Microwave Assisted Organic Synthesis
Where do we go from here?

Steve Jordan

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Escalating costs of drug discovery

- ***$802m*** **to bring a drug to market (Tufts Centre, 2001)**
- **2.5 fold increase over the last decade!**
- **Costs largely associated with increasing clinical costs**
- **R&D expenditure 'v' marketable drugs**
- **False screening results**
- ***Time for technology to realise its full potential!!***

  Hardware & informatics

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Evolution of Microwave Chemistry

1946	Microwave radiation was discovered as method of heating
1947	First commercial domestic microwave oven
1978	First microwave lab instrument developed to analyze moisture in solids
1980-82	Microwave radiation developed to dry organic materials
1983-85	Microwave radiation was used for chemical analysis processes such as ashing, digestion and extraction
1986	Gedye R. (Laurentian Univ. Canada); Majetich, G. (Univ. Georgia; USA) & Giguere, R. (Mercer Univ; USA) published papers relating to microwave radiation in chemical synthesis
2000	Introduction of the first commercial single-mode microwave system for high throughput organic synthesis
2005	Over 2000 publications on MAOS
2006-2010	....????

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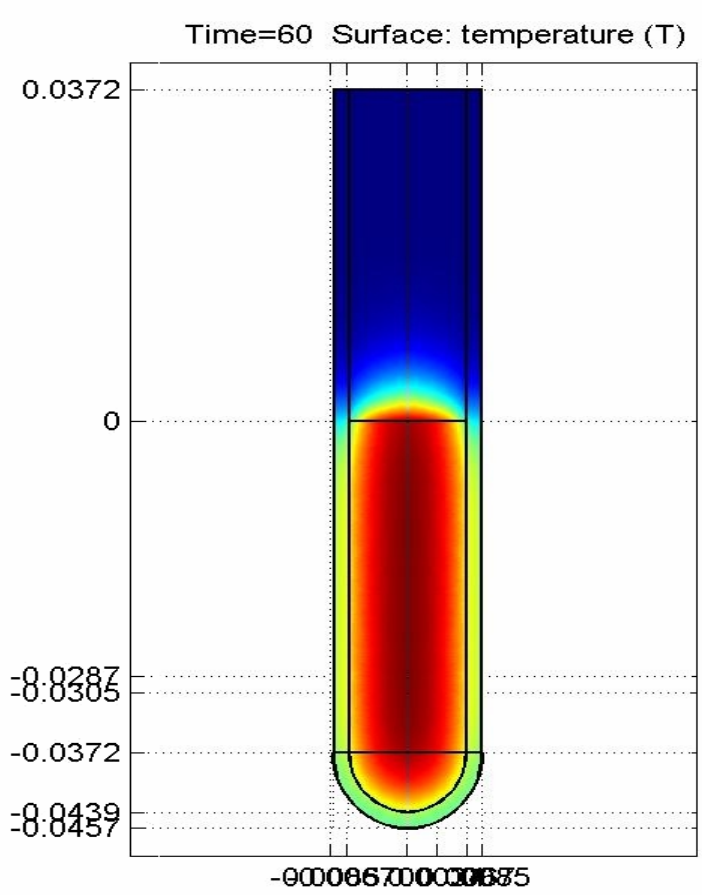
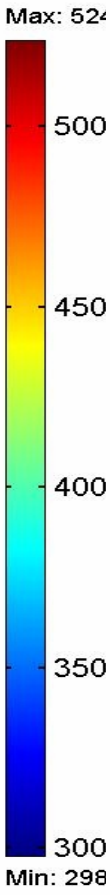
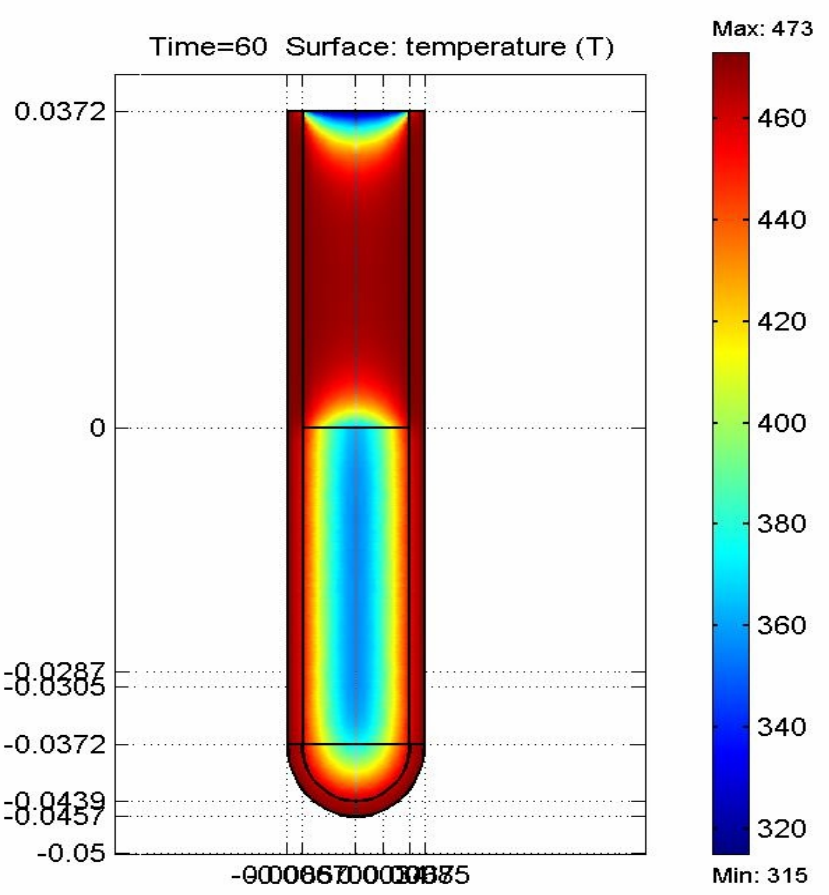
Microwave *vs* Conventional Heating







Microwave Heating **Conventional Heating**

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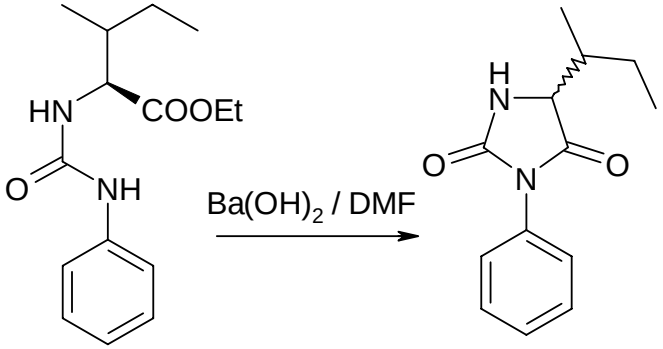
Advantages of Microwave Assisted Synthesis

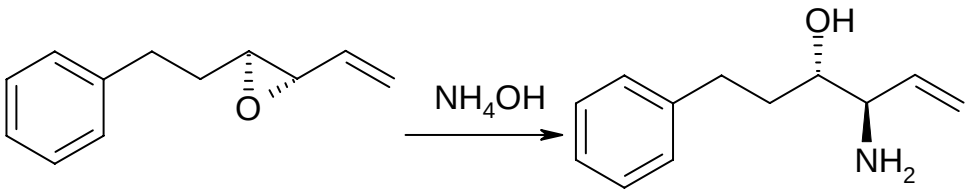
- Shorter reaction times
  - Rapid testing of creative ideas
  - Increased productivity
  - Higher yields, improved purity
- Expanded reaction diversity
  - Some difficult reactions made possible
- Less reagents and solvents
- Less reactive reagents
- Reproducible results
- Scalable conditions

Hydantoin Synthesis



Microwave Heating: 4 min; **90%** yield
Conventional Heating: 48 h; **54%** yield

Epoxide Ring Opening



Microwave Heating: 7 min; **93%** yield
Conventional Heating: 10 days; **13%** yield

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Unusual Findings!

- Reactions conventionally done in ice-baths (0 ^{o}C)
- Reactions and substrates with perceived sensitivity to “heat”

Can be successful via microwave “flash” high temperature heating!

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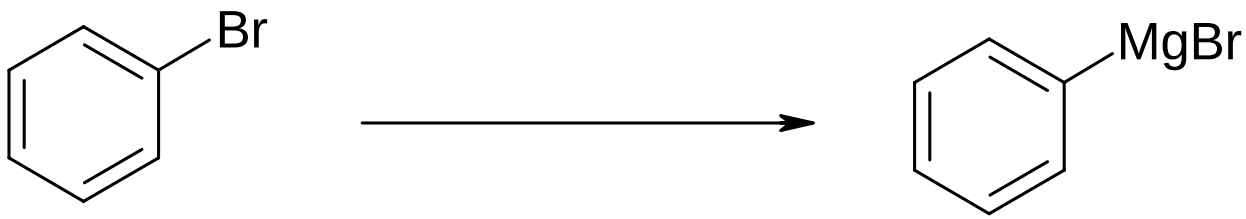
Preparation of Grignard reagent



89 %

Conventionally

- **0°C, hours**
- Et_2O
- Inert atmosphere

Microwaves

- **60°C, 10min**
- THF
- Normal atmosphere

Avoids the inconvenience of purging N_2 and ice baths.

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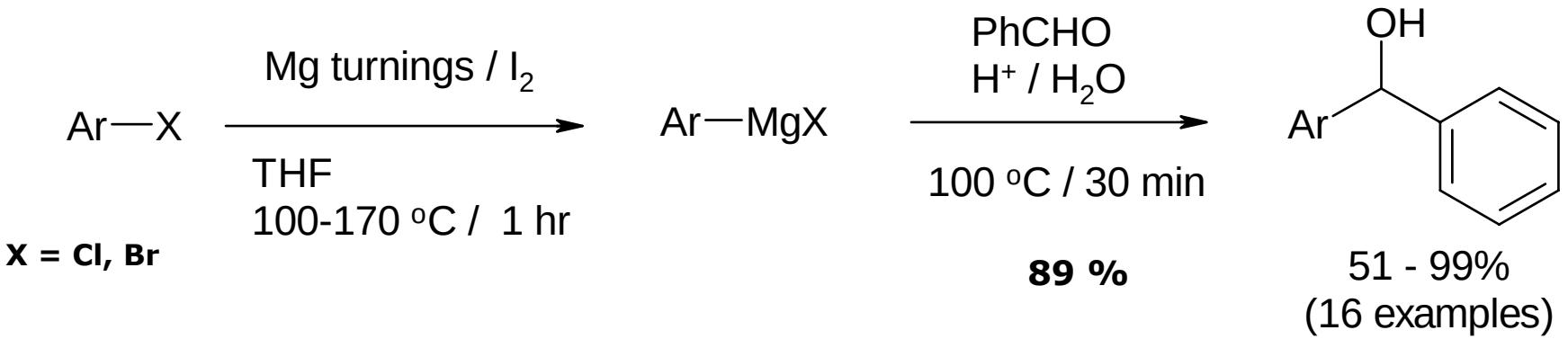
Biotage Pathfinder data

Grignard Reaction of Aryl Chlorides



Larhed, M. *et al. Synlett.*, 2005, 1596

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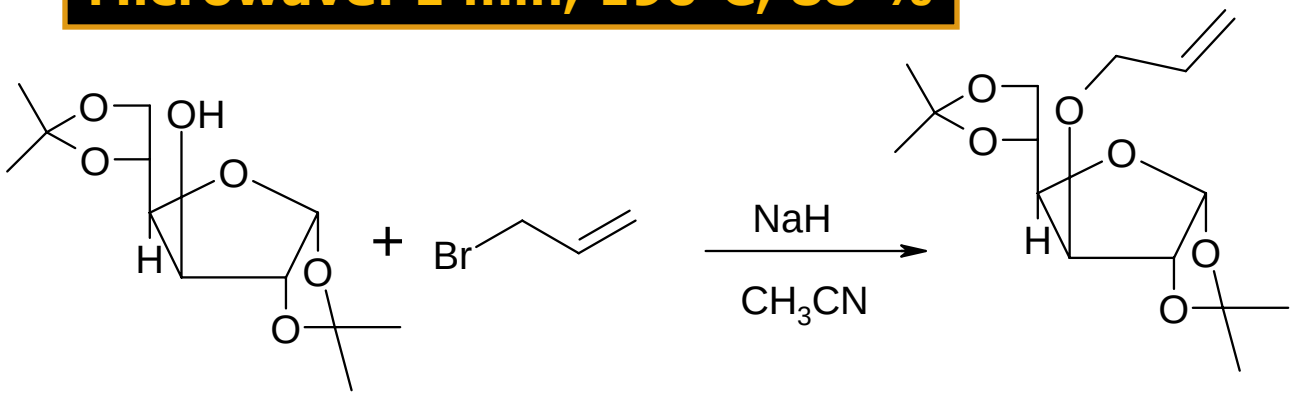
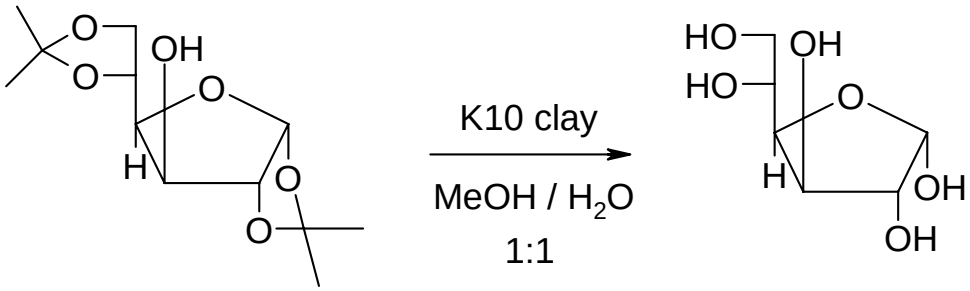
Carbohydrate Chemistry

Microwave: 1 min, 190°C, 88 %



Microwave: 3 min, 150°C, 91 %



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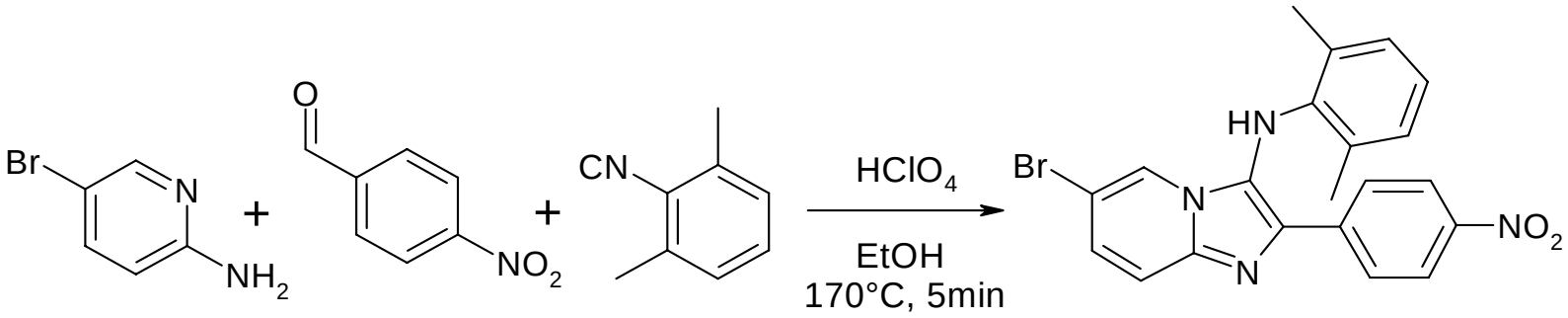
Söderberg, E.; Westman, J.; Oscarsson, S. *J. Carbohydrate Chem*. **2001**, *5*, 397-410

Biotage Pathfinder data

One-step, three-component synthesis of Imidazo[1,2-a] annulated Pyridine



Safety. Use of Perchloric acid as catalyst

1. Optimized on Emrys™ Liberator: **70%** yield
2. Directly scaled up 30 X: **68 %** yield (100% purity)

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Solid Supported Reagents in Solution Phase MAOS

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What slows down drug discovery?

1. Target and Synthesis Design
2. Reaction
3. Work-up - usually extraction & evaporation
4. Purification - usually chromatography
5. Spectral Analysis Registration

Bottlenecks (3) and (4) become even greater with microwave chemistry

J. C. Hodges, Pfizer Inc. ACS Spring Meeting, San Diego, 2001

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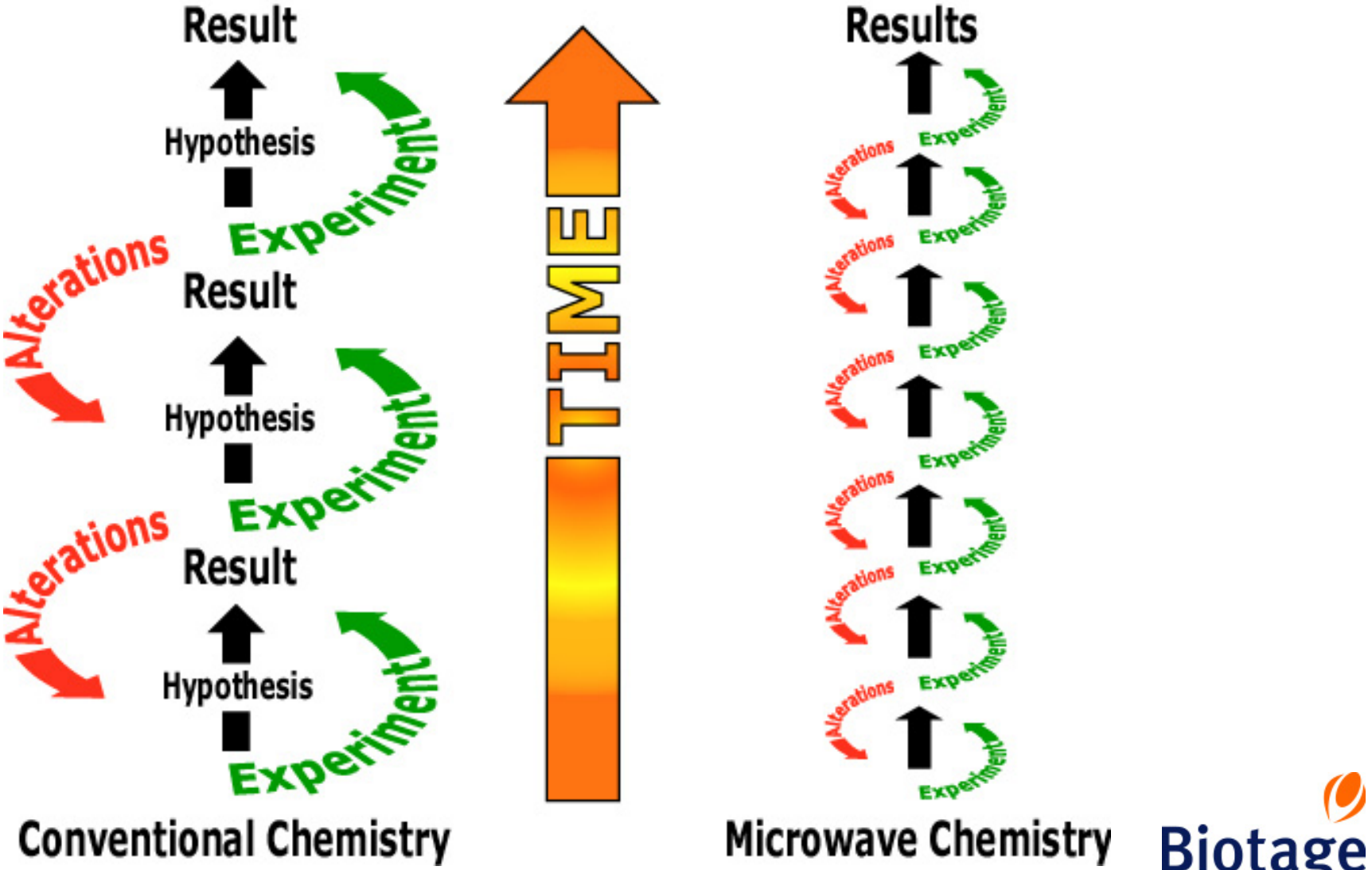
Reduce cycle-time

Fail Fast – Fail Cheaply



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Reagents for Important Reaction Families

- Reductive Amination
  - 30% of drugs in the Comprehensive Medicinal Chemistry (CMC) database are tertiary amines[1]
- Common Reagents for Amide Synthesis
  - 28% of compounds in the CMC database are carboxamides[1]
- Oxidizing agents
- Palladium Catalyst & Scavenger
- Acids and Bases

[1]Ghose, A. K.; Viswanadhan, V. V.; Wendoloski, J. J. *J. Comb. Chem*. **1999**, *1,* 55-68.

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Polymer Types

Resin	Advantages	Limitations
Polystyrene 1 - 2 % cross linked **(PS-)**	• Swell in organic solvents • High loading	Incompatible with water, alcohols
Macroporous Polystyrene **(MP-)**	• Compatible with all solvents • Low swelling • Faster washing and drying	Lower loading

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Biotage Polymeric Reagents

Bound Reagent	Solution Analog	Application
PS-TsCl	*p*-toluenesulfonyl chloride	Catch and Release
MP-TsOH	*p*-toluenesulfonic acid	Catch and Release
PS-DIEA	Hindered tertiary amine	Amine base
PS-NMM	N-methylmorpholine	Non-benzylic amine base
PS-TBD	TBD	Strong Base
PS-DMAP	DMAP	Catalyst, Catch and Release
MP-Carbonate	Ammonium carbonate	Base, Catch and Release
MP-Borohydride	Sodium borohydride	Reducing agent
MP-Cyanoborohydride	Sodium cyanoborohydride	Reductive amination
MP-Triacetoxyborohydride	Sodium triacetoxyborohydride	Reductive amination
MP-TsO-TEMPO	TEMPO	Oxidation of alcohols to carbonyls
PS-Carbodiimide	DCC	Coupling
PS-HOBt(HL)	1-hydroxybenzotriazole	Active ester, amide synthesis
PS-Triphenylphosphine	Triphenylphosphine	Mitsunobu/Wittig/halogenations
PS-PPh_3-Pd	Triphenylphosphine Palladium (0)	Palladium Catalyst

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Functional Group Stability Study
PS- and MP- resins

- The stability PS- and MP- based resins upon microwave heating studied
- Three most commonly used solvents were selected: DCM, THF, DMF
- Temperatures were selected to be higher than what would be used in an actual application
- Heating time was 5 and 15 min
- The resins were evaluated for:
  - Resin Capacity
  - Bead breaking/agglomeration
  - Volatile and non-volatile leachable decomposition products

Collaboration with Argonaut Technologies (now Biotage)

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Functional Group Stability Results for PS- and MP resins - SUMMARY

- PS- and MP- behaved similarly; PS- type swelled and occupied more volume

- In general the resins were stable to microwave heating and did not break or agglomerate

- No volatile or non-volatile leachable decomposition products was found over the range of solvents studied (DCM, THF and DMF)

- The capacities of the PS and MP-isocyanate and MP-triacetoxyborohydride resins was reduced by more than 70%

This does not mean that they cannot be used with microwave heating because
(a) the reaction would most probably be performed at a lower temp/time
(b) the reaction rates maybe faster than the decomposition rates

Collaboration with Argonaut Technologies (now Biotage)

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Functional Group Stability Results for PS- and MP resins

No	Resin Type	Std Capacity mmol/g	Resin Capacity mmol/g	Resin Shape (% Broken)
1	MP-Triacetoxyborohydride	2	0.66	1.5
2	MP-Carbonate	2.8	2.88	0
3	MP-TsOH	3.3	3.4	0
4	PS-Carbodiimide	1.15	1.23	0
5	PS-HOBt	1	0.99	1
6	PS-DIEA	3.9	3.9	30
7	PS-PPh3Pd	pass	pass	0
8	PS-trisamine	4.5	3.86	0
9	PS-Benzaldehyde	1.2	1.11	0

Condition: 1 g / 20 mL THF / 135 ^{o}C / 5 min

Collaboration with Argonaut Technologies (now Biotage)

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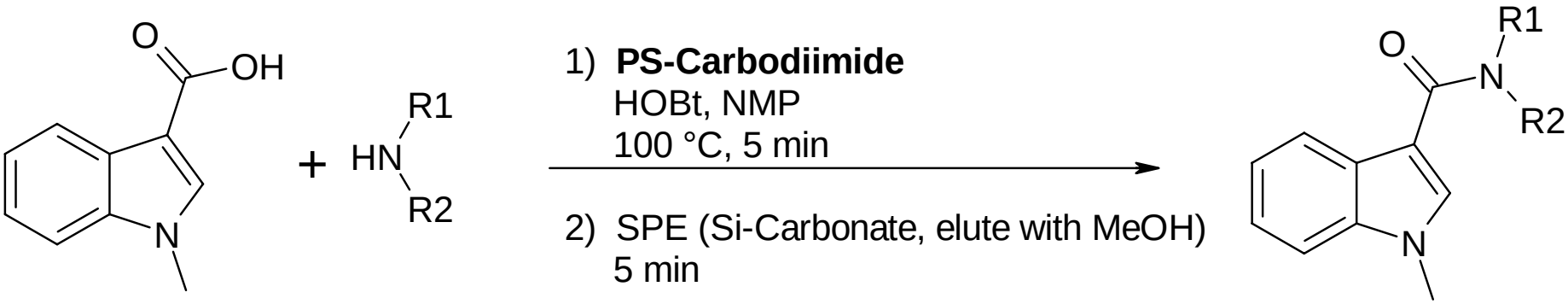
Amide Formation



- HOBt scavenged via Si-carbonate SPE
- Both synthesis and purification takes < 15 min
- 6 different amines were used

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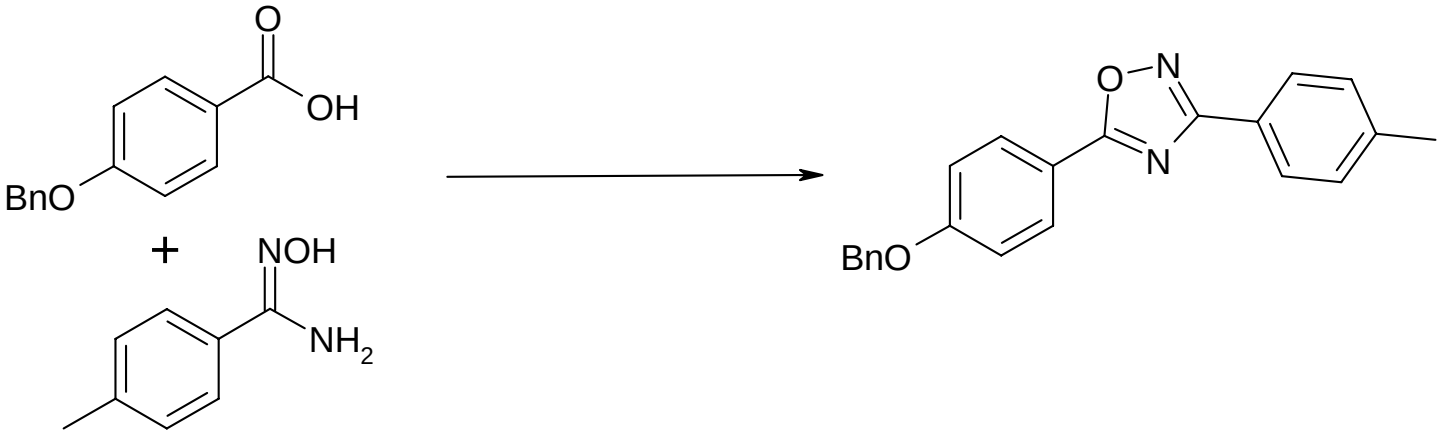
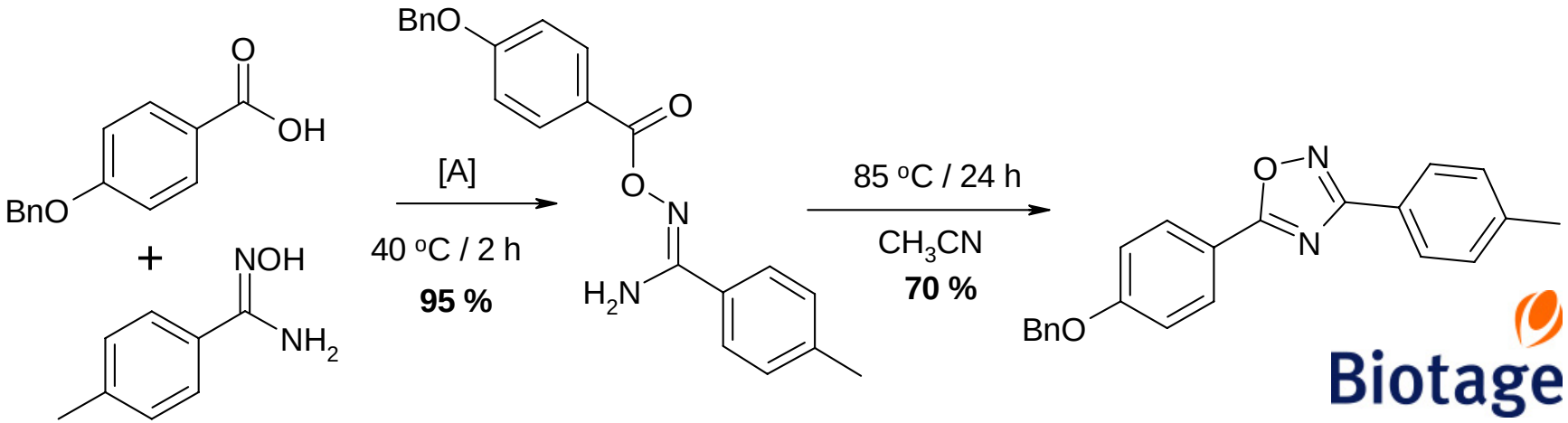
Sauer D.R. et al. *Org. Lett*. **2003**, *5*, 4721-4724.

Solid Supported Reagents
Oxadiazole synthesis



[A] PS-Carbodiimide (3 equiv); HOBt (1 equiv); DIEA (3 equiv); CH_3CN
130 °C / 30 min (83% yield)

Conventional Heating:



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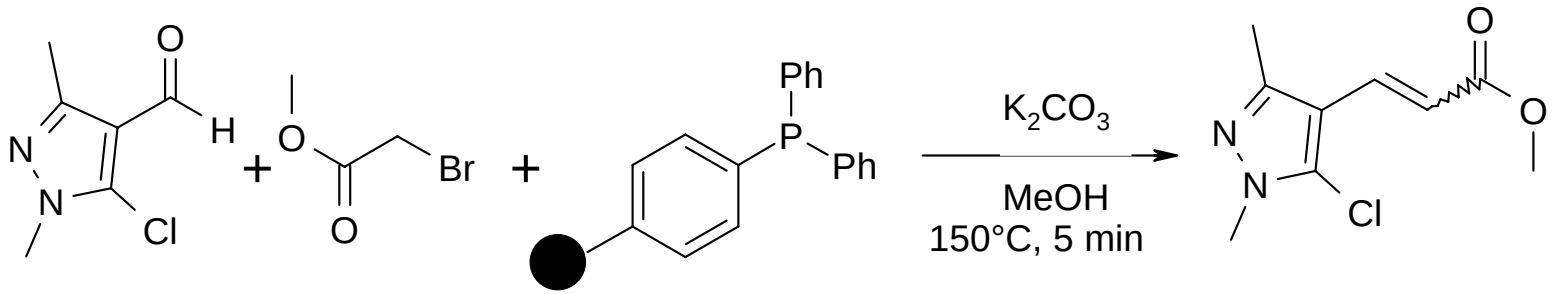
Wang, Y.; Miller, R.L.; Sauer, D. R. Djuric, S. W.; *Org. Lett.* 2005, *7(5)*, 925-928

Solid Supported Triphenylphosphine
One-pot Wittig olefination



Solid phase supported reagent. Heterogeneous solution

1. Developed & optimized on Emrys™ Liberator
2. Scaled up 30 times in Advancer; **92% yield (95% purity)**

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COMBINING

- Microwave Assisted Organic Synthesis (MAOS)
- Solid supported reagents
- Automated Flash purification

- Shorten “compound production” time
- Increase product purity
- Increase productivity

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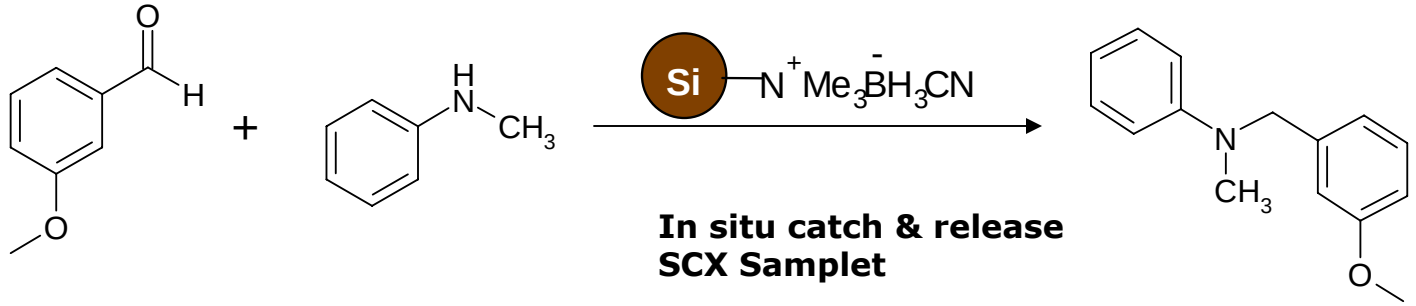
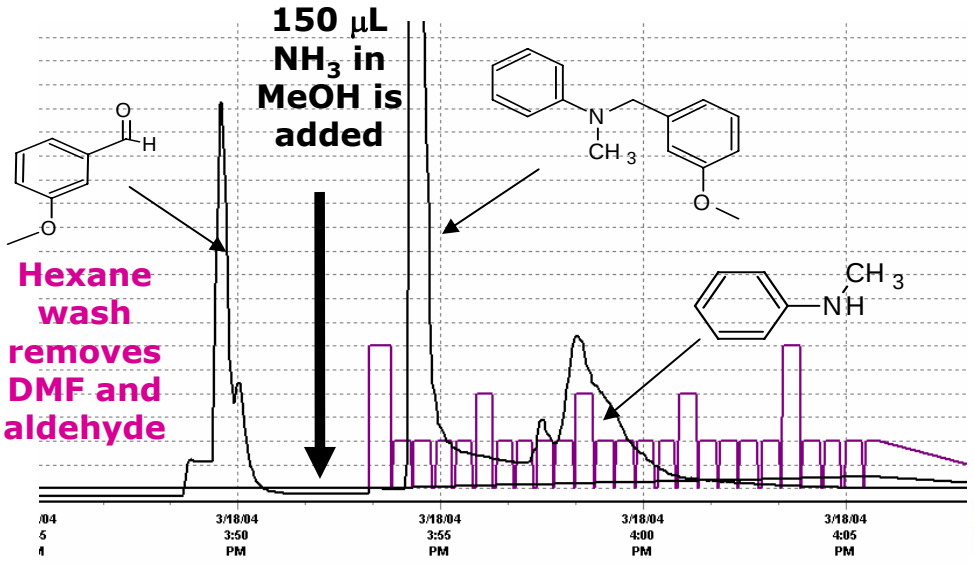
Simplified Workup & Purification

"Catch and Release" purification of Tertiary Amines



TLC of Reaction mixture



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Ghassemi, S. Biotage, Unpublished results

Simplified Workup & Purification
Catch/Release + Flash Technique

Reaction Mixture (in DMF)

SP

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Ghassemi, S. Biotage, Unpublished results

Where do we go from here

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Drivers for change---

- HTC/HTS has put increased pressure down stream ----- Process chemistry
- More compounds entering PRD ----need to respond quickly
- Many chemical routes now using MW technology
- Need to fail early----fail cheaply
- In the next 5 years many compounds come off patent
- A large number of API vendors now off-shore
  - **700 vs 3000**

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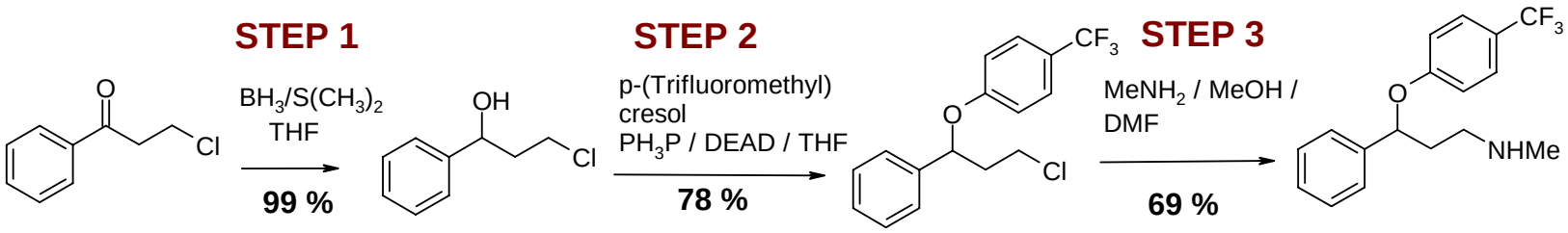
Fluoxetine

PROZAC™



	Microwave Assisted Synthesis	Conventional Synthesis
Step 1	100 °C; 2 min 20 sec	-25 °C; 7 h[1]
Step 2	120 °C; 5 min	23 °C; 18 h
Step 3	150 °C; 5 min	130 °C; 3 h

Overall Yield	**53 %**	**51 %**
Total Reaction Time	**12 min 20 sec**	**28 h**

** Ruda, K.; Katkevics, M.; Mutule, I; Ozola., V; Suna, E.*

(1) Brown, H.C. et al; J. Org. Chem. ***1988,*** *53, 2916-2920*

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What can we expect to see---

- More process chemistry done earlier and faster. Early scale-up group (1-5kg)
- Increasing use of MW technology in scale-up
- More Flow chemistry-----including MW/flow, Batch flow
- Use of solid support reagents, catalysts, scavengers in both the synthesis and purification
- New Polymer backbones
- Many new reagents/scavengers on Silica and Polymer supports
- **API vendors /Pharma---looking towards MW technology in large scale production**

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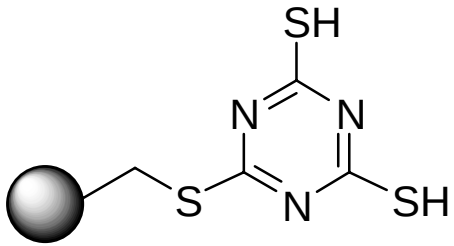
MP-TMT – New Palladium Scavenger



Macroporous polystyrene-2,4,6-trimercaptotriazine

- Bound TMT ligand on macroporous resin
- Scavenges Pd(II) and Pd(0), ligated palladium
- Effective in aqueous and non-aqueous solutions
- Useful for compound polishing
- Reduces residual palladium to low ppm levels

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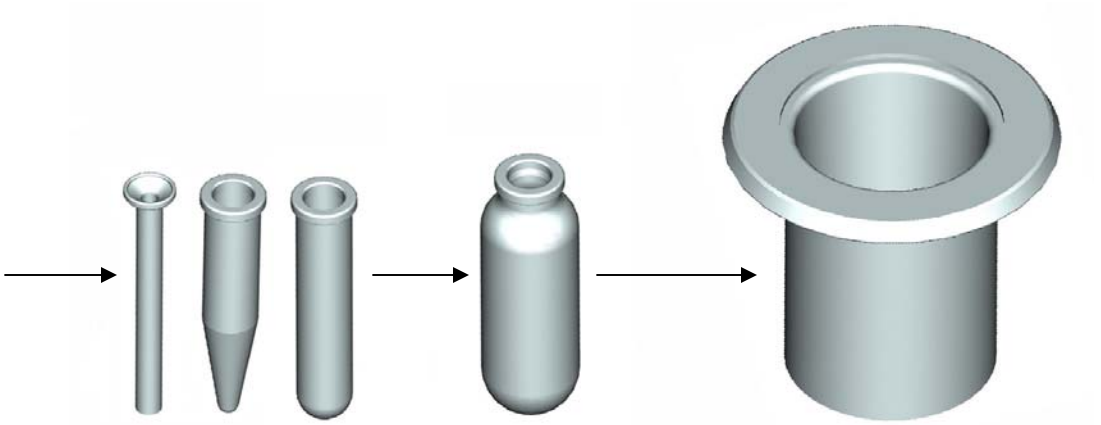
Microwave Reaction Scale-up



	0.2-5 ml mg-g	20 mL 1-10g	300 ml 10g-1kg
Biotage™ Pathfinder	**Initiator EXP** -Eight EXP -Sixty EXP	**Initiator EXP** - Eight EXP - Sixty EXP	**Advancer**

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SUMMARY

- MAOS is a versatile tool that speeds up the chemistry development process
- Adoption in to workflow simplifies and enhances the rate of discovery
- Allows access to reactions and conditions previously considered “impossible”
- Can be easily integrated with *Solid Bonded Reagents* and *Automated Flash Chromatography* eliminating the purification bottleneck

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QUESTION TO YOU....????

- What is the top 5 troublesome reagents that you would like to see in bound form?
- What are your top 5 work-up/purification bottlenecks? (eg. solvents, byproducts, reagents etc..)

Please drop of your list before leaving with a Biotage personnel

THANK YOU!!!

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