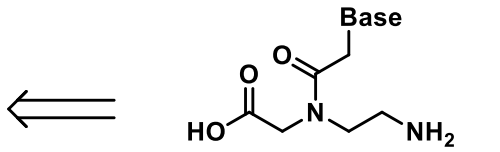


DNA
(DeoxyriboNucleic Acid)

- General structure of PNAs :



Peptidic Nucleic Acid
(PNA)



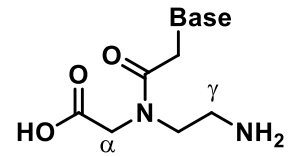
N-(2-aminoethyl)-glycine unit

Peter Nielsen
(University of Copenhagen)
(1991)

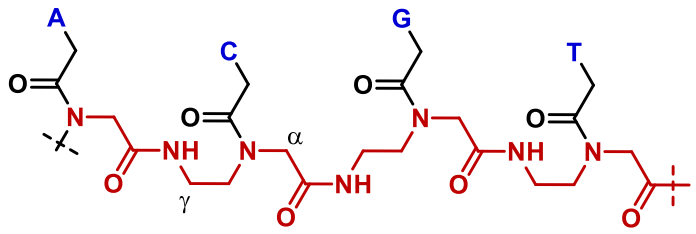
Nielsen, P. E.; *Chemistry & Biodiversity*, **2010**, 7, 786-805
Newell, G. E.; Sabourin, A.; Montchamp, J.-L.; Tetrahedron Letters, **2021**, 69, 152987

Peptide Nucleic Acids (PNAs)
Applications

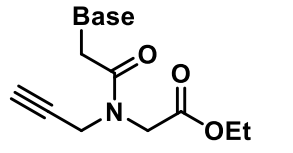
- Advantages
  - Higher stability
  - Ease of synthesis
  - Ease of derivatization
  - Higher affinity
- Applications
  - Antisense therapy
  - Gene editing
  - Fluorogenic probes
- Limitations
  - Solubility
  - Intracellular delivery
  - Rapid clearance



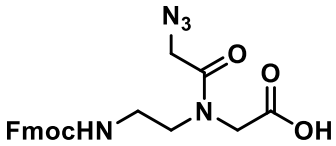
N-(2-aminoethyl)-glycine unit



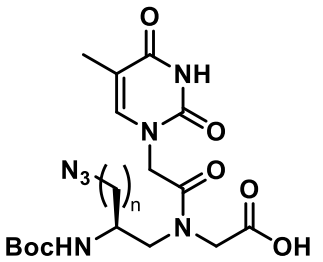
Peptidic Nucleic Acid
(PNA)



Base = T, C^{Cbz}, A^{Cbz}
(Howarth 2011)



(Hudson 2015)

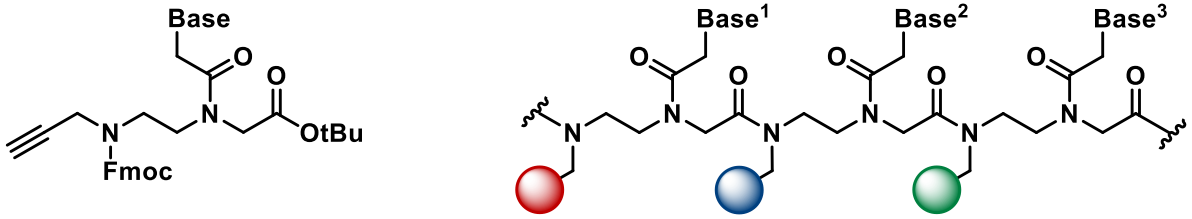


n = 1, 4
(Ganesh 2014)

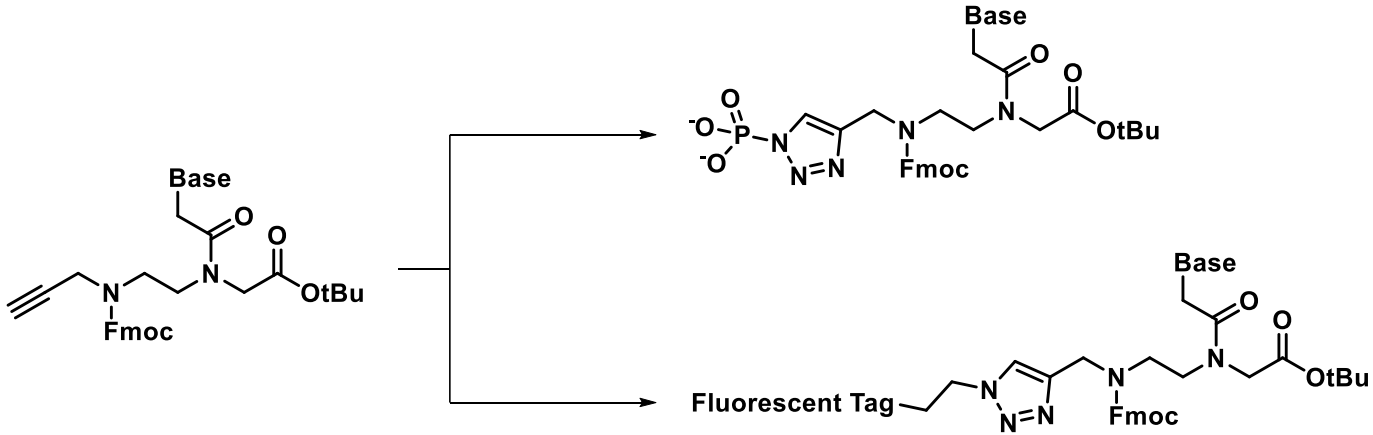
David P. Clark, Nanette J. Pazdernik; *Michelle R. McGehee, in Molecular Biology (Third Edition), 2019*
Newell, G. E.; Sabourin, A.; Montchamp, J.-L.; Tetrahedron Letters, **2021**, 69, 152987

Peptide Nucleic Acids (PNAs)
Our Monomer

- Structure:

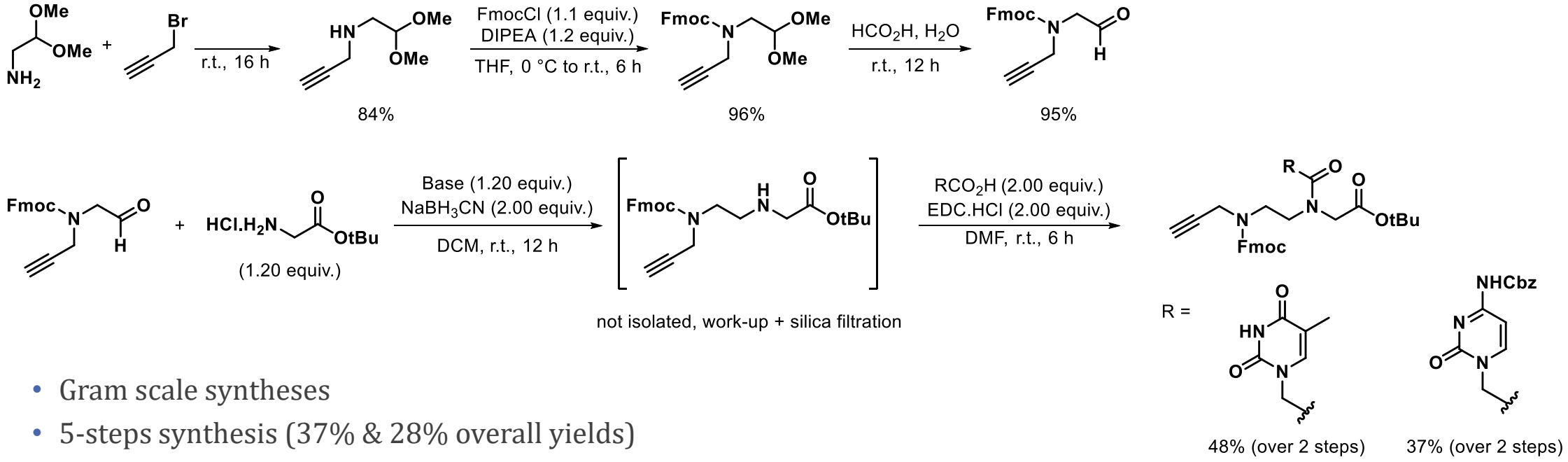


- Handle for functionalization (post/pre oligomerization): Click Chemistry
  - Charged groups
  - Fluorescent tag
  - Delivery vehicle



Peptide Nucleic Acids (PNAs)
Synthesis

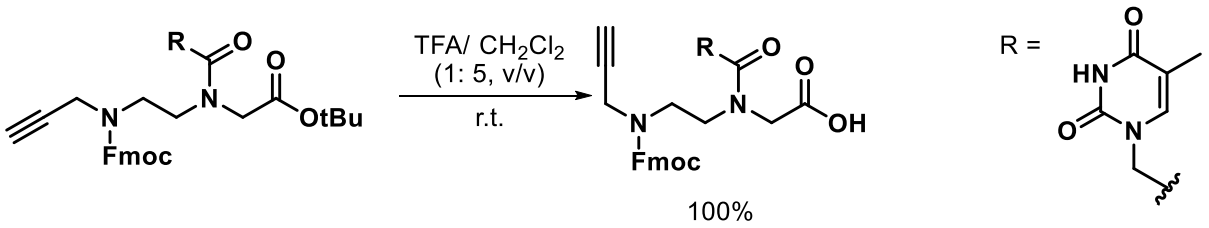
- Synthesis of the protected monomer



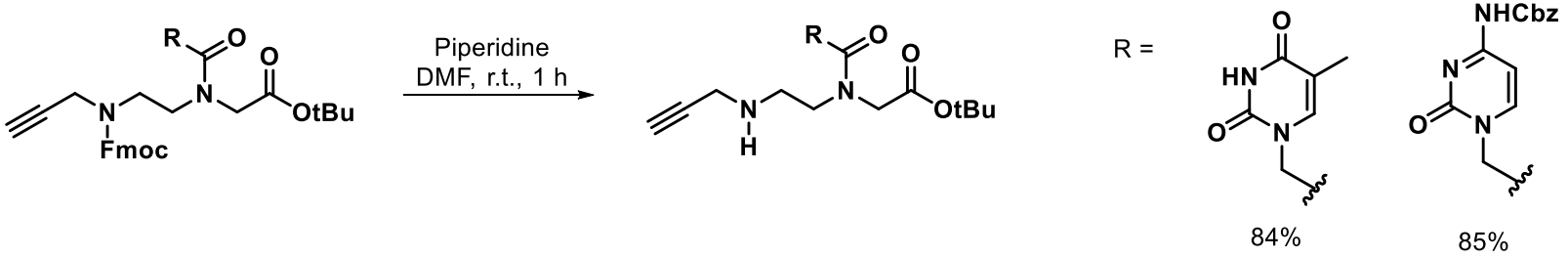
- Gram scale syntheses
- 5-steps synthesis (37% & 28% overall yields)
- Bench stable compounds

Peptide Nucleic Acids (PNAs)
Synthesis

- Deprotection of the various functional groups
  - tBu ester deprotection:



  - Fmoc deprotection



Peptide Nucleic Acids (PNAs)
Further work

- Other DNA/RNA bases
- Examples of Click chemistry
- Collaborations

Acknowledgements

Dr. Jean-Luc Montchamp & Grace E. Newell