The use and application of solid supported media in organic, medicinal and scale up chemistries

-leaping hurdles

Nathalie Huther, PhD

Biotage

Contents

- **Solid supported reagents and scavengers**
  - Background
- **Solid-supported reagents/scavengers**
  - Synthesis / Chemistry

    Pd-Catalyzed reactions inc Alloc Deprotection
    Supported Reductive Amination
    Etherification / N-Alkylation
    Amidation Synthesis
    Oxidation
  - Purification / Scavenging

    Metal Scavenging
    One Step Deprotection and purification
    Primary vs. Secondary amine scavenging
    One step Purify, Change solvent and Remove Metal

Brief History – The Supports: Resins

- 1838 First polymer modification (nitration of cellulose)
- 1839 First Lab Polymerisation of styrene

- 1910 First Polymer supported catalyst (amylase/ starch)
- 1935 Polar groups incorporated into polymers

- 1945 Ion Exchange Polymers, water purification

- 1963 Merrifield and first modern SPS / SPPS
- 1988 Split and Mix, the combinatorial revolution

Biotage

Brief History – The Supports: Silicas

- 1901 Concept of Chromatography Tsvet, chlorophylls
- 1952 Martin & Synge Partition Chromatography/ Plate theory
- 1950's Silica Catalysts in cracking, Butadiene Synthesis
- 1978 Still, Flash Column Chromatography
- 1980's- Increasing development of Silicas for use in organic and med chem applications.

Development of solid supports for use in organic / med chem. with or without microwave heating

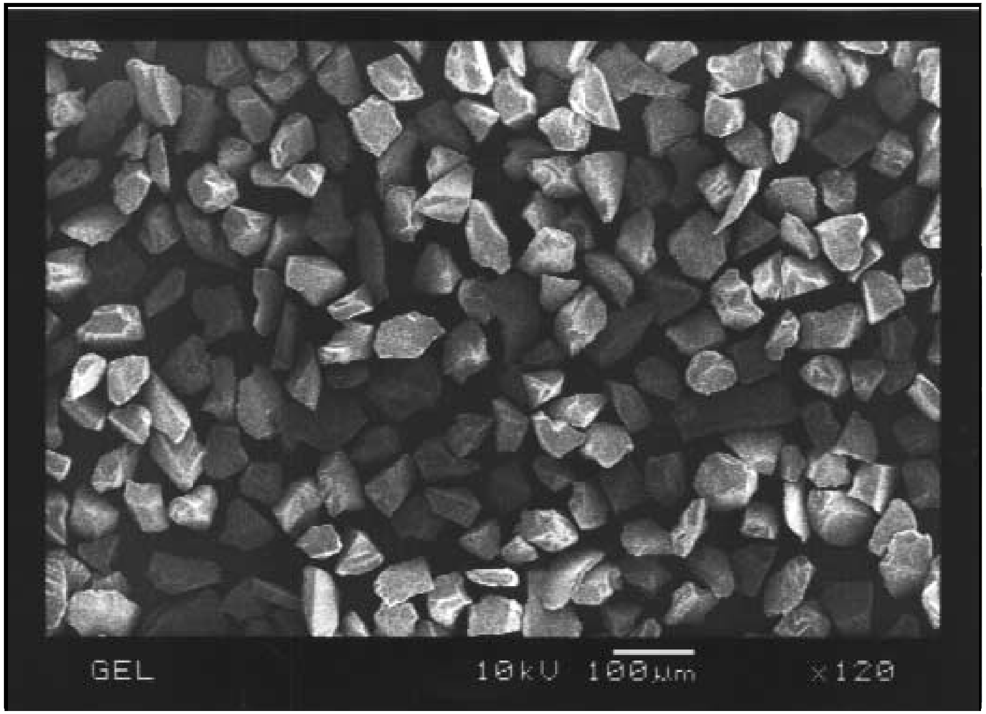
Biotage

Why are Solid Supports Useful?

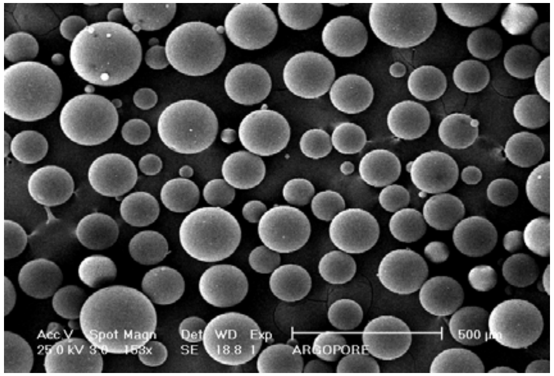
	Priority	
	Med Chem	**Larger Scale**
Reduction of Bench Time		
Easy and fast to dispense and use	☺☺☺	☺☺
Work flow enhancements / cost	☺☺	☺☺☺
Easy dispose / potentially recyclable	☺	☺☺☺
Health and Safety		
Removal of toxic by-products	☺☺	☺☺☺
Stable, Storage, much simpler	☺☺	☺☺
Safety / Health (TSE) statements	☺	☺☺
Chemistry		
Heterogeneous properties	☺☺	☺☺☺
Defined loadings	☺☺	☺☺☺
Enhanced chemistry	☺☺	☺☺☺

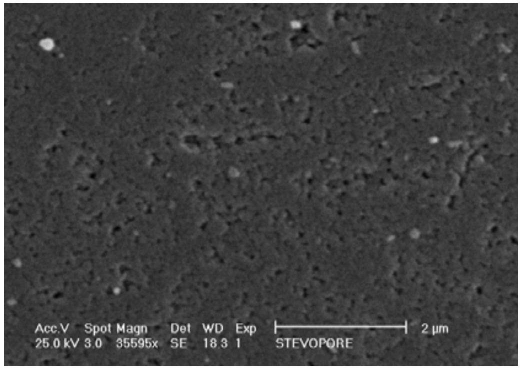
Biotage

Integration of Technology and Methods

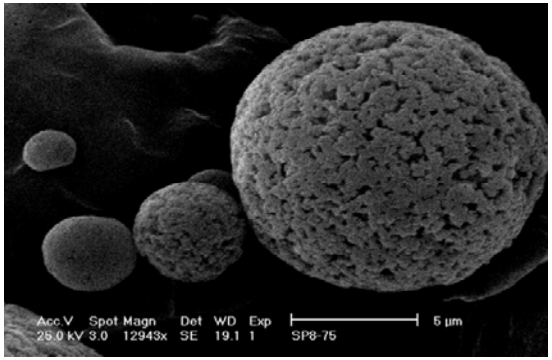


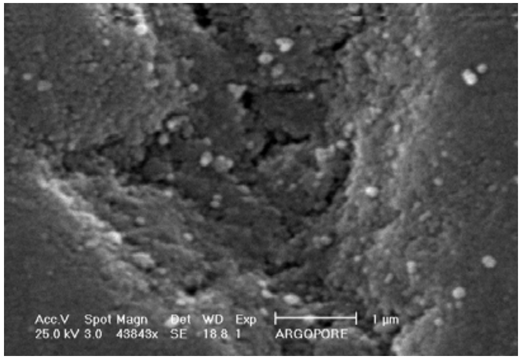
Resins and Silicas



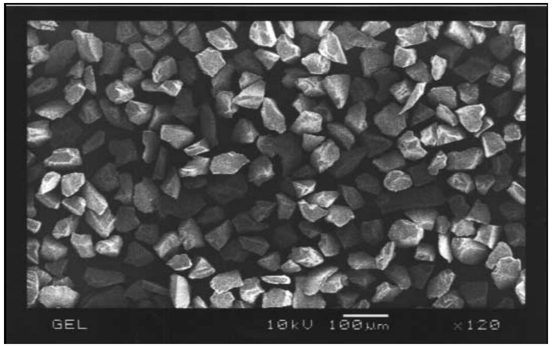


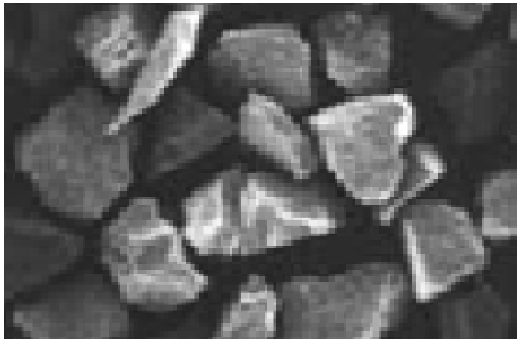
Insoluble, cross-linked
Polystyrene Spherical
50um – 1000um diameter
No Formal pore structure





Insoluble, cross-linked
Polystyrene Spherical
50um – 1000um diameter
Formal pore structure





Mostly surface orientated chemistry
Robust irregular shaped particles
Si-OH terminal groups
Insoluble polymer
Si-O-Si matrix

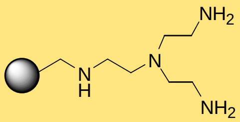
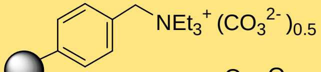
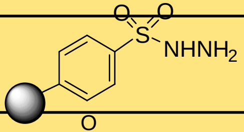
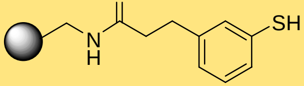
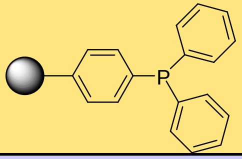
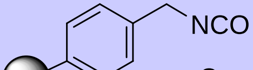
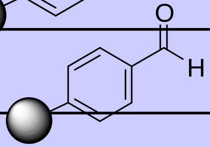
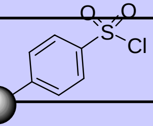
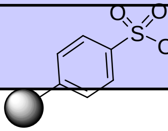
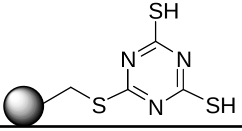
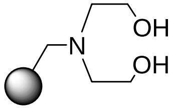
Biotage

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

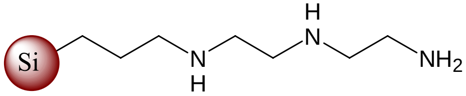
Biotage

Biotage Polymeric Scavengers

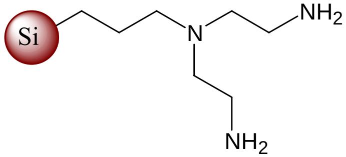
Electrophile	PS-Trisamine MP-Trisamine 	**Acyl halides, Sulfonyl halides, Isocyanates**
	MP-Carbonate 	**Carboxylic acids, Phenols**
	PS-Tosylhydrazide 	**Aldehydes, Ketones**
	PS-Thiophenol 	**Alkylating agents**
	PS-Triphenylphosphine 	**Alkyl halides**
Nucleophile	PS-Isocyanate MP-Isocyanate 	**1°, 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**

Silica-supported Reagents/Scavengers

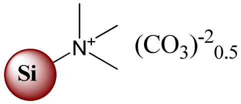
ISOLUTE® Si-Triamine



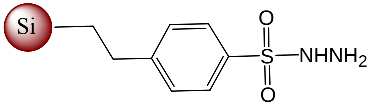
ISOLUTE® Si-Trisamine



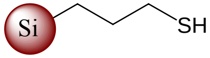
ISOLUTE® Si-Carbonate



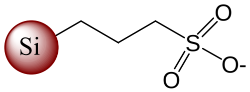
ISOLUTE® Si-Ts-Hydrazide



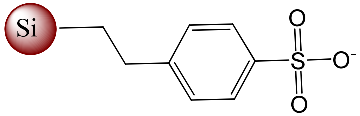
ISOLUTE® Si-Thiol



ISOLUTE® Si-Propylsulfonic acid (SCX-2)

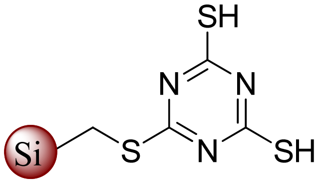


ISOLUTE® Si-EthylPhenyl sulfonic acid (SCX-3)



ISOLUTE® Si-TMT

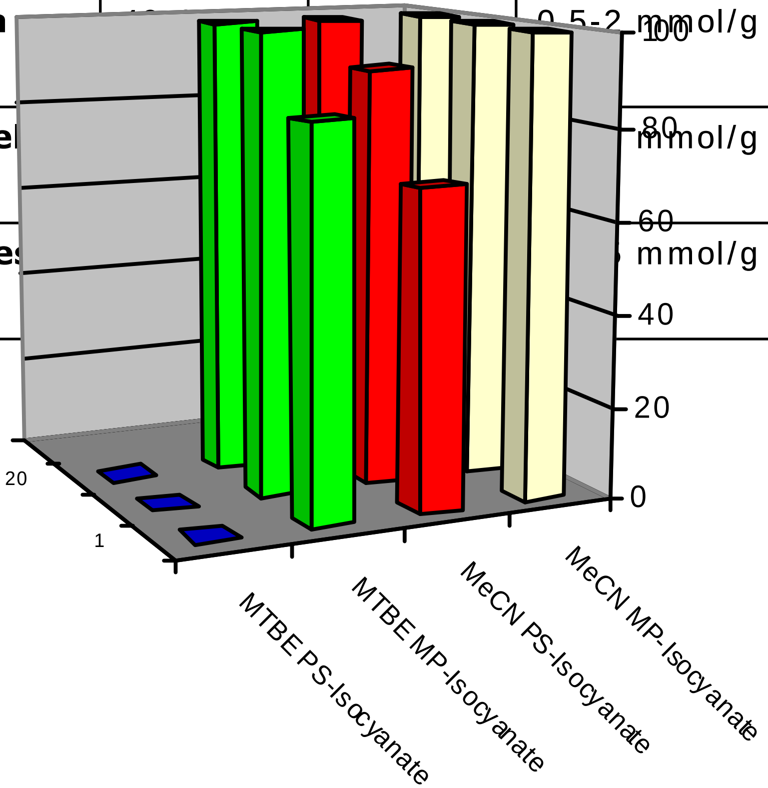
NEW!

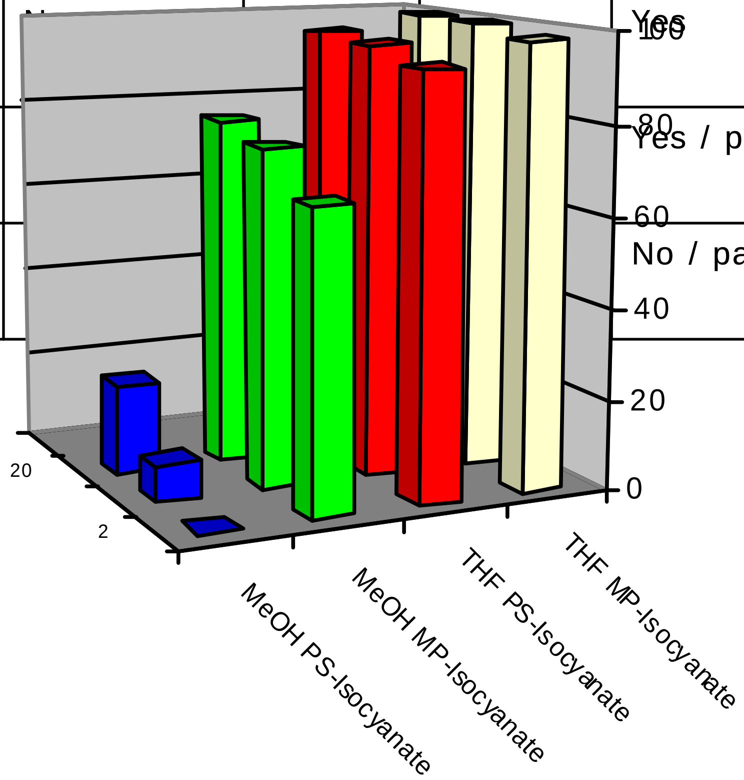


PS-, MP- and Si Supports – A Comparison

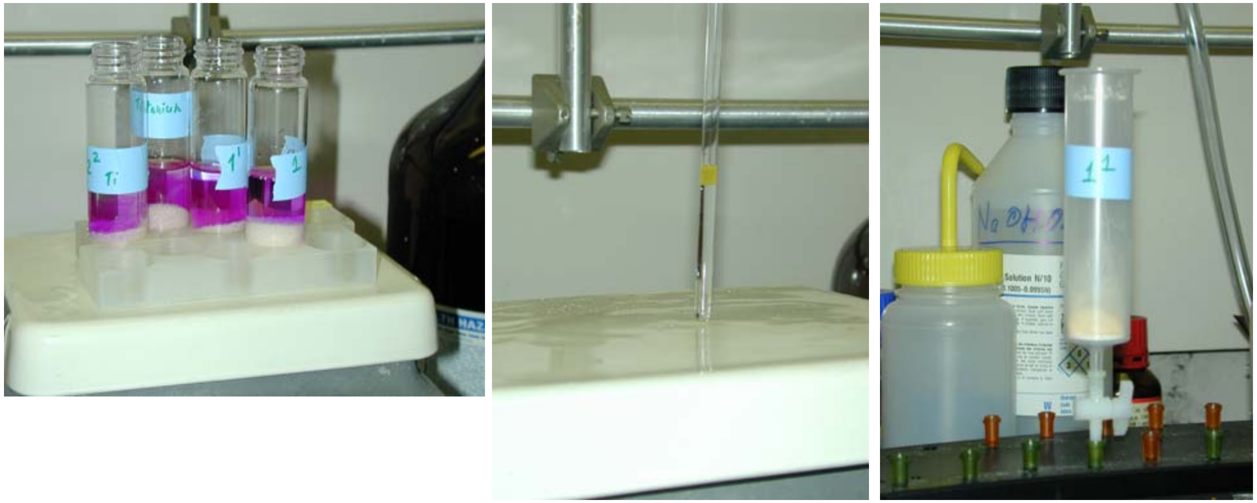
Material	Size	Volume	Loading	Swelling	Protic (polar)	Aprotic	Friability
Silica			0.5-2 mmol/g				Yes
PS ge			mmol/g				Yes / partial
MP re			mmol/g				No / partial

Scavenging Benzylamine: 3.5 Equiv. PS- or MP-Isocyanate/ RT





In the Laboratory



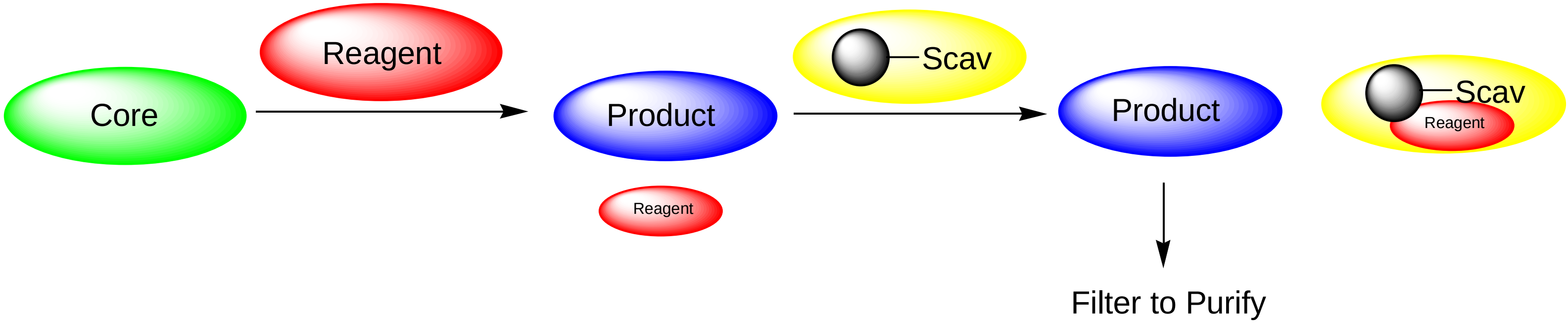
Standard lab equipment

Shaking, overhead, magnetic,

Microwave, ‘Blood Wheels’

Synthesis (Bound Reagents) / Purification (Scavengers)

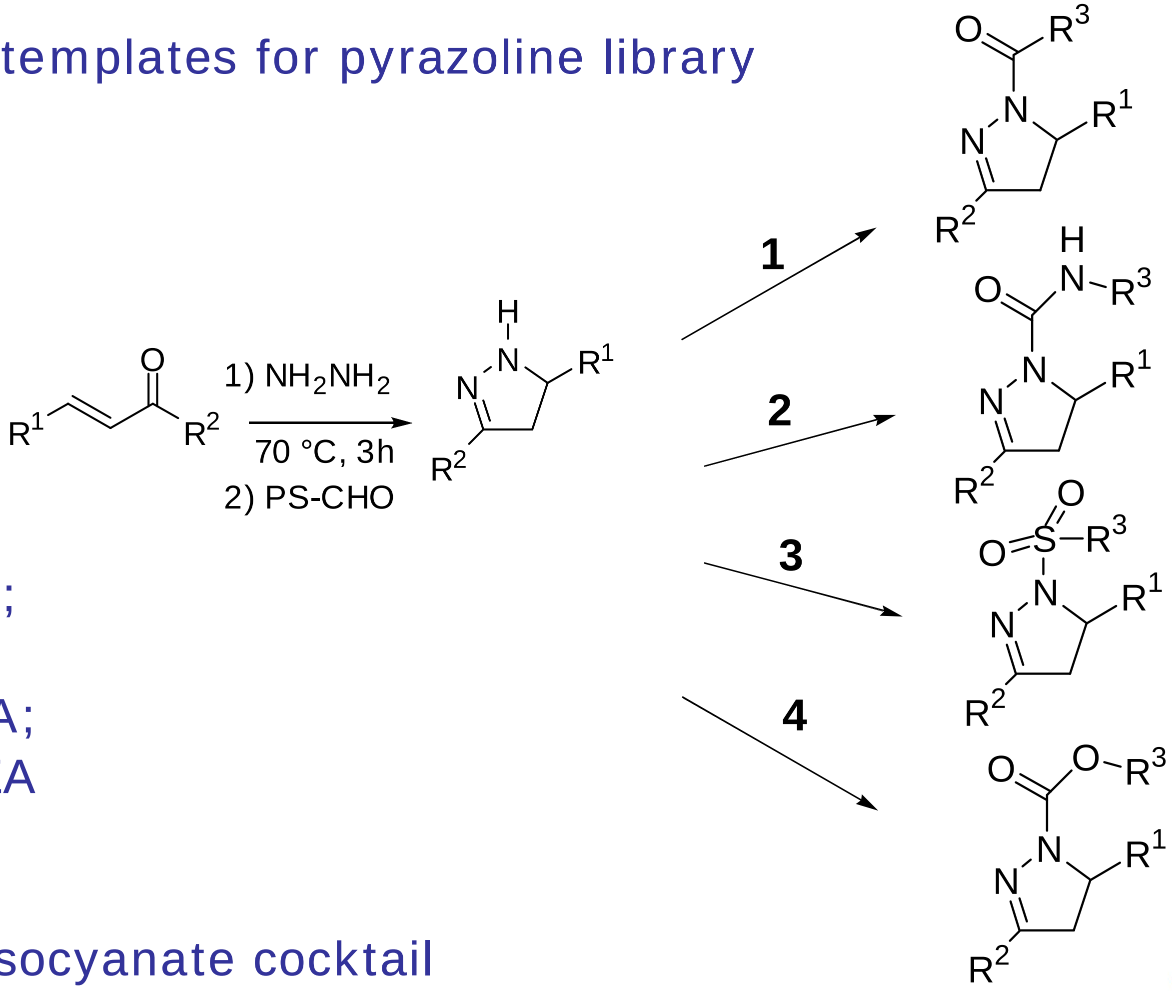
Scavengers



- Chemically-driven separation
- Resins added after reaction is completed (work-up)
- 2-5 equiv relative to excess reagent
- Purified product isolated by filtration, concentration
- Multiple scavengers in a single reaction step
  - Resin bound functional groups cannot react
  - Functional groups “incompatible” used simultaneously

N-Substituted Pyrazoline Libraries

Chalcones used as templates for pyrazoline library



Synthesis

1, R^3COCl, PS-DIEA;
2, R^3NCO;
3, R^3SO_2Cl, PS-DIEA;
4, R^3OCOCl, PS-DIEA

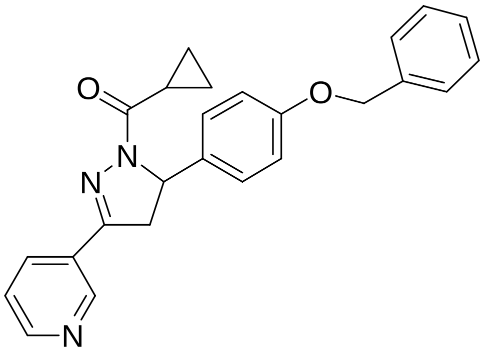
Purification

PS-Trisamine, PS-Isocyanate cocktail

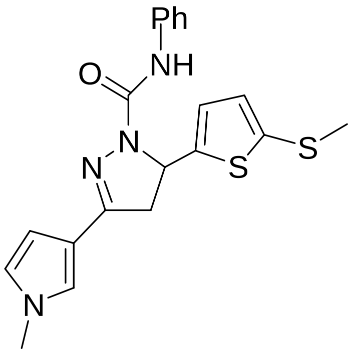
Bauer, U. *et al.* *Tetrahedron Lett.* **2000,** *41***,** 2713-2717

N-Substituted Pyrazoline Libraries

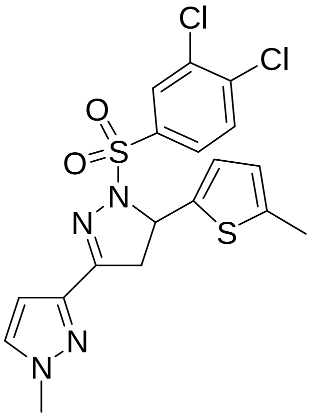
- 80 chalcones converted to 1500 derivatives
- Purities = 75 – 98%
- Representative structures



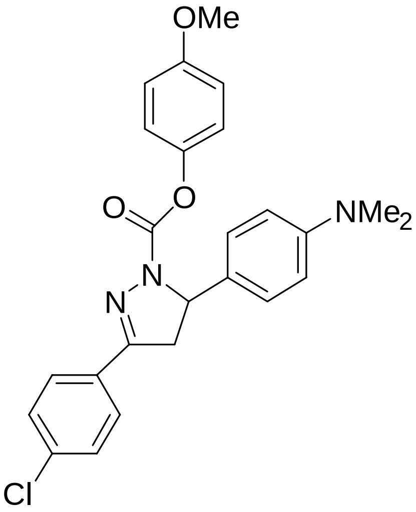
82% Yield
> 95% Purity



84 %Yield
91 %Purity



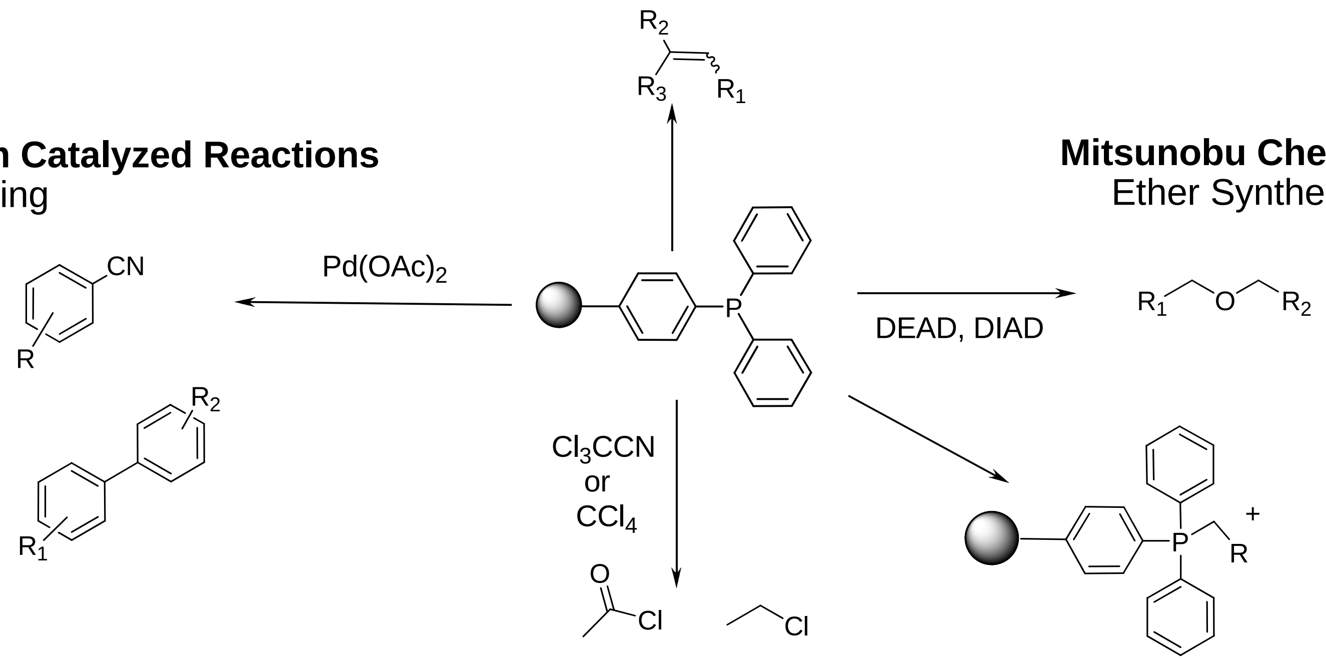
87 %Yield
89 %Purity



75 %Yield
88 %Purity

Biotage

PS-Triphenylphosphine



Wittig Chemistry
Alkene Synthesis

Palladium Catalyzed Reactions
C-C coupling

Mitsunobu Chemistry
Ether Synthesis

Scavenging
of Alkyl Halides

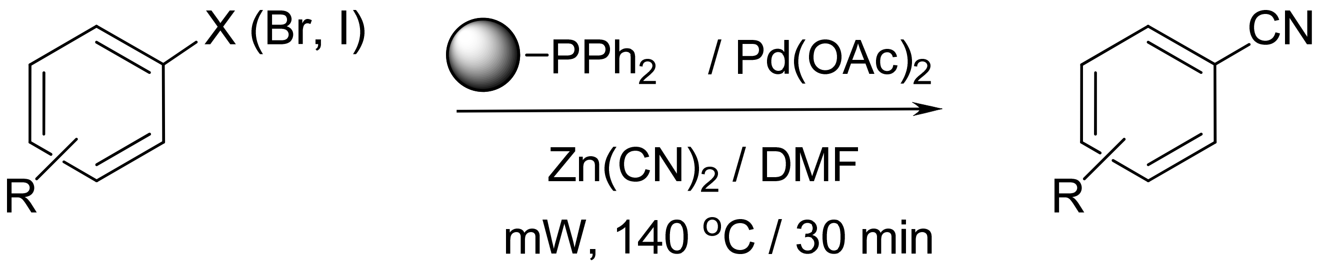
Chlorination
Formation of acid chlorides & alkyl halides

Advantage over Triphenylphosphine:

- Phosphines and oxide byproducts are resin bound and easily removed

Biotage

PS-Triphenylphosphine Palladium-assisted Cyanation



84-99 %

- Pre-mixing of Catalyst and Ligand was essential for optimal catalytic activity
  - *2 h; yellow color of Pd(OAc)$_2$ transferred to bead upon complexation*

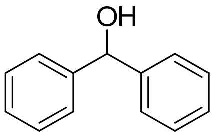
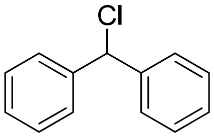
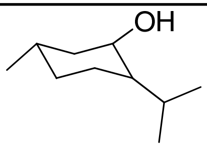
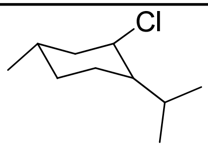
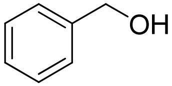
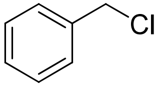
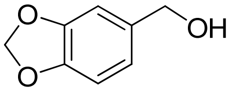
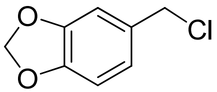
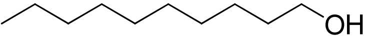
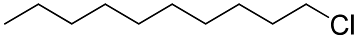
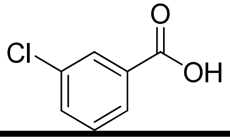
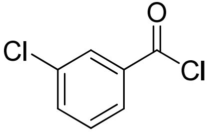
- Workup: (1) Filtration
  (2) Wash resin with Ether
  (3) Dry and evaporate organic layer

Srivastava, R.R. et al.; *Tetrahedron Lett.* 2004, *45,* 8895

Biotage

PS-Triphenylphosphine - Chlorination

$$\text{R-OH or R-CO}_2\text{H} \xrightarrow[\text{CCl}_4\text{, reflux}]{\text{PS-PPh}_2\text{ (2 equiv)}} \text{R-Cl or R-COCl}$$

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

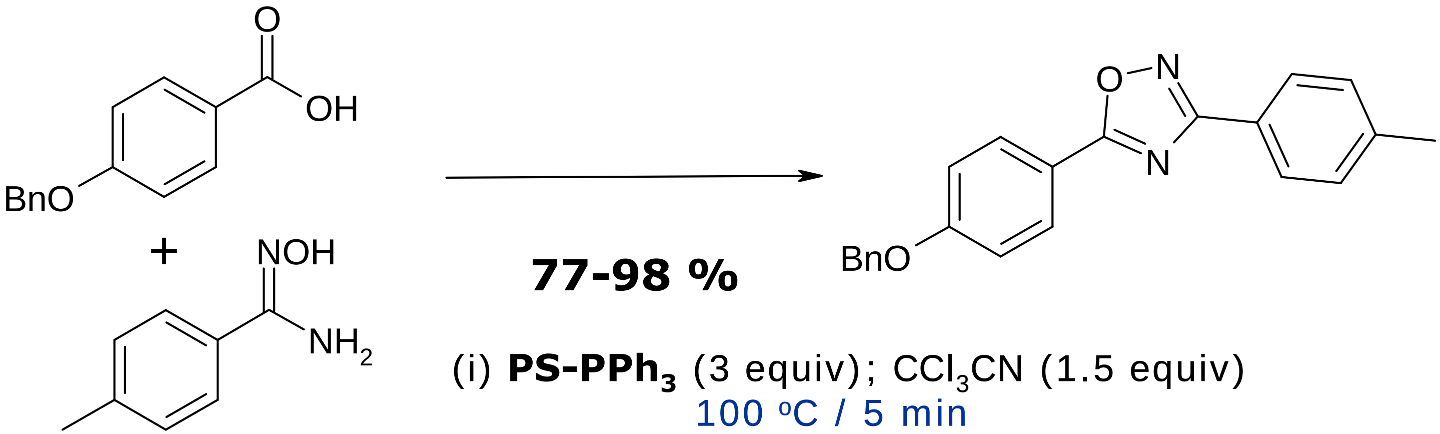
***28%@3hrs**

64%@16hrs

by ^{1}H NMR

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

PS-Triphenylphosphine Microwave-assisted Chlorination



77-98 %

(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

Acid Chloride formed in-situ, quantitative yields

React with aldoximes generating the oxadiazole

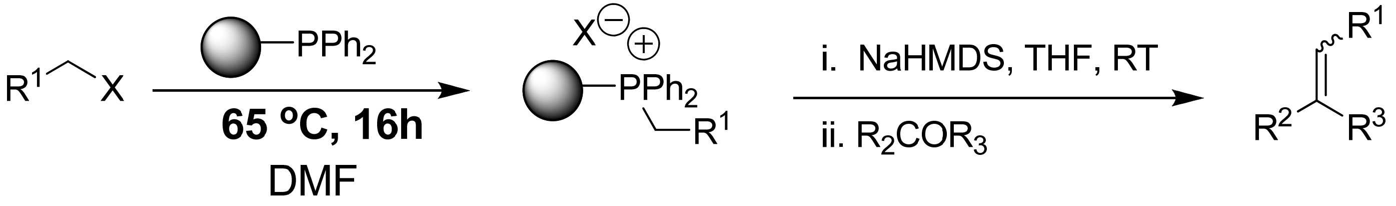
THF worked well – even in MW

One pot synthesis

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

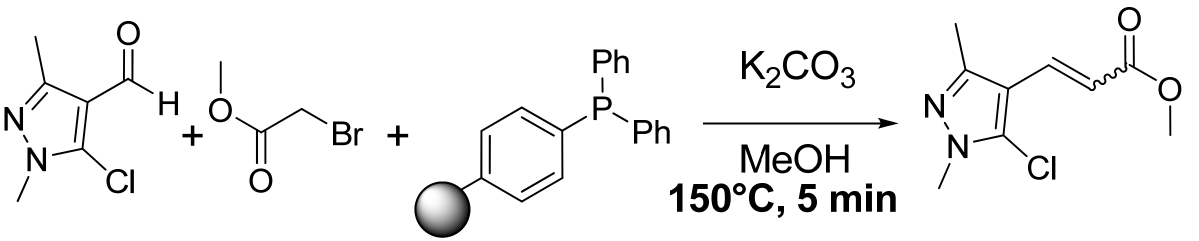
PS-Triphenylphosphine - Wittig

Traditional



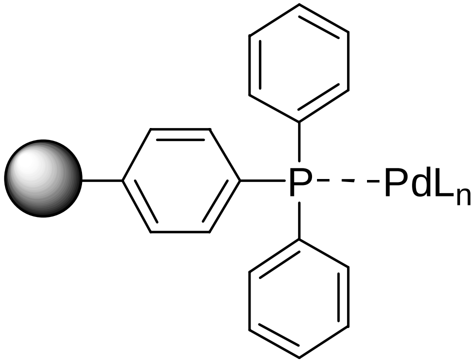
Microwave

(one-pot)



Westman, J. *Org. Lett*. **2001**, *3(23)*, 3745-3747.

PS-Triphenylphosphine-Pd(0)

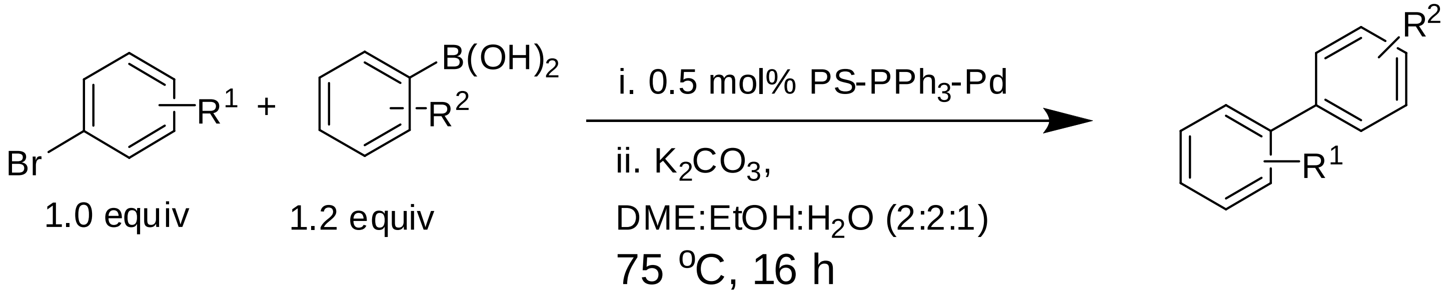


Bound Pd(0) Catalyst

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

Biotage

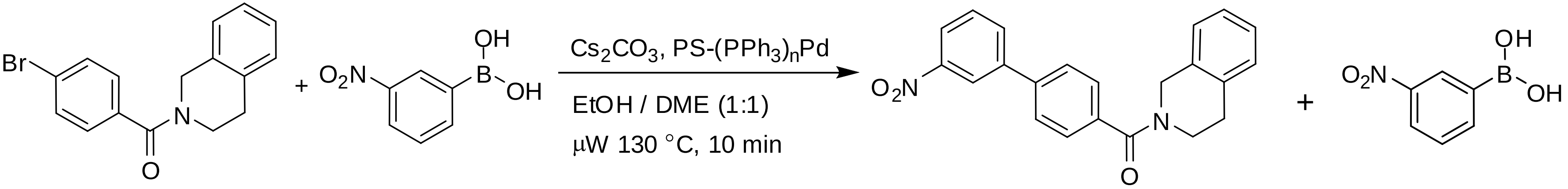
PS-PPh$_3$-Pd : Suzuki Coupling (Regular)

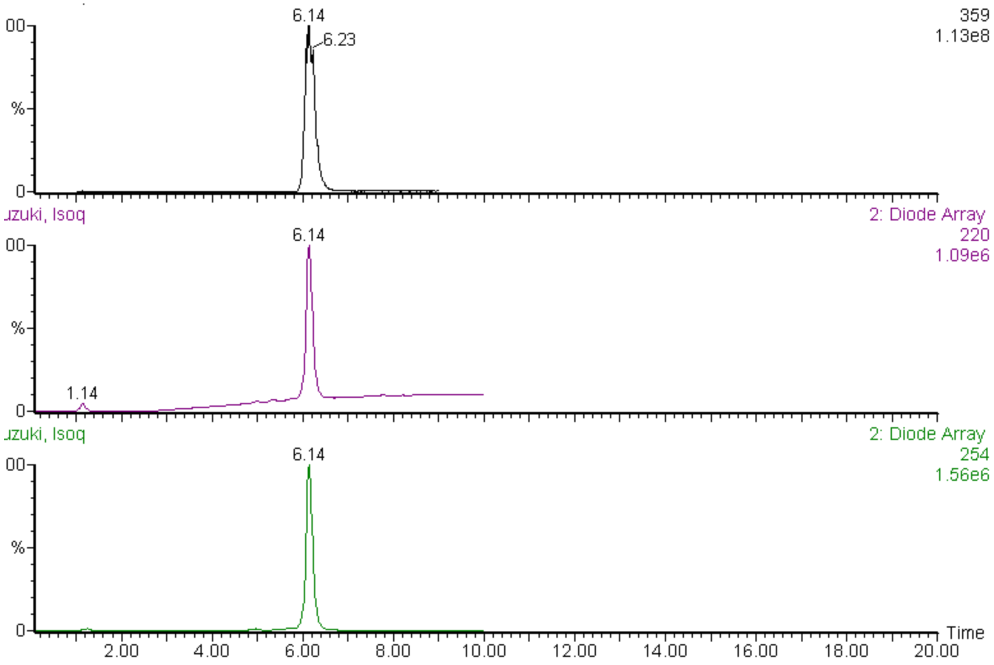


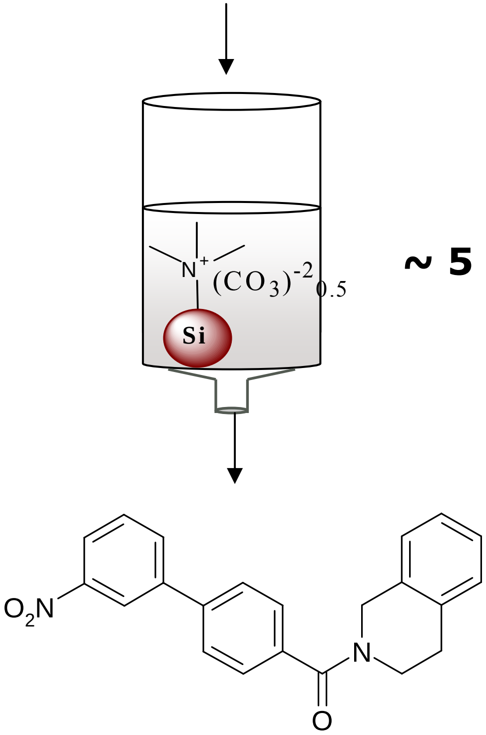
- Reactions performed under air, no inert conditions required
- Products isolated in high purity and yield
- Low palladium level in products (< 60 ppm)

Biotage

PS-PPh$_3$-Pd / Si-Carbonate: Enhanced Workflow



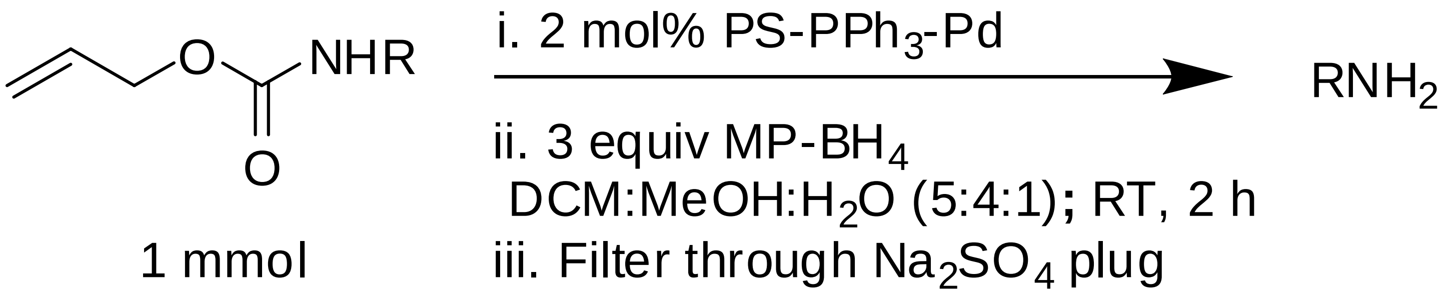




~ 5 mins

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

PS-PPh_3-Pd / MP-BH_4: N-Alloc Reductive Deprotection



1 mmol

i. 2 mol% PS-PPh_3-Pd

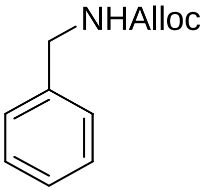
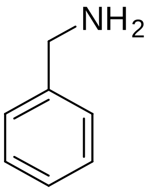
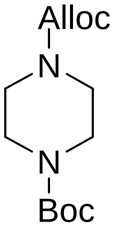
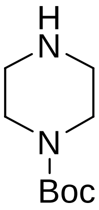
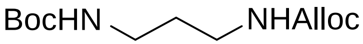
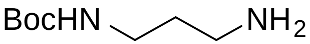
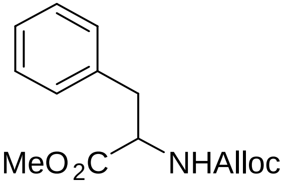
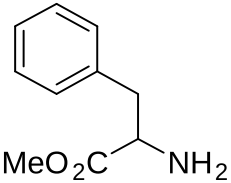
ii. 3 equiv MP-BH_4
DCM:MeOH:H_2O (5:4:1); RT, 2 h

iii. Filter through Na_2SO_4 plug

RNH_2

- Alloc orthogonal to Boc, Fmoc and Cbz groups
  - Applications in peptide, nucleoside and amino-sugar chemistry
- 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 conditions
- Low palladium level in products (< 100 ppm)
- Products isolated in high yield and purity

Reductive Deprotection of N-Alloc: Scope Studies

Entry	Substrate	Product Amine	Yield %	Purity %
1			85	98
2			82	97
3			79	97
4			90	99

Reaction scale: 1.0 mmol

Isolation = Filter through Na_2SO_4 plug, concentrate

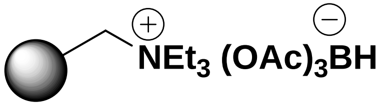
Reductive Amination - Methodologies

MP-BH(OAc)$_3$

Tolerates acid-sensitive groups: ketals, acetals

Secondary amines isolated as acetate

Tertiary amines as free base



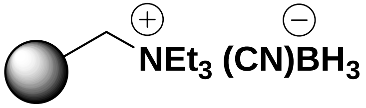
2 mmol/ g

MP-BH$_3$CN

Requires acetic acid

Similar reactivity and scope

Masked toxicity



2-3 mmol/ g

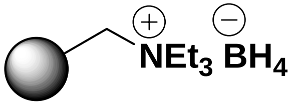
MP-BH$_4$ /Ti(^{i}OPr)$_4$

Suppresses over-alkylation (reactive carbonyls)

Enables use of:

- sterically hindered carbonyls i.e.. adamantyl ketones
- enolizable ketones e.g. acetophenone

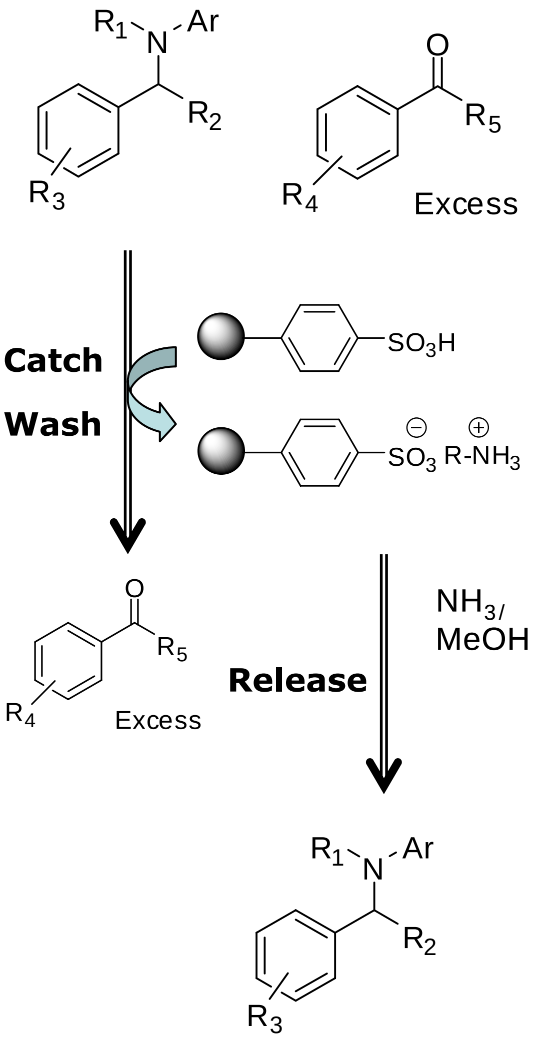
Titanium isopropoxide scavenged by PS-DEAM



3-3.2 mmol/ g

Reductive Amination
Supported Purification Strategies

Scenario 1



Excess

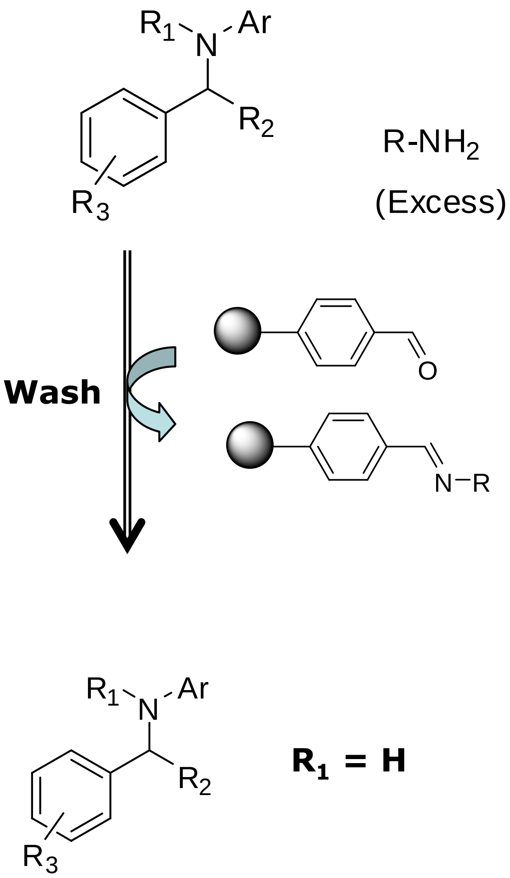
Catch

Wash

Excess

Release

Scenario 2

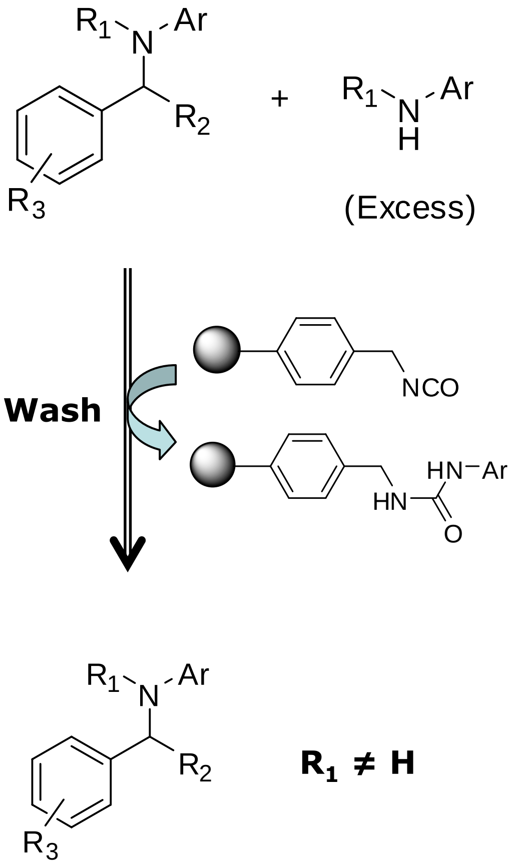


(Excess)

Wash

R_1 = H

Scenario 3



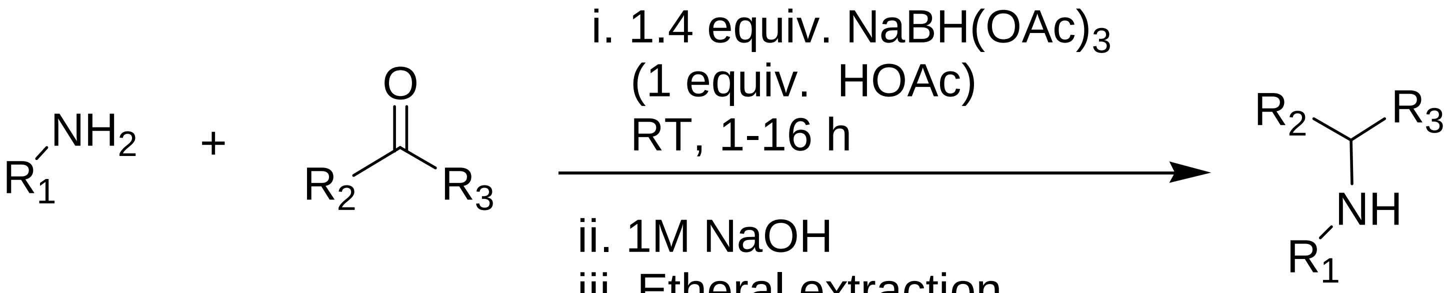
(Excess)

Wash

R_1 ≠ H

Synthesis of Secondary Amines

Typical solution-phase protocol



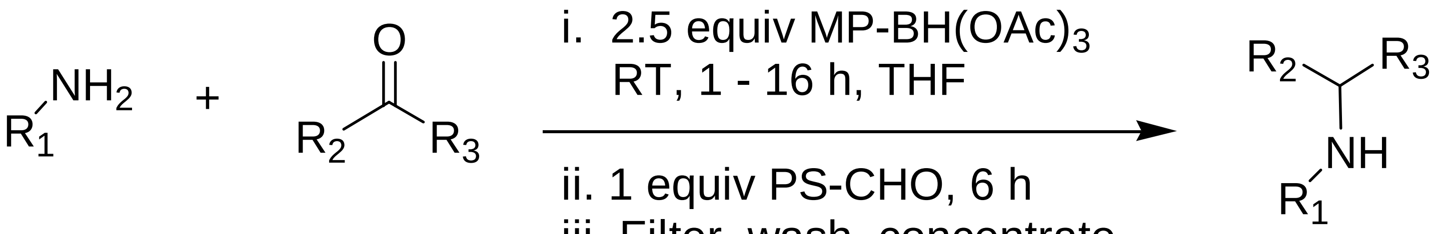
i. 1.4 equiv. $NaBH(OAc)_3$
(1 equiv. HOAc)
RT, 1-16 h

ii. 1M NaOH
iii. Etheral extraction
iv. Wash, dry
v. Column purification

1-1.2 equiv.

Pure product

Expedited bound reagent protocol



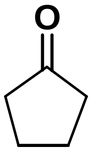
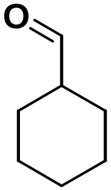
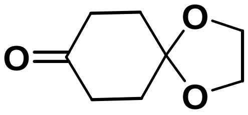
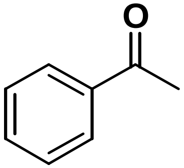
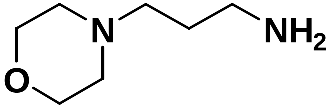
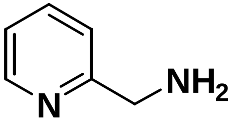
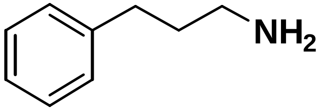
i. 2.5 equiv MP-$BH(OAc)_3$
RT, 1 - 16 h, THF

ii. 1 equiv PS-CHO, 6 h
iii. Filter, wash, concentrate

1-1.2 equiv.

Pure product

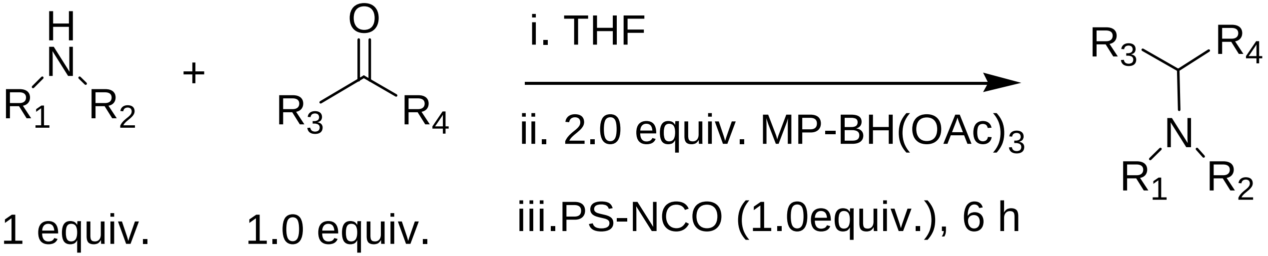
MP-BH(OAc)$_3$: Synthesis of Secondary Amines

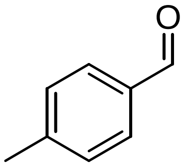
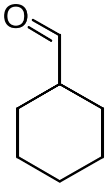
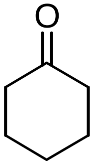
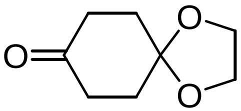
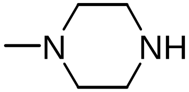
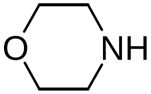
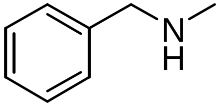
				
	93 (100)	77(84)*16*	77 (100)	69(98)
	93 (98)	90(96)*3*	91(100)	76(27)
	100 (100)	94 (88)*12*	54(100)	39(91)

%yield (%purity)*%overalkylation*

- Water of imine formation hydrolyzes ~ 1 equiv BH(OAc)$_3$
- Facilitates scavenging, additional HOAc not required

MP-BH(OAc)$_3$: Synthesis of Tertiary Amines



				
	97(100)	92(99)	88(100)	85(100)
	63(100)	90(99)	69(100)	64(100)
	67(100)	77(99)	82(100)	76(100)

%yield (%purity)

- Ketal tolerated
- Resin scavenger PS-NCO (1 equiv, 5- fold xs wrt amine)
- Product isolated as free amine
- Negligible B leaching
- PS-Isocyanate removes excess secondary amine

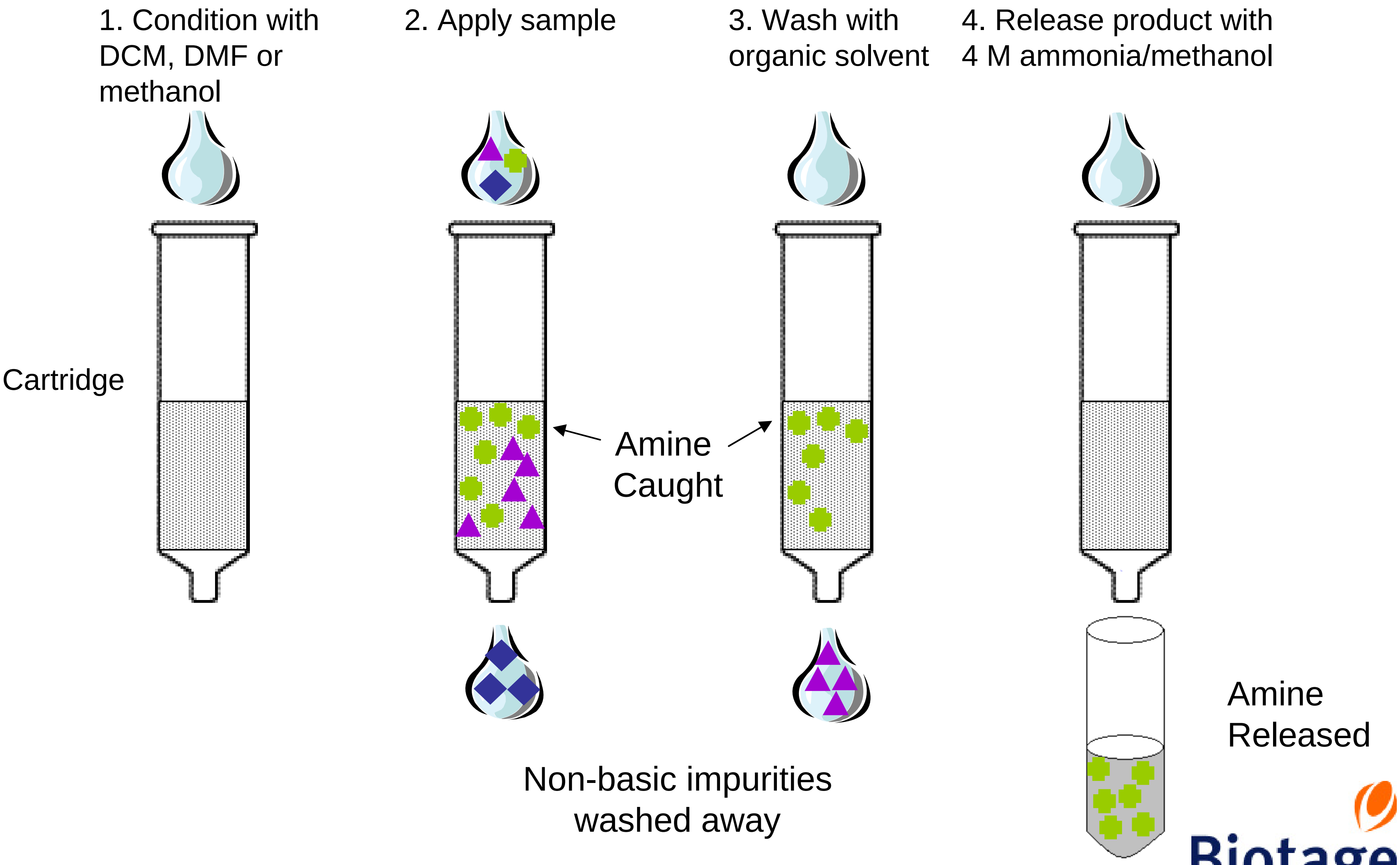
Bound Acid: MP-TsOH

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

Biotage

Cartridges for Amine Purification by Catch and Release



1. Condition with DCM, DMF or methanol

2. Apply sample

3. Wash with organic solvent

4. Release product with 4 M ammonia/methanol

Cartridge

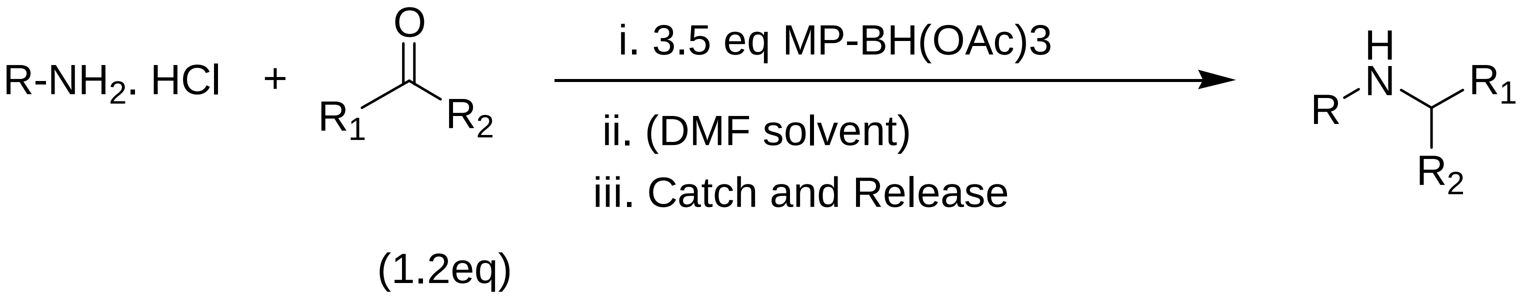
Amine Caught

Non-basic impurities washed away

Amine Released

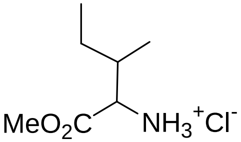
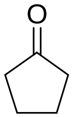
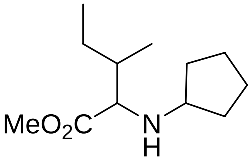
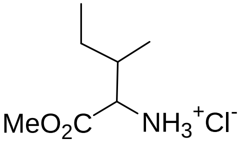
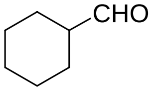
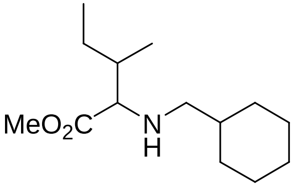
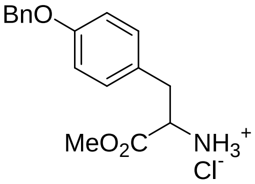
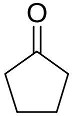
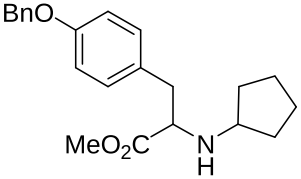
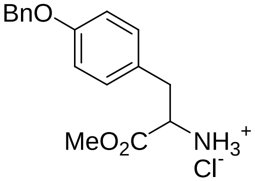
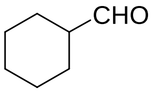
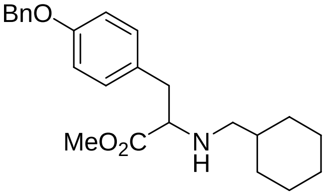
Biotage

MP-BH(OAc)$_3$: HCl salts and DMF - Summary

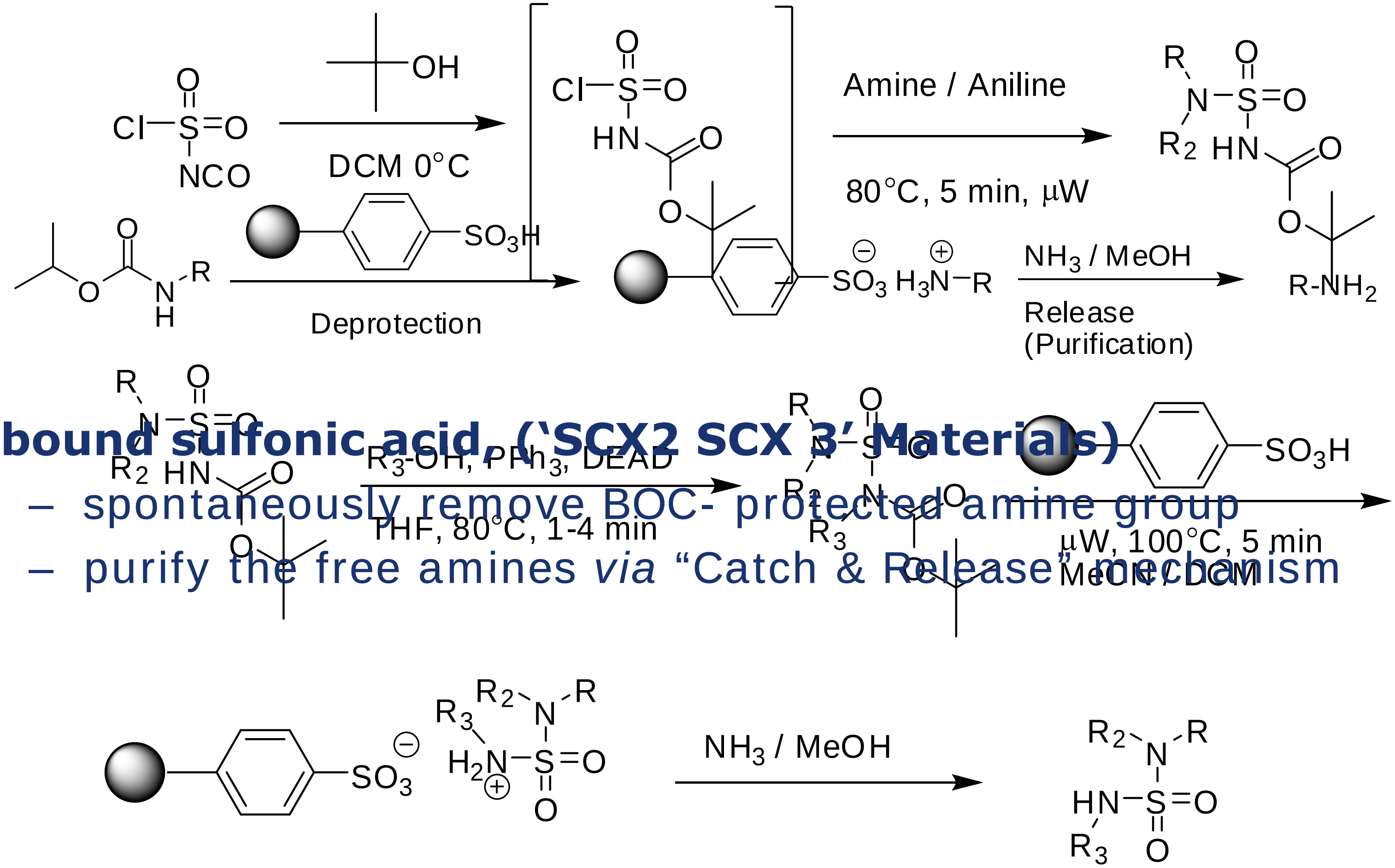


- Amines available as HCl salts
- Amines not soluble in THF
- Extra equiv of MP-BH(OAc)$_3$ required
- “Catch and Release” – 2 Birds / One Stone
  1. Purifies product
  2. Removes DMF

MP-BH(OAc)$_3$: HCl salts and DMF

Starting Amine	Carbonyl Compound	Product Amine	%Yield (isolated)	% Purity
			59	98
			93	99
			60	93
			74	98

Simultaneous BOC-deprotection & Amine Purification : Unsymmetrical Sulfamides

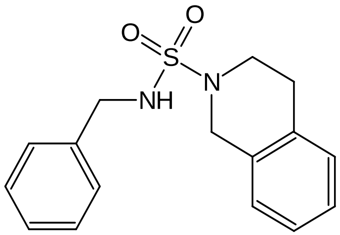
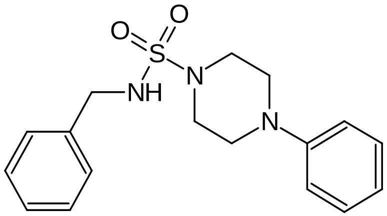
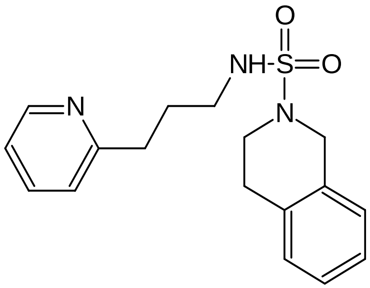


Si bound sulfonic acid, ('SCX2 SCX 3' Materials)

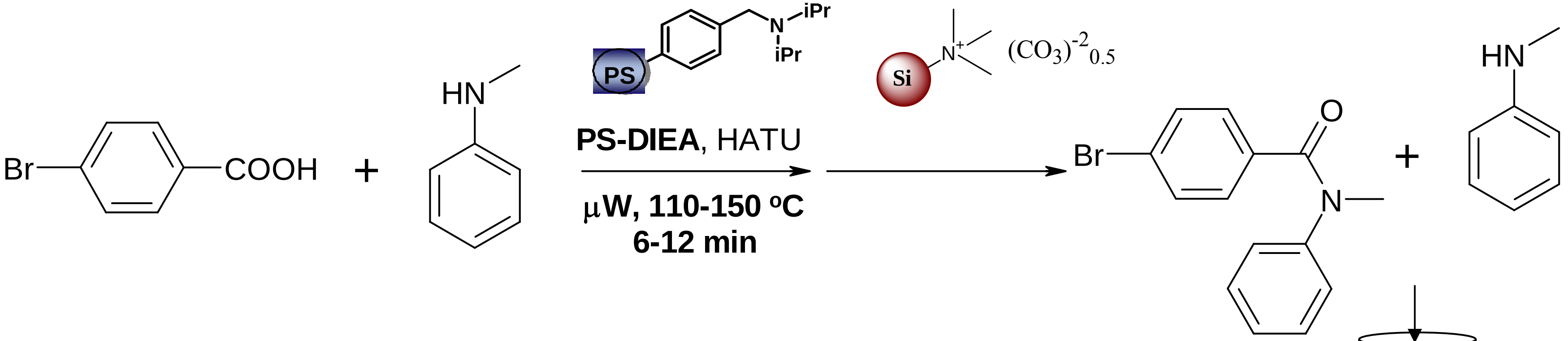
- spontaneously remove BOC- protected amine group
- purify the free amines *via* "Catch & Release" mechanism

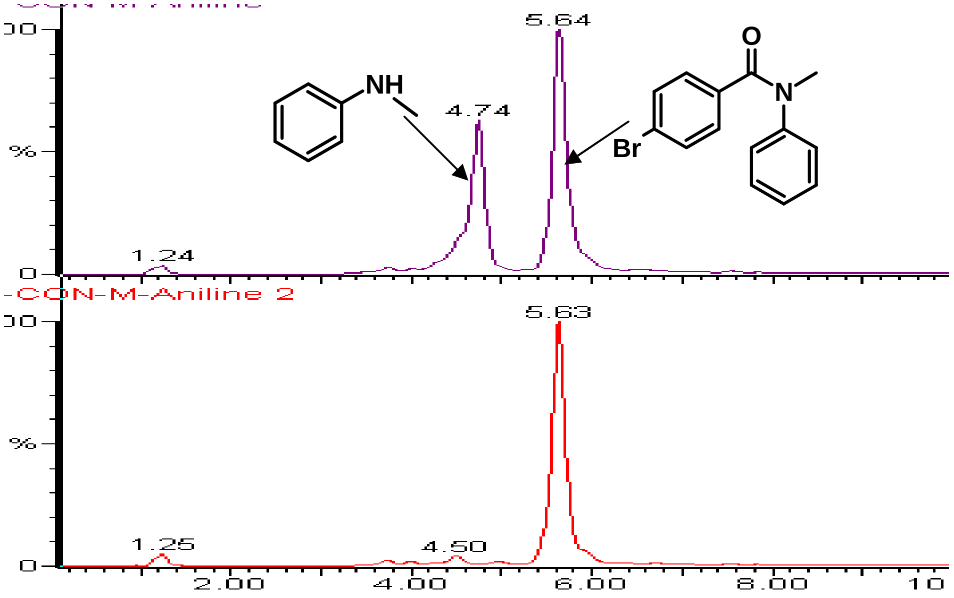
Ghassemi, S. *et al. Molecular Diversity*, **2005**, *9*, 295-299

Unsymmetrical Sulfamides

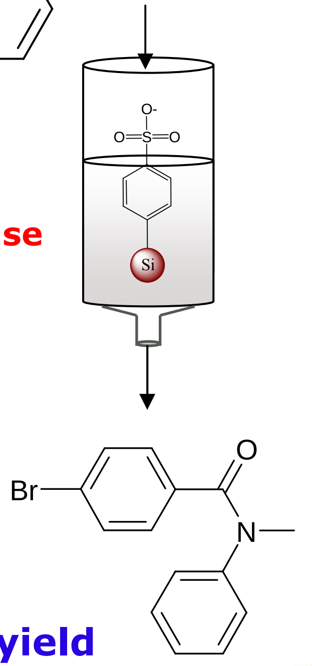
Products	% Isolated Yield	% HPLC Purity
	**72**	**99**
	**92**	**98**
	**89**	**99**

PS-DIEA, Si-Carbonate, Si-TsOH
Rapid Amidation and workup





Catch & Release



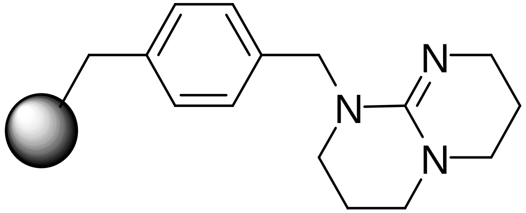
59% yield
97 % Purity

Biotage

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

PS-TBD

- PS-bicyclic guanidine (1,5,7- triazabicyclo[4.4.0]dec-5-ene)



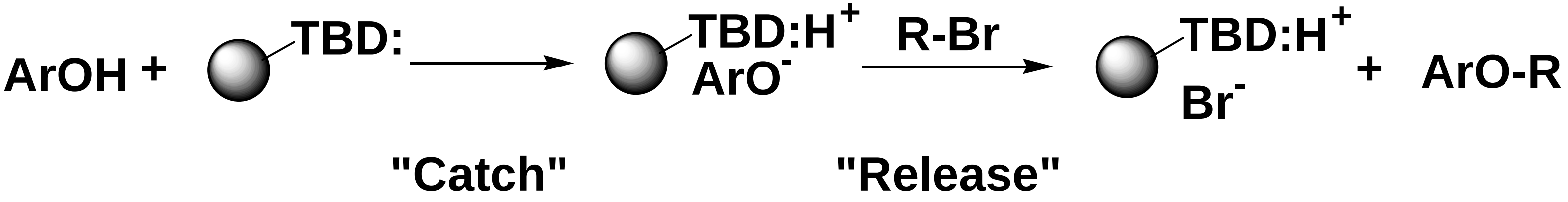
- Stronger base than PS-DIEA, PS-NMM
- Deprotonation of moderately acidic hydrogens, pKa 13-15
- Applications Include:
- Alkylation of phenols, amines, active methylenes
- Esterification of carboxylic acids

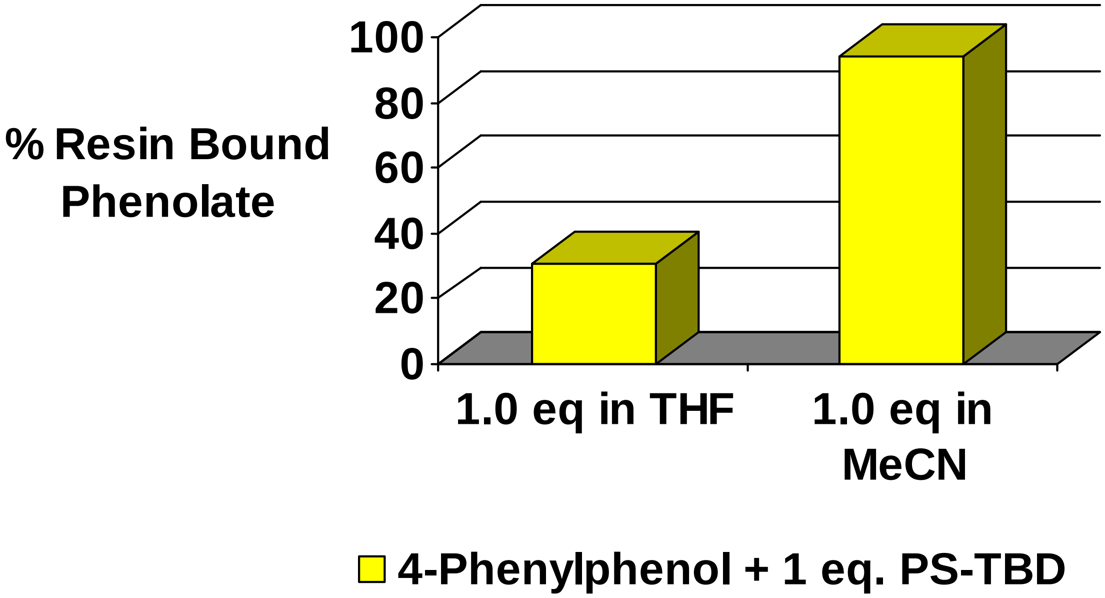
Morrissey, M.; Mohan, R.; Xu, W. Tetrahedron Lett 1997, 38,7337

Organ, M.G.; Dixon, C.E. Biotechnol. Bioeng. (Comb. Chem) 2000, 71, 71-77

PS-TBD

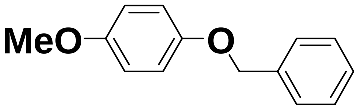
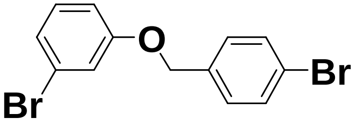
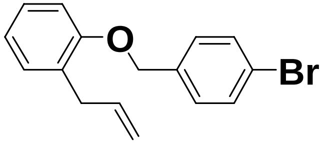
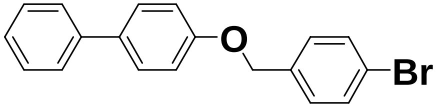
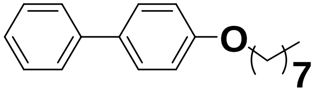
Catch and Release





PS-TBD: Williamson Ether Synthesis

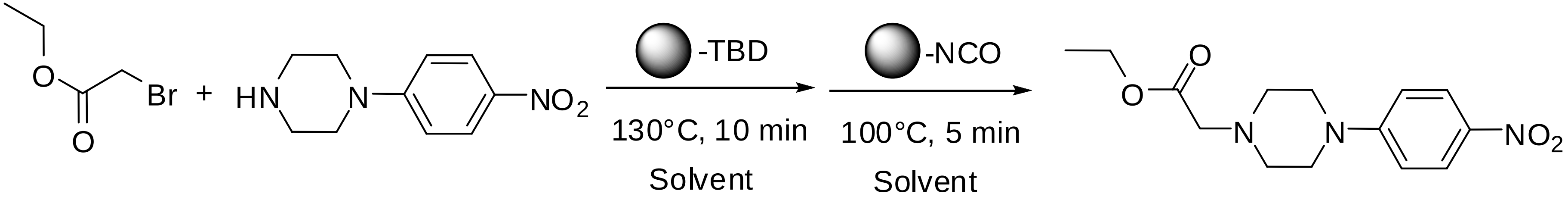
$$\underset{(1.1\ \text{equiv.})}{\text{Ar-OH}} \xrightarrow[\text{ii. RBr (1.0 equiv.)}]{\text{i. PS-TBD (3.0 equiv.)}} \text{ArOR}$$

Product	MeCN 55C, 16 hrs		THF 25C, 16 hrs	
	Purity %	*Yield %*	*Purity %*	*Yield %*
	**100**	**91**	**100**	**90**
	**100**	**90**	**17**	**45**
	**100**	**95**	**89**	**38**
	**100**	**90**	**100**	**77**
	**100**	**85**	**100**	**91**

Original Conditions: See Williamson, A. *Justus Leibigs Ann. Chem*. **1851,** *77*, 37-49, 81, 373.

Resin combinations / Microwaves

PS-TBD, MP-Isocyanate



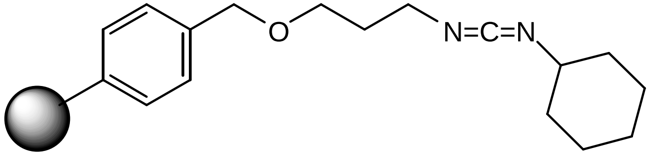
Amine Alkylation

Faster cycle times, enhanced scavenging

Lundin, R. www.biotagepathfinder.com

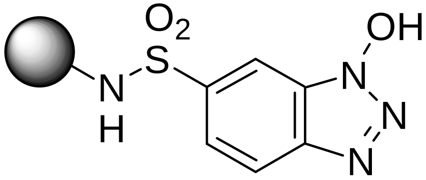
Amide Synthesis: Reagent Comparison

- **PS-Carbodiimide - Coupling Agent**



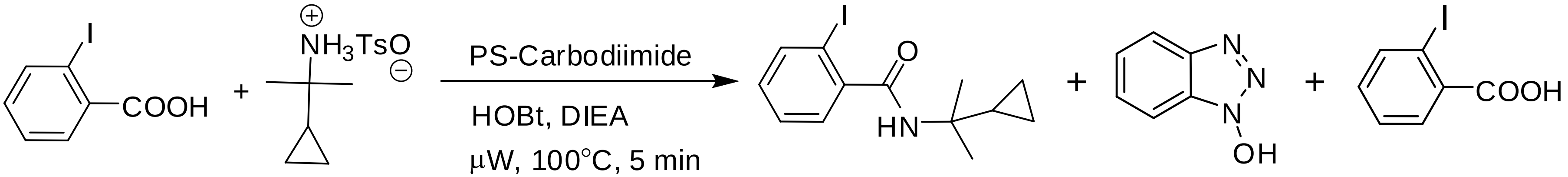
  - One-step amide synthesis
  - Scavenging may be required
  - Rearrangement to acylisourea can be problematic ---Can be solved by addition of HOBt

- **PS-HOBt - Active Esters**

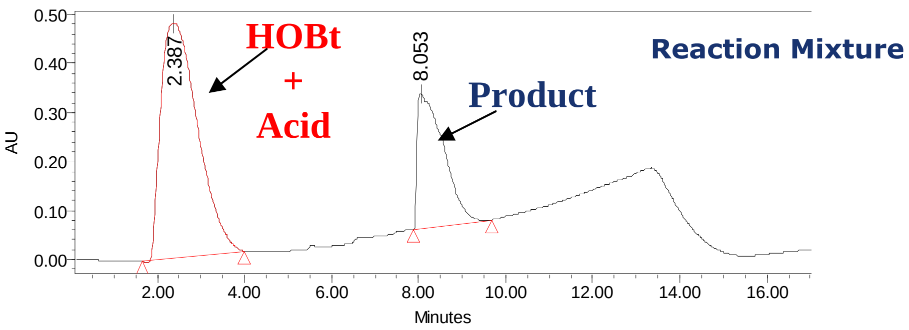


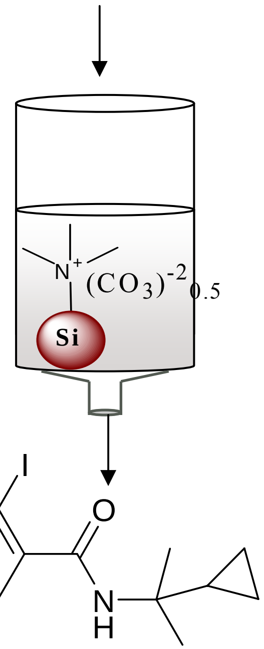
  - Two-step process
  - Amine = limiting reagent in acylation, affords high purity amides
  - Storable reactive intermediate

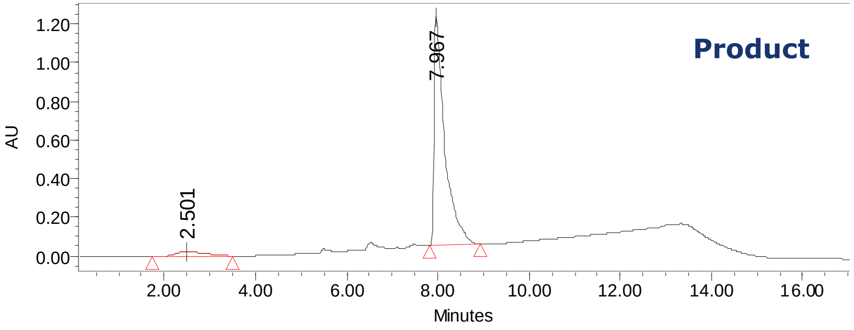
PS-Carbodiimide/ Si-CO_3 Rapid Acylation & Purification



Unreacted acid





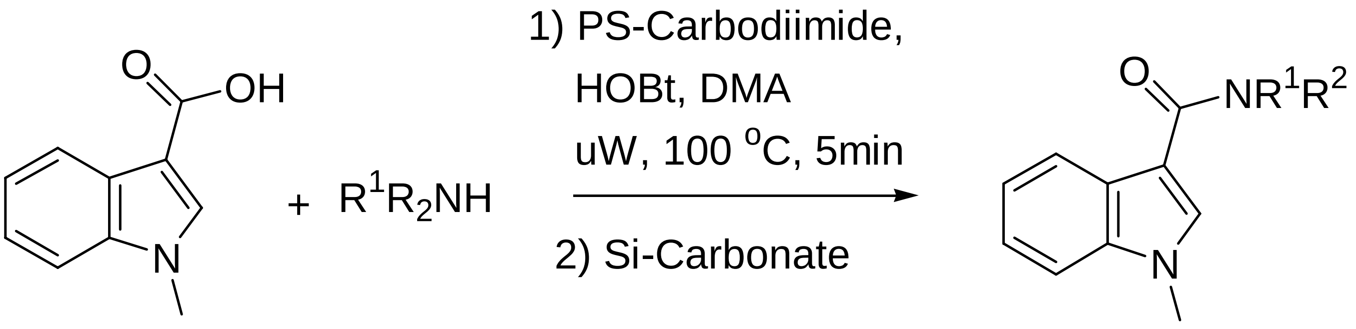


99% yield, 98 % Purity

Synthesis + Purification ~ 10 mins

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

PS-Carbodiimide:Microwave Assisted Synthesis



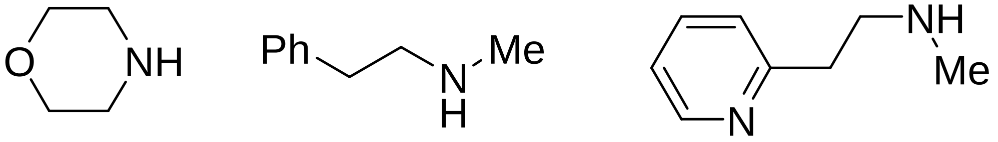
1) PS-Carbodiimide,
HOBt, DMA
uW, 100 °C, 5min

2) Si-Carbonate

98% Yield
98% purity
< 15 min

R^1R_2NH =

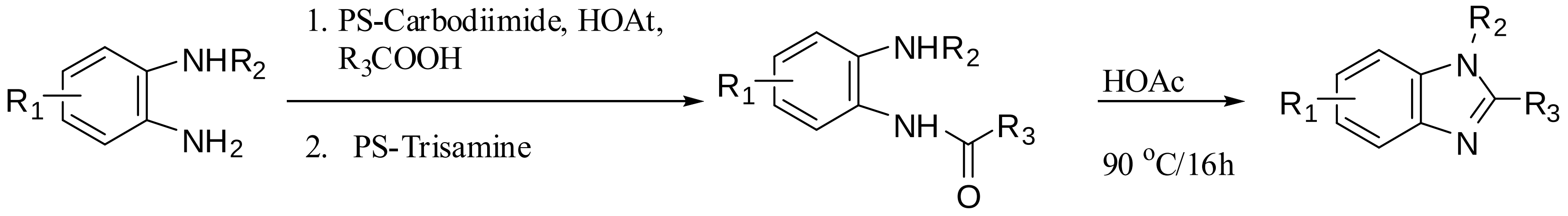
$BnNH_2$



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

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

PS-Carbodiimide for Benzimidazole Synthesis



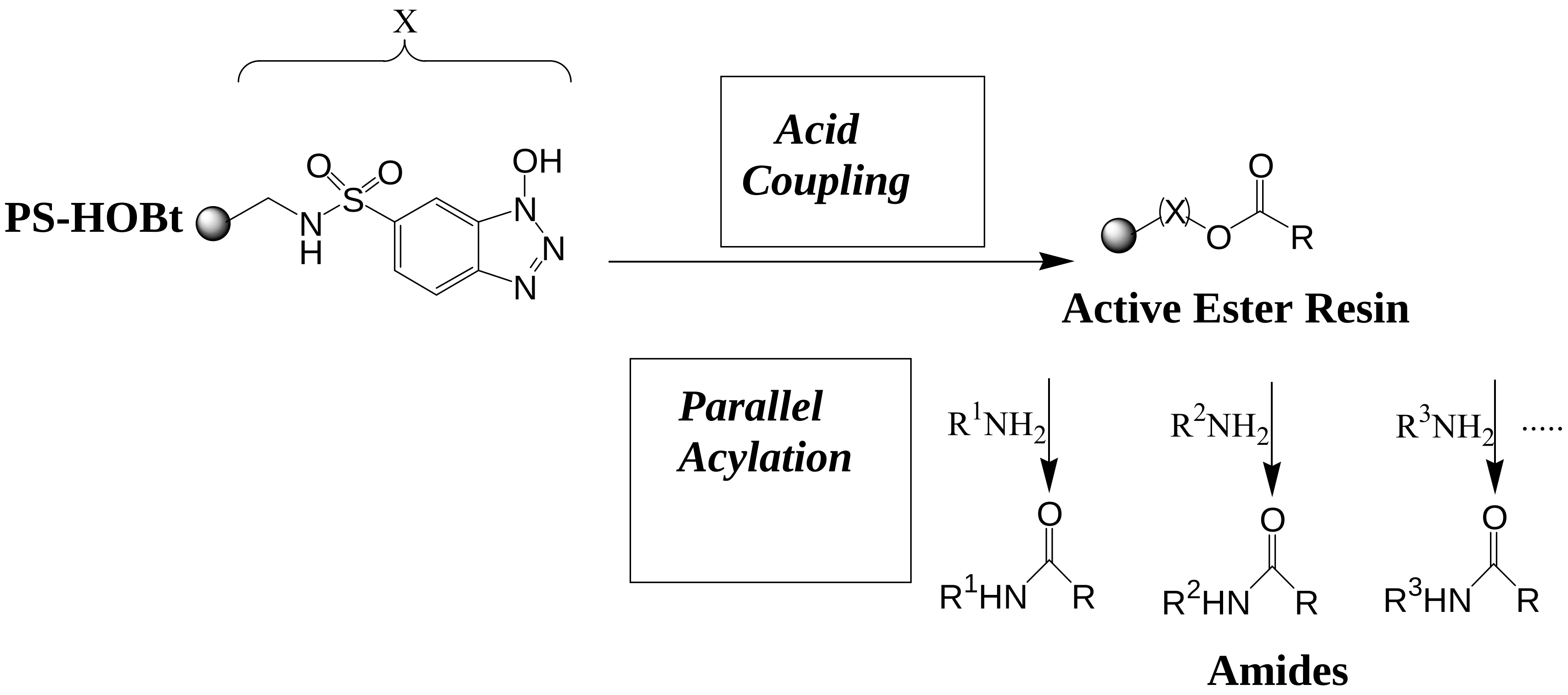
- Applied to selective acylation of diamine
    - Imidates, thioimidates, acyl halides failed
    - HOAt performed better than HOBt
    - 70% conversion with HOBt

- Applied to library of 96 1,2-diarylbenzimidazoles
    - >95% purity for 85% of products

Yun, Y.K.; Porco, J.A.; Labadie, *J. SynLett*. **2002,** *5*, 739-742.

Biotage

Amides From Active Ester Resins



PS-HOBt

Acid Coupling

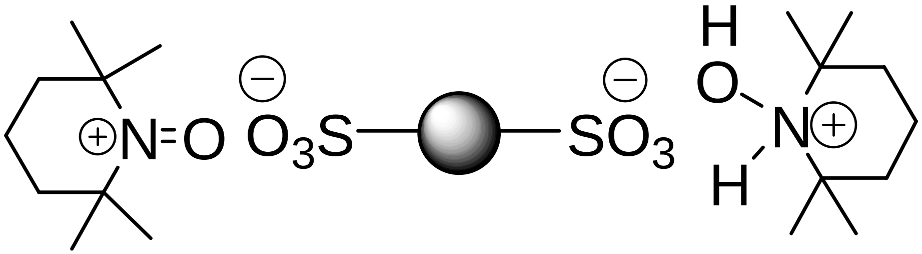
Active Ester Resin

Parallel Acylation

Amides

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

MP-TsO-TEMPO
Bound Oxidizing Agent

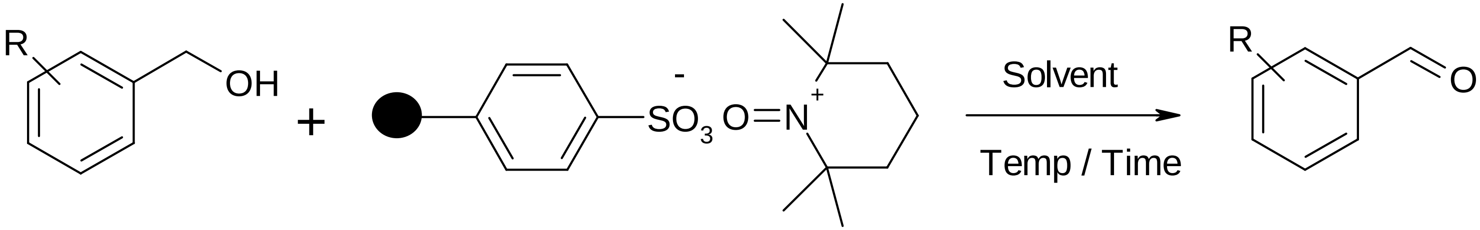


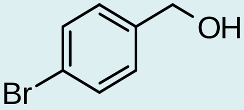
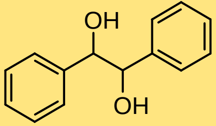
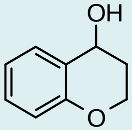
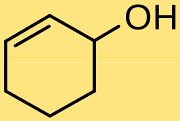
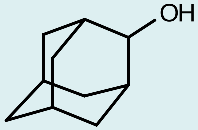
MP-TsO-TEMPO
(As provided)

- 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

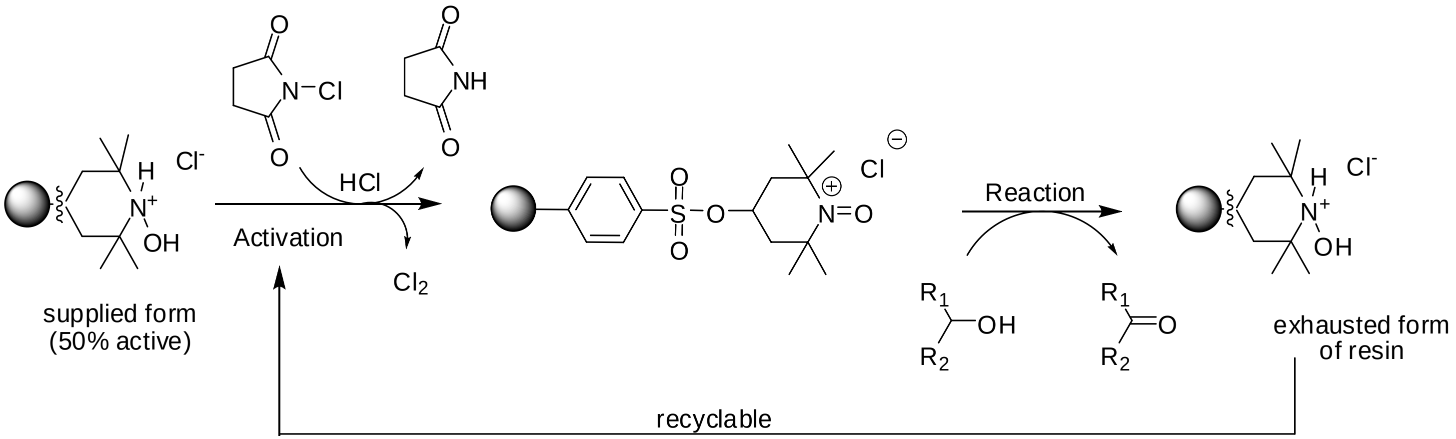


Alcohol	Method	Solvent	Temp	Time	Yield
	Non-μW	CH_3CN	rt	16 h	95 %
	μW	**DCM**	**100 ºC**	**10 min**	**100 %**
	Non-μW	CH_3CN	rt	16 h	99 %
	μW	**DCM**	**60 ºC**	**2 h**	**100 %**
	Non-μW	CH_3CN	rt	16 h	70 %
	μW	**DCM**	**60 ºC**	**5 min**	**93%**
	Non-μW	DCM	rt	16 h	70 %
	μW	**DCM**	**60 ºC**	**1.5 min**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

Lundin, R. *www.biotagepathfinder.com*

PS-TEMPO - pipeline

PS-sulphonic ester linked 2,2,6,6-tetramethylpiperidine-1-oxyl species



Biotage

Pharmaceutical Metal Limits

- Current acceptable limits:

Metal	Concentration (ppm)	
	Oral	Parenteral
Pt, Pd, Ir, Rh, Ru, Os	5	0.5
Mo, V, Ni, Cr	10	1
Cu, Mn	15	1.5
Zn, Fe	20	2

- Permitted limits of metals in API, fine and speciality chemicals will continue to decline

- New technology required to meet this challenge

Biotage

Metal Scavenger Selection Table

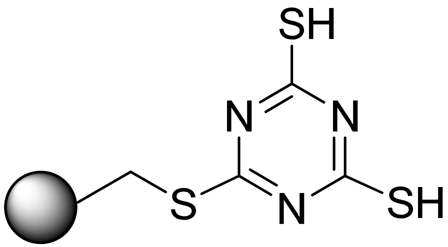
	Catalyst & Solvent							
	$Pd(OAc)_2$	$Pd(OAc)_2$	$(Ph_3P)_2PdCl_2$	$Pd(PPh_3)_4$	$Ru(C_{43}H_{72}Cl_2P_2)$ (Grubbs)	$Rh(PPh_3)_3Cl$	$CuSO_4$	$C_{10}H_{14}NiO_4$
	CH_3CN	DMF:THF (1:1)	DMF:THF (1:1)	$DMF:THF:CH_3CN$ (1:2:1)	DMF:THF (1:1)	DMF:THF (1:1)	DMF	DMF
Media	% scavenged*							
Si-Thiol	100	100	94	100	43	66	99	54
Si-TsOH (SCX3)	100	100	92	100	49	71	97	85
Si-Propylsulfonic acid (SCX2)	100	95	0	100	50	80	100	81
Si-Triamine	100	100	100	100	96	29	100	92
Si-Trisamine	100	100	100	100	90	28	93	91
MP-TMT	100	100	100	100	82	41	0	74
MP-Trisamine	100	100	100	99	93	27	100	91
PS-Thiophenol	0[a]	100	100	100	90	55	95	76
PS-Trisamine	0[a]	100	100	100	95	18	100	94
$PS-NH_2$	0[a]	100	100	99	82	20	64	93
PS-TBD	0[a]	100	100	100	70	44	85	56
PS-DEAM	0[a]	100	55	0	31	32	100	47
$PS-PPh_3$	0[a]	100	100	98	84	41	97	3

* % Catalyst scavenged from 6mL of 1000ppm catalyst solution by 0.5g media when stirred for 2 h at room temperature

[a] PS-based resins require swelling solvents for activity. No scavenging was observed in CH3CN, due to lack of swelling whereas 100% scavenging was observed in DMF-THF(1:1).

Biotage

MP-TMT – Palladium Scavenger

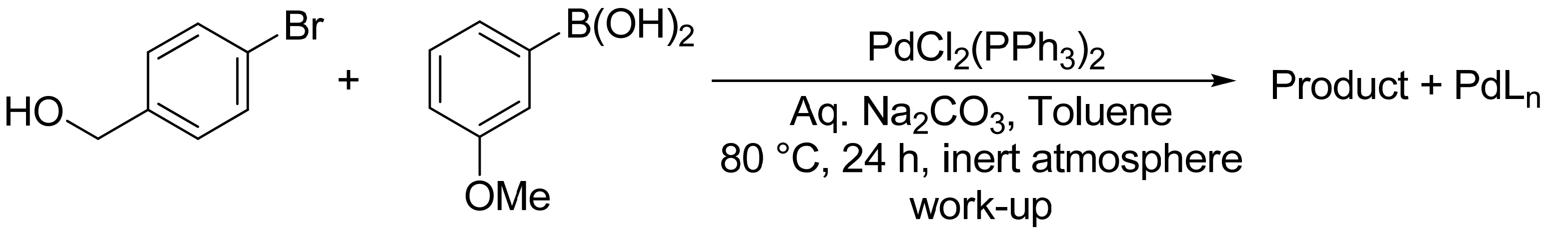


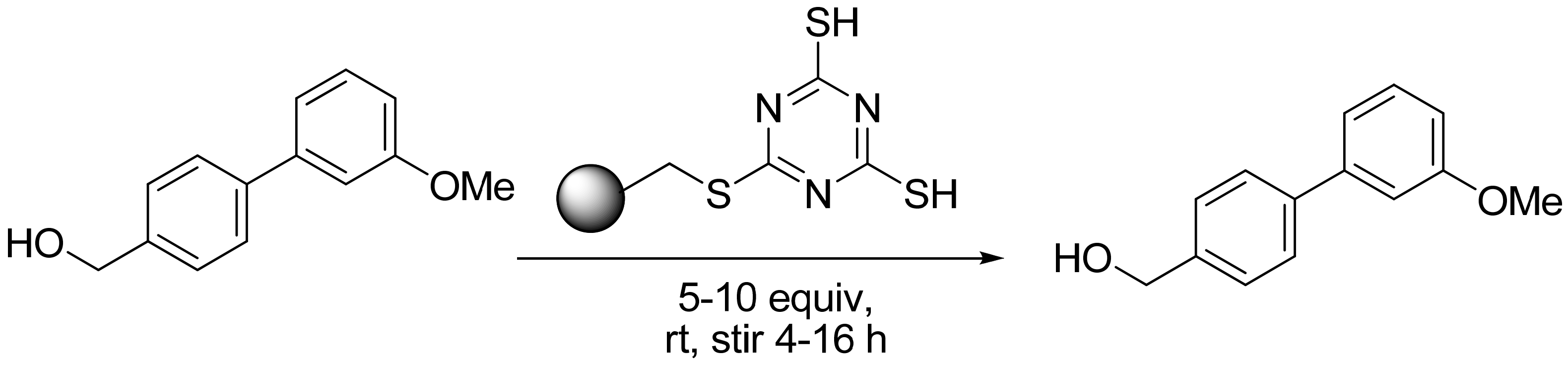
Macroporous polystyrene-2,4,6-trimercaptotriazine

- 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

Biotage

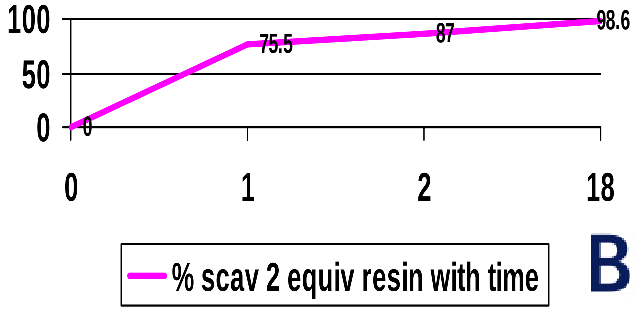
Palladium Scavenging: Advances





33400 PPM Pd (ICP)

<190 PPM Pd (ICP)



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

Merck metal scavenger screen results

Merck-Rahway screened 30-different scavengers for a palladium-catalyst removal process. Merck picked Biotage MP-TMT as the clear winner for this application

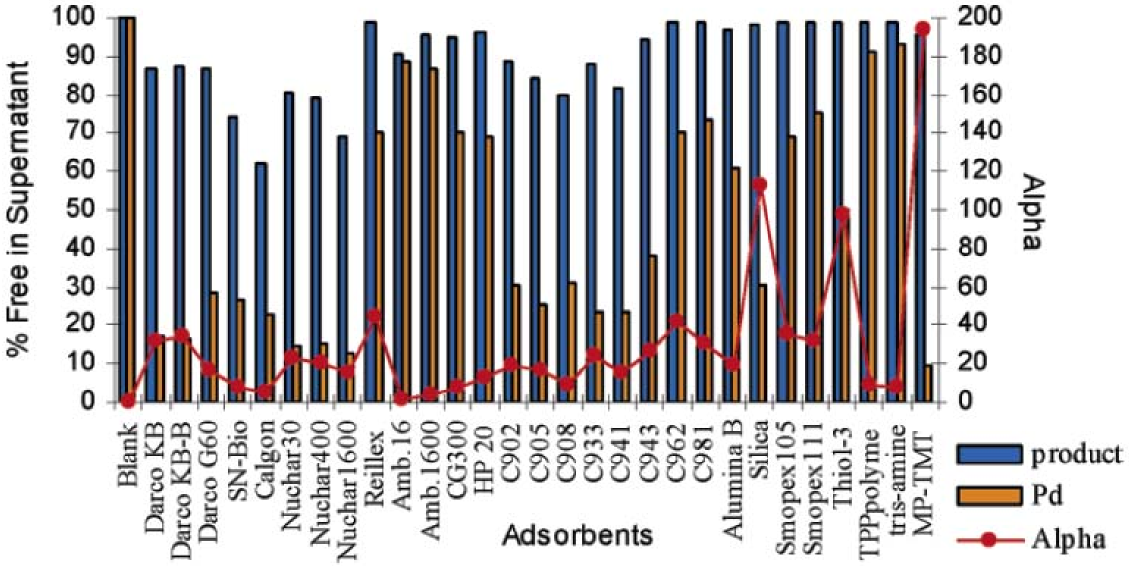
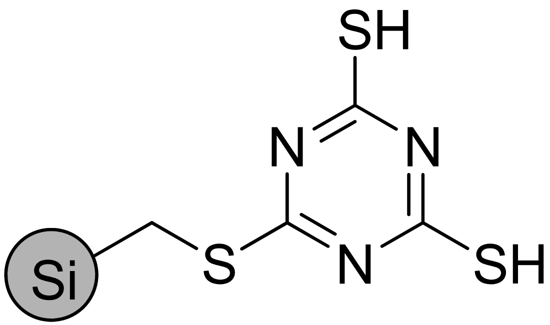


Figure 6. **Selective removal of palladium from the process stream coming from workup of Suzuki−Miyaura biaryl coupling reaction. Adsorbent screening conducted at 50 wt % loading.**

Alpha is the ratio of metal removed divided by the ratio of product lost.
High Alpha is strongly preferred solution, with low levels of metal and high yield of product

Welch, C.; *OPRD*, **2005**, *9*, 198-205

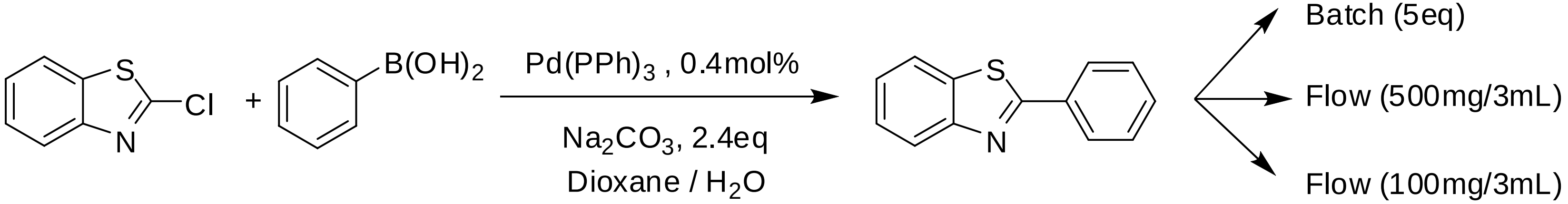
NEW: ISOLUTE® Si-TMT



- Typical capacity 0.3 mmol/g
- Ultrapure analytical grade silica backbone
- Chemically stable
- Reduces Pd residues to the lower ppm levels
- Available in multikilo quantities

Si-TMT initial chemical application work

Si-TMT : Synthesis of Benzothiazoles



	Batch Studies 5eq media	Flow (cartridge) scavenging 500mg/3mL	 100mg/3mL
Si-Thiol (Biotage)	91%	86%	45%
Si-Thiol (competitor)	82%	91%	45%
Si-TMT (Biotage)	>99%	>99%	95%

S.Rana, Unpublished Results, Biotage 2008,

Method as per: Heo,Y.; Song, Y.S.; Kim, B.T.; Heo, J. Tetrahedron Lett. 47 (2006), 3091-3094

How should I decide which backbone to use?

The choice of backbone depends on what best fits the workflow.

MP-polymers	Si-reagents
Do not swell	Do not swell
200-300 Å size particles	60 Å size particles
Wide range of solvents	Wide range of solvent
Low loading	Low loading
Ideal for batch mode	Ideal for filtration
More expensive	Less expensive

Biotage

Summary: Biotage Metal Scavengers

- Biotage metal scavengers remove transition metals to levels approved by FDA guidelines prior to clinical trials
- Biotage offers both silica and polymer based metal scavengers for both filtration and batch processing
- MP-TMT, Si-Thiol and Si-TMT are available in multi-kilo quantities
  - At cost effective prices
  - Within a few weeks of order
- TSE certified

Biotage