

Rapid Compound Production: Microwave Assisted Synthesis, Workup & Purification

*Farah Mavandadi, Ph.D.
Product Manager*

Topics

- **Microwave-assisted organic synthesis**
 - Advantages
 - Scope
- **Solid supported reagents and scavengers**
 - History and Concept of use
 - Advantages in solution phase synthesis
 - Microwave stability
- **Key Transformations using solid-supported reagents/scavengers**
 - Pd-catalyzed reactions
 - PS-Triphenylphosphine
 - Acid catalyzed Reactions
 - Base Catalyzed reaction
 - Amidation
 - Reductive Amination
 - Oxidation

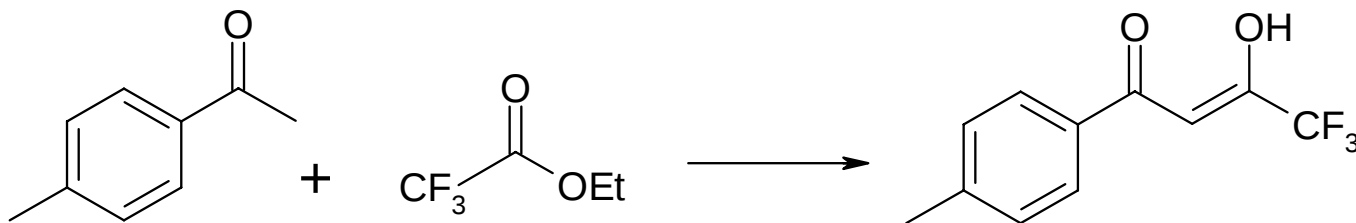
Tools for Accelerating Drug Discovery

MAOS

2004-2005



Advantage of MAOS NON-Organometallic Reactions



Solvent	Base	Temp	time	Yield
MTBE	NaOMe	25 °C	14 h	25 %
DMF	NaH	25 °C	5 days	88 %
DME	NaH	100 °C	2 h	60 %
DME	NaH	160 °C	10 min	95 %

SCOPE OF MICROWAVE SYNTHESIS

- Most room temperature & elevated temperature reactions
- Reactions in Polar and Non-polar solvents
- Metal catalyzed and gaseous reactions

**REACTION OPTIMIZATION
IS KEY TO SUCCESS**

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 greater with microwave chemistry

Purification Techniques

PURIFICATION

Crystallisation

Separation

Liquid-Liquid
Clean-up

Filtration

Distillation

➤ Flash
Chromatography

➤ HPLC



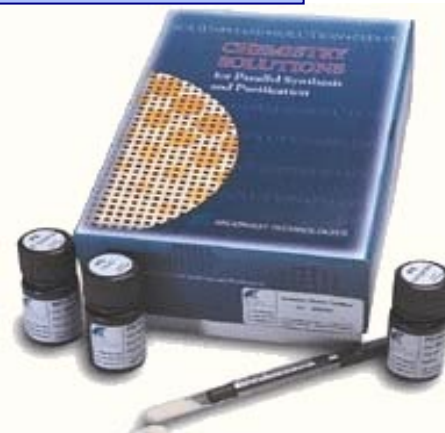
➤ Solid phase
extraction (SPE)

➤ Solid-supported
liquid extraction

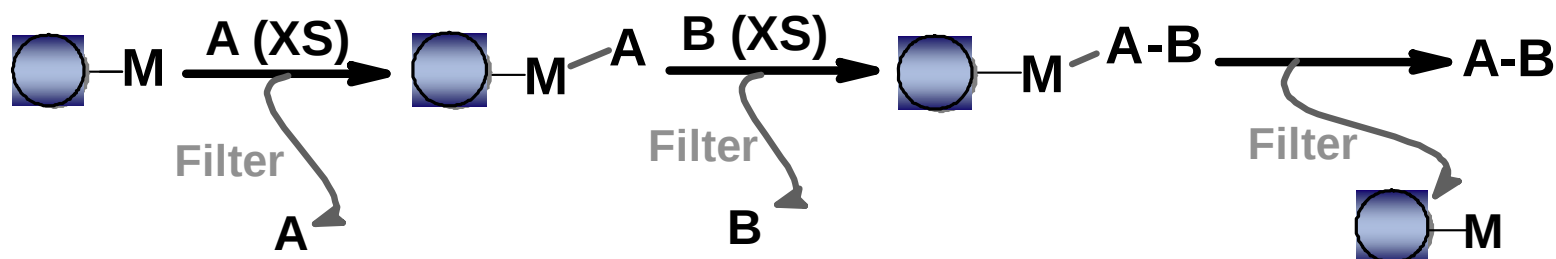


➤ Solid-bound
reagents

➤ Solid-bound
scavengers

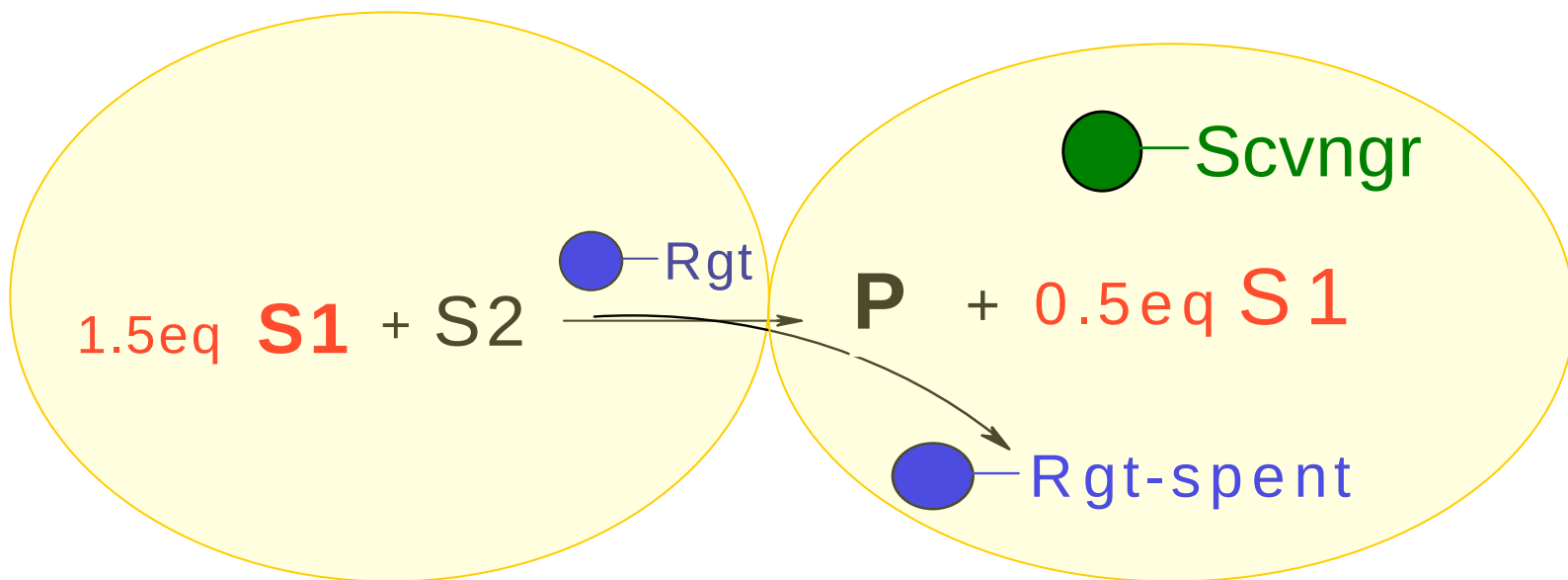


Solid Supported Organic Synthesis



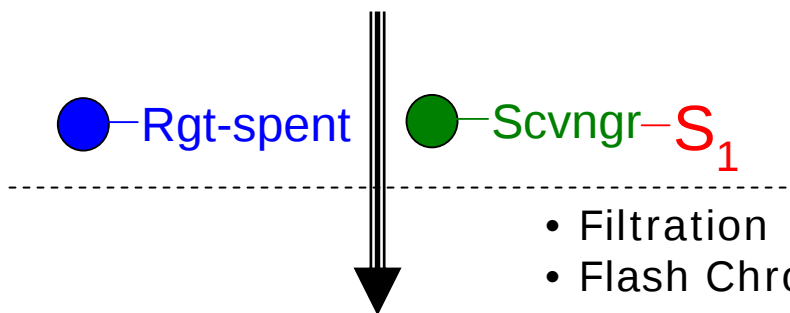
- Excess reagents help drive reactions to completion
- Minimal workup is needed, usually by filtration
- Extra steps of anchoring and cleaving the target molecule to the resin
- Difficulty in real time monitoring of the reaction progress
- Slow reaction kinetic

Solid-Bound Reagents & Scavengers Mode of Action



Solution Phase Synthesis

- Conventional
- Microwave-assisted

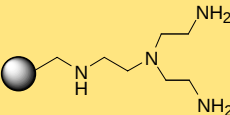
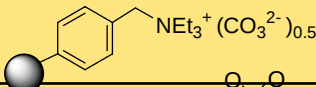
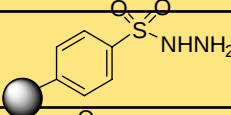
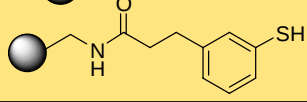
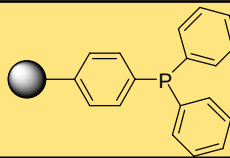
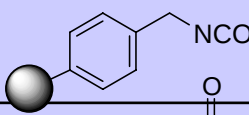
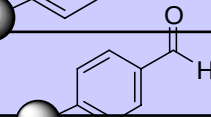
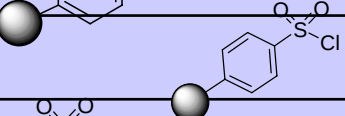
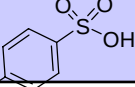
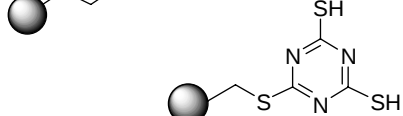
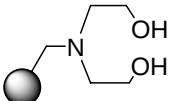


- Filtration
- Flash Chromatography

Biotage Resin Reagents

Bound Reagent	Solution Analog	Application
PS-TsCl	p-toluenesulfonyl chloride	Catch & Release
MP-TsOH	p-toluenesulfonic acid	Catch & Release
PS-DIEA	Hindered tertiary amine	Amine base
PS-NMM	N-methyl morpholine	Non-benzylic base
PS-TBD	TBD	Strong Base
PS-DMAP	DMAP	Catalyst, Catch & Release
MP-Carbonate	Ammonium carbonate	Base, Catch & Release
PS-Triphenylphosphine	Triphenylphosphine	Mitsunobu/Wittig/Halogenation
PS-PPh ₃ -Pd	Triphenylphosphine Pd(0)	Palladium Catalyst
PS-Carbodiimide	DCC	Coupling Agent
PS-HOBt (HL)	HOBt	Coupling agent
MP-Borohydride	Sodium borohydride	Reducing Agent
MP-Cyanoborohydride	Sodium cyanoborohydride	Reducing agent
MP-Triacetoxymorohydride	Sodium triacetoxymorohydride	Reducing agent
MP-TsO-TEMPO	TEMPO	Oxidizing Agent

Biotage Polymeric Scavengers

Electrophile	PS-Trisamine MP-Trisamine		Acyl halides, Sulfonyl halides, Isocyanates
	MP-Carbonate		Carboxylic acids, Phenols
	PS-Tosylhydrazide		Aldehydes, Ketones
	PS-Thiophenol		Alkylating agents
	PS-Triphenylphosphine		Alkyl halides
Nucleophile	PS-Isocyanate MP-Isocyanate		1°, 2° amines, hydrazine
	PS-Benzaldehyde		1° amines
	PS-Tosyl chloride		Anilines, Alcohols
	MP-Tosic acid		Amines, Anilines
Metal	MP-TMT		Pd (0)
	MP-DEAM		Ti(IV), Sn(IV), Boronic acids

Solution Phase Resins: Introductory Kit

NEW! Launched Sept 18, 2006

Contains resin samples for:

Amidation

PS-Carbodiimide (3g; 1.1-1.3 mmol/g)
PS-HOBt(HL) (3g; 0.9-1.0 mmol/g)
Rgt-ACTU (3g)
MP-TsOH(65) (3g; 3.5-4.5 mmol/g)
MP-Carbonate (3g, 2.5-2.8 mmol/g)

Reductive Amination

MP-Triacetoxyborohydride (3g; 1.8-2.0 mmol/g)
MP-Cyanoborohydride (3g; 2.0-2.3 mmol/g)
MP-TsOH(65) (3g; 3.5-4.5 mmol/g)
PS-Isocyanate (3g, 1.1-1.4 mmol/g)
MP-Isocyanate (3g, 0.9-1.3 mmol/g)
PS-Benzaldehyde (3g, 1.1-1.3 mmol/g)

Coupling

PS-Triphenylphosphine (3g; 1.8-2.2 mmol/g);
PS-PPh₃-Pd (1g, 0.08-0.1 mmol/g)
MP-TsOH(65) (3g; 3.5-4.5 mmol/g)
MP-Carbonate (3g, 2.5-2.8 mmol/g)
PS-DEAM (3g; 1.5-1.8 mmol/g)

Oxidation

MP-TsO-TEMPO (3g; 0.8-1.0 mmol/g)

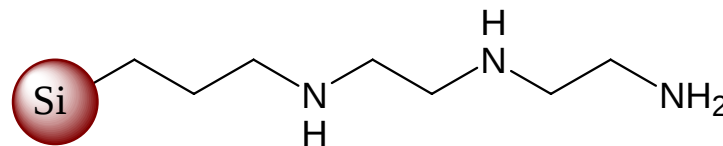


BIOTAGE INTRODUCES

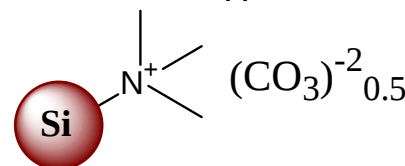
Silica-supported Reagents/Scavengers

NEW!

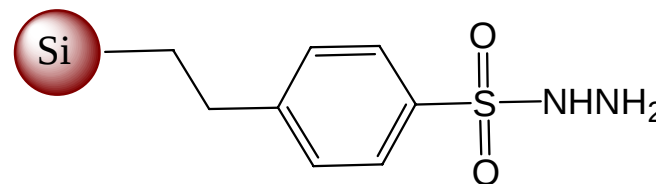
ISOLUTE® Si-Triamine



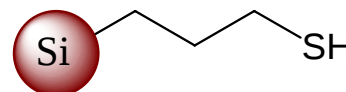
ISOLUTE® Si-Carbonate



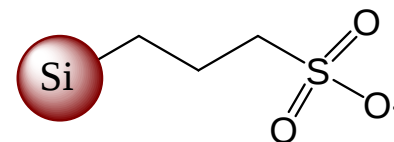
ISOLUTE® Si-Ts-Hydrazine



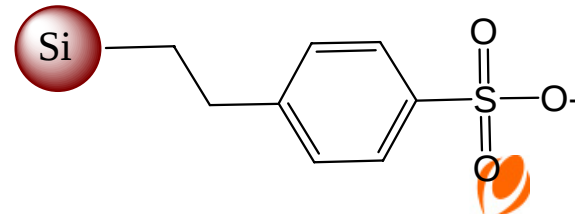
ISOLUTE® Si-Thiol



ISOLUTE® Si-Propylsulfonic acid (SCX-2)

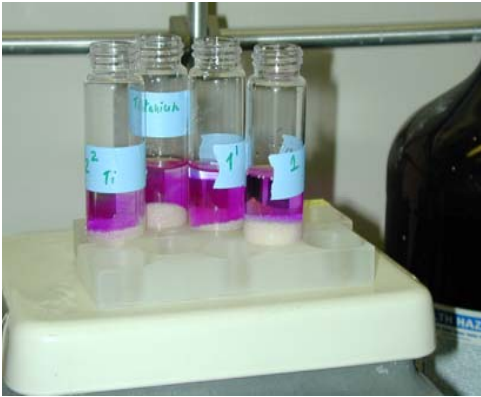


ISOLUTE® Si-EthylPhenyl sulfonic acid (SCX-3)




Biotage

In the Laboratory



- Use standard lab equipment
- Shaking, overhead or magnetic

Advantages of Solid-supported Reagents/Scavengers

- Drive reaction to completion using excess reagents
- Remove spent and excess reagent by filtration
- Perform one-pot multi-step reactions
- Mix “incompatible” functionalities
- Real time reaction progress monitoring (TLC/LC-MS)
- Eliminate problems with small molecule reagents
- Toxicity, byproducts difficult to eliminate

Slow reaction kinetics

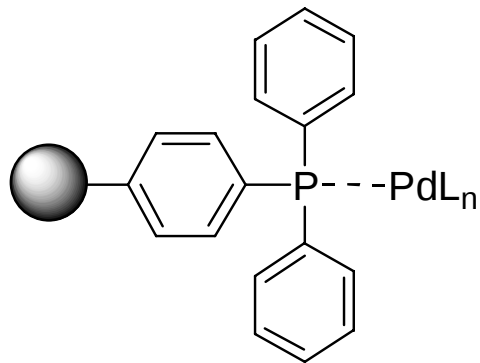


Key Transformations

Solid-supported reagents/Scavengers

- Pd Catalyzed reactions
- PS-Triphenylphosphine
- Acid catalyzed Reactions
- Base Catalyzed reaction
- Amidation
- Reductive Amination
- Oxidation

PS-Triphenylphosphine-Pd(0)

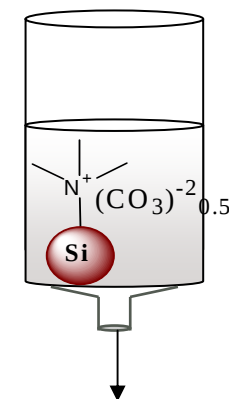
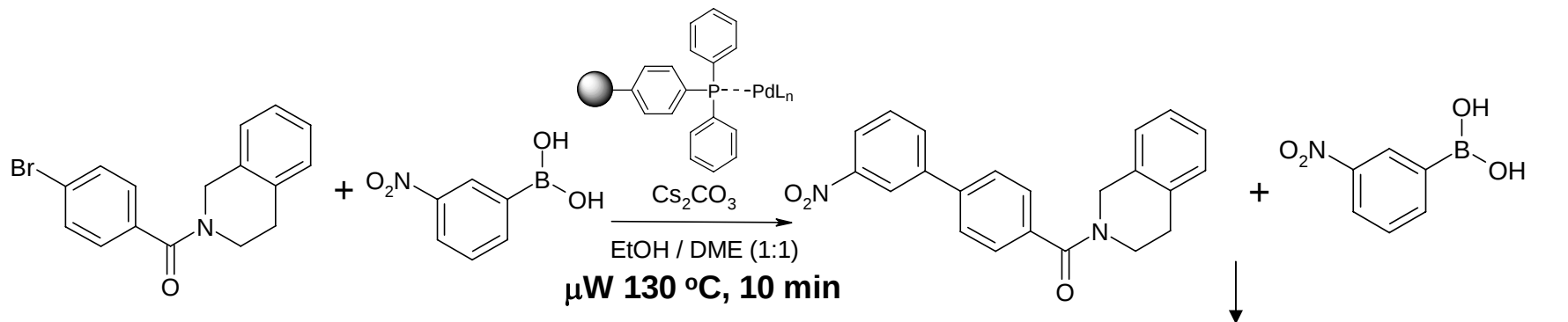


Bound Pd(0) Catalyst

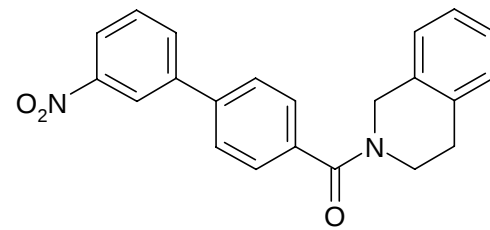
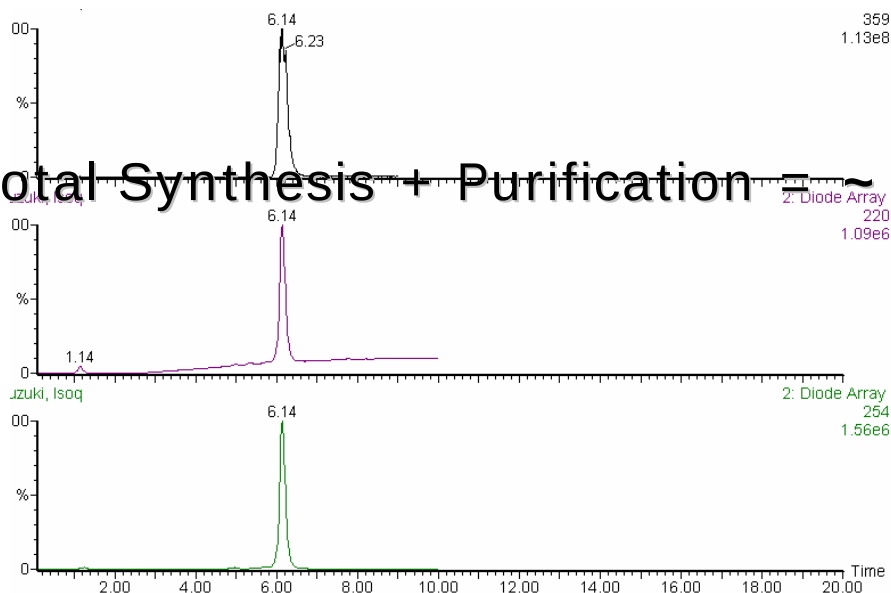
- Stable to air, light and moisture
- Easy Handling
- Shelf-stable at room temperature
- No “Hot Spot” – minimizes vial breakage in MAOS
- Simplified product isolation
- Low Pd levels in product (< 100ppm)

PS-PPh₃-Pd & ISOLUTE® Si-Carbonate

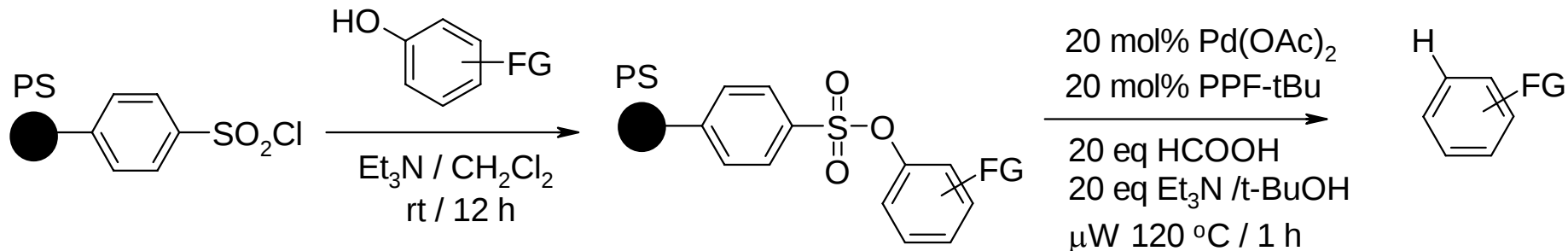
Rapid Suzuki Reaction & Workup



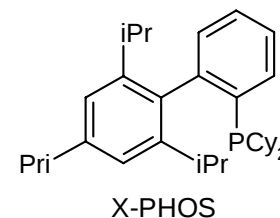
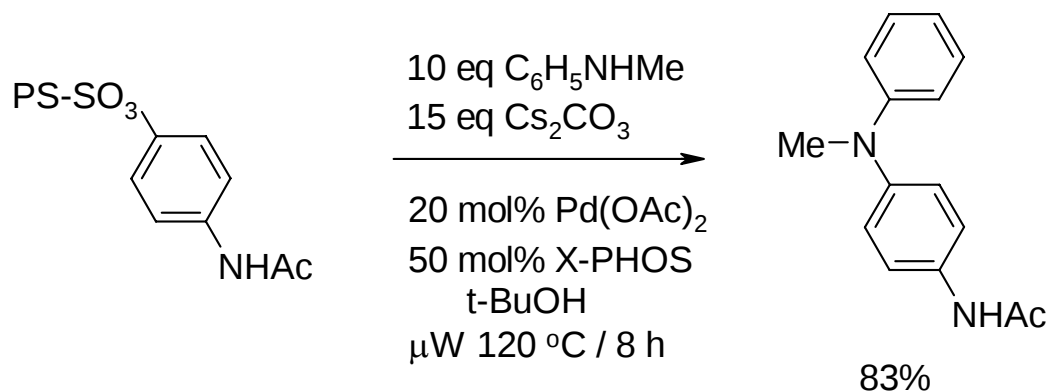
Total Synthesis + Purification = ~ 15 min



PS-TsCl: Palladium assisted deoxygenation and Multifunctionalization of Phenols



FG = 4-NHAc (92%), 2-NHAc(quant), 3-NHAc (89%)
 4-OCH₂CO₂tBu (80%), 4-SCH₂CO₂tBu (82%)
 4-(CH₂)₂CMe₂OH (85%)
 4-CH₂CH(NHBoc)CO₂Me (68%)
 4-OMe-4-CH₂OH (64%)



Key Microwave-Assisted Transformations

Solid-supported reagents/Scavengers

- Pd Catalyzed reactions
- **PS-Triphenylphosphine**
- Acid catalyzed Reactions
- Base Catalyzed reaction
- Amidation
- Reductive Amination
- Oxidation

PS-Triphenylphosphine

PS-Triphenylphosphine

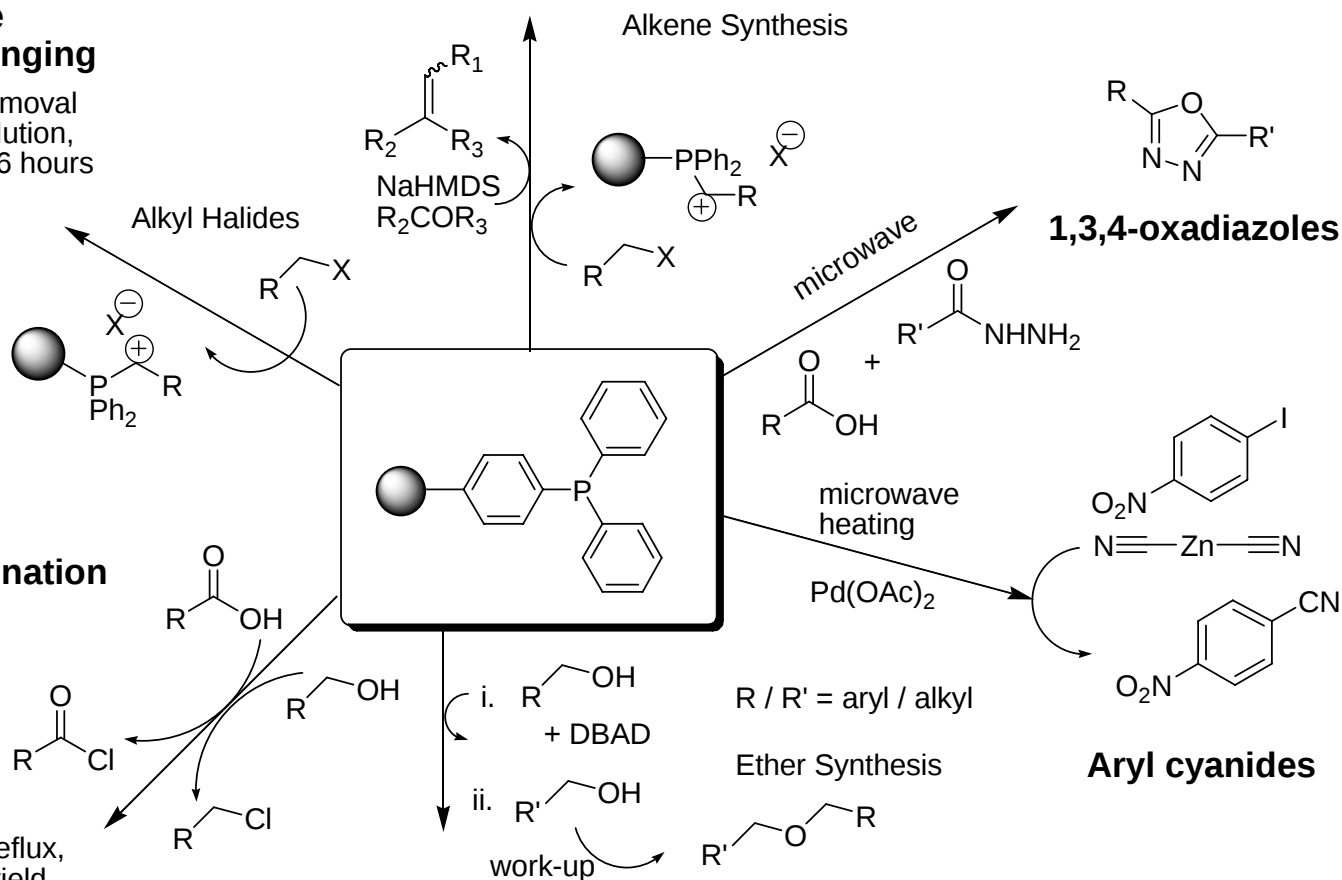
Wittig Chemistry

Halide Scavenging

100% removal
from solution,
RT, 6-16 hours

Chlorination

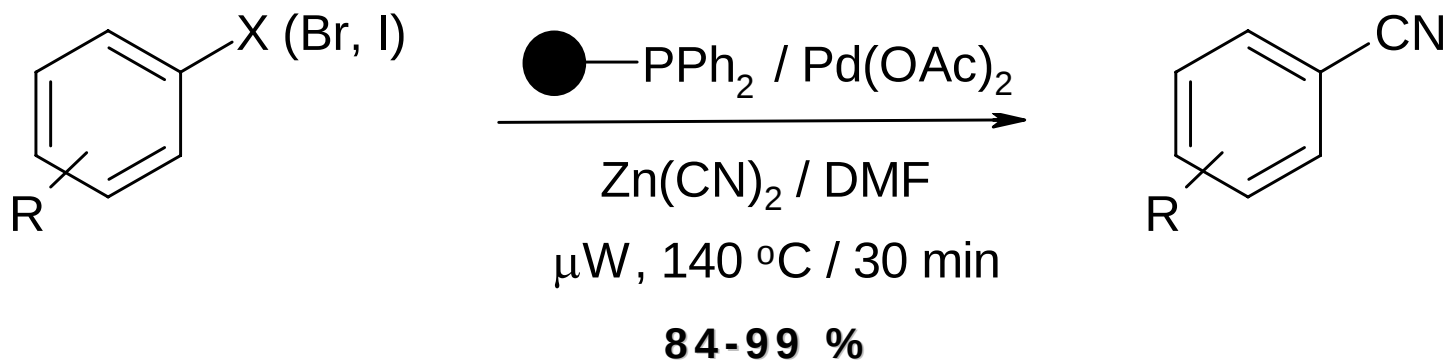
3 hrs, reflux,
100% yield
100% purity



Mitsunobu Chemistry

75-95% yield, 100% purity, RT conditions

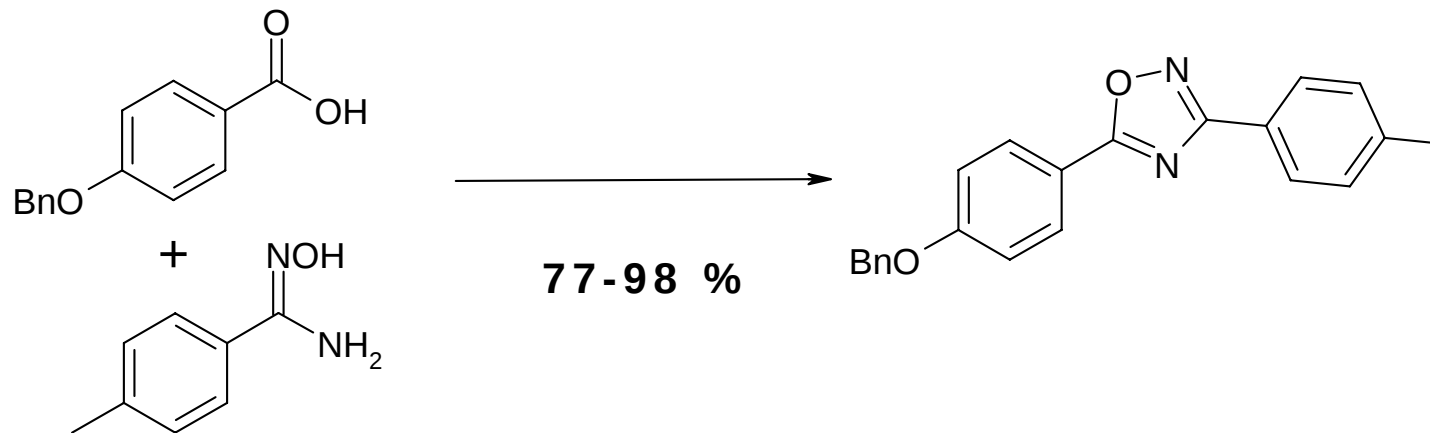
PS-Triphenylphosphine Palladium-assisted Cyanation



- Premixing of Catalyst and Ligand was essential for optimal catalytic activity
- 2 h; yellow color of Pd(OAc)_2 transferred to bead upon complexation
- Workup:
 - (1) Filtration
 - (2) Wash resin with Ether
 - (3) Aqueous wash of filtrate
 - (4) Dry and evaporate organic layer

PS-Triphenylphosphine

Microwave-assisted Chlorination

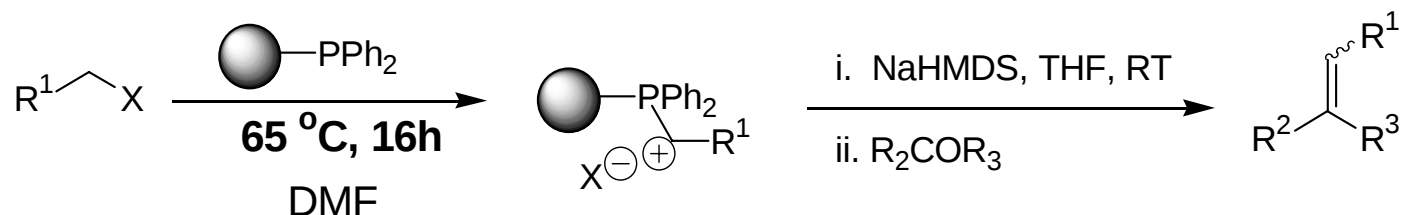


(i) **PS-PPh₃** (3 equiv); CCl₃CN (1.5 equiv)
100 °C / 5 min

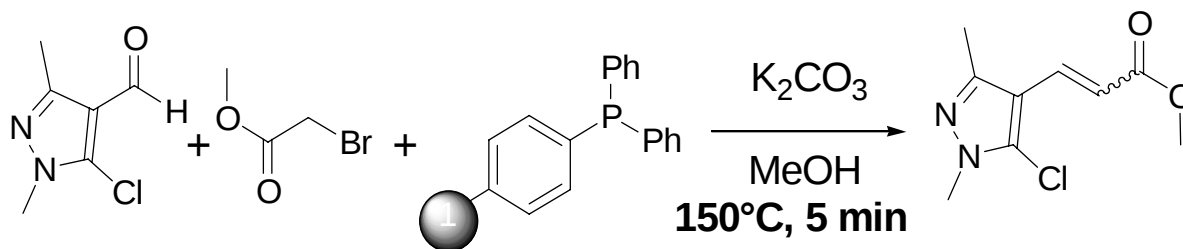
(ii) DIEA (2 equiv); Aldoxime; THF
150 °C / 15 min

PS-Triphenylphosphine - Wittig

Traditional



**Microwave
(one-pot)**



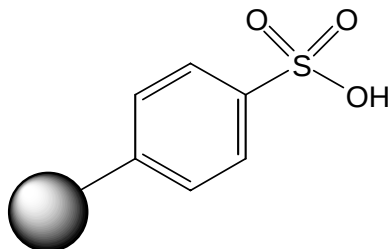
Key Microwave-Assisted Transformations

Solid-supported reagents/Scavengers

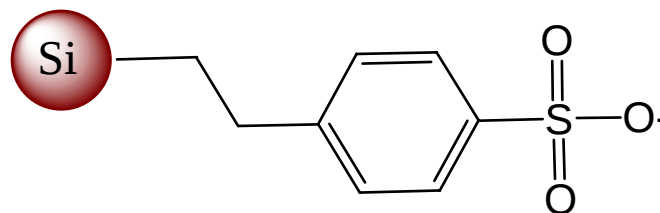
- Pd Catalyzed reactions
- PS-Triphenylphosphine
- **Acid catalyzed Reactions**
- Base Catalyzed reaction
- Amidation
- Reductive Amination
- Oxidation

Bound Acid: MP-TsOH

ISOLUTE® Si-TsOH



MP-TsOH

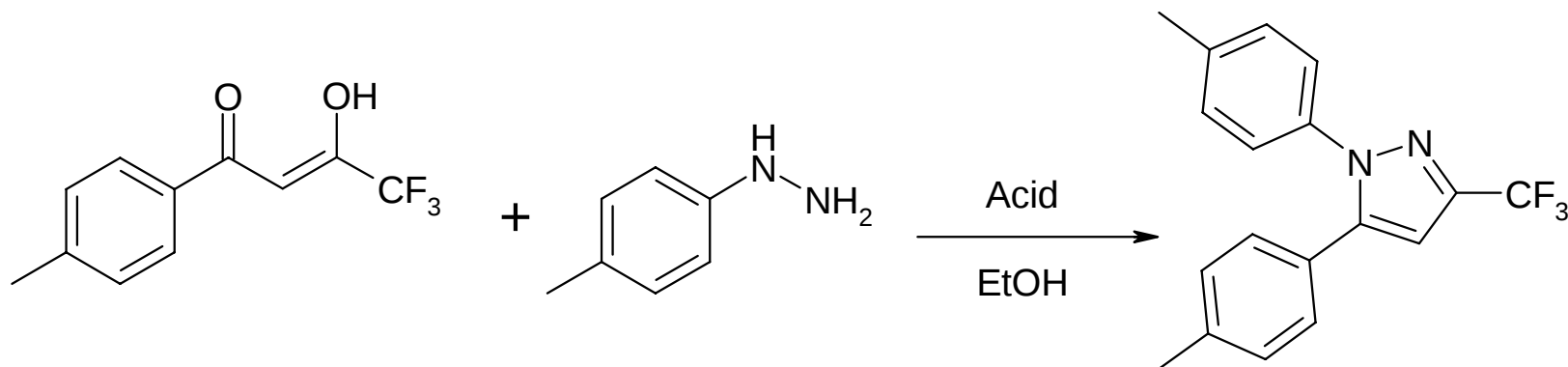


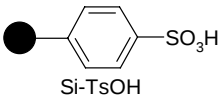
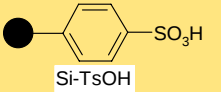
ISOLUTE® Si-TsOH

- Bound sulfonic acid equivalent
- Applications:
 - Acid catalyst
 - Cleavage of acid sensitive groups eg BOC-
 - Scavenger for amines & basic compounds
 - Catch and Release purifications

Solid-supported TsOH

Microwave-assisted Pyrazole Synthesis

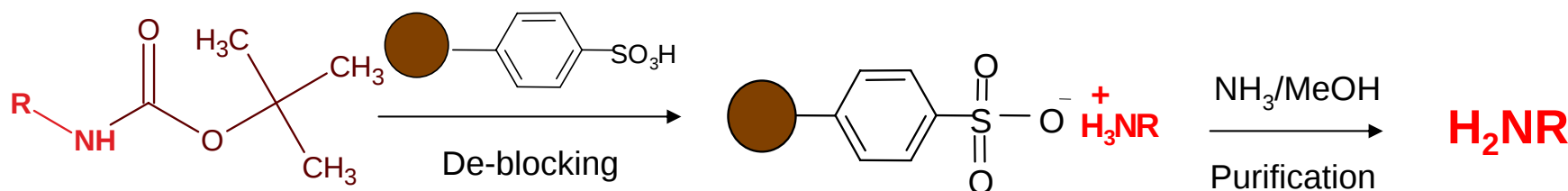


Entry	Acid	Method	Temp	time	Yield
1	p-TsOH	Non- μ W	100 °C	7 h	95 %
2	p-TsOH	μ W	160 °C	5 min	61 %
3	 Si-TsOH	Non- μ W	100 °C	6 h	84 %
4	 Si-TsOH	μ W	160 °C	5 min	95 %



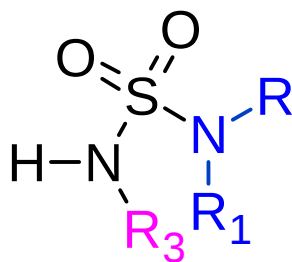
Biotage

Simultaneous BOC-deprotection & Amine Purification



Acidic Si-phenylsulfonic acid (Si-TsOH)

- spontaneously remove BOC- protected amine group
- purify the free amines *via* “Catch & Release” mechanism



Unsymmetrical sulfamides

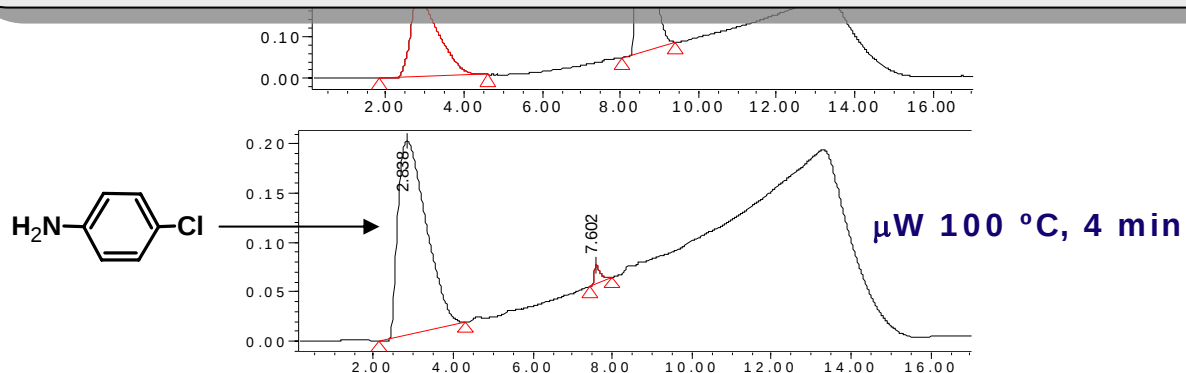
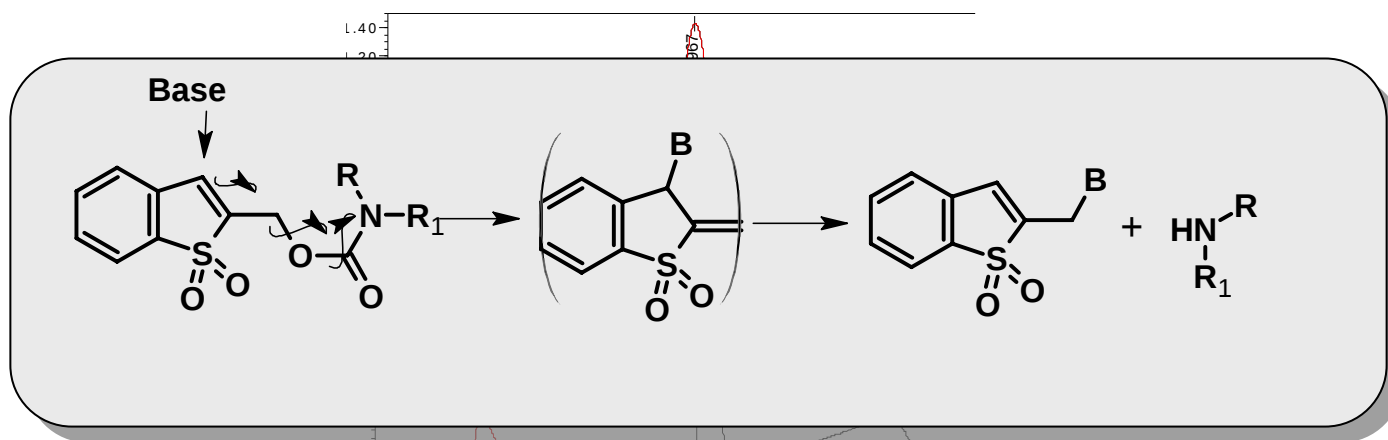
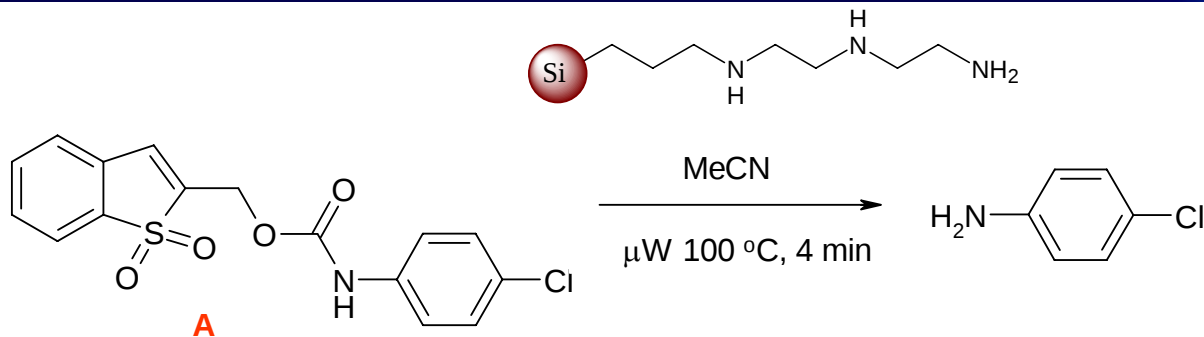
Key Microwave-Assisted Transformations

Solid-supported reagents/Scavengers

- Pd Catalyzed reactions
- PS-Triphenylphosphine
- Acid catalyzed Reactions
- **Base Catalyzed reaction**
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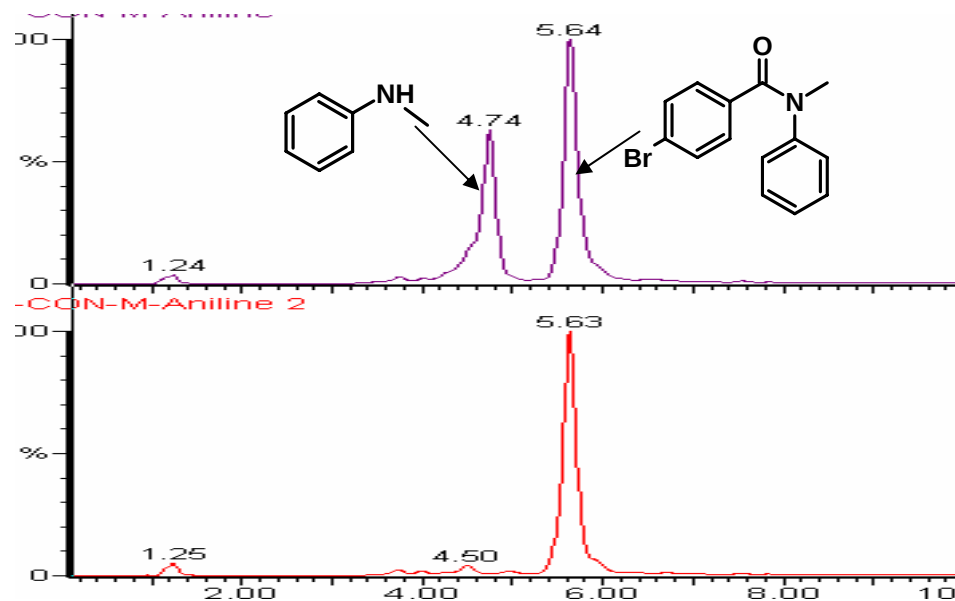
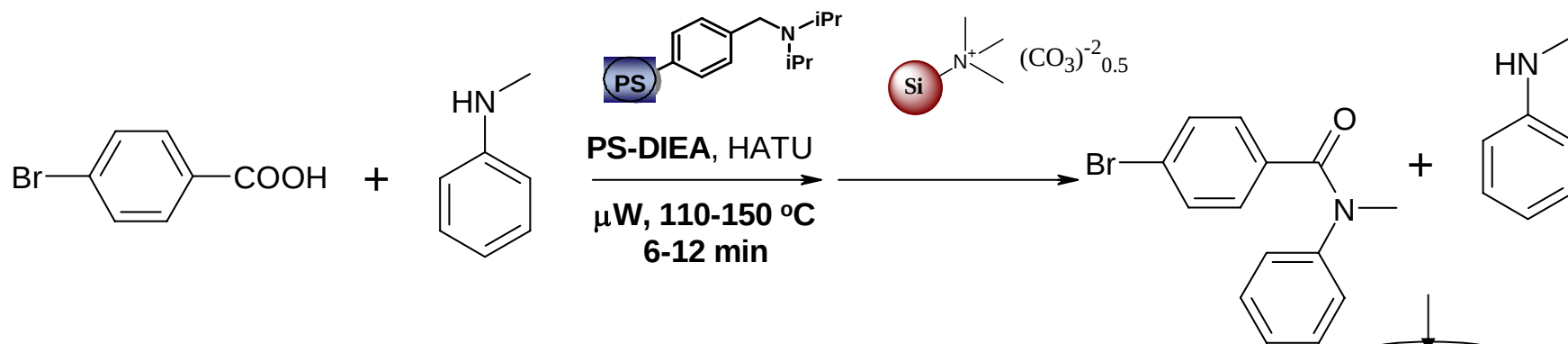
ISOLUTE® Si-Triamine

BSMOC-group Cleavage

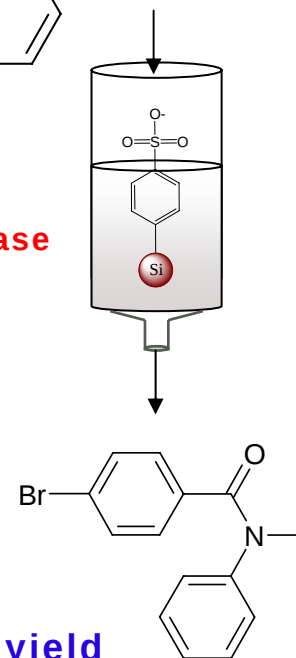


PS-DIEA, Si-Carbonate, Si-TsOH

Rapid Amidation and workup



Catch & Release



59 % yield
97 % Purity


Biotage

Key Microwave-Assisted Transformations

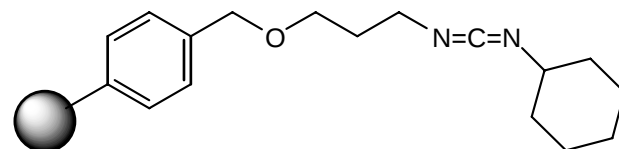
Solid-supported reagents/Scavengers

- Pd Catalyzed reactions
- PS-Triphenylphosphine
- Acid catalyzed Reactions
- Base Catalyzed reaction
- **Amidation**
- Reductive Amination
- Oxidation

Amide Synthesis: Reagent Comparison

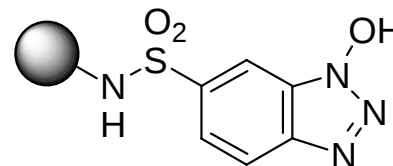
- **PS-Carbodiimide - Coupling Agent**

- One-step amide synthesis
- Scavenging may be required
- Rearrangement to acylisourea can be problematic



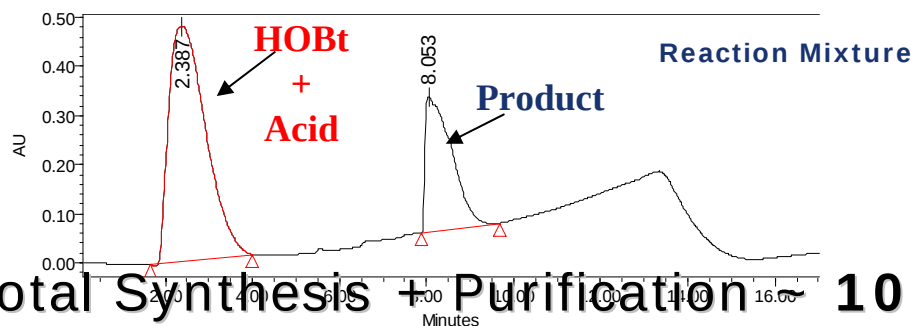
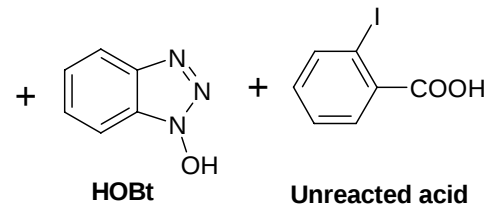
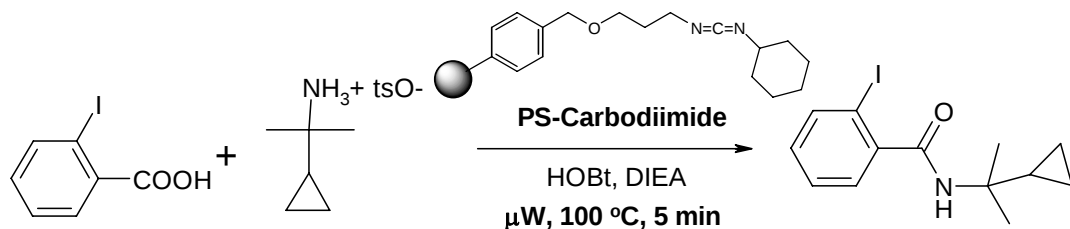
- **PS-HOBt - Active Esters**

- Two-step process
- Amine = limiting reagent in acylation, affords high purity amides
- Storable reactive intermediate

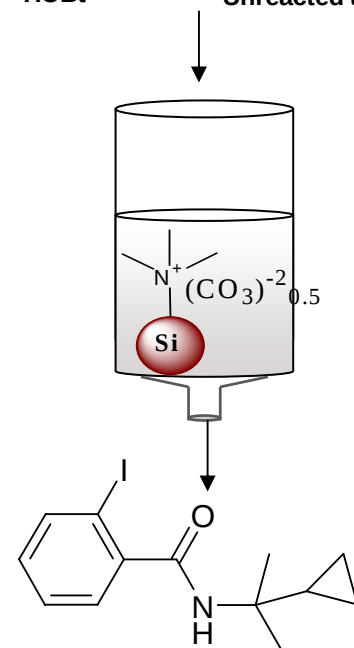
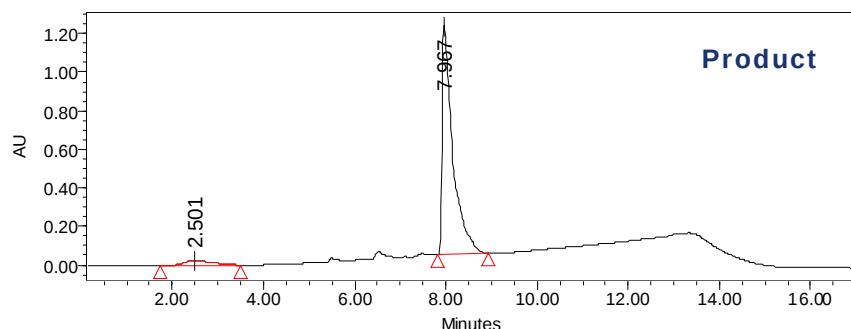


PS-Carbodiimide & ISOLUTE® Si-Carbonate

Rapid Acylation & Purification of Amines

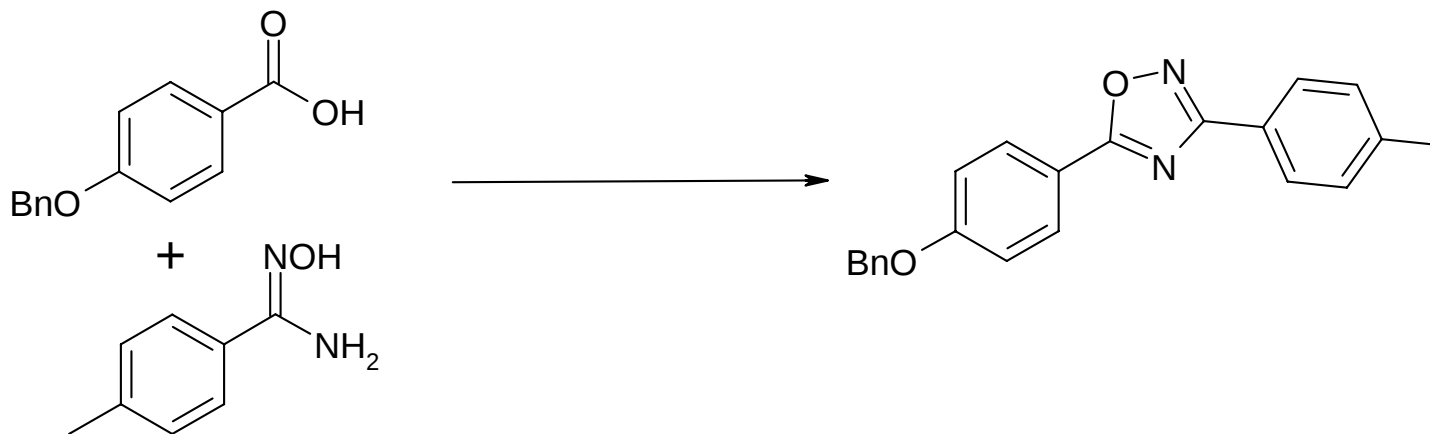


Total Synthesis + Purification ~ 10 mins



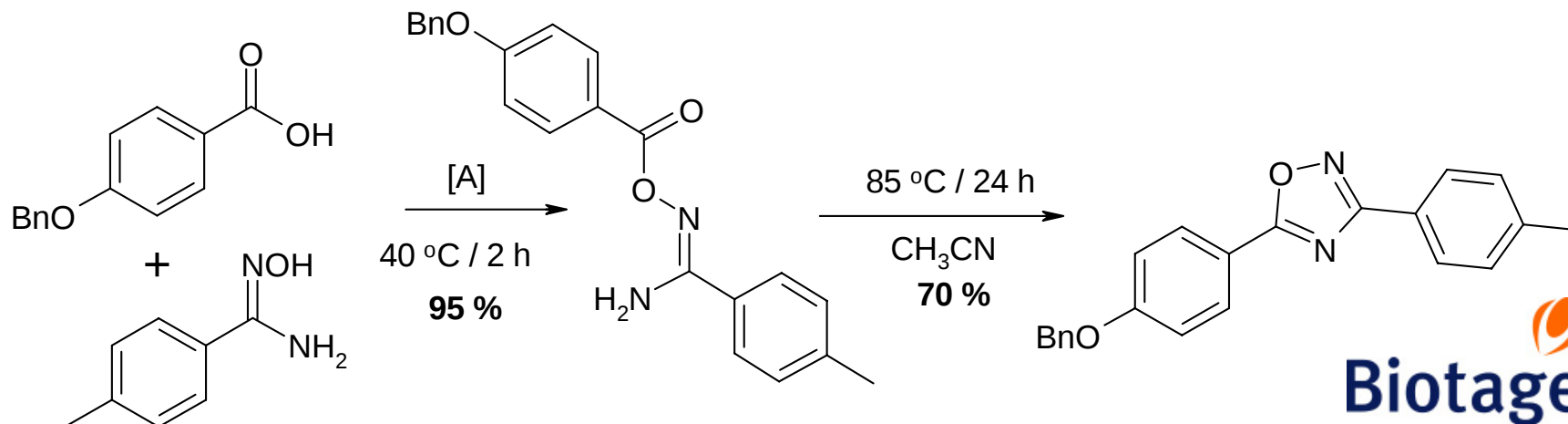
99 % yield
98 % Purity

PS-Carbodiimide Oxadiazole synthesis



PS-Carbodiimide (3 equiv); HOBt (1 equiv); DIEA (3 equiv); CH₃CN
130 °C / 30 min (83% yield)

Conventional Heating:




Biotage

Key Microwave-Assisted Transformations

Solid-supported reagents/Scavengers

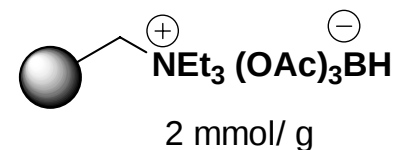
- Pd Catalyzed reactions
- PS-Triphenylphosphine
- Acid catalyzed Reactions
- Base Catalyzed reaction
- Amidation
- **Reductive Amination**
- Oxidation

Bound Reagents

Reductive Amination

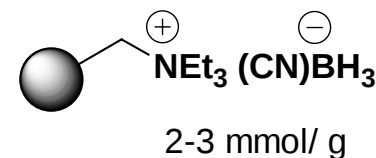
MP-BH(OAc)₃

- Tolerates acid-sensitive groups: ketals, acetals
- Secondary amines isolated as acetate
- Tertiary amines as free base



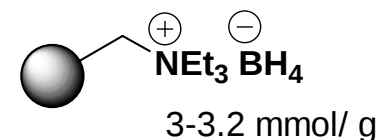
MP-BH₃CN

- Requires acetic acid
- Similar reactivity and scope
- Masked toxicity
- Very little pressure build up with MAOS



MP-BH₄ / Ti(iOPr)₄

- Suppresses over-alkylation with reactive carbonyls
- Enables use of:
 - sterically hindered carbonyls ie. adamantyl ketone
 - enolizable ketones eg acetophenone
- Titanium isopropoxide scavenged by PS-DEAM



MP-CNBH₃ Reductive Amination



Amine	Carbonyl	Conv. Yield	μW Yield
		79 %	98 %
		91 %	85 %
		39 %	77 %
		63 %	79 %
		69 %	73 %

Conventional condition:

- (1) THF
- (2) room temp, 16 h

Microwave condition:

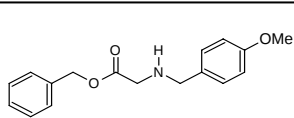
- (1) DCM
- (2) 110°C , 5-7 min

Microwave-Assisted Amine Synthesis

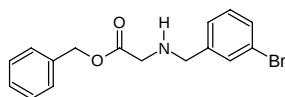
Method A: 2 eq. 1 M NaCNBH₄

Method B: 2 eq. Si-CN BH₄

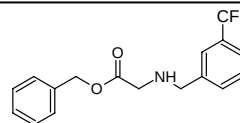
Method C: 2 eq. PS-CN BH₄



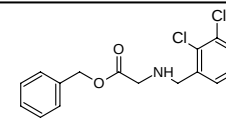
Method A **79 %**



83 %



84 %



68 %

Method B **74 %**

79 %

85 %

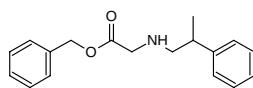
63 %

Method C **72 %**

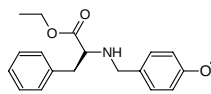
80 %

73 %

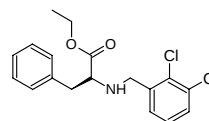
59 %



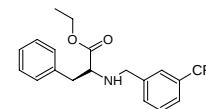
Method A **85 %**



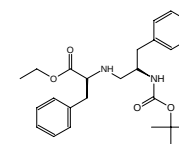
89 %



88 %



88 %



75 %

Method B **79 %**

84 %

80 %

78 %

73 %

Method C **80 %**

80 %

77 %

81 %

65 %



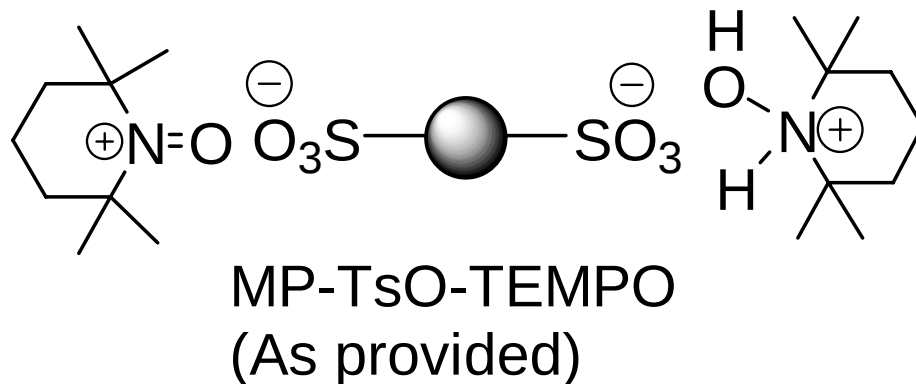
Key Microwave-Assisted Transformations

Solid-supported reagents/Scavengers

- Pd Catalyzed reactions
- PS-Triphenylphosphine
- Acid catalyzed Reactions
- Base Catalyzed reaction
- Amidation
- Reductive Amination
- **Oxidation**

MP-TsO-TEMPO

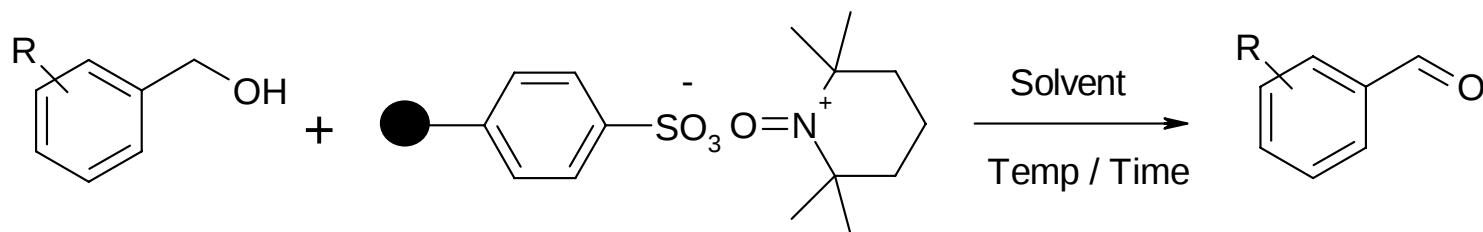
Bound Oxidizing Agent

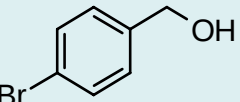
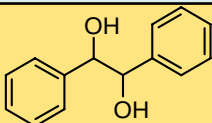
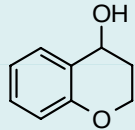
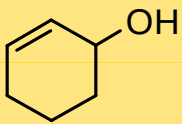
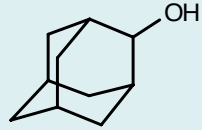


- MP-TsO-TEMPO is a bound oxoammonium sulfonate
- Oxidation of benzylic, allylic, acetylenic and cyclic secondary alcohols
- Highly controlled reaction. No over-oxidation to acid.
- Stable
- Resin is a mixture of active oxoammonium and reduced hydroxylammonium species.

MP-TsO-TEMPO

Oxidation of Alcohols



Alcohol	Method	Solvent	Temp	Time	Yield
	Non- μ W	CH ₃ CN	rt	16 h	95 %
	μ W	DCM	100 °C	10 min	100 %
	Non- μ W	CH ₃ CN	rt	16 h	99 %
	μ W	DCM	60 °C	2 h	100 %
	Non- μ W	CH ₃ CN	rt	16 h	70 %
	μ W	DCM	60 °C	5 min	93 %
	Non- μ W	DCM	rt	16 h	70 %
	μ W	DCM	60 °C	1.5 min	100 %
	Non- μ W	DCM	rt	16 h	100 %
	μ W	DCM	60 °C	2.5 min	100 %



Biotage

SUMMARY

- MAOS is a versatile tool for ***accelerating synthesis***
- *Solid bonded Reagents and Scavengers* significantly ***reduces the work-up and purification bottleneck***
- Combining MAOS with *Solid bonded Reagents and Scavengers* can accelerate ***total compound production time***

University Promotion



University Bundle 1 – Initiator 1 EXP

INITIATOR 1 EXP_ Version 2.0 with high powered 400 watt magnetron delivers the most precise heating control of any microwave synthesis instrument on the market. Additional features include front mounted USB port, built-in computer with touch-screen interface, and set-up wizard that guides users and automatically converts conventional parameters to microwave conditions.

Description	Part #	List (USD)	University (USD)
Initiator 1 EXP	355302	26,000	
Vial Starter Kit			
(0.5 – 2 mL) Qty 100	352016	413	
(2 – 5 mL) Qty 100	351521	325	
(10-20 mL) Qty 50	354833	495	
Solution Phase Resins Introductory Kit	800038	663	
3g Each of the following 14 resins: PS-Carbodiimide, PS-HOBt (HL), RGT-ACTU, MP-Triacetoxyborohydride, MP-Cyanoborohydride, PS-PPh3, PS-PPh3-Pd 1g, MP-TsO-TEMPO, PS-Isocyanate, MP-Isocyanate, PS-Benzaldehyde, MP-TsOH(65), MP-Carbonate, PS-DEAM Argoscoop			
Installation and Training	SER-IN1-IN	750	
Pathfinder (1 Lincense, 1yr Subscription)	355239	395	
Total		\$29,041	\$15,000*

University Promotion



University Bundle 2 – Initiator 8 EXP

INITIATOR Eight The 8-position sample bed provides automation to medicinal chemists for rapid optimization of reaction conditions and analog synthesis. The ability to use both large and small vials provides the medicinal chemist flexibility and the ability to rapidly scale-up compounds of interest.

Description	Part #	List (USD)	University (USD)
Initiator 8 EXP	355323	35,000	
Vial Starter Kit			
(0.5 – 2 mL) Qty 100	352016	413	
(2 – 5 mL) Qty 100	351521	325	
(10-20 mL) Qty 50	354833	495	
Solution Phase Resins Introductory Kit	800038	663	
Same as above			
Installation and Training	SER-IN8-IN	750	
Pathfinder (1 Lincense, 1yr Subscription)	355239	395	
Total		\$38,041	\$22,500*

Thank You for Your Attention!