Microwave-initiated living free radical polymerization: Optimization of the preparative scale synthesis of Rasta resins.

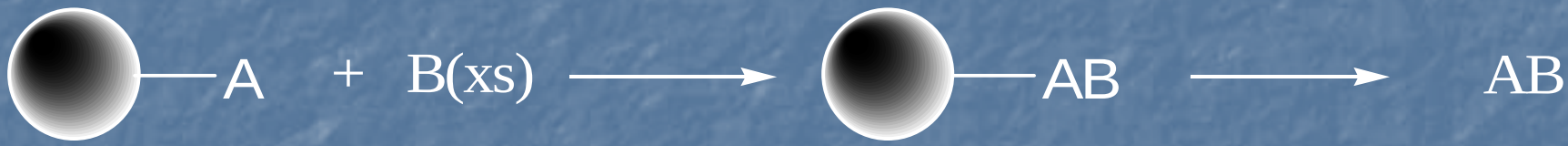
Presented by Joe Pawluczyk
Merck Research Laboratories

Microwave Synthesis and Other Enabling Tools & Technologies in Drug Discovery
University of Pennsylvania
Thursday October 19, 2006

Overview

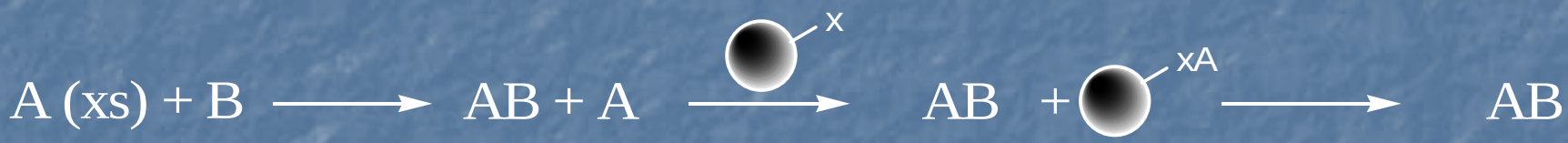
- Historical background of SPOS
- Introduction and description of Rasta resins and LFRP
- Microwave initiated LFRP in synthesis of Rasta resins
- Microwave preparative scale synthesis of Rasta resins in the Biotage Advancer
- Summary

Solid Phase Organic Synthesis



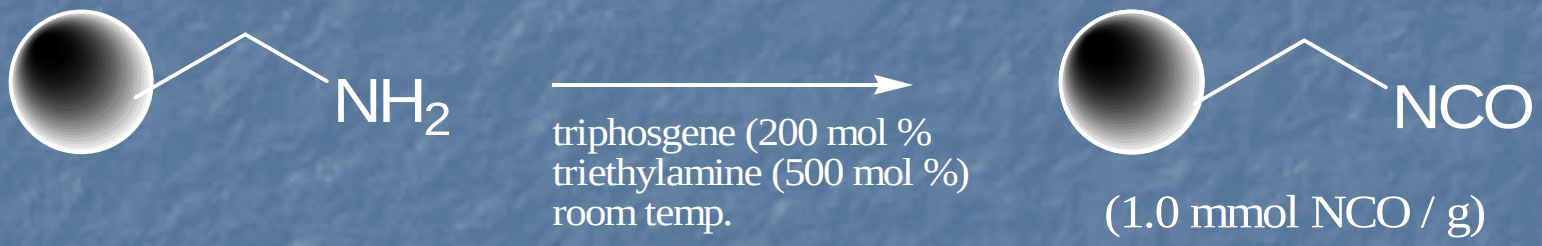
- methodology by Merrifield over 40 years ago
- gave birth to the field of combinatorial chemistry
- limitations: limited chemistry solution: solution-phase

Solid-Supported Scavengers



- solid-supported reagents to aid in purification
- published by Kaldor ***(Tet Lett Vol 37, No 4, pp7193-7196 (1996)***
- Hodges publishes paper on Polymer-Supported Quenching
  *(JACS **1997**, 119 4882-4886)*

Methylisocyanate for Amines



- the highest loading possible with commercially available resin

- for scavenging, want highest loading of functionallity as possible

- maximal reproducible loading achieved was 1.5 mmol/g

- disadvantage: urea cross linking vs isocyanate formation at higher loading. Uses expensive and hazardous reagents.

In Search of ...

- Hodges et al *J. Comb Chem 2000, 2, 80-88*
- Begin investigating polymerization of isocyanate bearing monomers
- Investigate living free radical polymerization

Living Free-Radical Polymerization

- Defined in the 1950's as the process of chain polymerization that proceeds in the absence of irreversible chain-termination.
- Realized by anionic polymerization (1950)
- Did not really emerge until the 1980's, the first successful form was nitroxide-mediated polymerization (NMP)

Living Free-Radical Polymerization

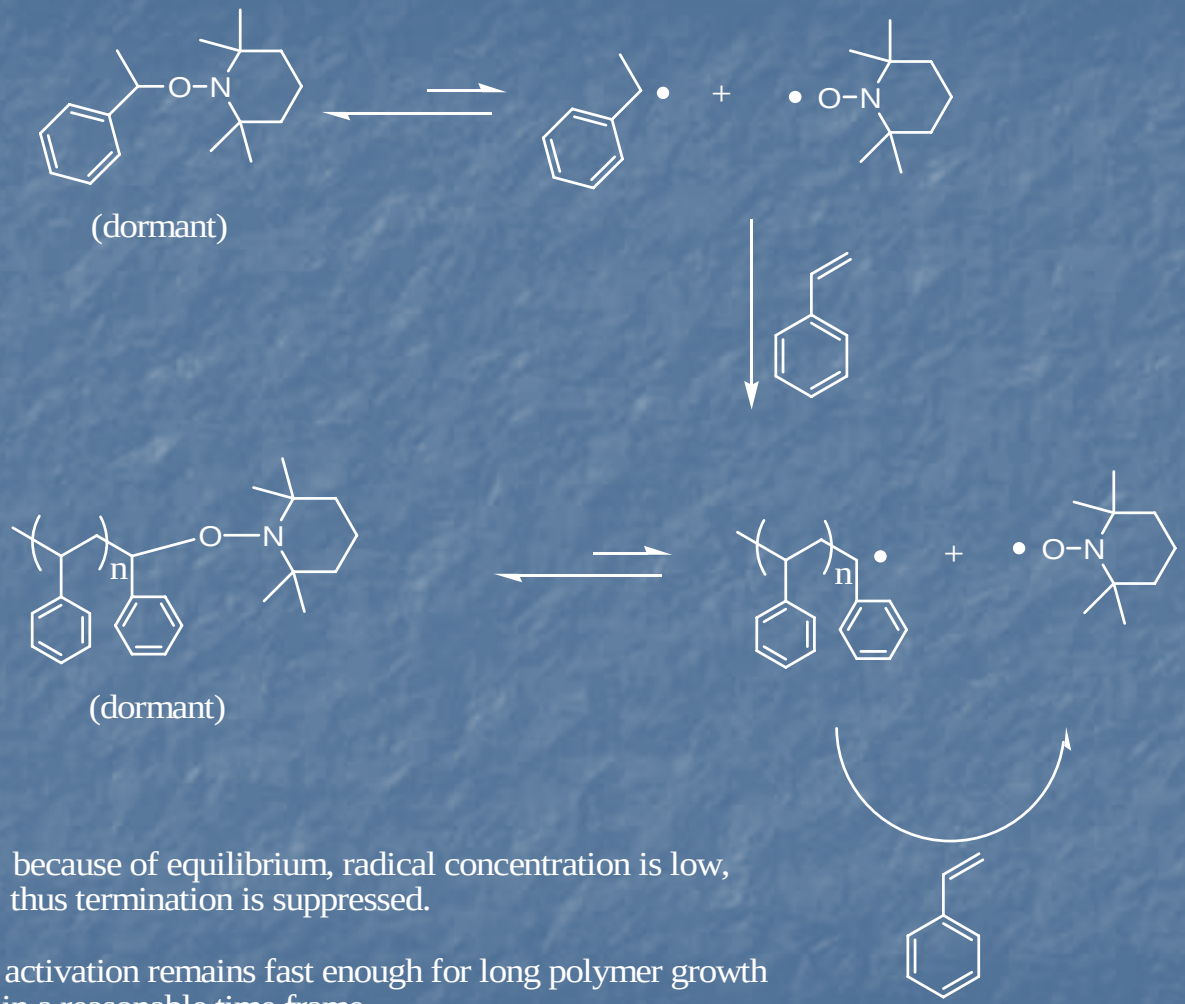
- polymer chain remains dormant until reactivated then a second monomer may be introduced. Equilibrium exists between dormant and active species.

- method provides end-group control and enables synthesis of macromolecules (ie block copolymers) by sequential addition of monomers.

- advantage: all chains are approximately the same if initiation is rapid on the time scale of monomer consumption.

Adash & Russell *Chemistry in New Zealand* vol 69 pp8 2004

Nitroxide-mediated Polymerization

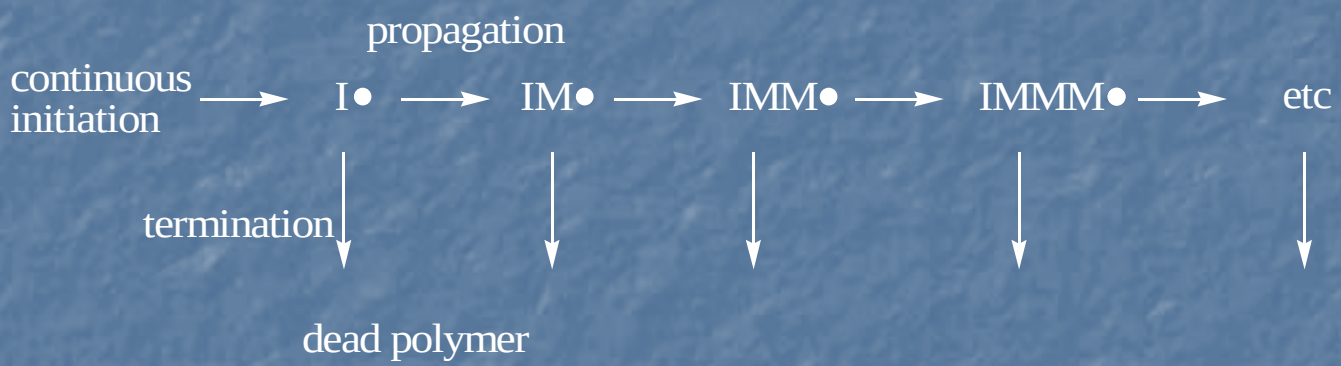


- because of equilibrium, radical concentration is low, thus termination is suppressed.

- activation remains fast enough for long polymer growth in a reasonable time frame.

Adash & Russell *Chemistry in New Zealand* vol 69 pp8 2004

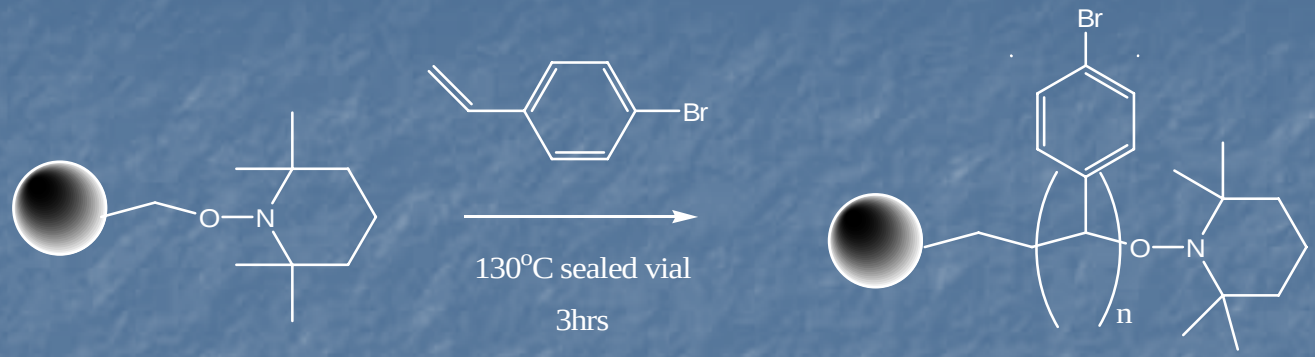
Conventional Free-Radical Polymerization



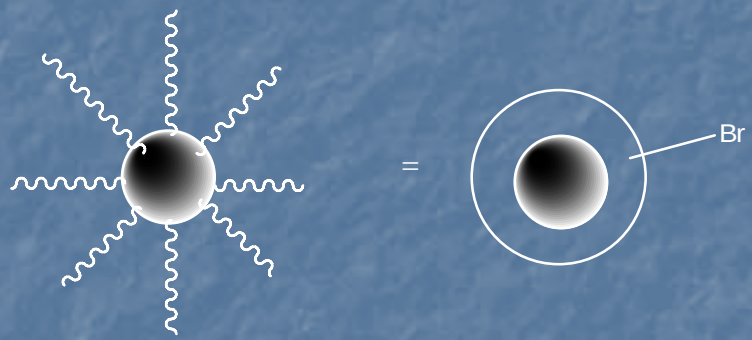
- many commercial polymers are prepared this way.
- allows for a wide range of monomers to be used under mild conditions
- disadvantage: polymer product is polydiverse

Adash & Russell *Chemistry in New Zealand* vol 69 pp8 2004

Proof of Concept



"Rasta resin"



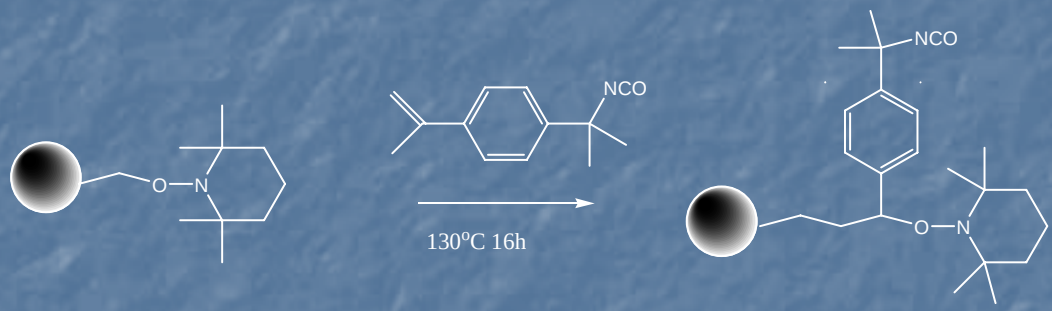
Results:

visibly larger bead with linear polymers

9- fold increase in mass

40.4% Br by elemental analysis (5.05 mmol/g loading)

Isocyanate Rasta Resin



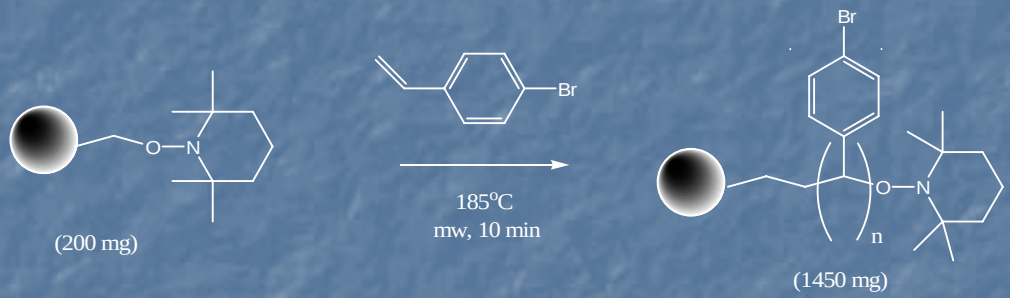
Results:

- workup of resin resulted in a disappointing 1.0 mmol NCO/g
- were able to achieve a Rasta resin through copolymeriaztion with styrene (~2.5 mmol NCO/g)
- successful investigation as an amine scavenger

5 Rasta resins are commercially available through Aldrich !

Microwave-initiated LFRP

Wisnoski et al *Tetrahedron Letters* 44 (2003) 4321-4325

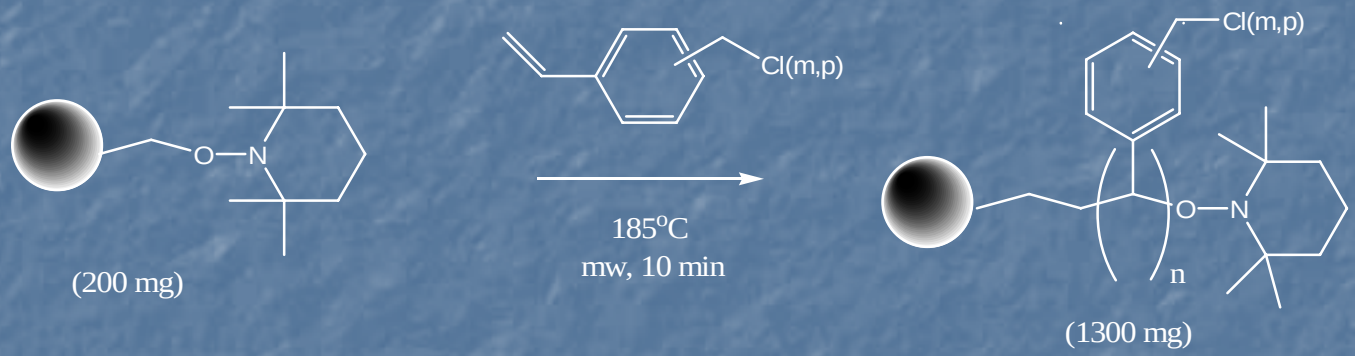


Results:

microwave preparation	**conventional preparation**
7.2 fold increase of mass	9 fold increase of mass
5.5 mmol/g loading (44% Br)	5.0g mmol/g (40.4% Br)
192um ⟶ ~ 550 um	75-150 um ⟶ 250um
spherical	spherical

Rasta Merrifield Resin

Wisnoski et al *Tetrahedron Letters* 44 (2003) 4321-4325

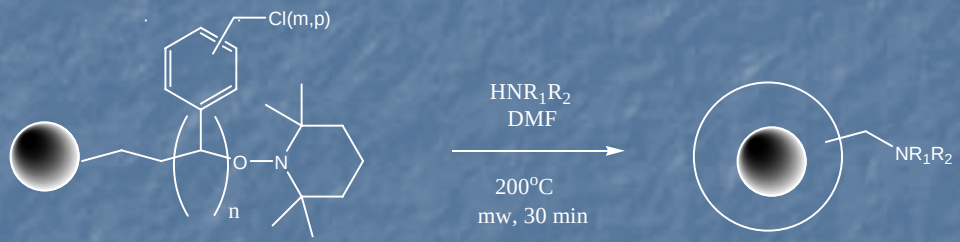


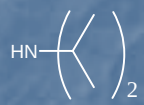
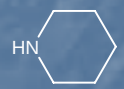
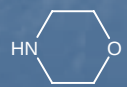
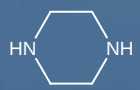
Initial run provided a 6.5 fold increase of mass and a loading level of 5.9 mmol/g (20.8% Cl)

Subsequent runs gave an average 6 fold increase of mass and ~5.8 mmol/g loading (23% Cl)

Rasta Amines

Wisnoski et al *Tetrahedron Letters* 44 (2003) 4321-4325

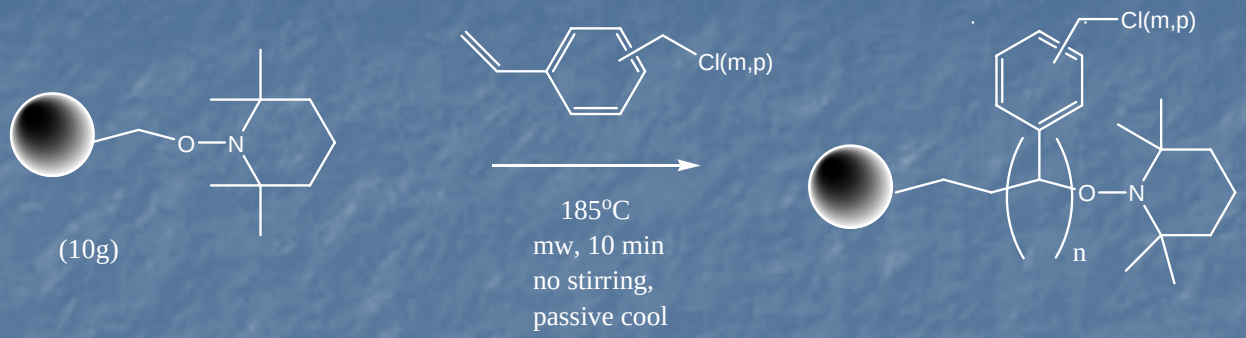


Amine	Loading
NEt	5.0 mol/g
	4.5 mmol/g
	5.0 mmol/g
	4.2 mmol/g
	4.2 mmol/g

Can we scale up ?

Can we scale up ?

Scale-up of Merrifield Rasta resin



Results:

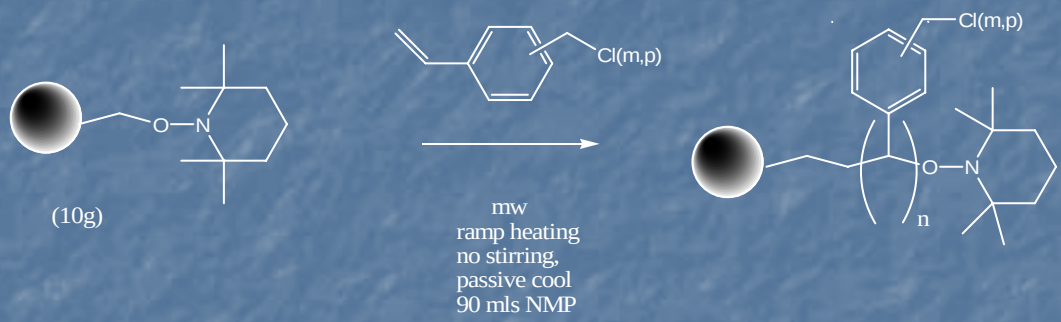
- initial run disappointing: reaction crashed cooled, internal temperature reached 225°C, fused polymeric mass

- repeat conditions, used ramp heating (.5°C/sec). Again crash cooled, temperature exceeded 200°C, polymeric mass

- repeat conditions, now add 90 mls NMP. Crashed cooled

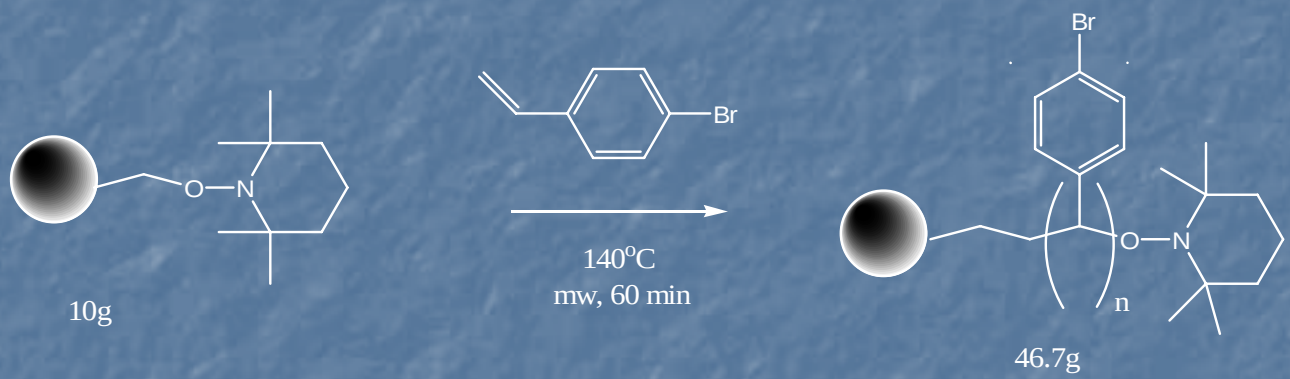
-reduced temperature to 140°C and increased time to 60 min
Recovered 50.55g of resin with a loading of 5.43mmol/g
(small scale produced a loading of 5.8 mmol/g)

Optimization of Temperature



Conditions	Results
15 mim @ 170°C	crashed cooled (186°C)
30 min @ 160°C	41g resin 5.3 mmol/g
15 min @ 160°C	37.23g resin 5.45 mmol/g
10 min @ 160°C	32.20g resin 5.23mmol/g
5 min @ 160°C	28.96g resin 4.85 mmol/g

Microwave-initiated LFRP



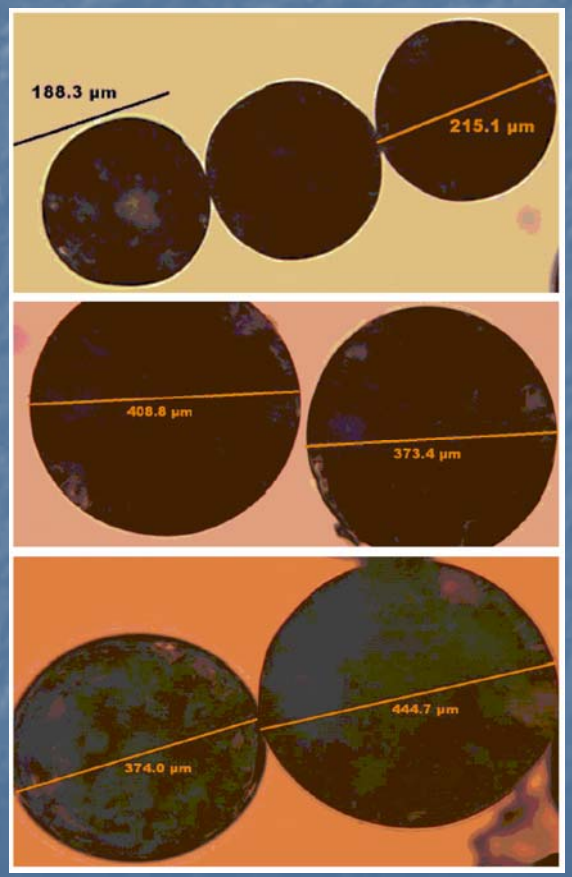
10g

46.7g

Results:

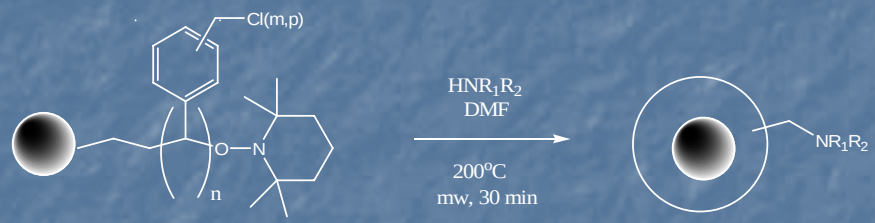
scale up	**microwave preparation**	**conventional preparation**
4.6 fold	7.2 fold increase of mass	9 fold increase of mass
3.85 mmol/g (30.45%)	5.5 mmol/g loading (44% Br)	5.0g mmol/g (40.4% Br)
370um to 450um	192um → ~ 550 um	75-150 um → 250um
spherical	spherical	spherical

Rasta Resins

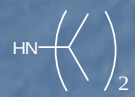
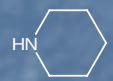
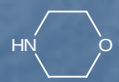
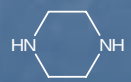


- PS – TEMPO resin
- Bromide
- Merrifield

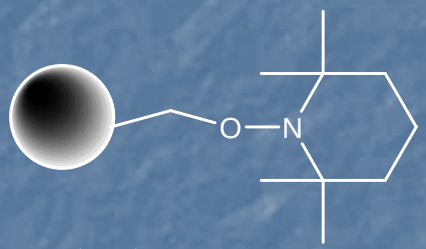
Rasta Amines



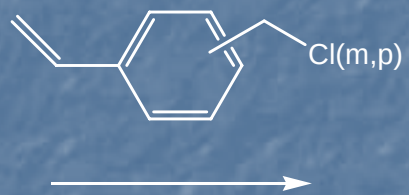
10g

Amine	Small scale	Large scale
NEt_2	5.0 mmol/g	4.5 mmol/g
	4.5 mmol/g	3.28 mmol/g
	5.0 mmol/g	4.51 mmol/g
	4.2 mmol/g	4.44 mmol/g
	4.2 mmol/g	3.17 mmol/g

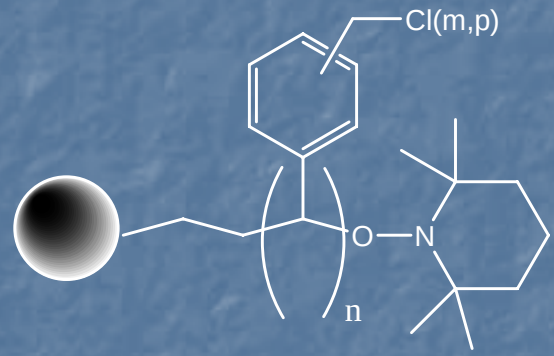
How Much ?



(30g)



mw
60 min@140°C
ramp heating
no stirring,
passive cool
100 mls NMP



116g

- unbreakable solid mass in core of rxn vessel

- 5.23 mmol/g loading

Conclusion

- Used LFRP to develop Rasta resins
- Microwave energy assisted in creating high loading Rasta resins
- A new scalable protocol that affords multi-gram quantities of custom Rasta resins.

Acknowledgements

- Craig Lindsley

- Deanne Jackson Rudd
- Ray McClain
- James Mulhearn
- Chris Denicola