Towards a Synthetic Genetic Polymer

Noam Prywes and Kyle Strom
ILASOL
April 11th, 2018

Towards a Synthetic Genetic Polymer

Noam Prywes and Kyle Strom
ILASOL
April 11th, 2018

Is there an alternative to DNA?

All of life on earth uses DNA as a data storage medium

What alternatives exist and what can we imagine?

Is there an alternative to DNA?

Two conditions to replace DNA:

1) Stores arbitrary information

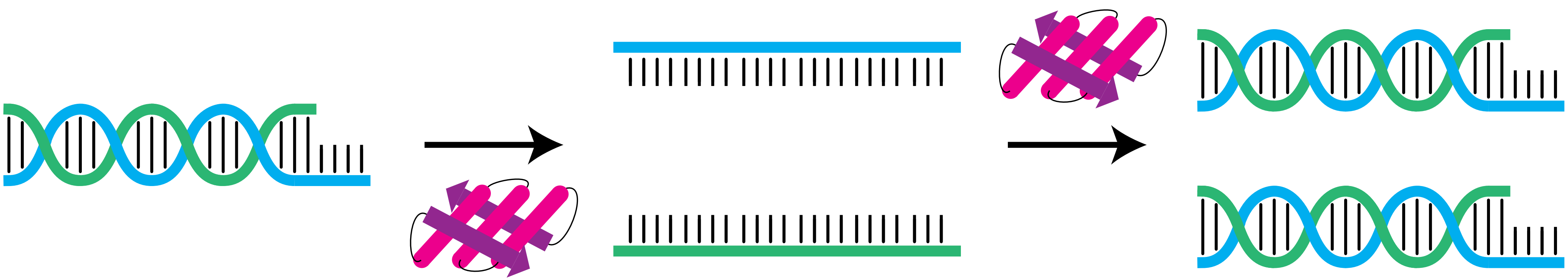
2) Can be copied

How is information copied?

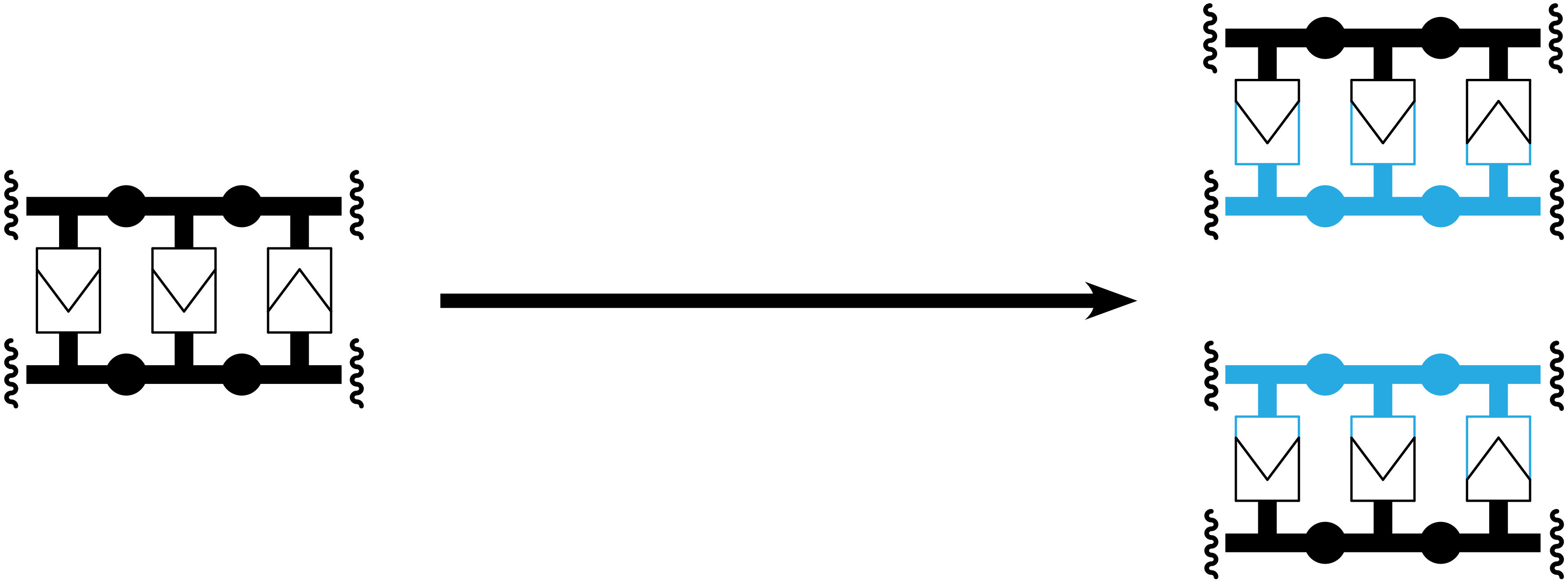
DNA replication is semiconservative

-Complementary strands form a duplex

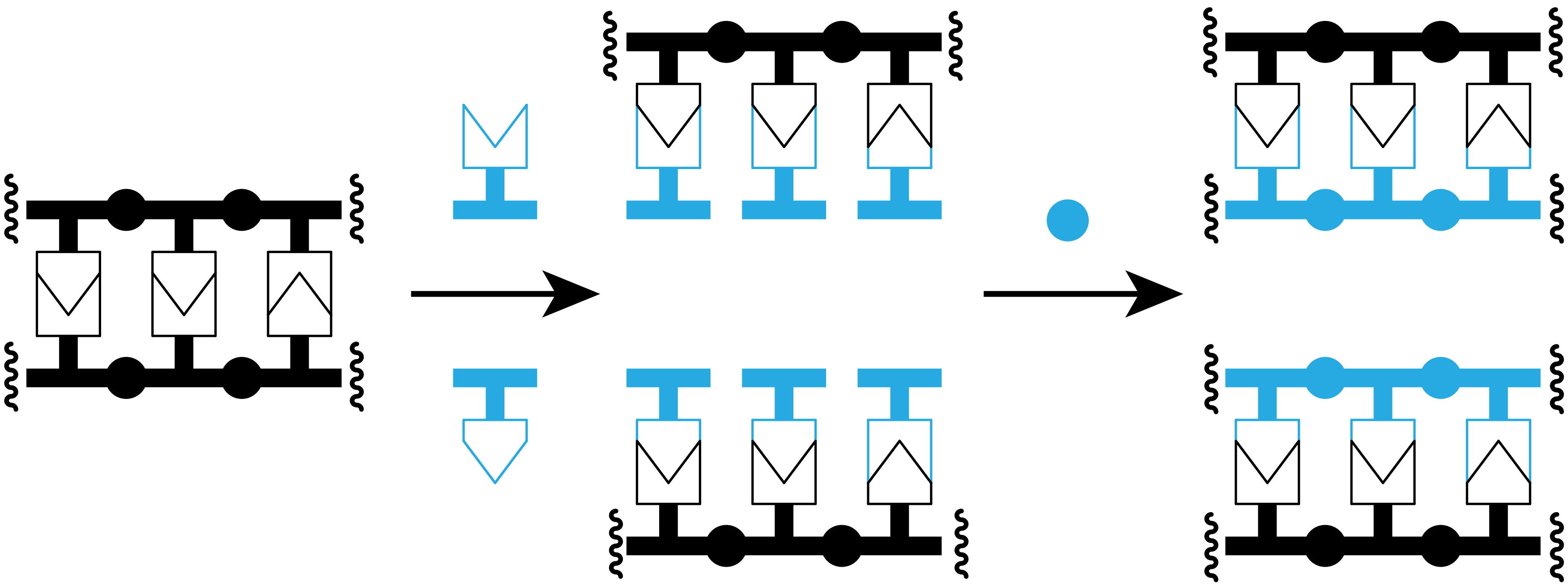
-One strand can template the chemical synthesis of its complement



Alternative hereditary polymer



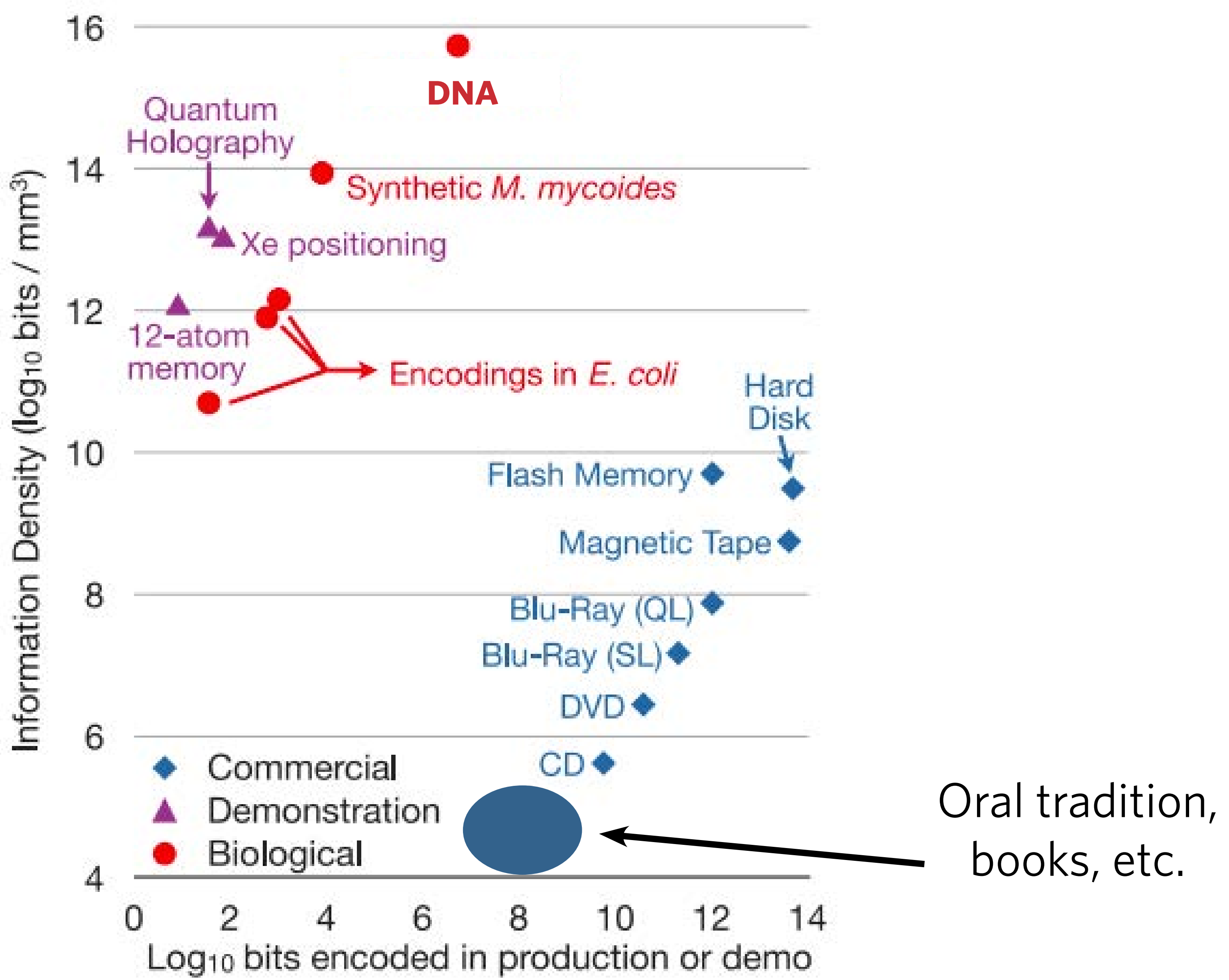
Alternative hereditary polymer



Why would we want to do this?

1) Unprecedented data storage capabilities

Data storage



Church, G. M.; Gao, Y.; Kosuri, S. Science 2012, 337, 1628.

Why would we want to do this?

1) Unprecedented data storage capabilities

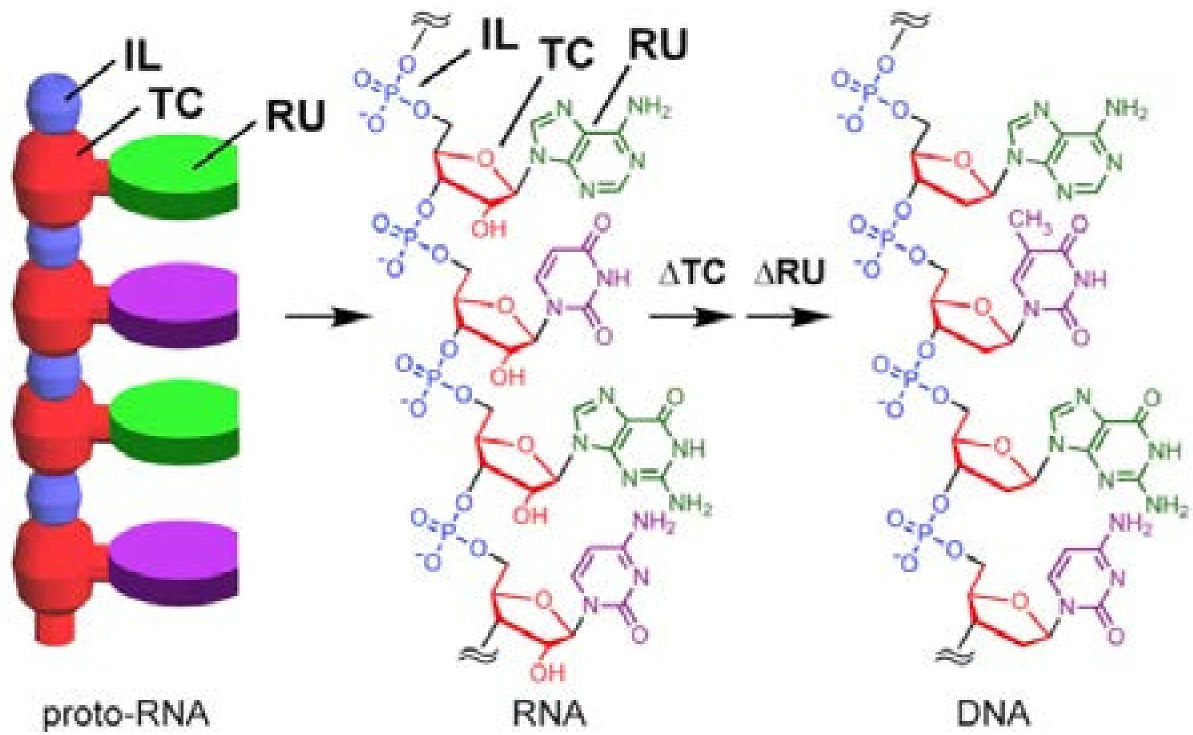
2) Explore the space of possible genetic polymers
- -How big is this space?
- -Are nucleic acids uniquely suitable?

Generalized genetic polymer

Trifunctional connector (TC)

Recognition units (RU)

Ionized linkers (IL)

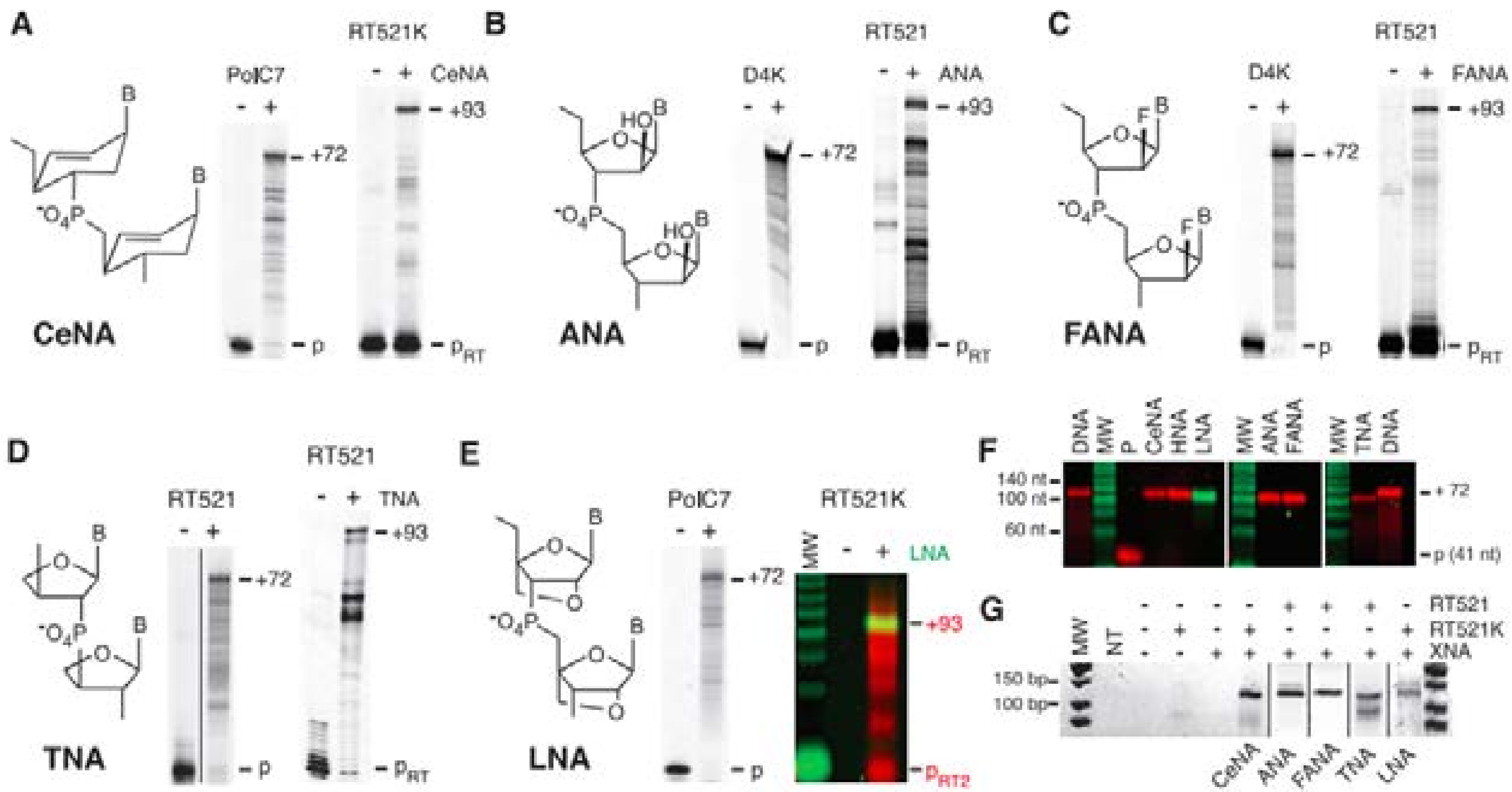


*Not the only way to store information in a molecule

Hud, N. V.; Cafferty, B. J.; Krishnamurthy, R.; Williams, L. D. Chem Biol 2013.

Previous attempts

-Mostly modified nucleic acids



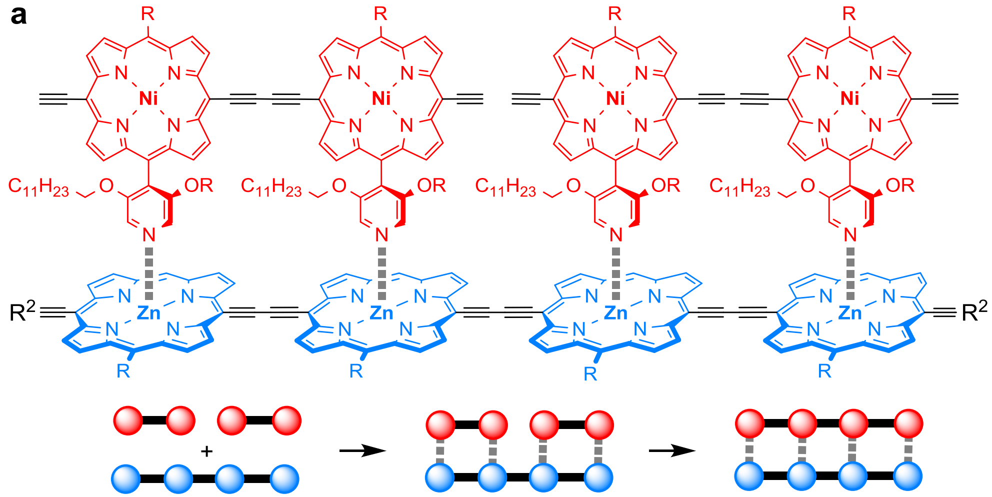
Pinheiro, V. B.; Taylor, A. I.; Cozens, C.; Abramov, M.; Renders, M.; Zhang, S.; Chaput, J. C.; Wengel, J.; Peak-Chew, S.-Y.; McLaughlin, S. H.; Herdewijn, P.; Holliger, P. Science 2012, 336, 341–344.

Previous attempts

Porphyrin-metal bonding

Templated Copying
(Kamonutthipaijit and Anderson)[18]

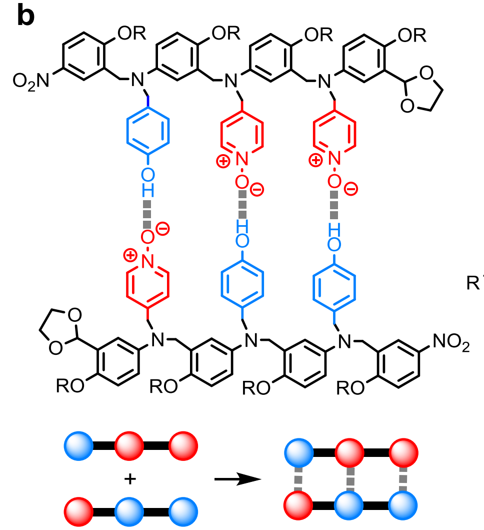
a



Hydrogen bonding

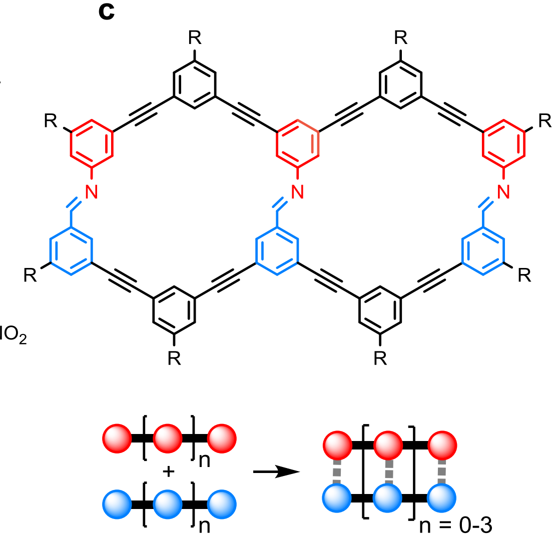
Sequence-Defined Duplexes
(Hunter et. al.)[17]

b



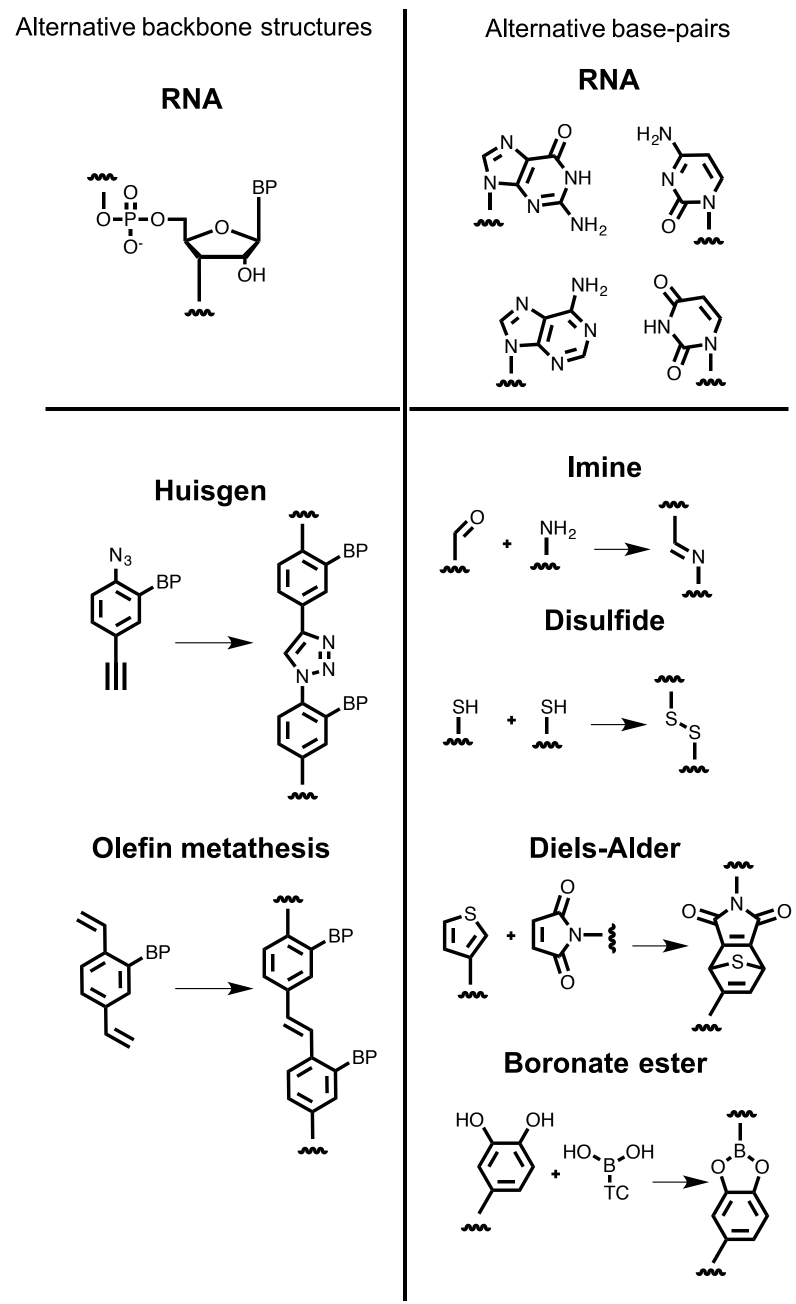
Homopolymeric Duplexes
(Moore et. al.)[20]

c



Imines

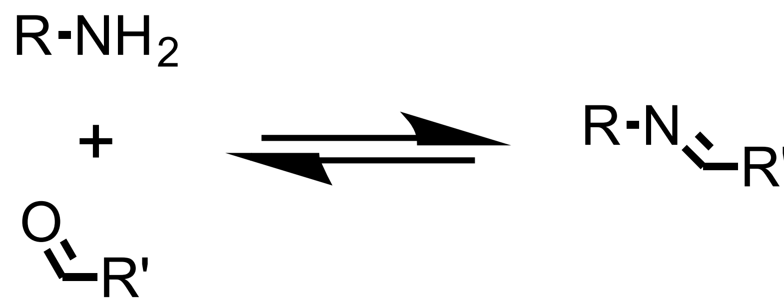
Alternative chemical reactions



Alternative hereditary polymer

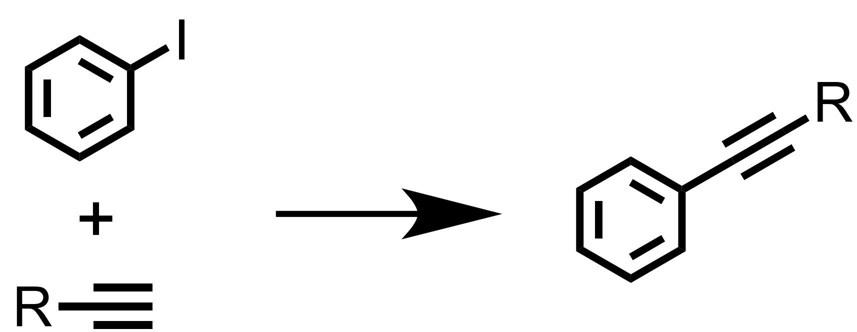
Base pair:

Schiff

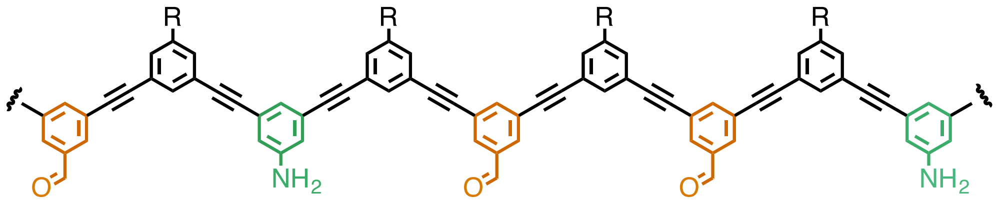


Backbone:

Sonogashira

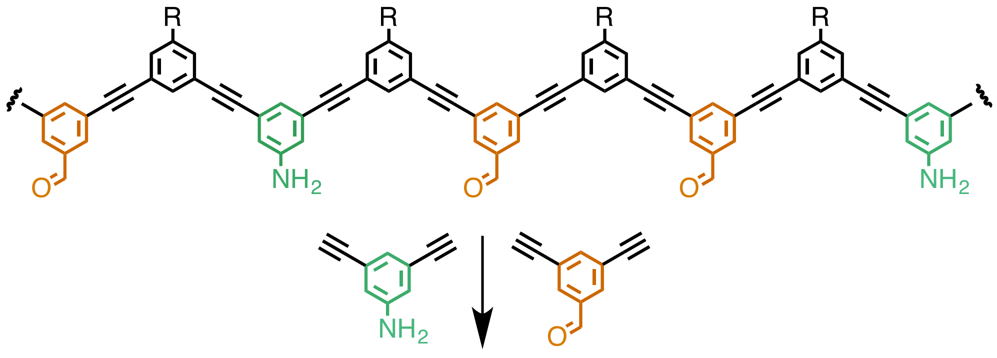


Alternative hereditary polymer

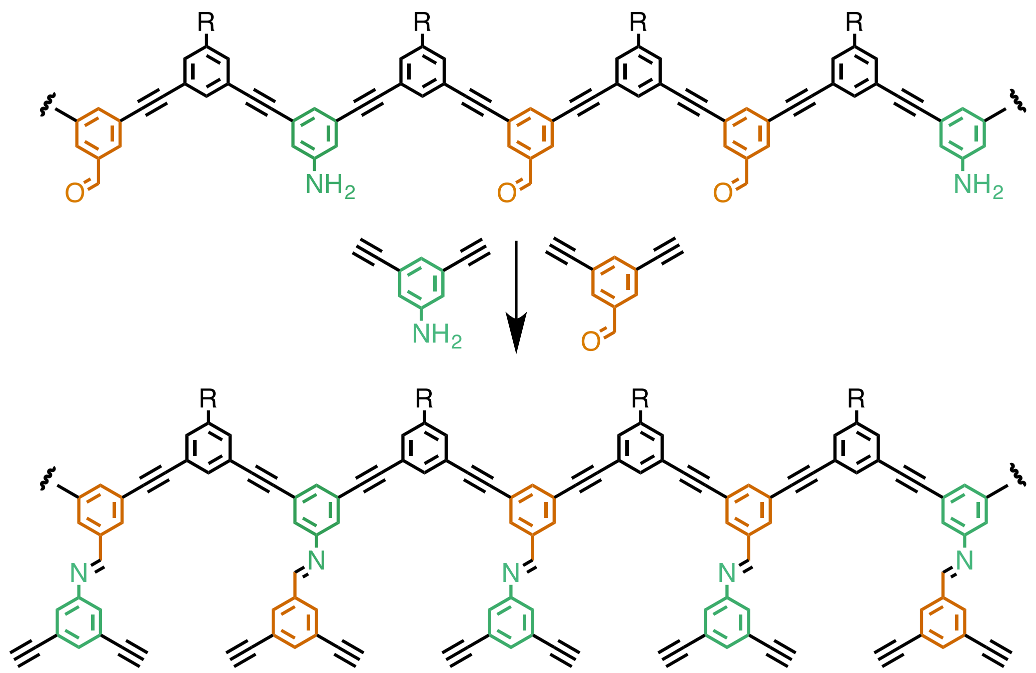


1 0 1 1 0

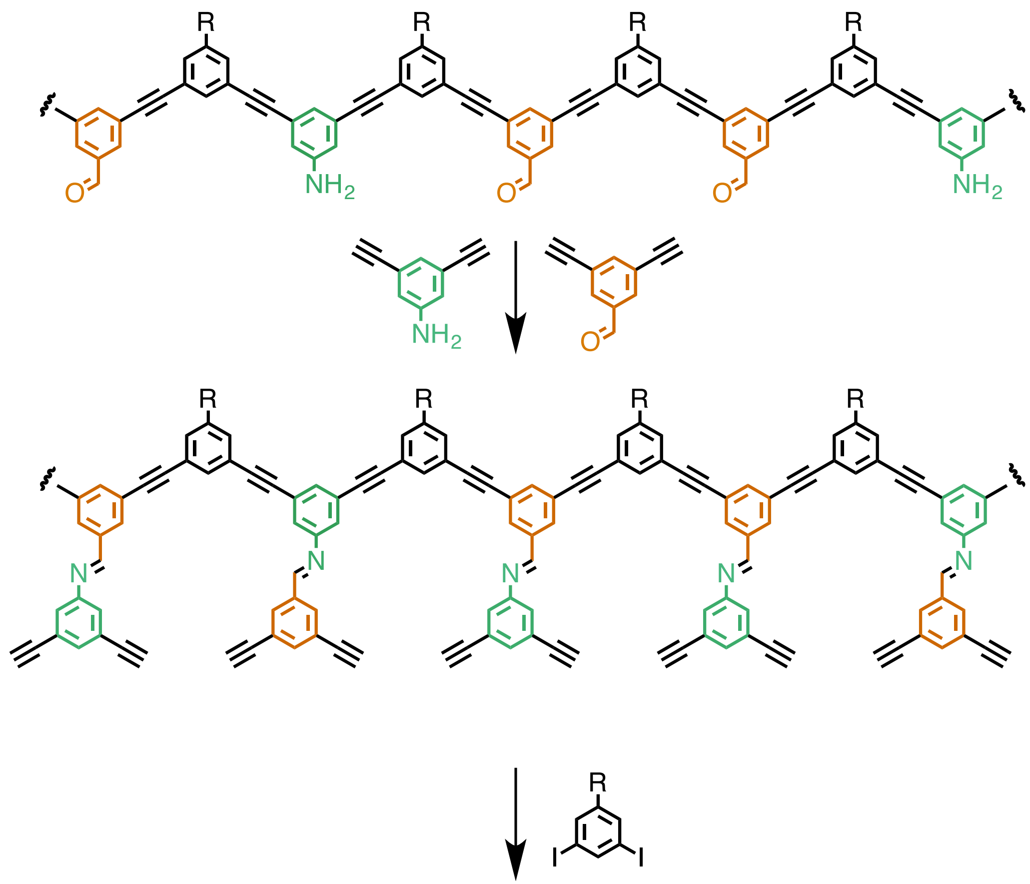
Alternative hereditary polymer



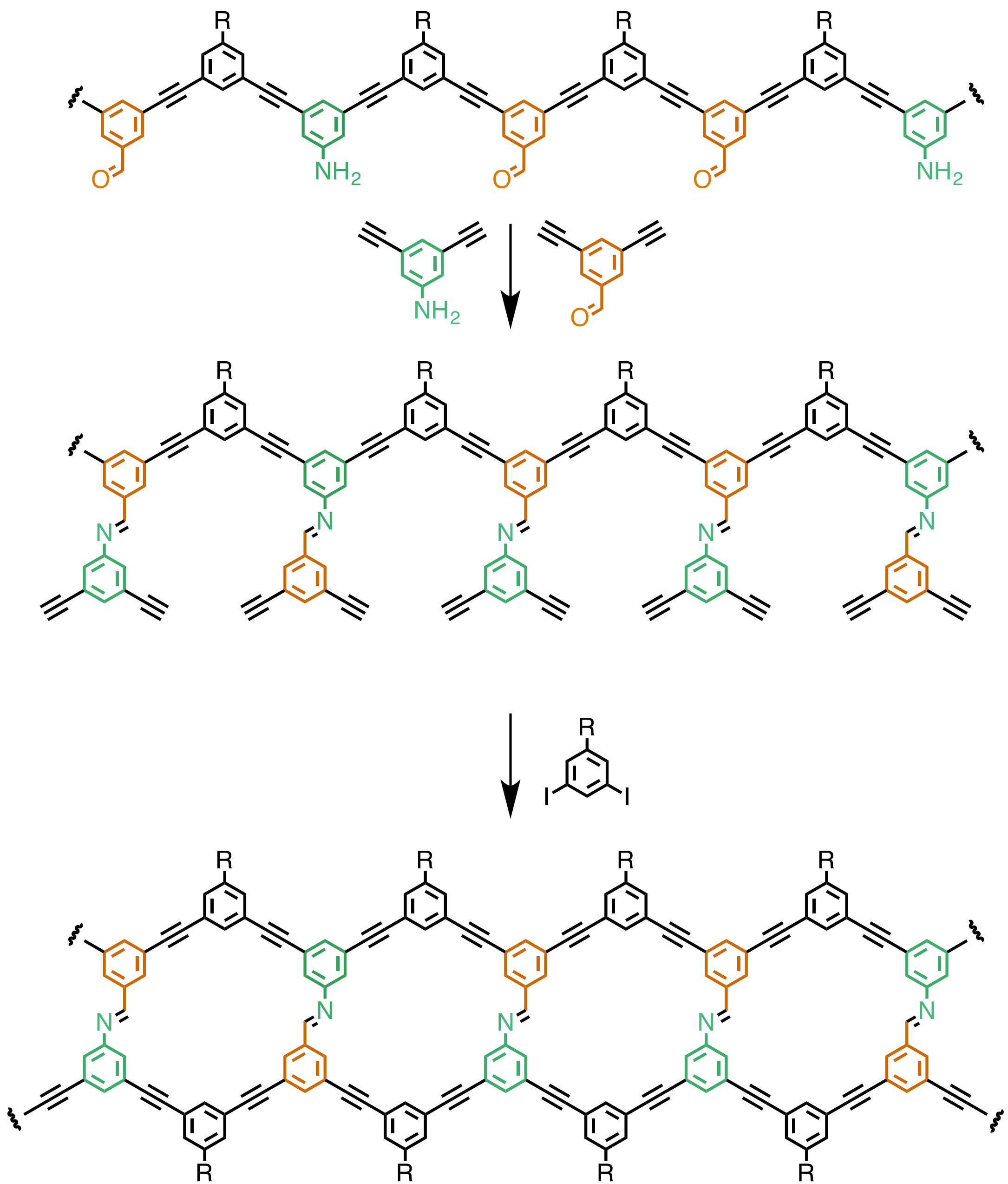
Alternative hereditary polymer



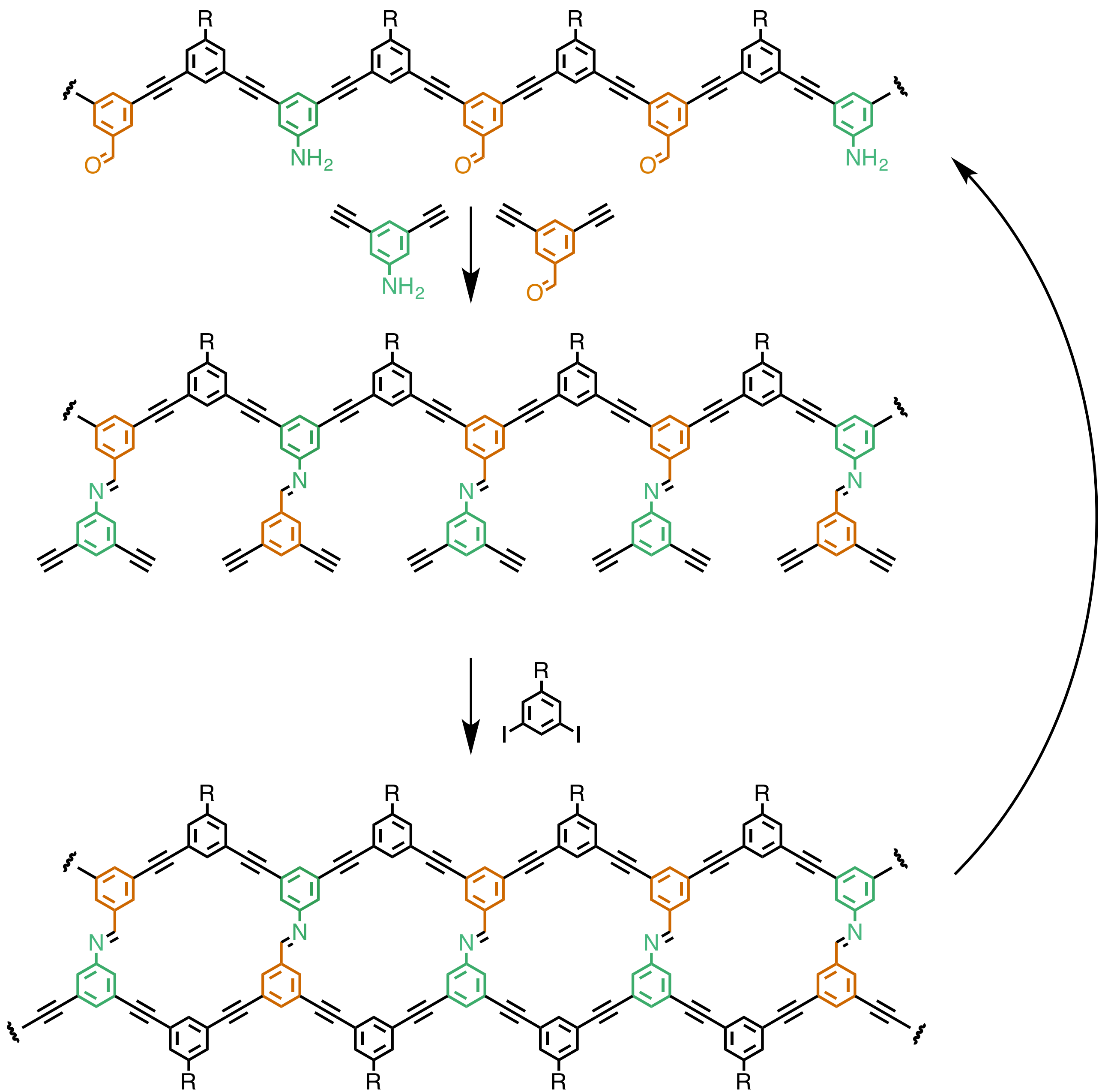
Alternative hereditary polymer



Alternative hereditary polymer



Alternative hereditary polymer



Differences with respect to NAs

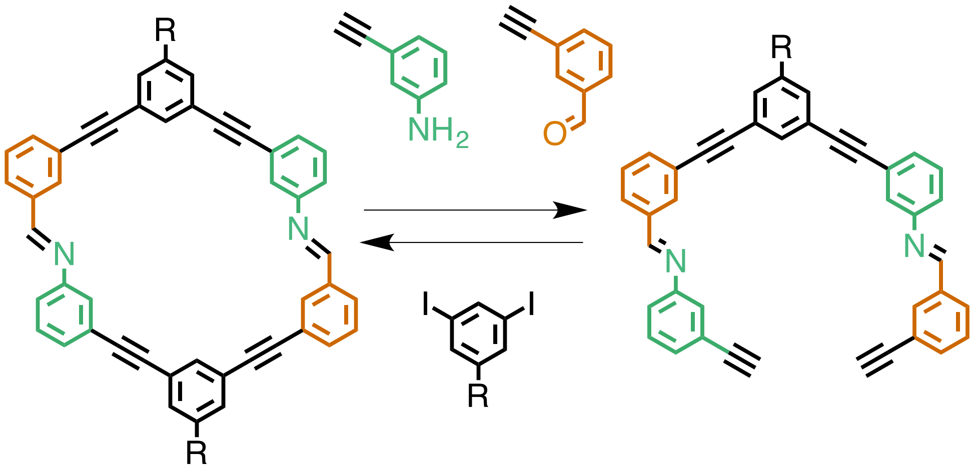
In design:

-Binary rather than tetranary
-Symmetric

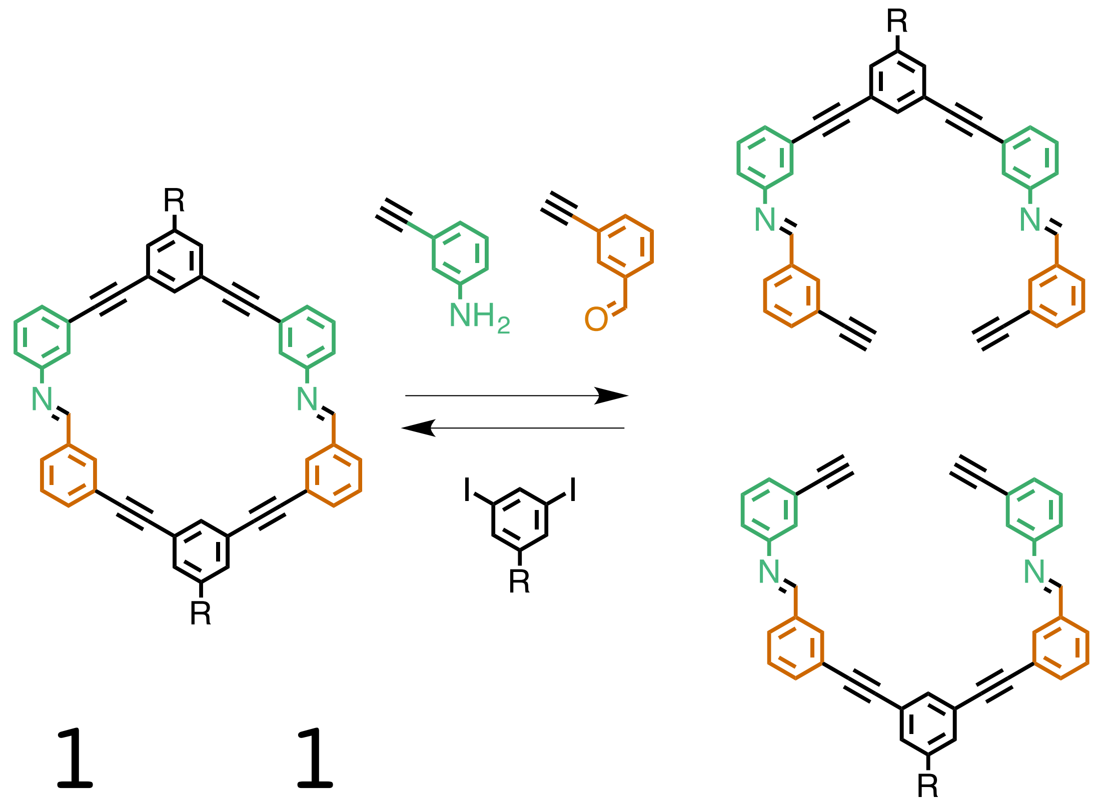
Chemically:

-Covalent base pairs
-Insoluble in water
-No enzymes

Model dimers

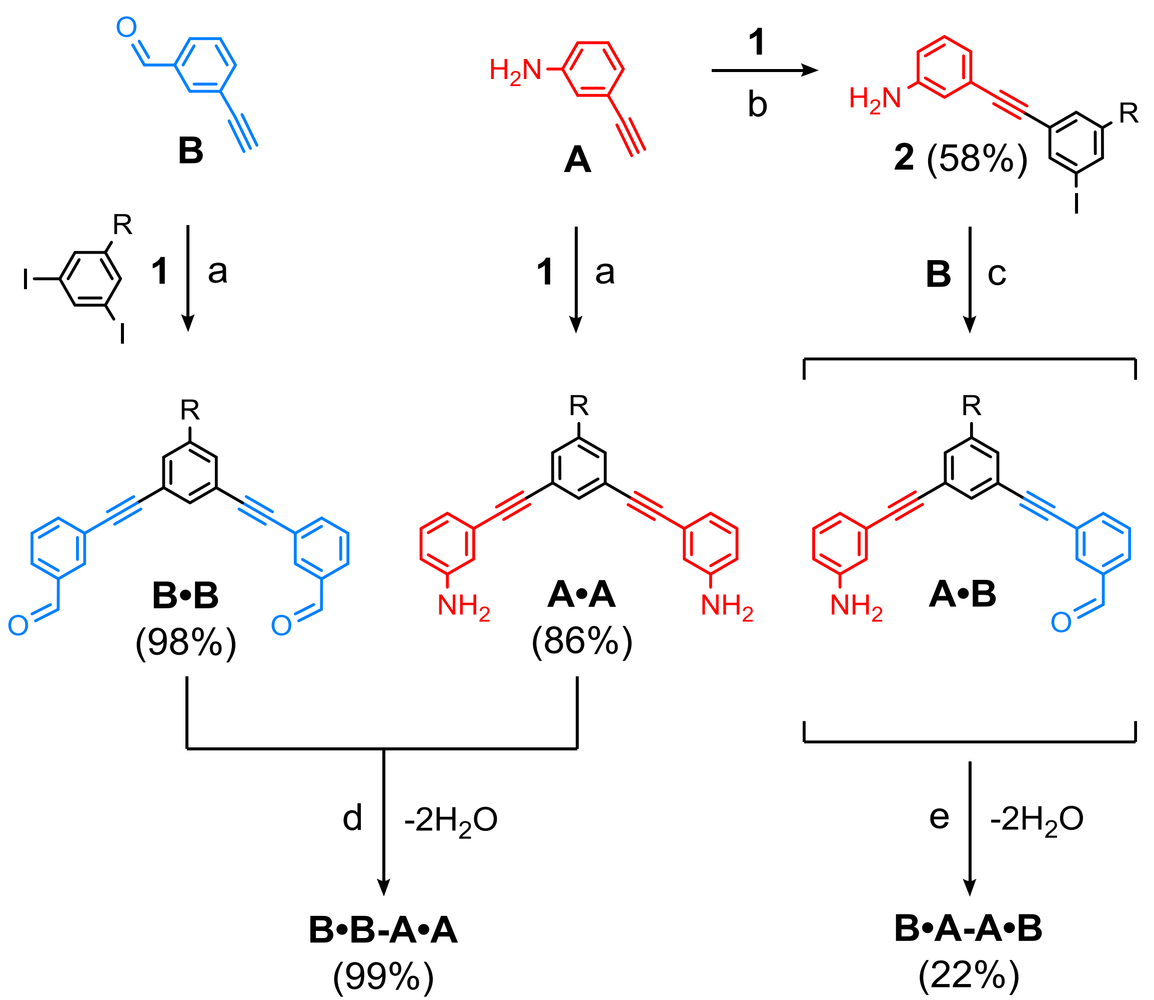


0 1



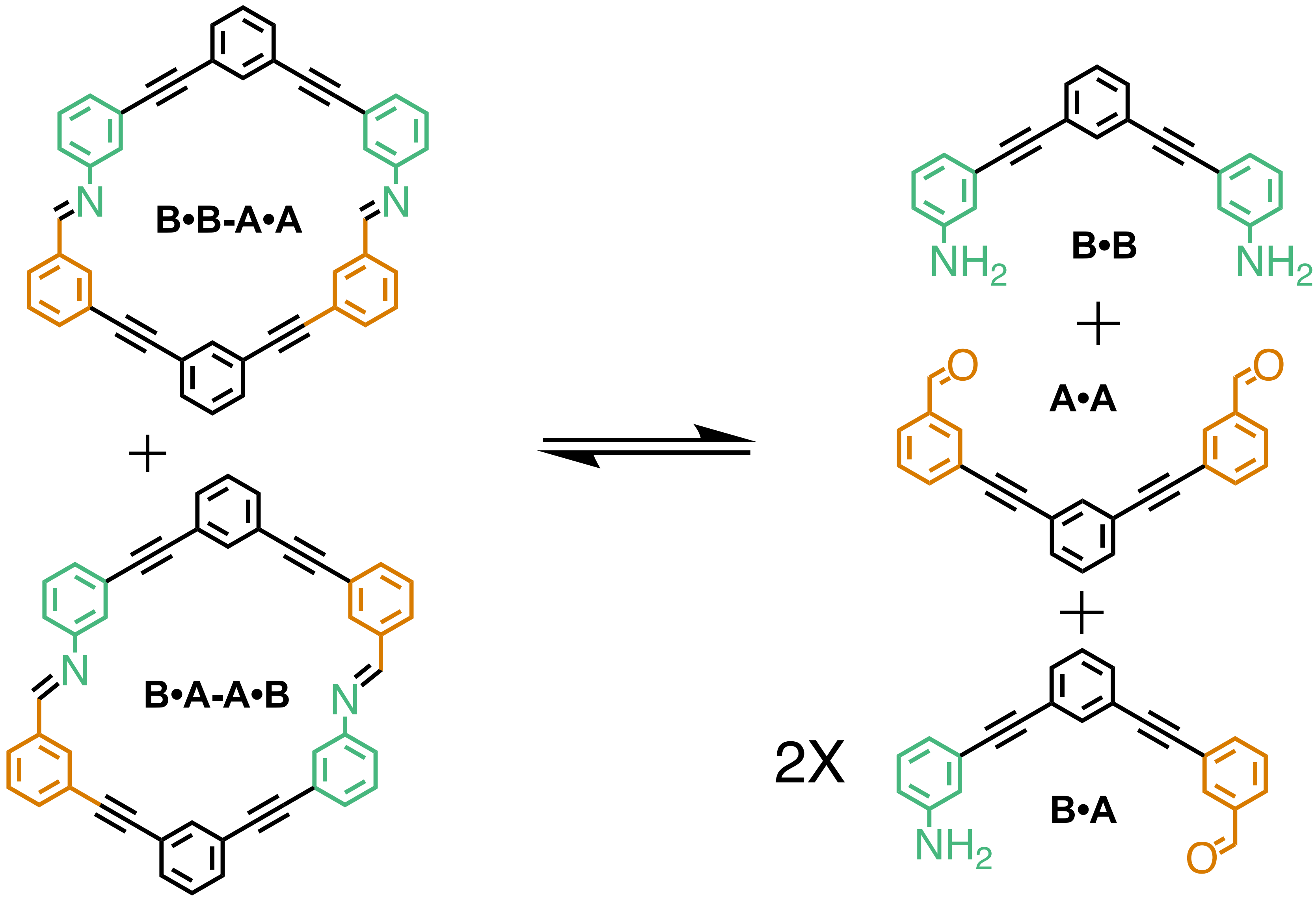
1 1

Model dimers

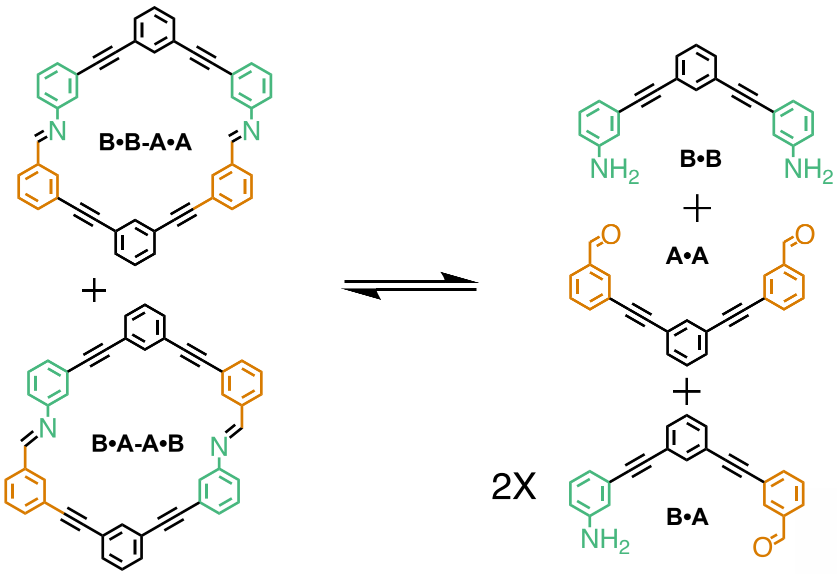


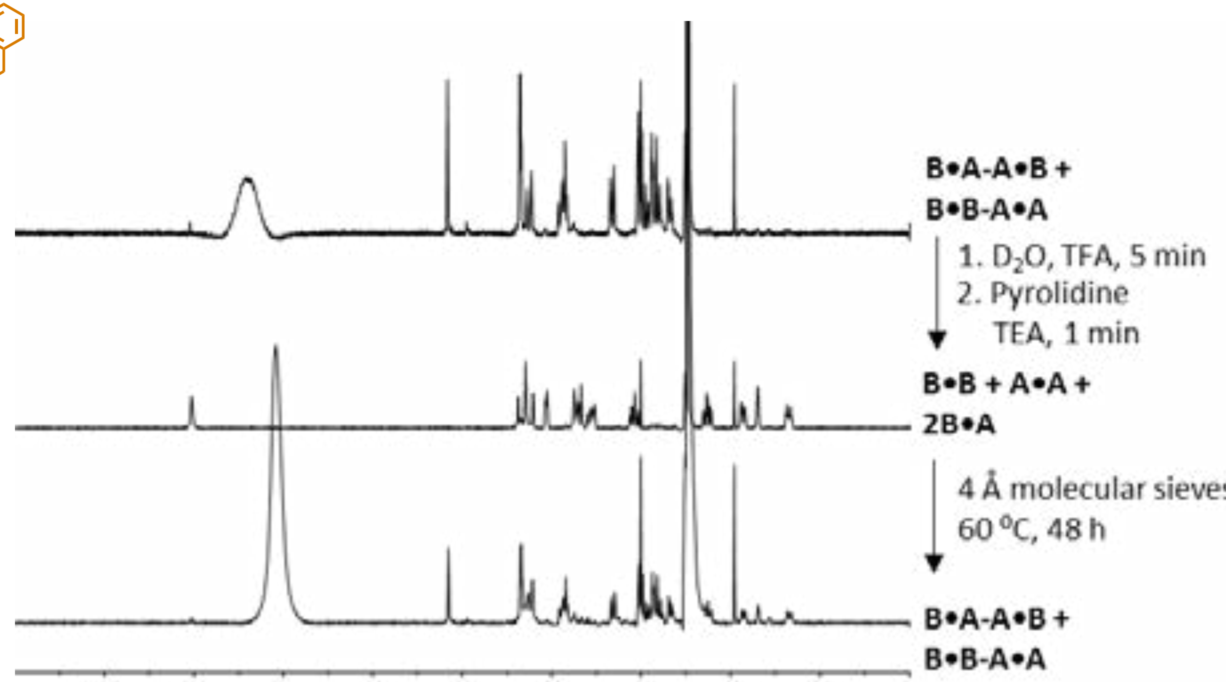
R = $CO_2(CH_2CH_2O)_2CH_3$

Reversible duplex formation

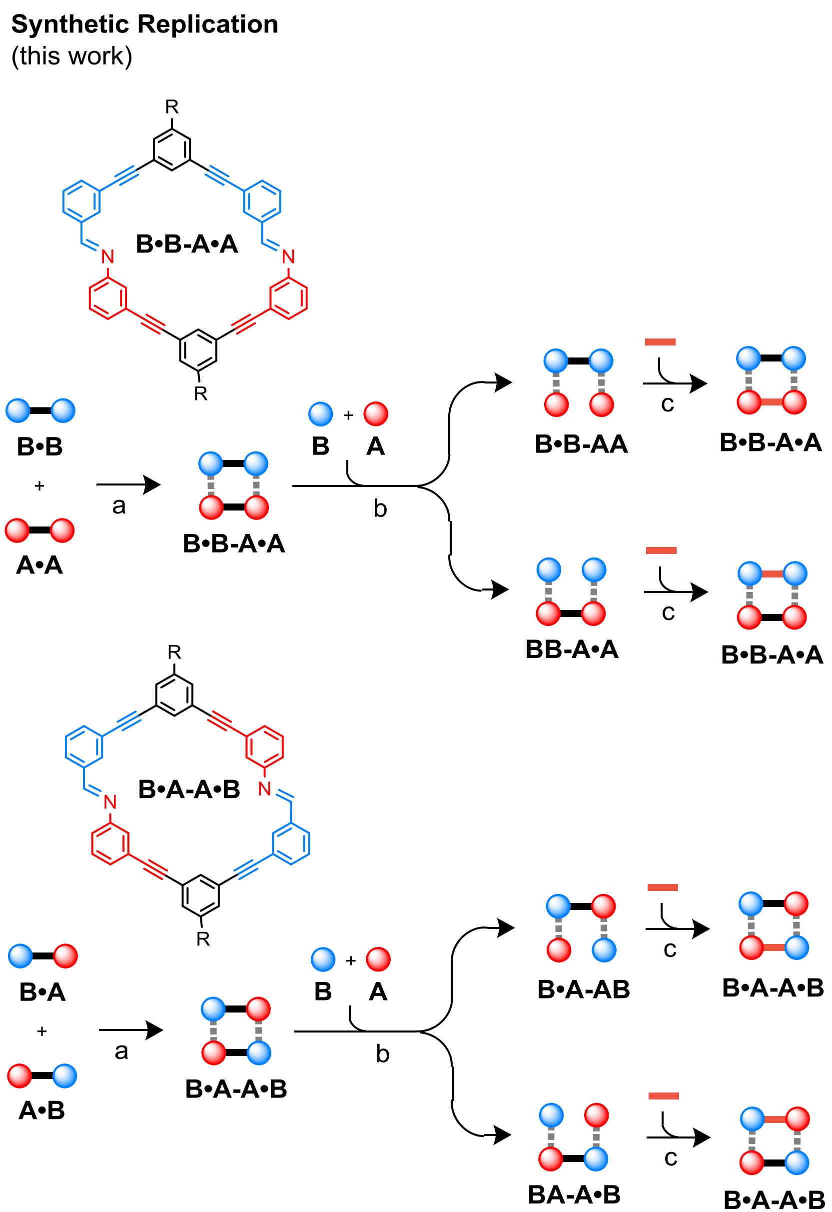


Reversible duplex formation

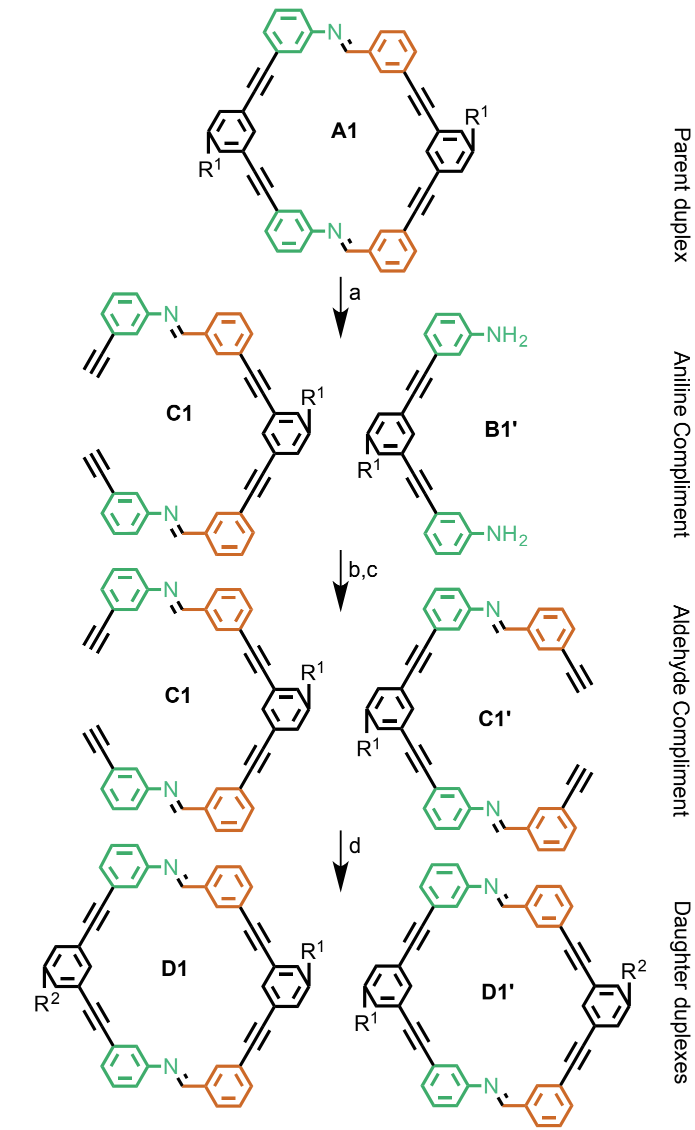




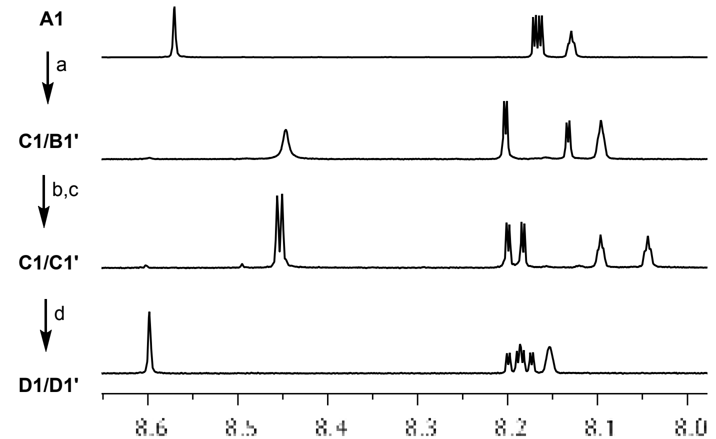
Model dimers



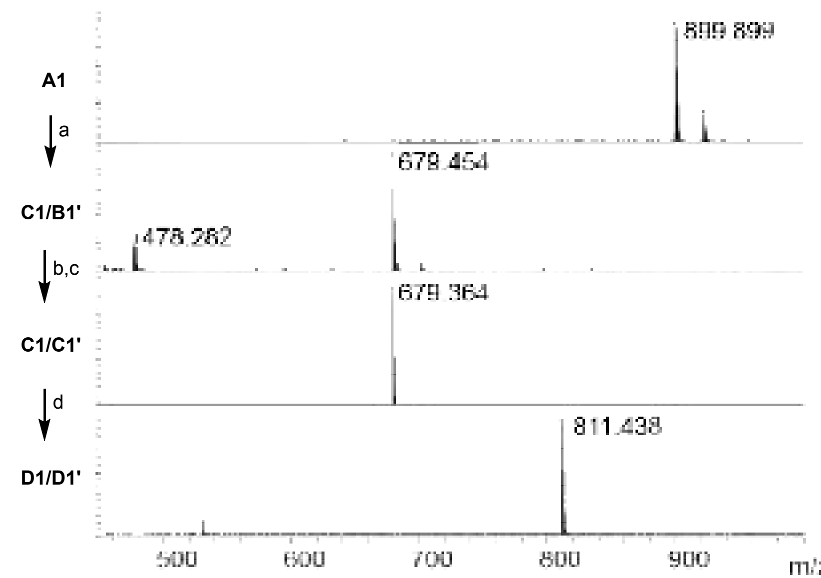
Homodimer



$R^1 = CO_2(CH_2CH_2O)_2CH_3$, $R^2 = CO_2CH_3$



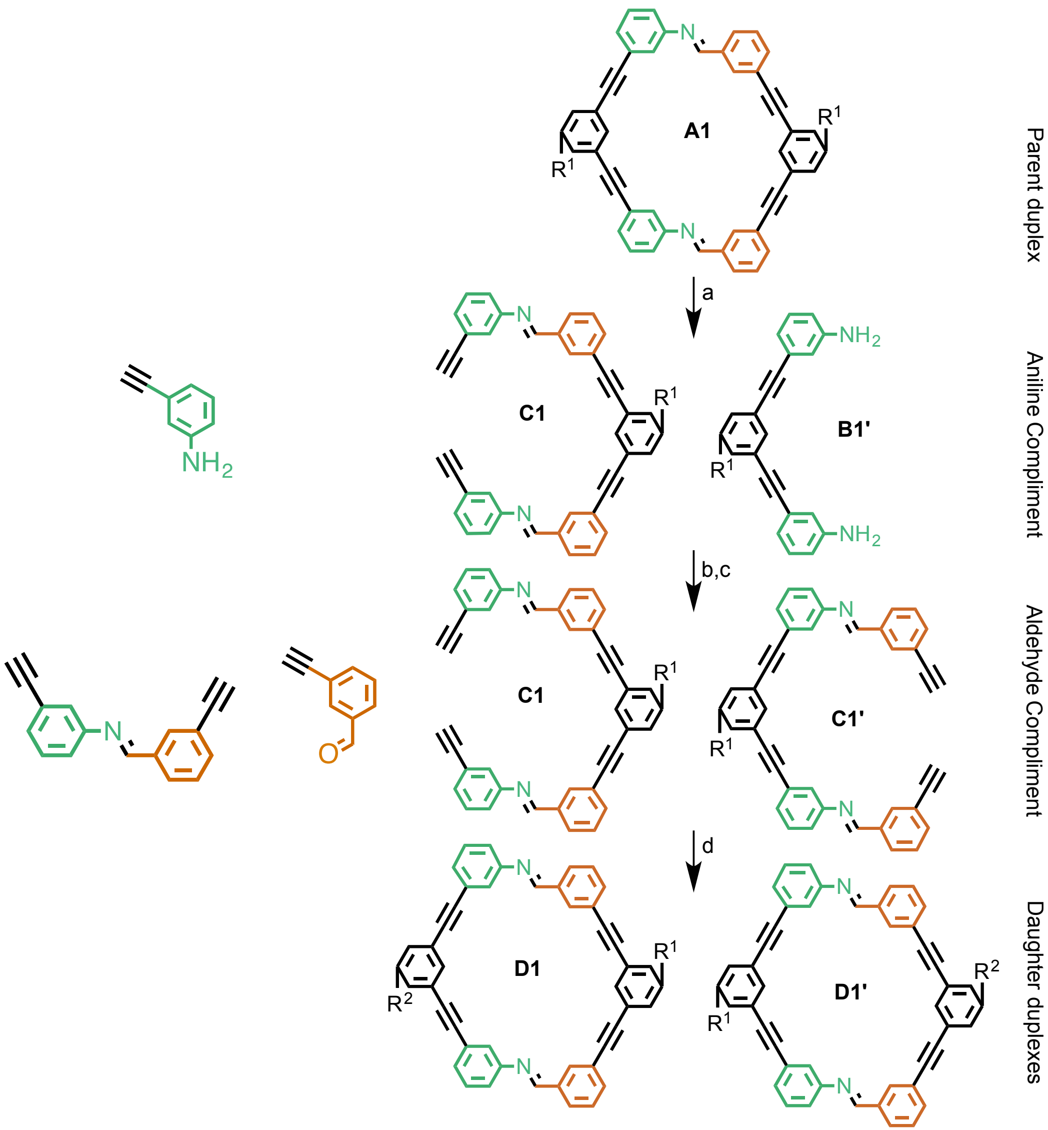
NMR expansion of downfield aromatic and immine protons for steps a-d. From left to right, imine protons, *meta* ester protons, *meta* imine (carbon side) singlet.



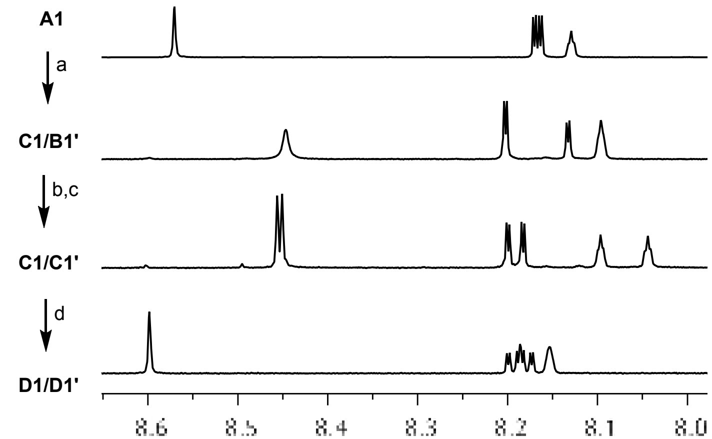
MALDI TOF spectra for steps a-d.

Steps a and b were conducted in an NMR tube containing 0.5 mL 0.02% TFA/CDCl3 and 10 mg 4 Å mol. sieves, starting with 0.01 M macrocycle. a) 30 equiv 3-ethynylaniline. b) 60 equiv 3-ethynylbenzaldehyde. c) 2x10-2 mbar, 120 °C, neat. d) 5 equiv methyl 3,5 diiodobenzoate, 1 equiv Pd(PPh3)4, 0.5 equiv CuI, 6 uM degassed DMF, 60° C.

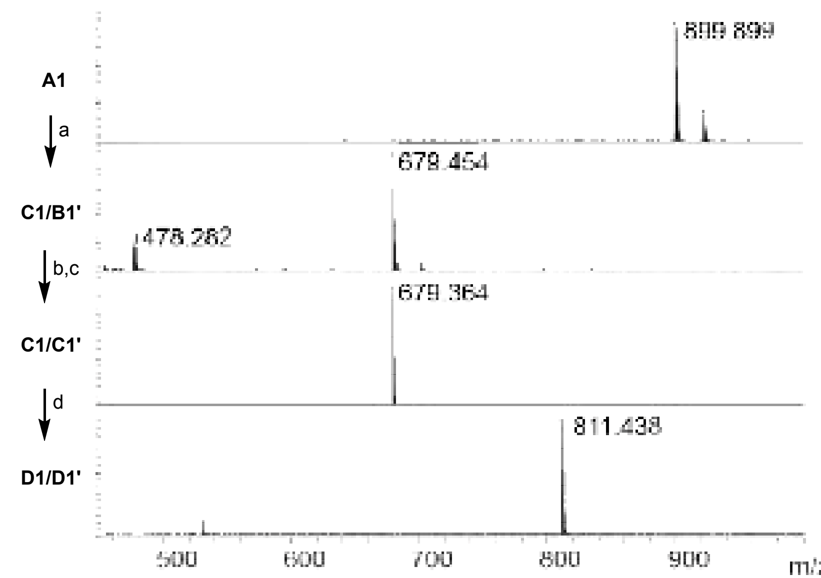
Homodimer



$R^1 = CO_2(CH_2CH_2O)_2CH_3$, $R^2 = CO_2CH_3$



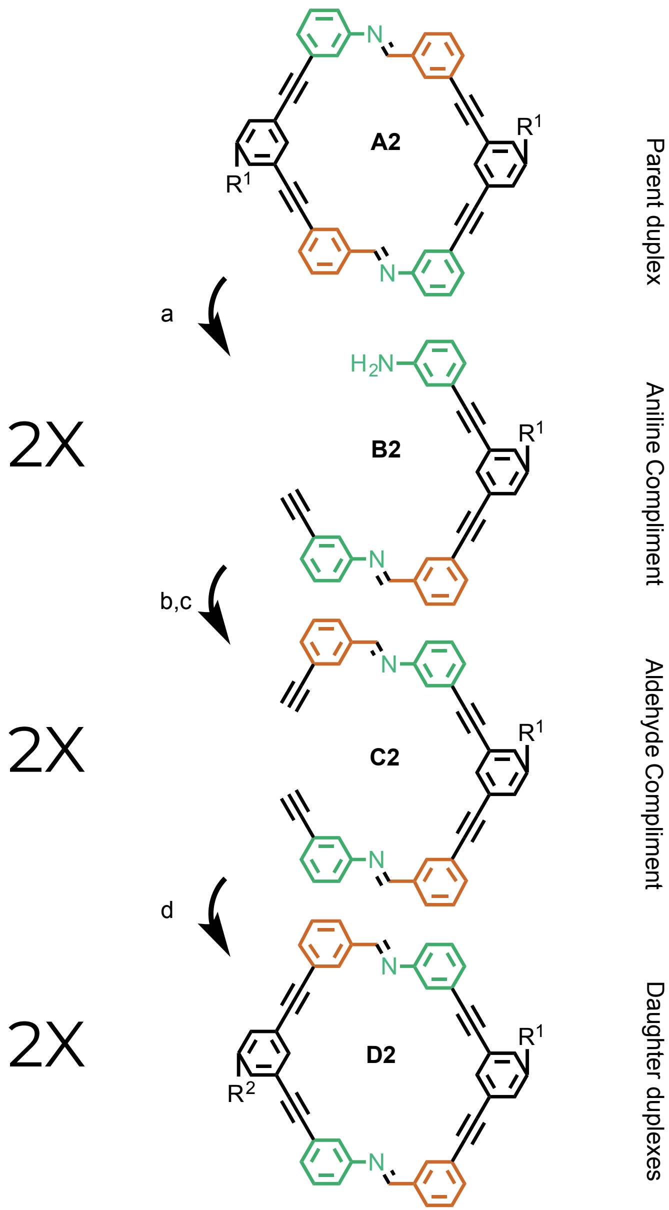
NMR expansion of downfield aromatic and immine protons for steps a-d. From left to right, imine protons, *meta* ester protons, *meta* imine (carbon side) singlet.



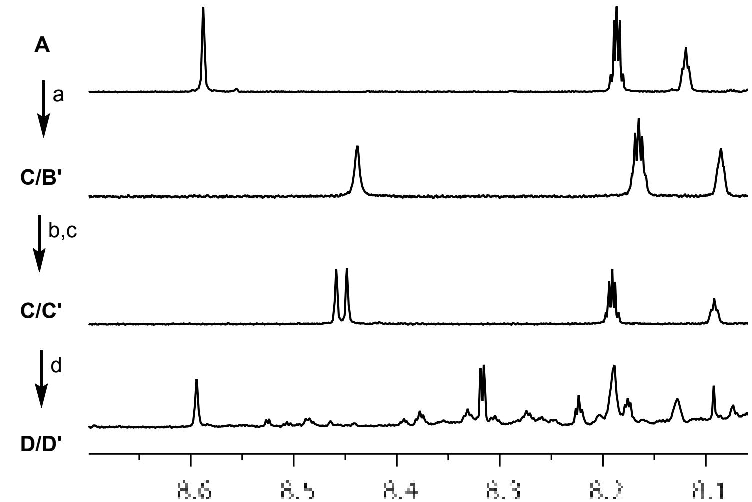
MALDI TOF spectra for steps a-d.

Steps a and b were conducted in an NMR tube containing 0.5 mL 0.02% TFA/CDCl3 and 10 mg 4 Å mol. sieves, starting with 0.01 M macrocycle. a) 30 equiv 3-ethynylaniline. b) 60 equiv 3-ethynylbenzaldehyde. c) 2x10-2 mbar, 120 °C, neat. d) 5 equiv methyl 3,5 diiodobenzoate, 1 equiv Pd(PPh3)4, 0.5 equiv CuI, 6 uM degassed DMF, 60° C.

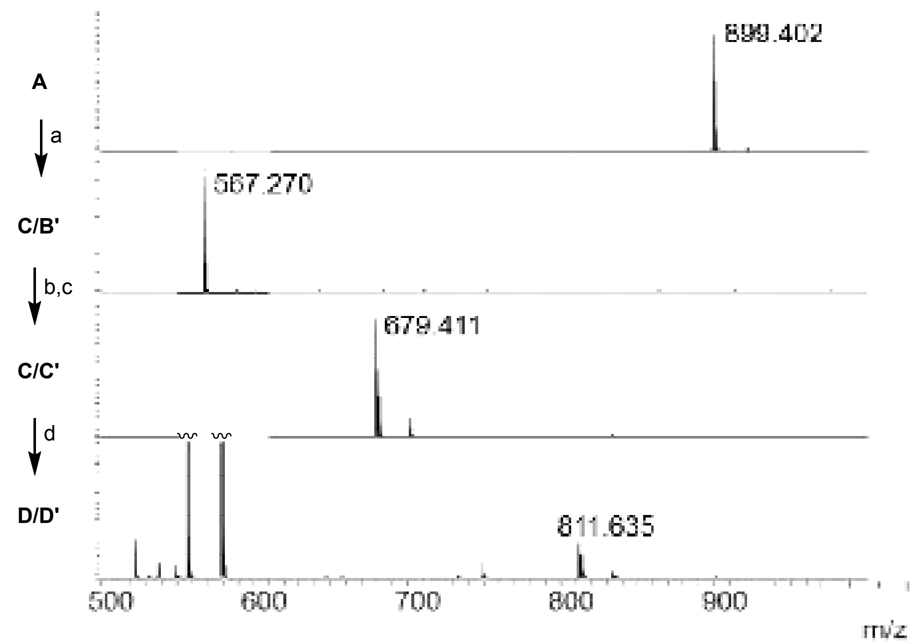
Heterodimer



$R^1 = CO_2(CH_2CH_2O)_2CH_3$, $R^2 = CO_2CH_3$



NMR expansion of downfield aromatic and immine protons for steps a-d. From left to right, imine protons, *meta* ester protons, *meta* imine (carbon side) singlet.



MALDI TOF spectra for steps a-d.

Steps a and b were conducted in an NMR tube containing 0.5 mL 0.02% TFA/CDCl3 and 10 mg 4 Å mol. sieves, starting with 0.01 M macrocycle. a) 30 equiv 3-ethynylaniline. b) 60 equiv 3-ethynylbenzaldehyde. c) 2x10-2 mbar, 120 °C, neat. d) 5 equiv methyl 3,5 diiodobenzoate, 1 equiv Pd(PPh3)4, 0.5 equiv CuI, 6 uM degassed DMF, 60° C.

Future work

Longer polymers - information storage

Alternative base pairs/backbones

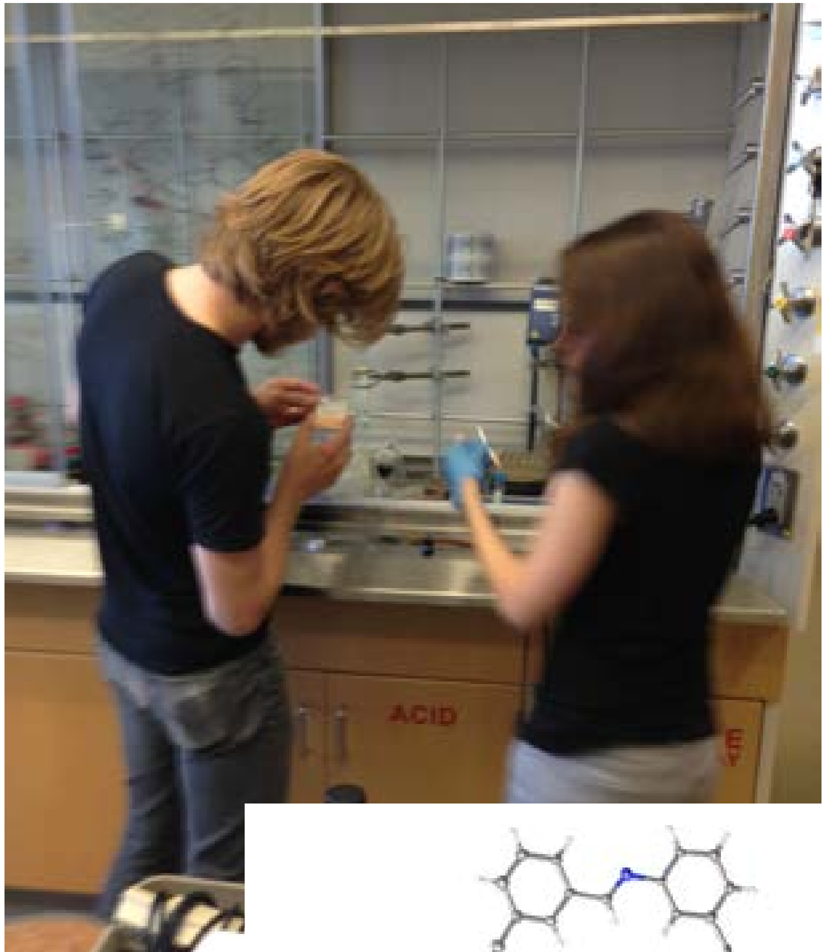
Function - selections for binders or catalysts

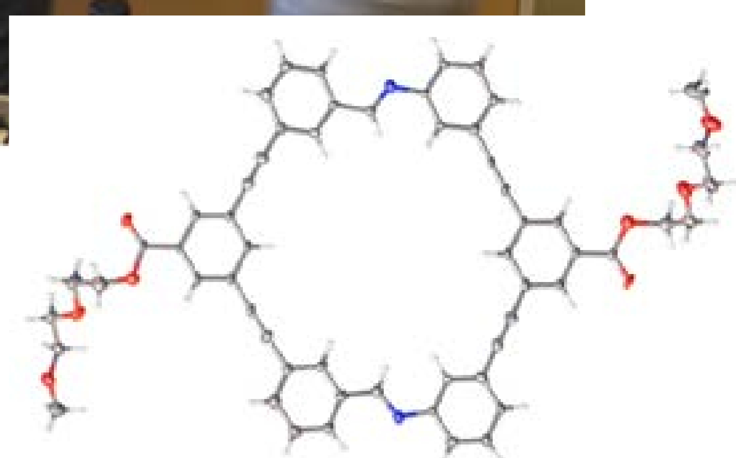
Translation - from one synthetic polymer to another

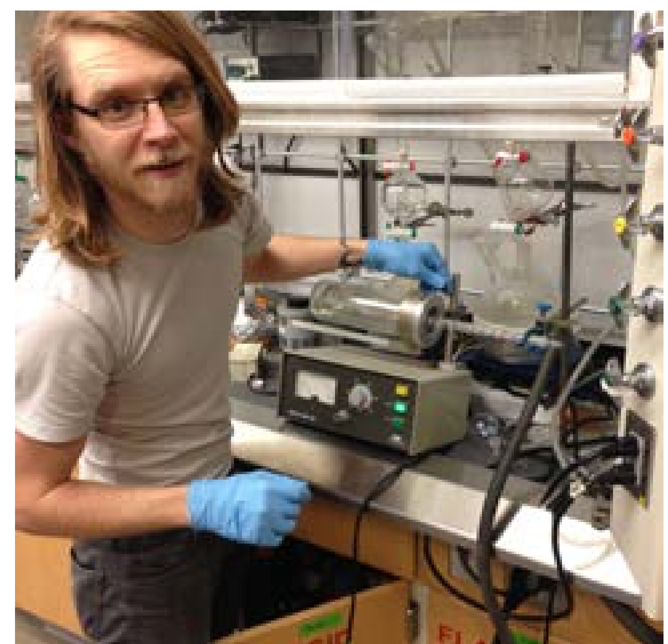
Vesicles

Acknowledgements

Kyle





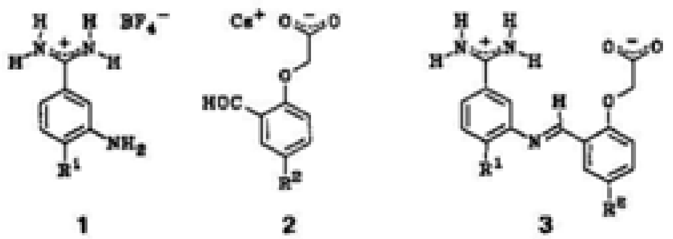


Questions?

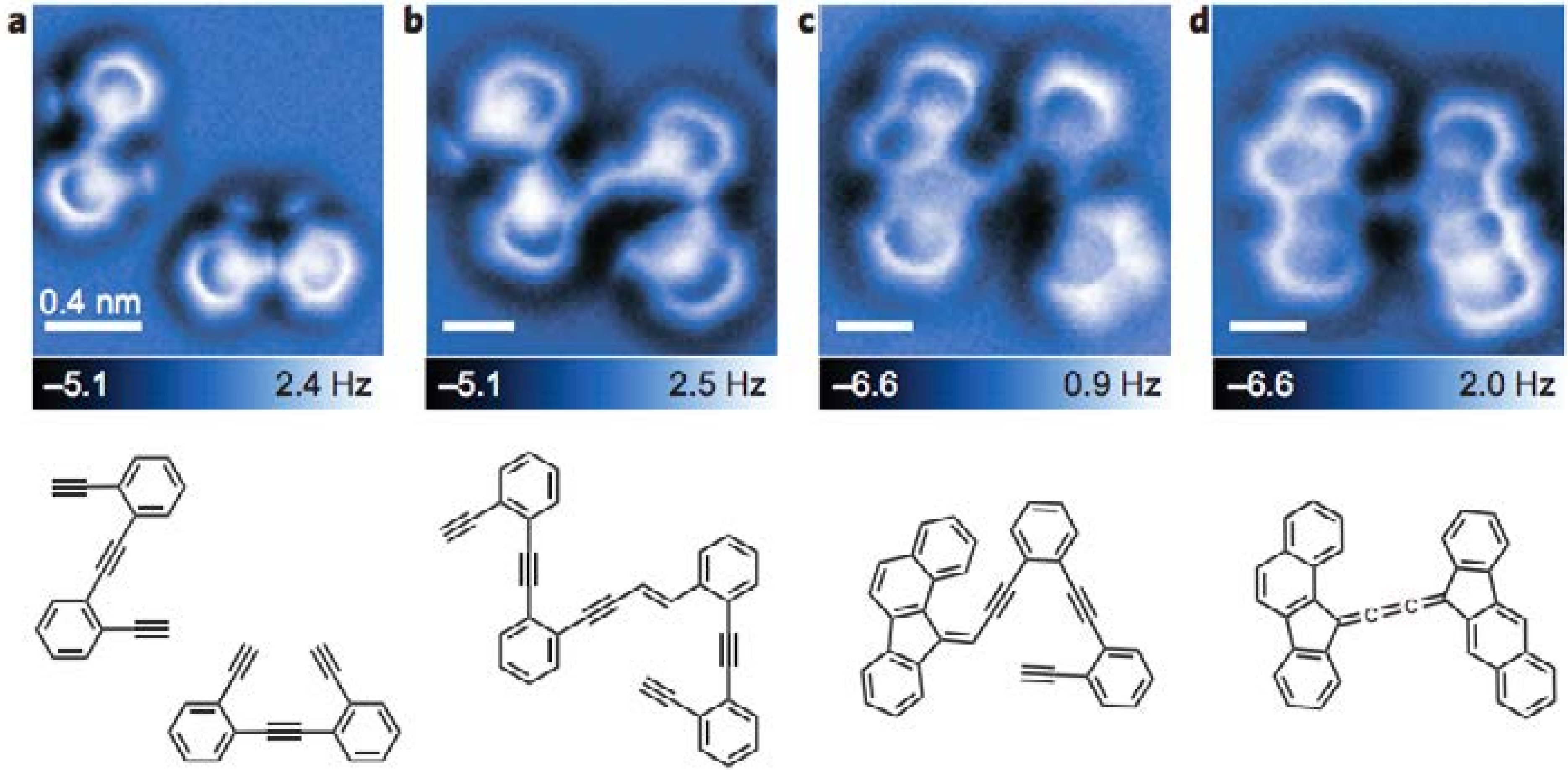
Previous attempts

Without nucleic acids:

Electrostatic connections (Terfort 1992)



AFM "sequencing"



1 2b 3c 4c

Riss, A. et al. Imaging single-molecule reaction intermediates stabilized by surface dissipation and entropy. Nature Chem 1–6 (2016). doi:10.1038/nchem.2506