Accelerating Drug Discovery: Enabling Tools and Techniques

Steve Jordan
Director R&D Chemistry
Biotage

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Synthesis and Purification Workflow

Synthesis	Work up and initial Purification	Final Purification
• **Bound Reagents**	▪ **Scavengers** ▪ **Catch & Release**	▪ **Flash Chromatography** ▪ **Preparative RP HPLC**

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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 greater with microwave chemistry

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

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What Tools are available today

The Tool Box

1. Polymer supported reagents
2. Polymer supported scavengers
3. Silica supported Reagents
4. Silica supported Scavengers
5. Microwave heating
6. Automated purification systems

How can we use these effectively

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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-Triacetoxyborohydride	Sodium triacetoxy borohydride	Reducing agent
MP-TsO-TEMPO	TEMPO	Oxidizing Agent

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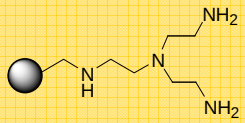
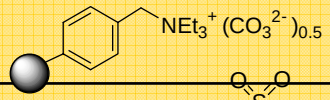
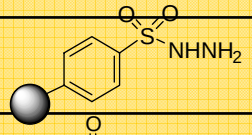
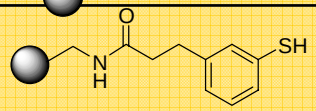
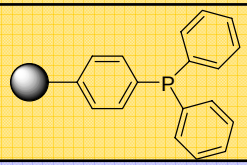
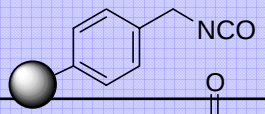
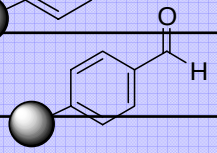
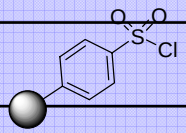
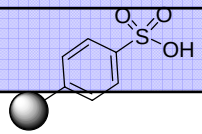
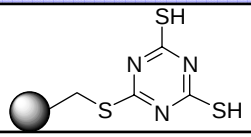
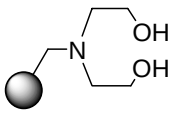
Biotage Polymeric Scavengers

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 	**1º, 2º amines, hydrazine**
	PS-Benzaldehyde 	**1º amines**
	PS-Tosyl chloride 	**Anilines, Alcohols**
	MP-Tosic acid 	**Amines, Anilines**
Metal	MP-TMT 	**Pd (0)**
	MP-DEAM 	**Ti(IV), Sn(IV), Boronic acids**

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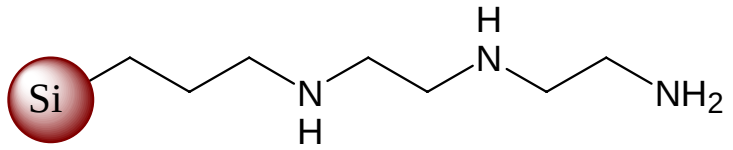
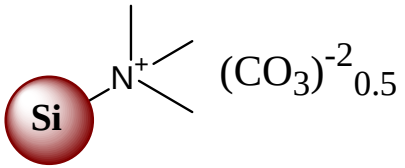
Silica-supported Reagents/Scavengers

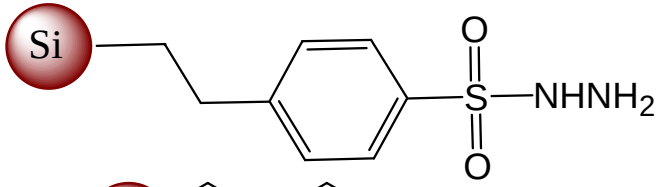
ISOLUTE® Si-Triamine



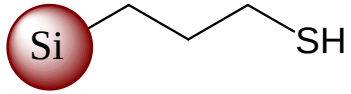
ISOLUTE® Si-Carbonate



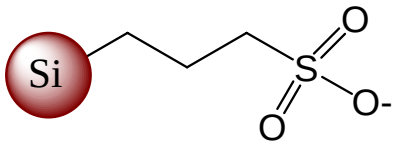
ISOLUTE® Si-Ts-Hydrazine



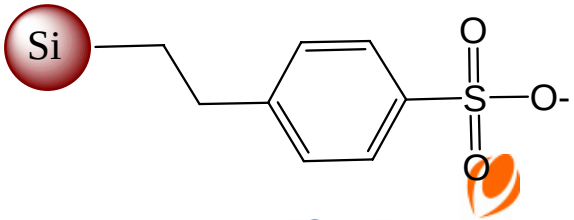
ISOLUTE® Si-Thiol



ISOLUTE® Si-Propylsulfonic acid (SCX-2)



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



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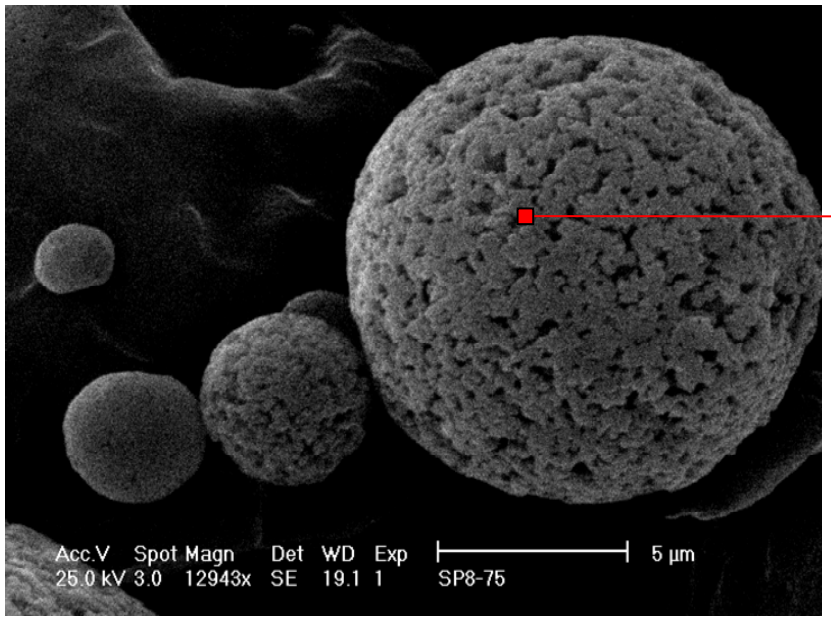
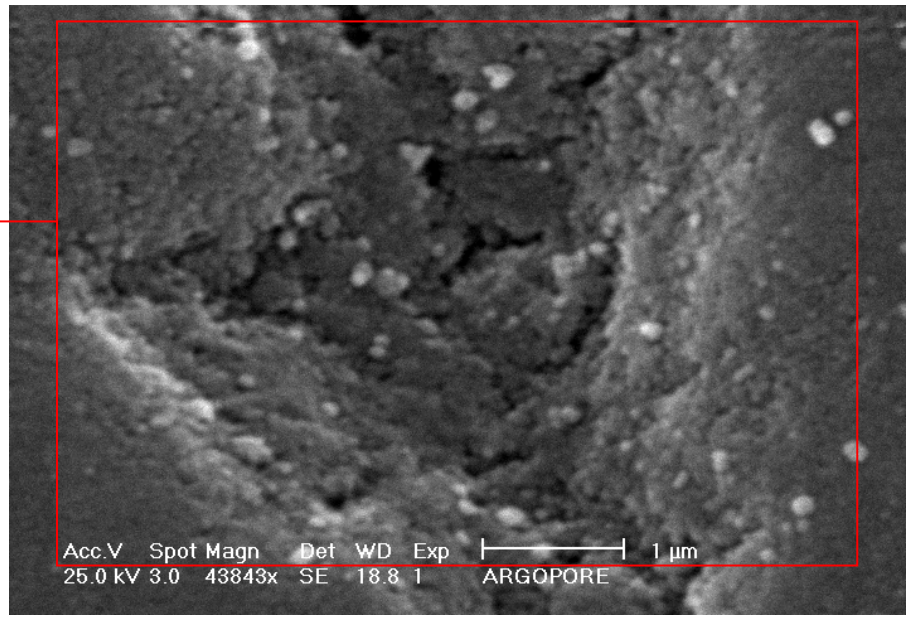
Surface Images of an MP-Resin





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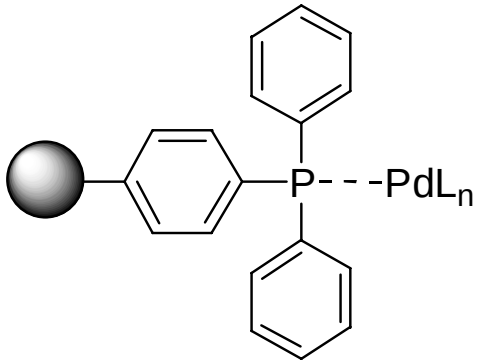
PS-Triphenylphosphine-Pd(0)



Bound Pd(0) Catalyst

- Stable to air, light and moisture
- Easy Handling
- Shelf-stable at room temperature
- Simplified product isolation
- Low Pd levels in product (< 100ppm)

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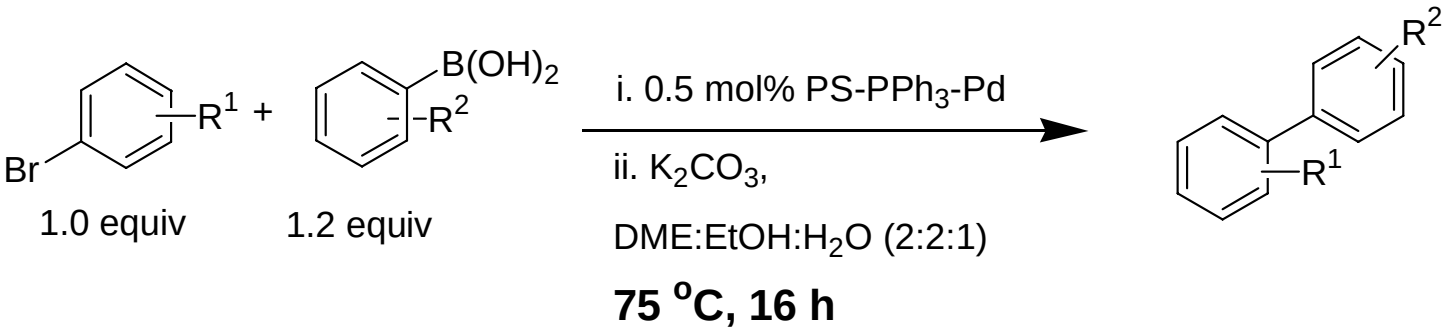
PS-PPh_3-Pd : Suzuki Coupling (Traditional)



- Reactions performed under air, no inert conditions required
- Products isolated in high purity and yield
- Low palladium level in products (< 60 ppm)

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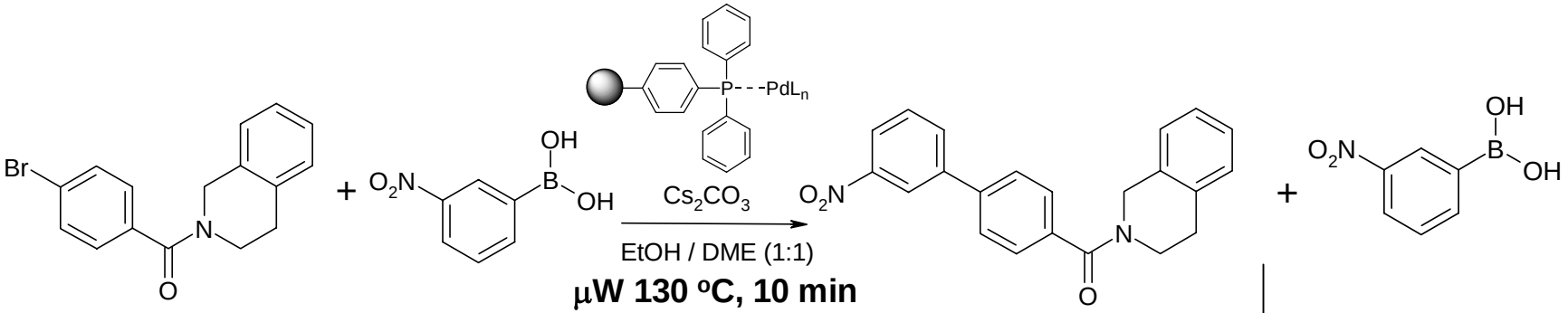
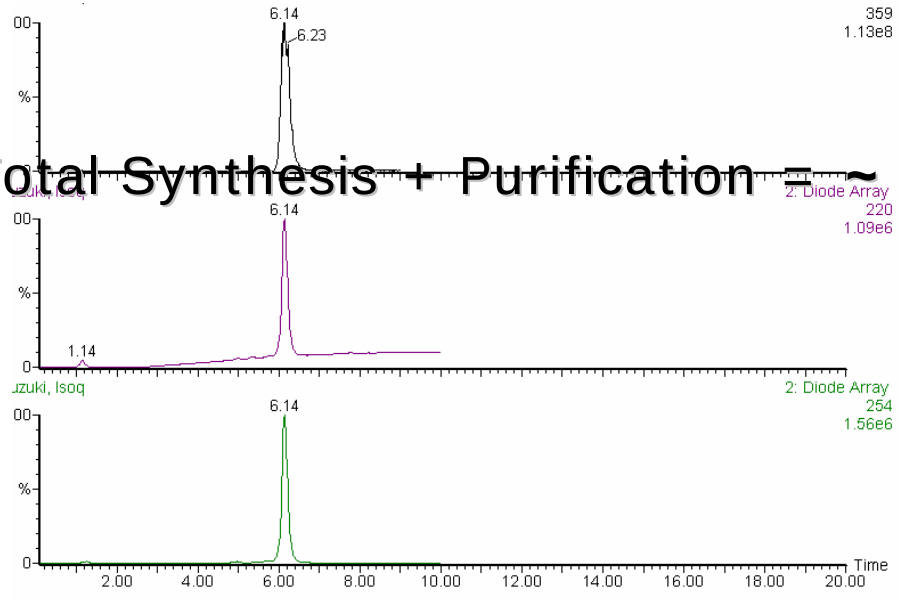
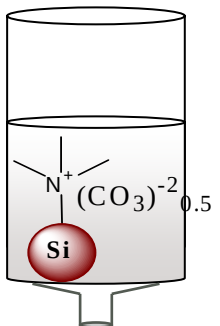
PS-PPh_3-Pd & ISOLUTE® Si-Carbonate
Rapid Suzuki Reaction & Workup

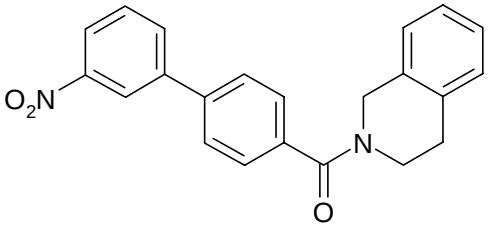




Total Synthesis + Purification = ~ 15 min



~ 5 mins



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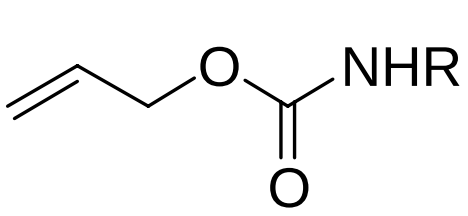
Ghassemi, S. ACS, Atlanta, GA, March **2006**

PS-PPh_3-Pd and MP-BH_4: Reductive Deprotection of N-Alloc



1 mmol

i. 2 mol% PS-PPh_3-Pd

ii. 3 equiv MP-BH_4

DCM:MeOH:H_2O (5:4:1)**; RT, 2 h**

iii. Filter through Na_2SO_4 plug

RNH_2

- Alloc orthogonal to Boc, Fmoc and Cbz groups
- Current Pd(0) catalyst drawbacks:
  - Formation of N-allylated by-product
  - Aqueous work-up
  - High Pd level in products
- Reactions performed under air at rt, no inert condition
- Products isolated in high yield and purity
- Low palladium level in products (< 100 ppm)

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Key Microwave-Assisted Transformations
Solid-supported reagents/Scavengers

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

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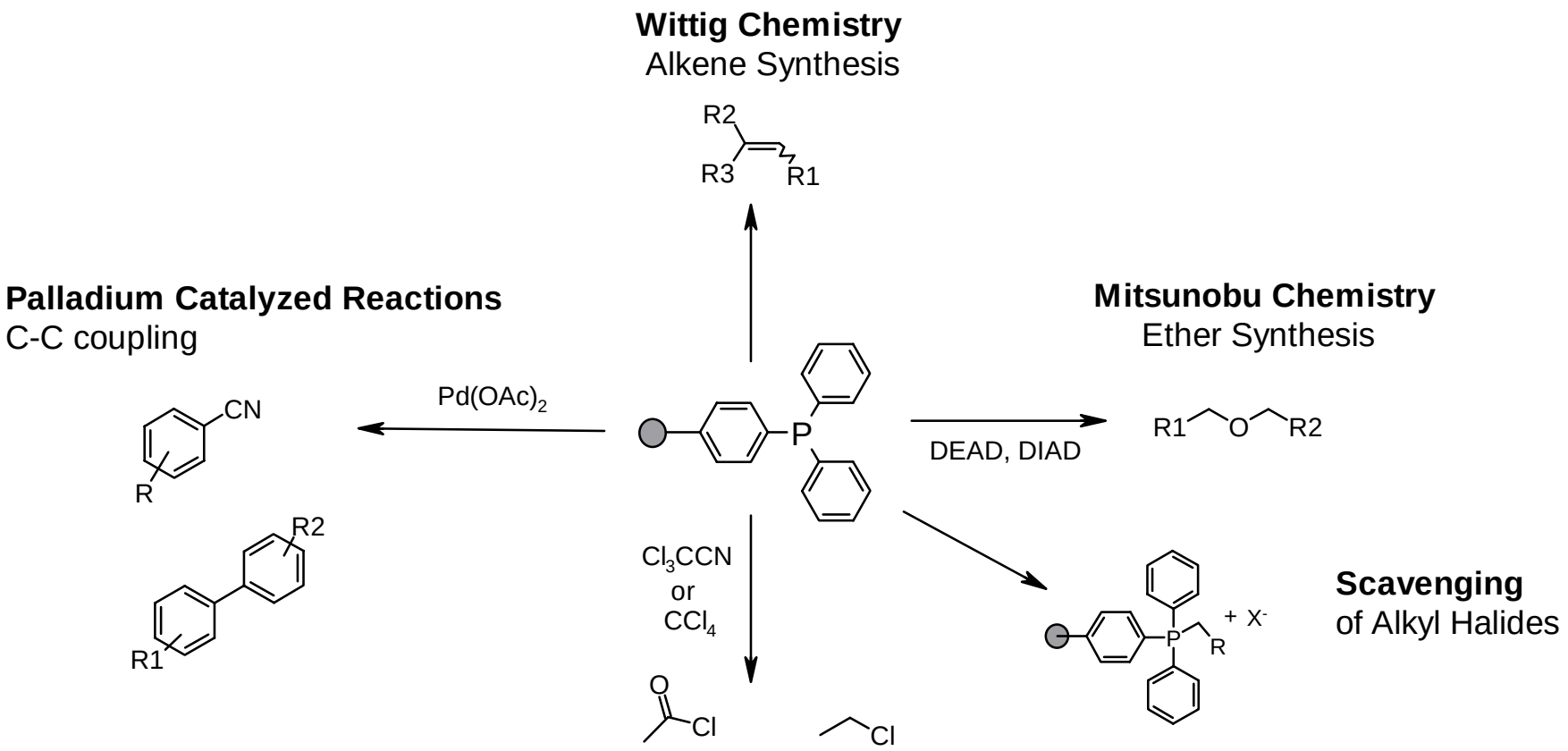
PS-Triphenylphosphine



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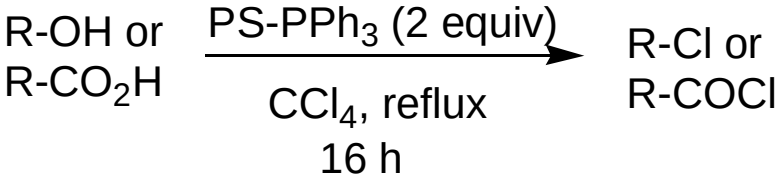
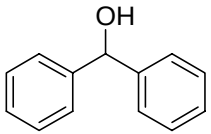
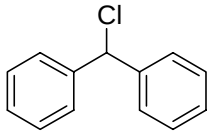
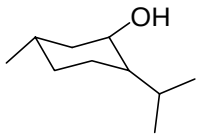
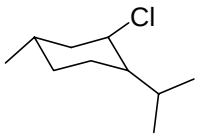
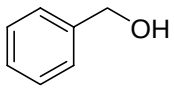
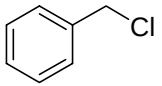
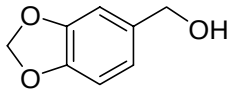
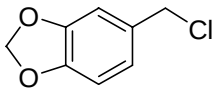
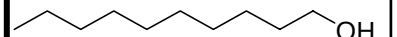
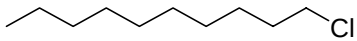
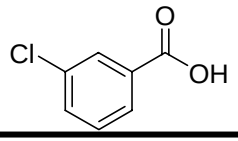
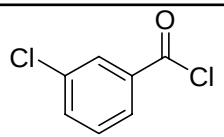
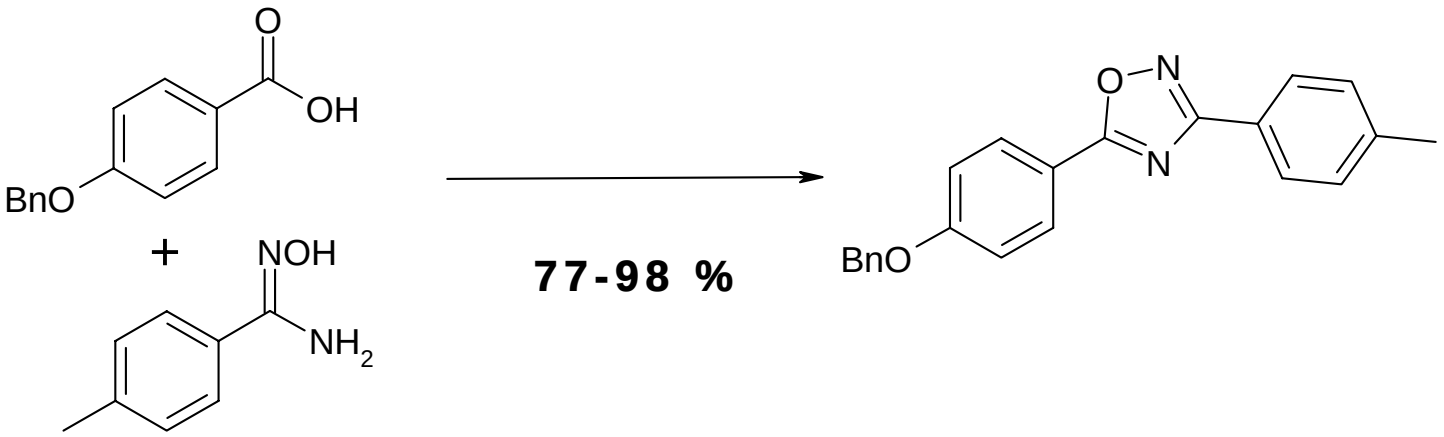
PS-Triphenylphosphine - Chlorination



Alcohol	Product	Yield %	% Purity
		98	95
		74	64
		100	100
		100	100
		100	100
		73	90

From Rana, S., Gooding, O., Labadie, J. **2003** Unpublished optimized procedures

PS-Triphenylphosphine
Microwave-assisted Chlorination



(i) **PS-PPh$_3$** (3 equiv); CCl_3CN (1.5 equiv)
100 °C / 5 min

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

Wang, Y.; Miller, R.L.; Sauer, D. R. Djuric, S. W.; R uj 1#Ohww1 2005, : +8 , / 925-928

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Key Microwave-Assisted Transformations
Solid-supported reagents/Scavengers

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

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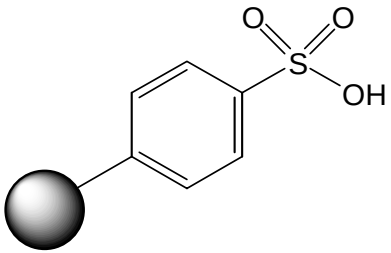
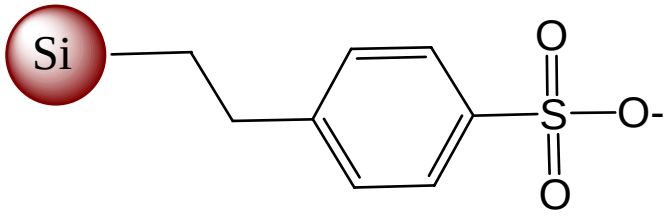
Bound Acid: MP-TsOH
ISOLUTE® Si-TsOH



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

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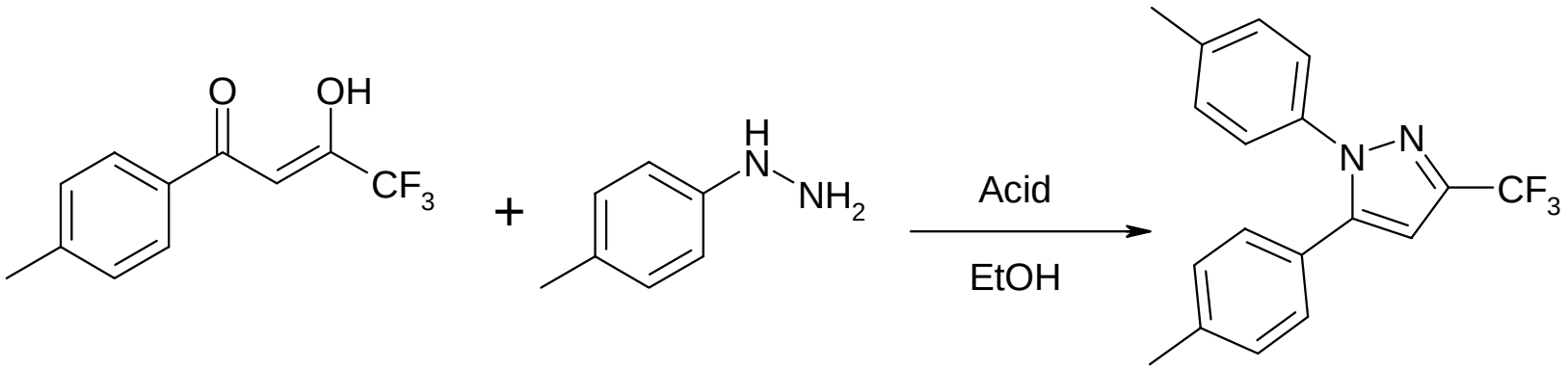
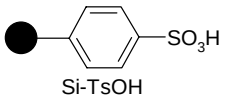
Solid-supported TsOH
Microwave-assisted Pyrazole Synthesis



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

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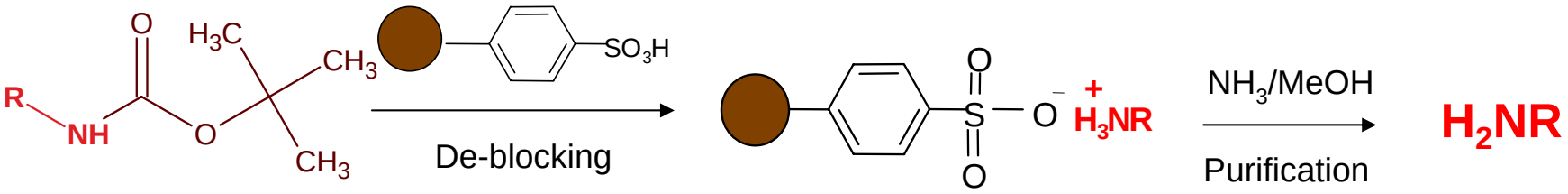
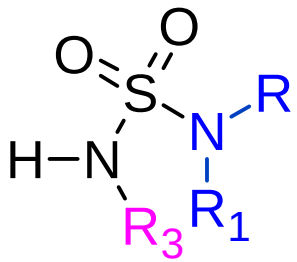
Humphries, P. hw#dq Whwudkhgurq#Ohww, **2006** 7: /#2443-2446

Simultaneous BOC-deprotection & Amine Purification



Acidic Si-phenylsulfonic acid (Si-TsOH)

- spontaneously remove BOC- protected amine group
- purify the free amines yld "Catch & Release" mechanism



Unsymmetrical sulfamides

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* Ghassemi, S. *et al. Molecular Diversity*, **2005**, *9*, 295-299

Key Microwave-Assisted Transformations
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- **Base Catalyzed reaction**
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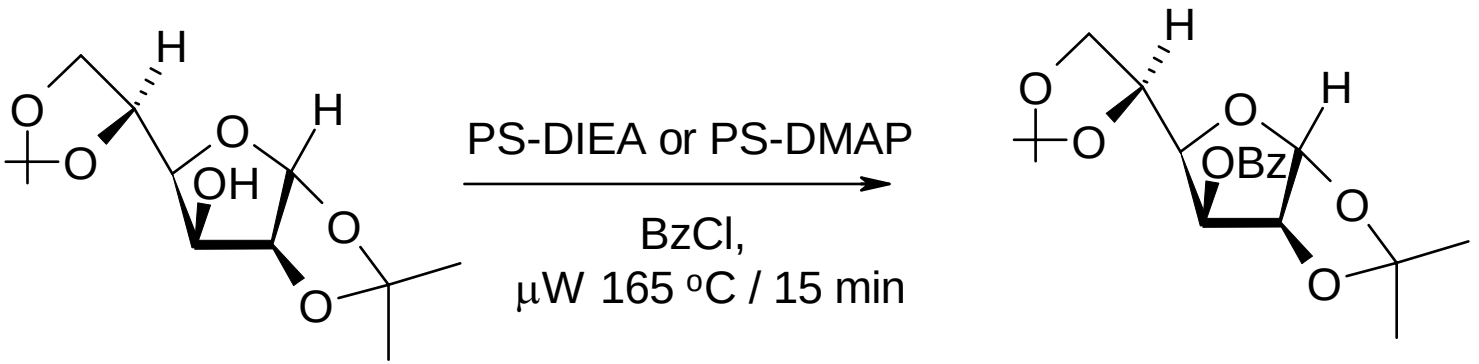
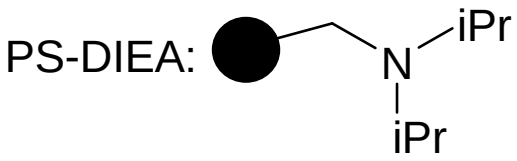
- Oxidation

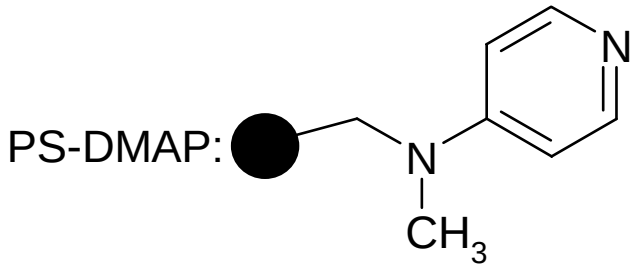
Biotage

PS-DIEA

Acylation of Carbohydrates





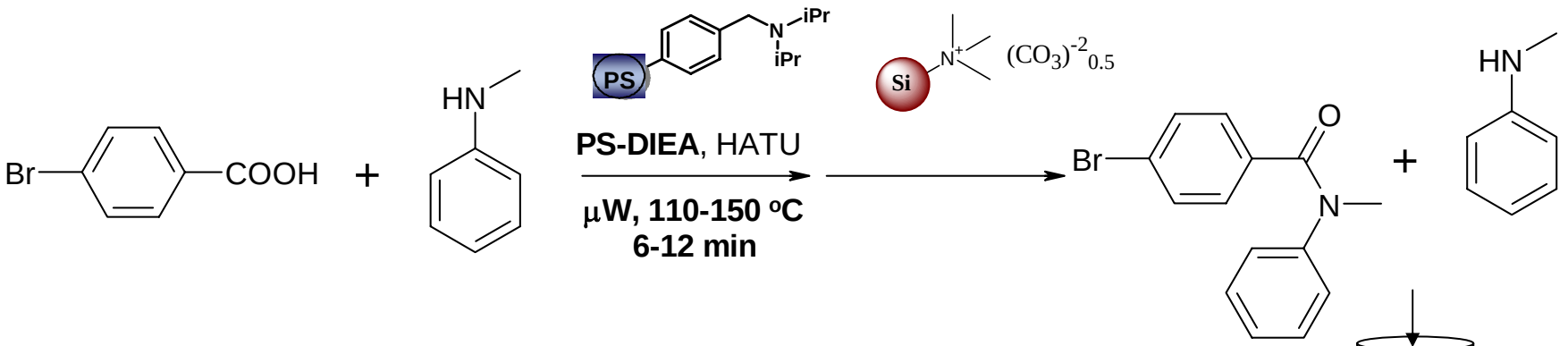


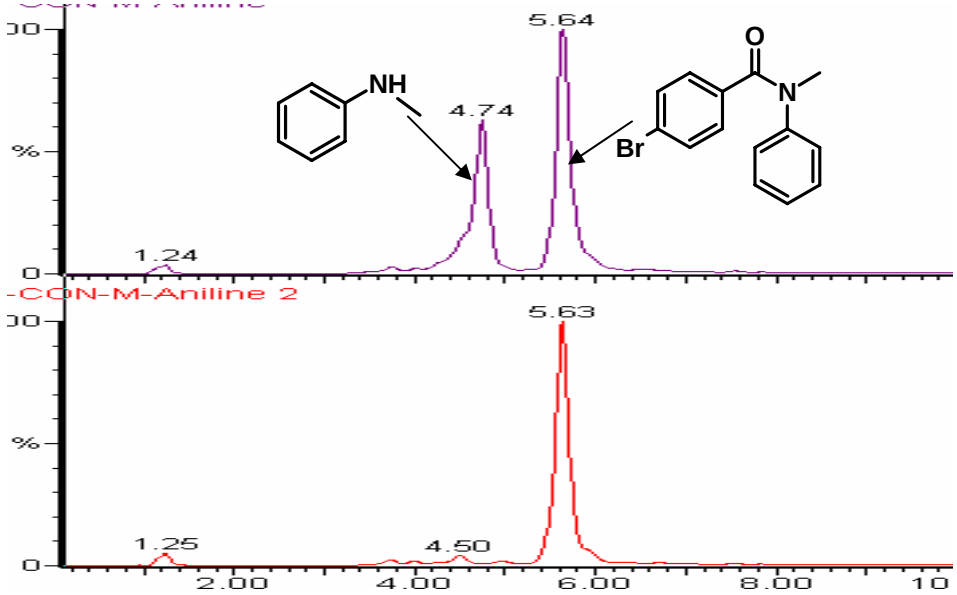
Biotage

Soederberg, E. hw#do M1#Fduerk|gu1#Fkhp . **2001**, 53, 397-410.

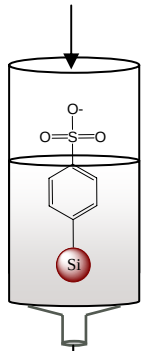
PS-DIEA, Si-Carbonate, Si-TsOH

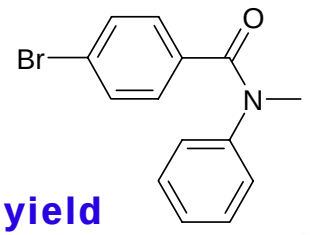
Rapid Amidation and workup





Catch & Release





59 % yield
97 % Purity

Biotage

Ghassemi, S. ACS, Atlanta, GA, March **2006**

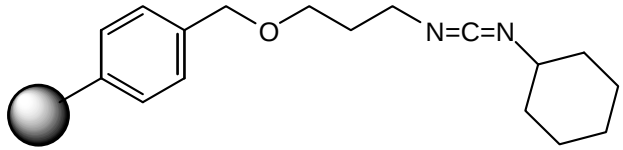
Key Microwave-Assisted Transformations
Solid-supported reagents/Scavengers

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

Biotage

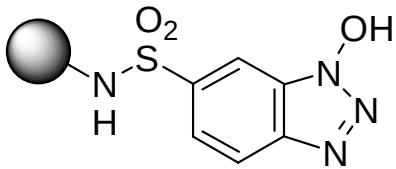
Amide Synthesis: Reagent Comparison

- **PS-Carbodiimide - Coupling Agent**



  - One-step amide synthesis
  - Scavenging may be required
  - Rearrangement to acylisourea can be problematic ---Can be solved by addition of HOBt

- **PS-HOBt - Active Esters**

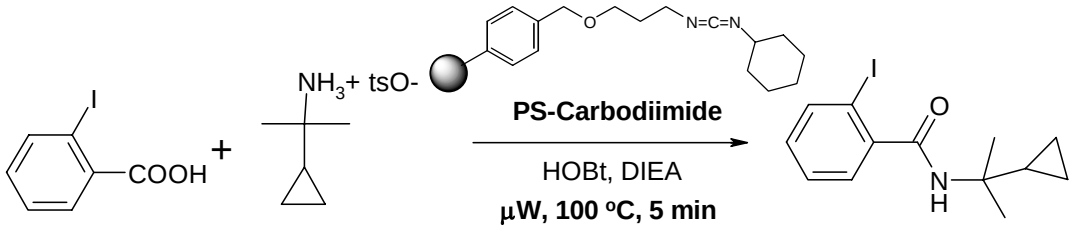


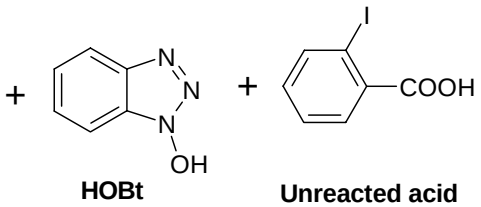
  - Two-step process
  - Amine = limiting reagent in acylation, affords high purity amides
  - Storable reactive intermediate

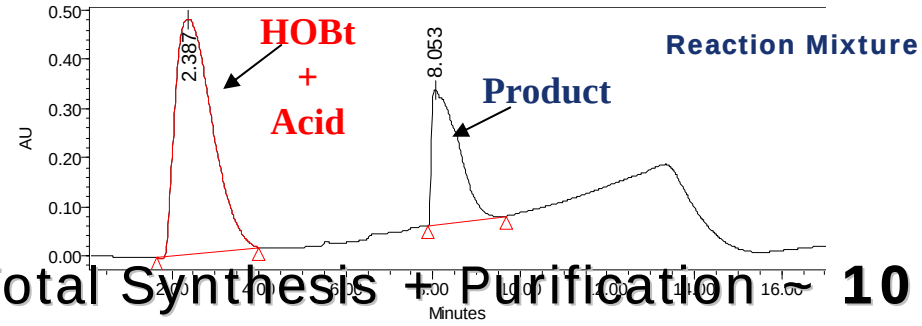
Biotage

PS-Carbodiimide & ISOLUTE® Si-Carbonate

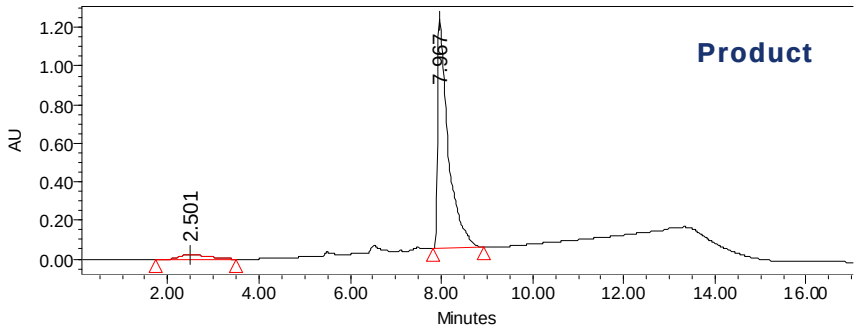
Rapid Acylation & Purification of Amines

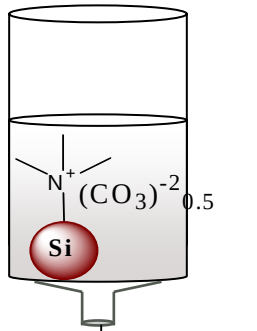


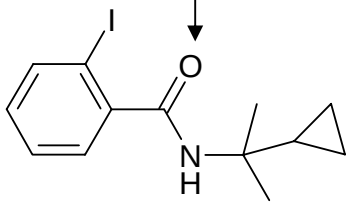




Total Synthesis + Purification ~ 10 mins





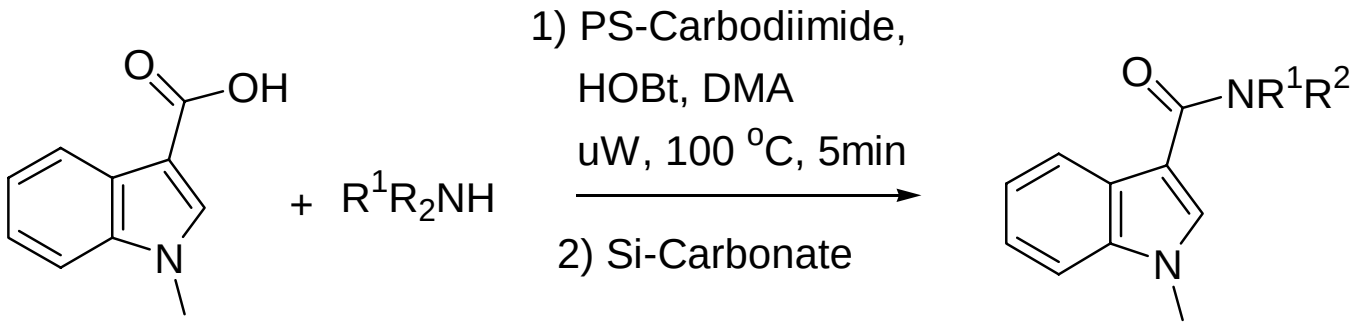


99% yield
98 % Purity

Ghassemi, S. ACS, Atlanta, GA, March **2006**

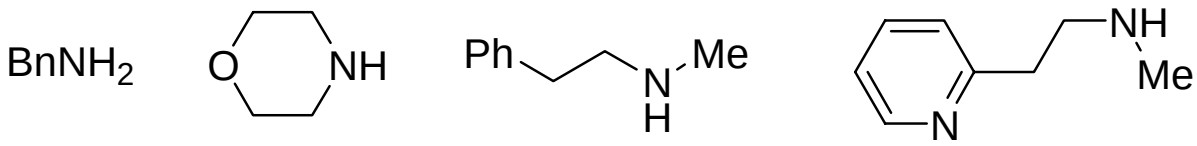
Biotage

PS-Carbodiimide:Microwave Assisted Synthesis



98% Yield
98% purity
< 15 min

R^1R_2NH =

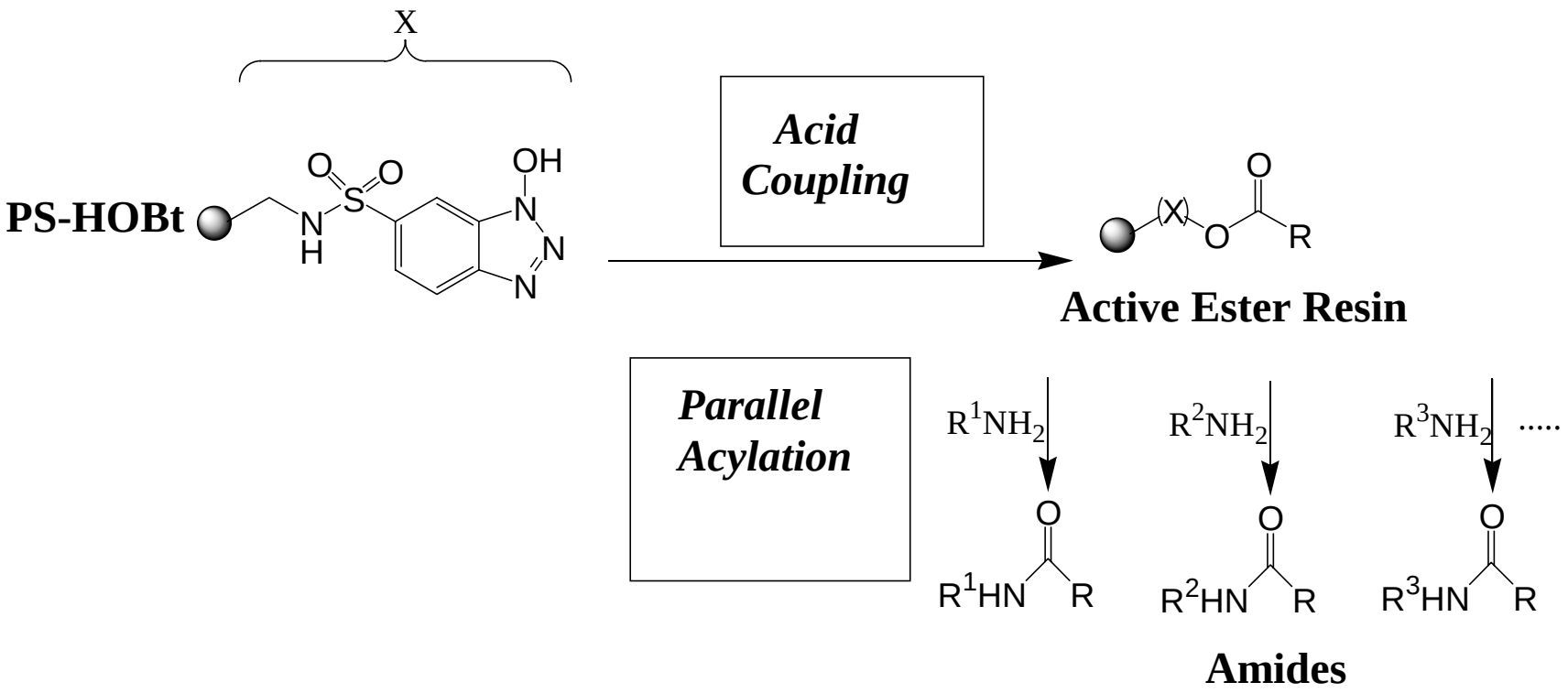


- High yield, high purity using filtration, Si-CO_3 cartridge based purification

•D. Sauer et.al. Organic Letters 2003, 24, 4721-4724

Biotage

Amides From Active Ester Resins



PS-HOBt: Pop, I.E. et al., *J. Org. Chem.* **1997**, *62*, 2594

Biotage

Key Microwave-Assisted Transformations
Solid-supported reagents/Scavengers

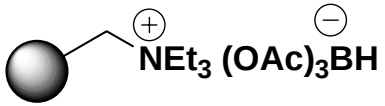
- Pd Catalyzed reactions
- PS-Triphenylphosphine
- Acid catalyzed Reactions
- Base Catalyzed reaction
- Amidation
- **Reductive Amination**
- Oxidation

Biotage

Bound Reagents
Reductive Amination

MP-BH(OAc)$_3$

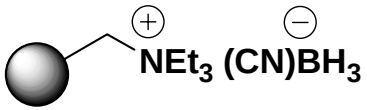
- Tolerates acid-sensitive groups: ketals, acetals
- Secondary amines isolated as acetate
- Tertiary amines as free base



2 mmol/ g

MP-BH$_3$CN

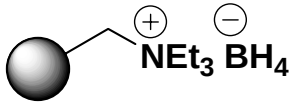
- Requires acetic acid
- Similar reactivity and scope
- Masked toxicity
- Very little pressure build up with MAOS



2-3 mmol/ g

MP-BH4 /Ti(iOPr)4

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

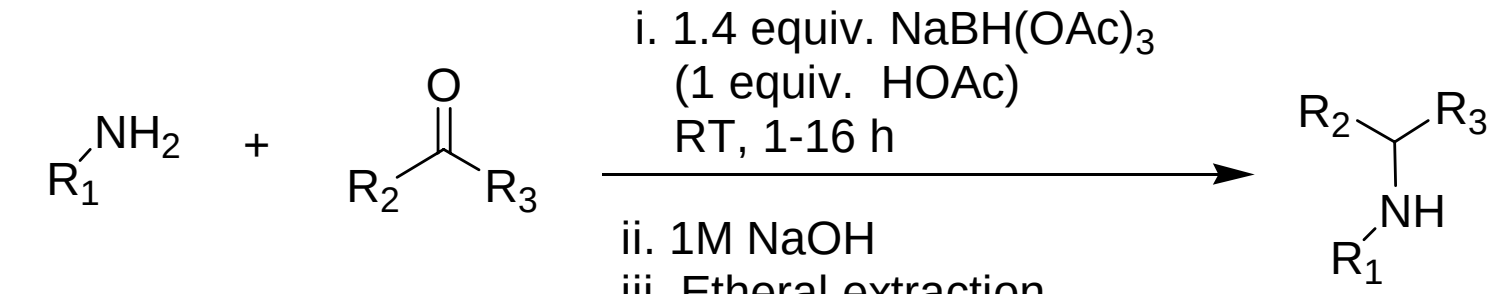


3-3.2 mmol/ g

Biotage

Synthesis of Secondary Amines

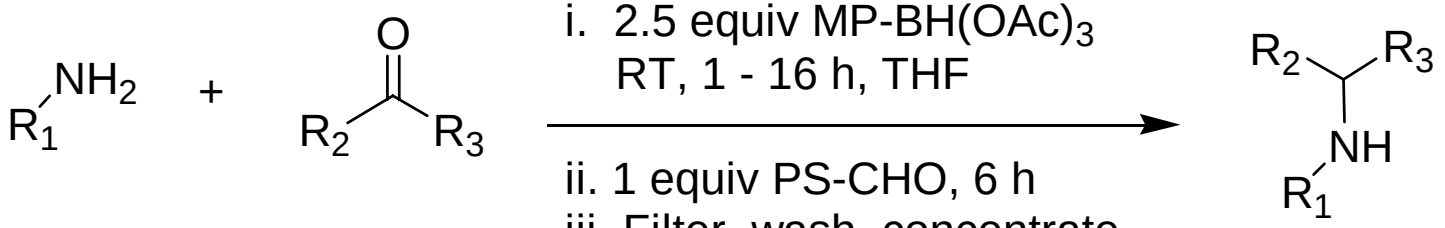
- Typical solution-phase protocol



1-1.2 equiv.

Pure product

- Expedited bound reagent protocol

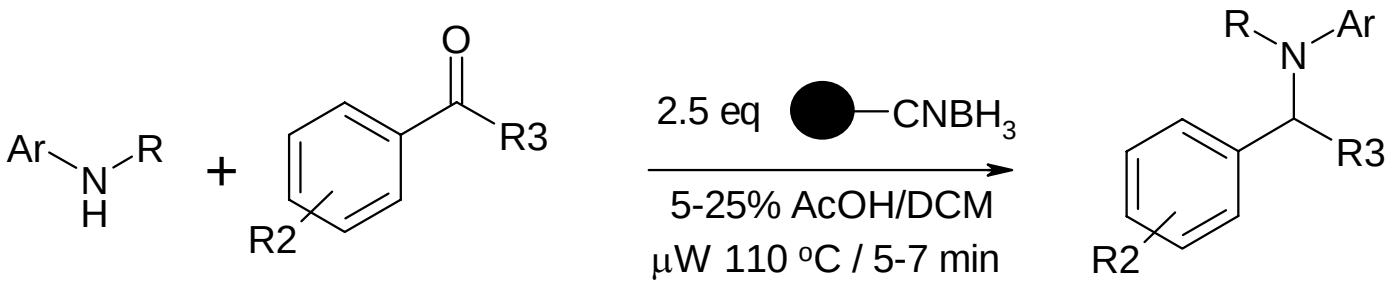


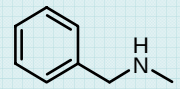
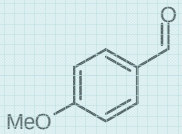
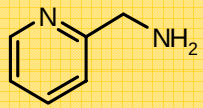
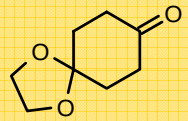
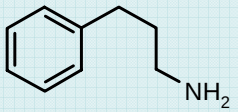
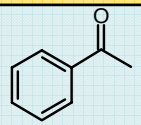
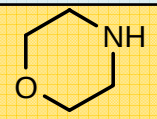
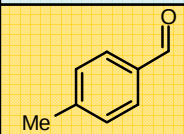
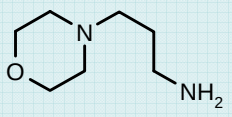
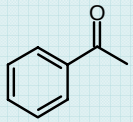
1-1.2 equiv.

Pure product

Biotage

MP-$CNBH_3$
Reductive Amination



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

Pannagiotis, P. www. elrwdjhsdwkilqghulfrp

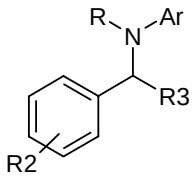
Frqyhqwlrqdo#frqglwlrq=
(1) THF
(2) **room temp, 16 h**

P lfurz dyh#frqglwlrq=
(1) DCM
(2) **110 °C, 5-7 min**

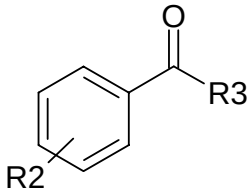
Biotage

MP-$CNBH_3$ – Reductive Amination Purification Strategies - summary

Scenario 1

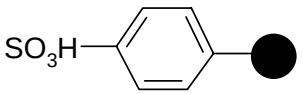


2º or 3º amine
Product



Excess Carbonyl

"Catch & Release"



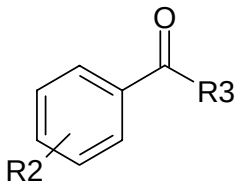
MP-TsOH

Product
NH_3+ SO_3-

NH_3-MeOH

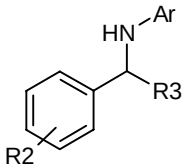
Product
NH_3+

2º or 3º amine

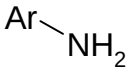


Excess Carbonyl

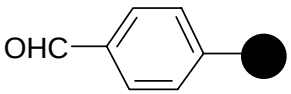
Scenario 2



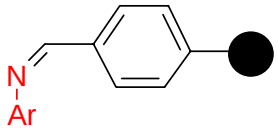
2º amine
Product



Excess 1º amine



PS-Benzaldehyde

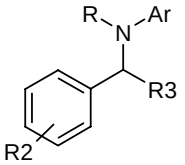


xs 1º amine

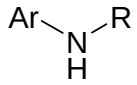
Product
NH+

2º amine

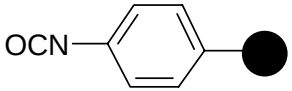
Scenario 3



3º amine
Product

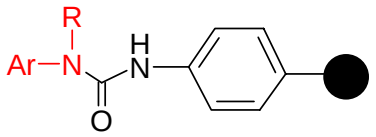


Excess 2º amine



PS-Isocyanate
MP-Isocyanate

xs 2º amine



Product
NH+

3º amine

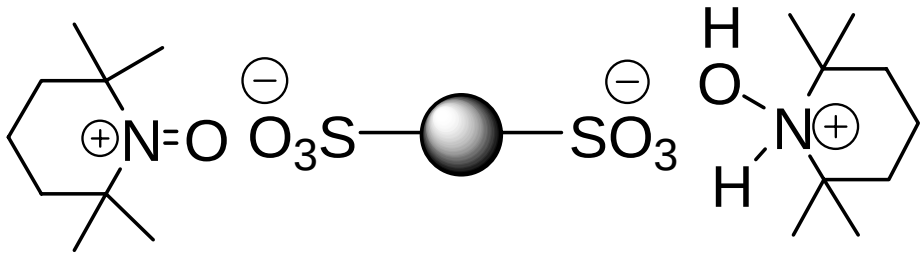
Biotage

Key Microwave-Assisted Transformations
Solid-supported reagents/Scavengers

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

Biotage

MP-TsO-TEMPO
Bound Oxidizing Agent

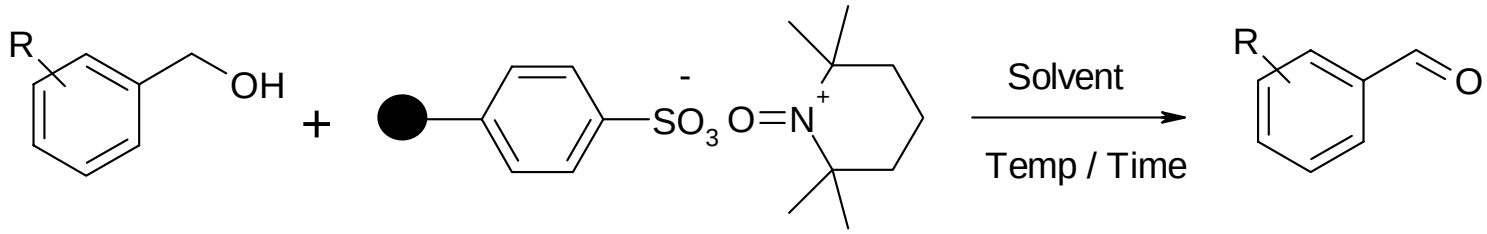


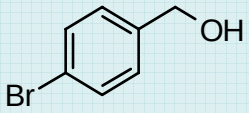
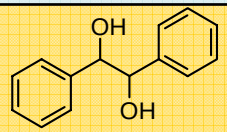
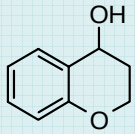
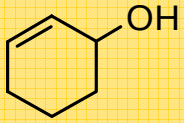
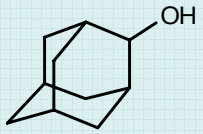
MP-TsO-TEMPO
(As provided)

- 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.

Biotage

MP-TsO-TEMPO
Oxidation of Alcohols

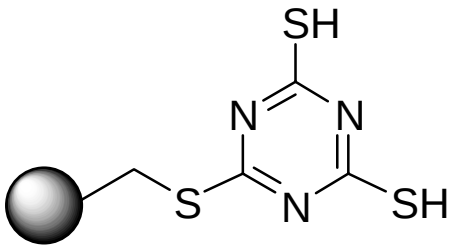


Alcohol	Method	Solvent	Temp	Time	Yield
	Non-μW	CH_3CN	rt	16 h	95 %
	μW	**DCM**	**100 °C**	**10 min**	**100 %**
	Non-μW	CH_3CN	rt	16 h	99 %
	μW	**DCM**	**60 °C**	**2 h**	**100 %**
	Non-μW	CH_3CN	rt	16 h	70 %
	μW	**DCM**	**60 °C**	**5 min**	**93%**
	Non-μW	DCM	rt	16 h	70 %
	μW	**DCM**	**60 °C**	**1.5 min**	**100 %**
	Non-μW	DCM	rt	16 h	100 %
	μW	**DCM**	**60 °C**	**2.5 min**	**100 %**

Biotage

Lundin, R. z z z 1elrwdjhsdwkilqghu1frp

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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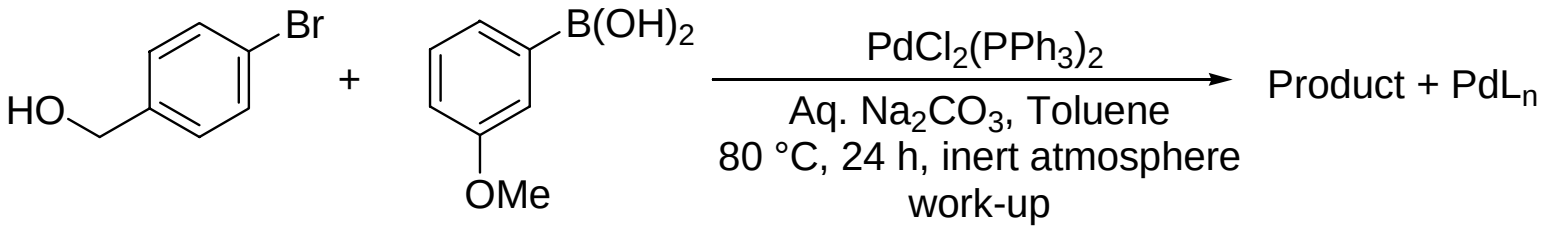
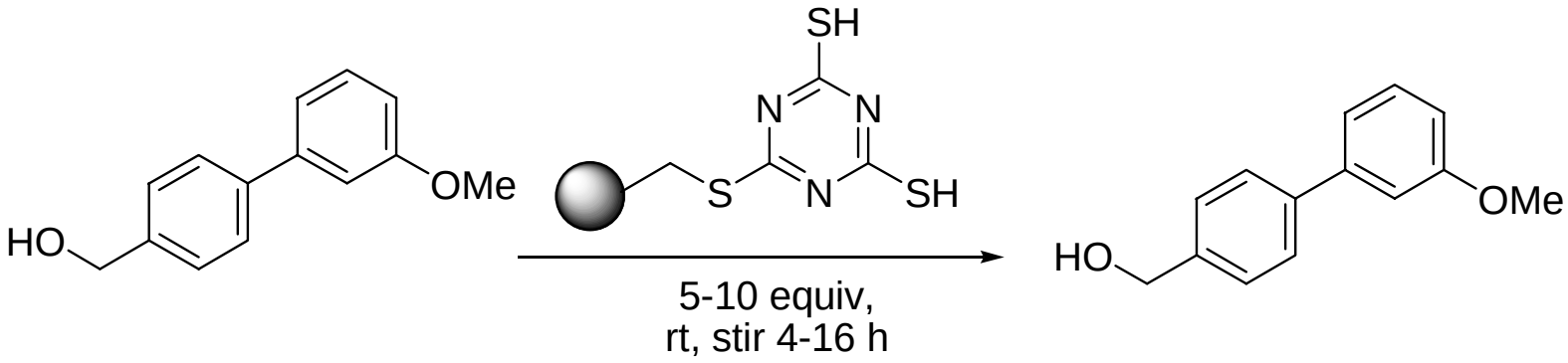
Palladium Scavenging: Advances

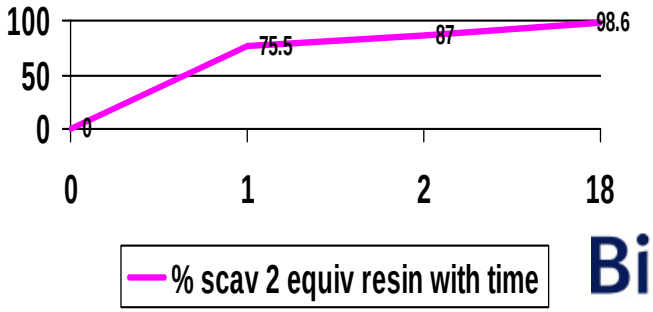




33400 PPM Pd (ICP)

<190 PPM Pd (ICP)

- Scavenges ligated palladium
- Aqueous and non-aqueous
- Next generation backbone



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SPE
Solid Phase Extraction

- **Purification------Catch and release technology**

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Bound Acid: MP-TsOH

MP-TsOH

- Bound sulfonic acid equivalents
  - Highly cross-linked polystyrene based
- Scavenges amines, basic compounds
- Catch and Release purifications
  - Catch amines, basic heterocycles
  - Wash impurities
  - Release amine with ammonia/methanol

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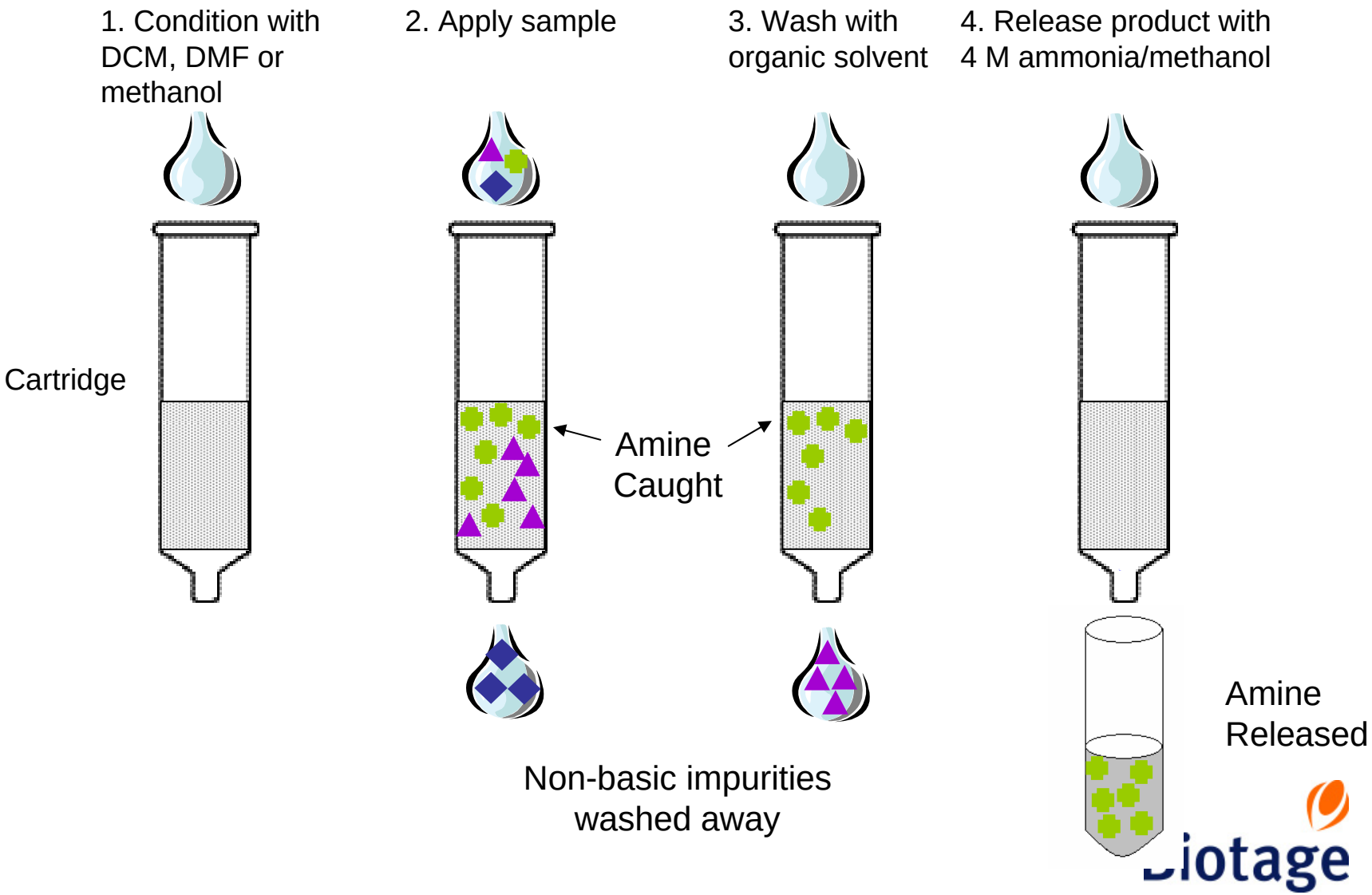
Cartridges for Amine Purification by Catch and Release



Thank you for your attention

Biotage