Microwave-Assisted Synthesis Utilizing Supported Reagents: Rapid & Versatile Synthesis of Pharmaceutically Relevant Molecules

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Outline

(i) High Speed Celebrex® Analogue Synthesis

(ii) Evaluation of Encapsulated Pd Catalysts

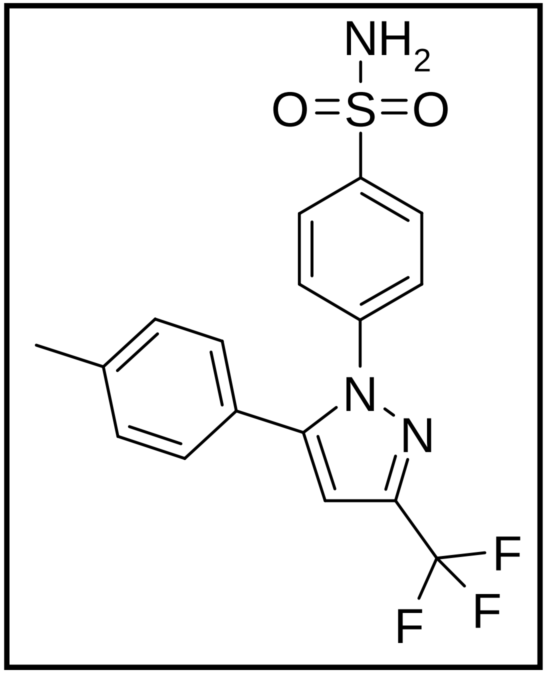
(iii) Project A – Utilization of Silica-Based Reagents For Piperidine Elaborations

(iv) Project B – Elaboration of 2-Chloro pyridines

Introduction to Celebrex®

Arthritis currently affects >43 million people with symptoms such as pain, inflammation and stiffness in the joints.

Celebrex® is the first COX-2 specific inhibitor approved for treating a broad range of painful conditions such as osteoarthritis, rheumatoid arthritis and acute pain.

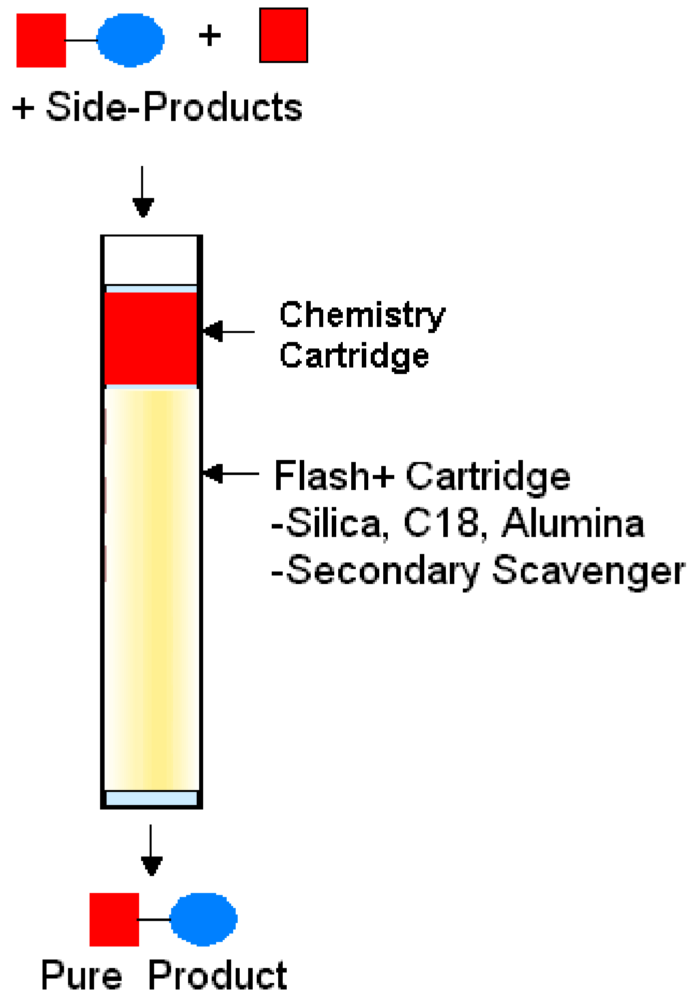


Silica-Based Reagents & Samplets

Samplets

Si-Based Scavengers — Si-TsOH

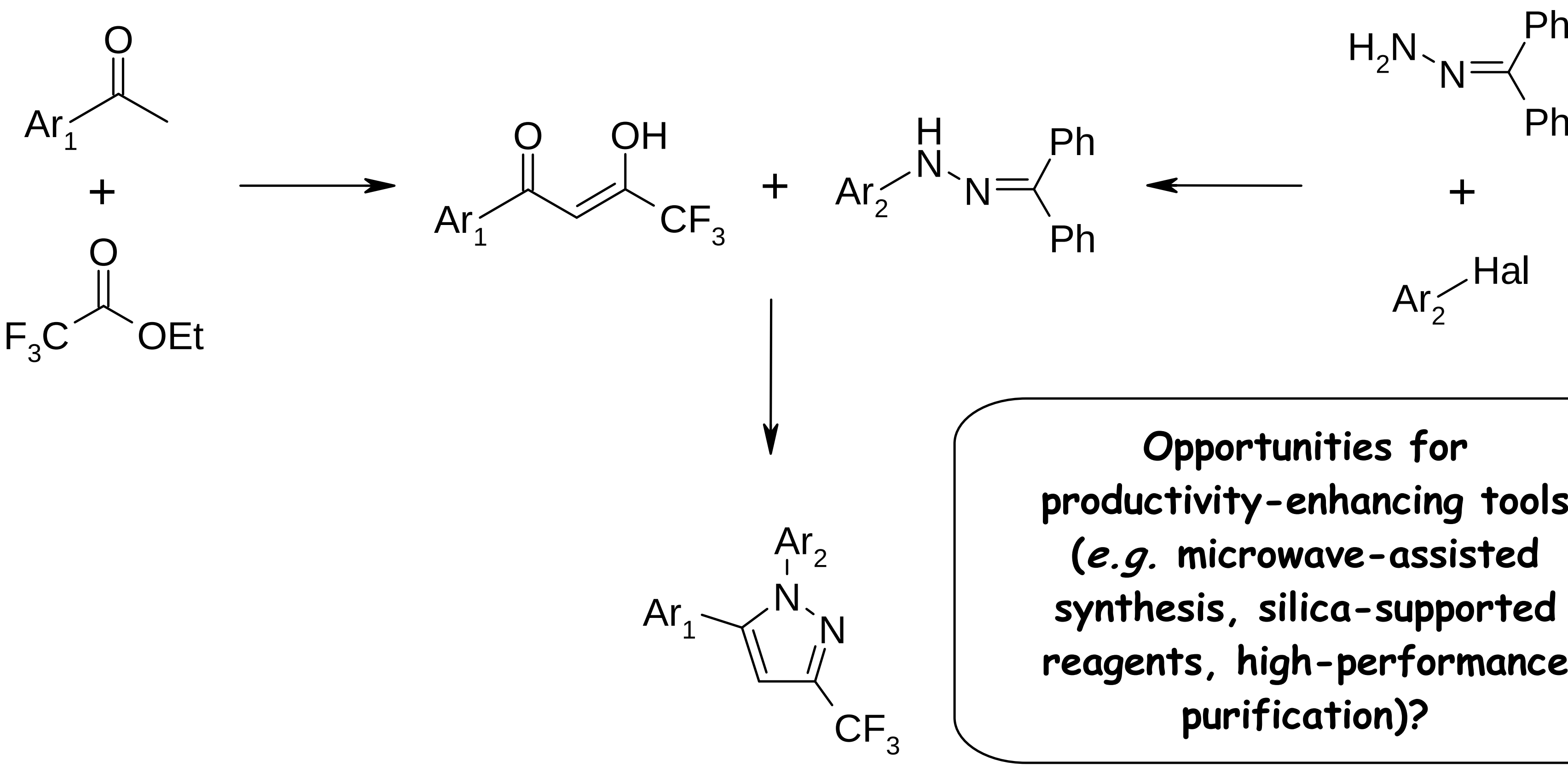
- Uniform particle size distribution facilitates filtration and bed stability.
- Thermally Stable - compatible with microwave synthesis.
- High surface area improves capacity and reactivity.



Catch and Release Method

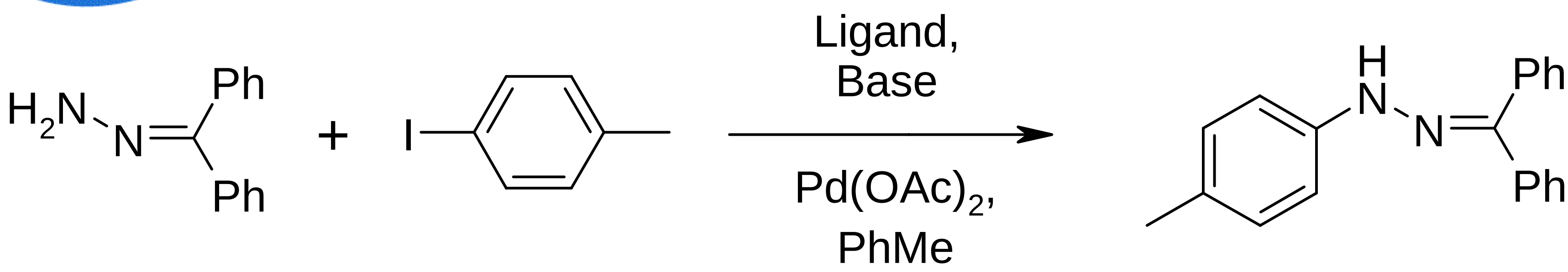
- Retain product.
- Retain impurities.

Synthesis of Celebrex® Analogues



Opportunities for productivity-enhancing tools (*e.g.* microwave-assisted synthesis, silica-supported reagents, high-performance purification)?

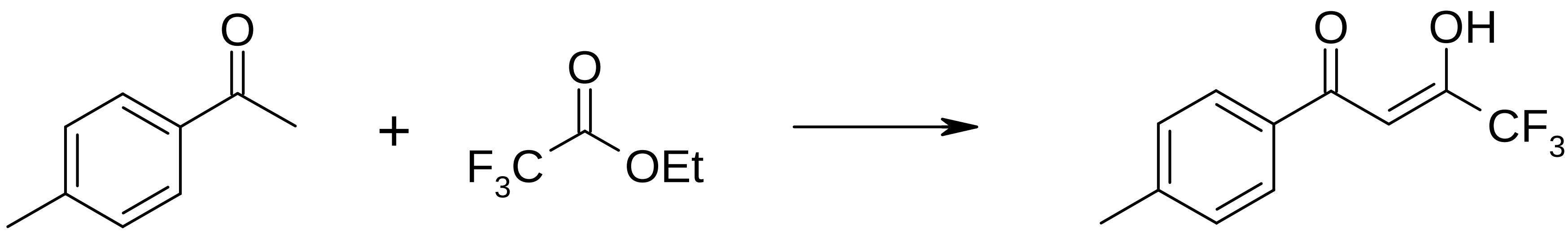
Aryl Amination Optimization



Ligand	Base	Conditions			Product Results
		Method	Temp (°C)	Time	
DPPF	NaO^{t}Bu	Thermal	100	4 hrs	40%
DPPF	NaO^{t}Bu	Microwave	170	3 hrs	No Product
DPPF	Cs_2CO_3	Microwave	170	40 min	No Product
BINAP	NaO^{t}Bu	Microwave	170	4 hrs	45%
HBF_4-P(^{t}Bu)$_3$	**NaO^{t}Bu**	**Microwave**	**170**	**30 min**	**45%**
HBF_4-P(^{t}Bu)$_3$	Cs_2CO_3	Microwave	170	10 min	43%
HBF_4-P(^{t}Bu)$_3$	NaO^{t}Bu	Thermal	100	24 hrs	No Product
HBF_4-P(^{t}Bu)$_3$	**Cs_2CO_3**	**Thermal**	**100**	**8 hrs**	**65%**

Hartwig, J. F. *et al. Angew. Chem. Int. Ed.* **1998**, *37*, 2090.
Buchwald, S. L. *et al. Acc. Chem. Res.* **1998**, *31*, 805.

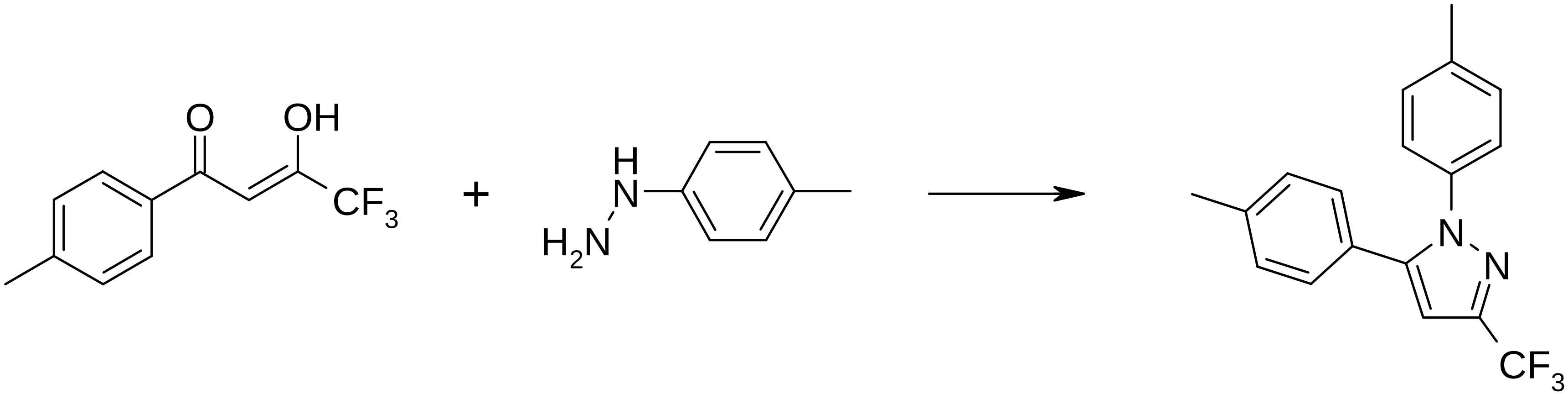
Enolate Reaction Optimization



Base	Solvent	Conditions			Yield (%)
		Method	Temp (°C)	Time	
25% NaOMe	MTBE	Thermal	25	14 hrs	25
NaH (60% in oil)	**DMF**	**Thermal**	**25**	**5 days**	**88**
NaH (60% in oil)	DME	Thermal	100	2 hrs	60
NaH (60% in oil)	**DME**	**Microwave**	**160**	**10 min**	**95**

Penning, T.D. *et al. J. Med. Chem.* **1997**, *40*, 1347.

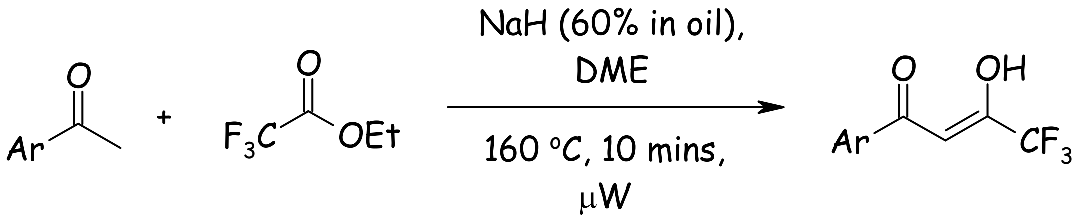
Cyclization Reaction Optimization

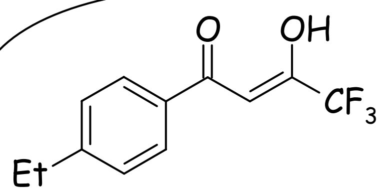


Acid	Conditions			Yield (%)
	Method	Temp (°C)	Time	
p-TsOH	**Thermal**	**100**	**7 hrs**	**95**
	Microwave	160	5 min	61
Loose Si-TsOH	Thermal	100	6 hrs	84
	Microwave	**160**	**5 min**	**95**
Samplet Si-TsOH	Oven	110	64 hrs	38

Penning, T.D. *et al. J. Med. Chem.* **1997**, *40*, 1347.

Parallel Enolate Reactions





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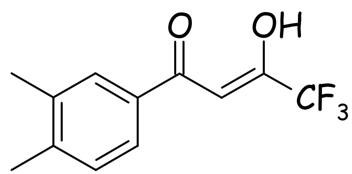

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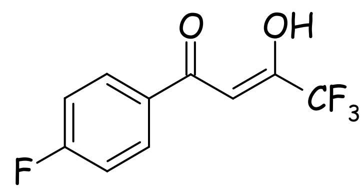

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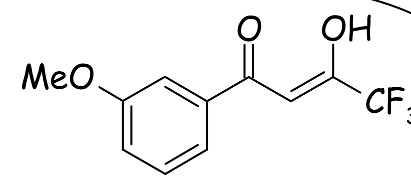

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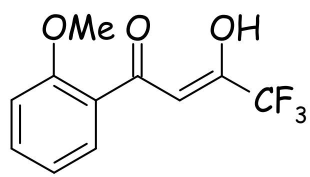

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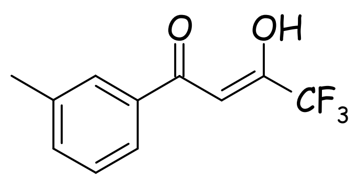

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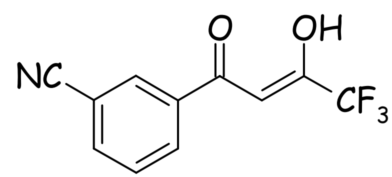

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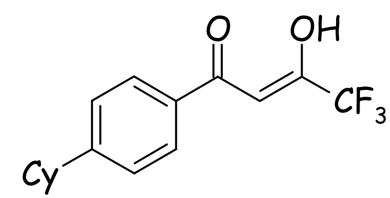

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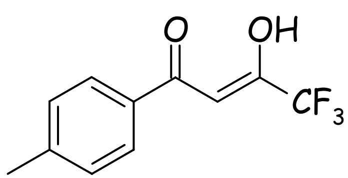

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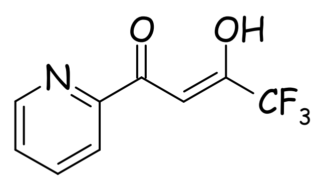

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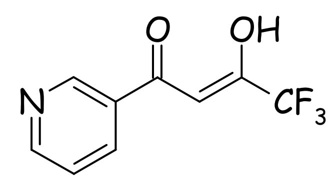

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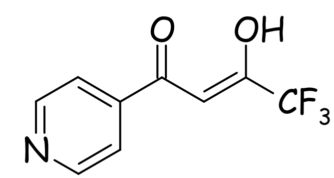

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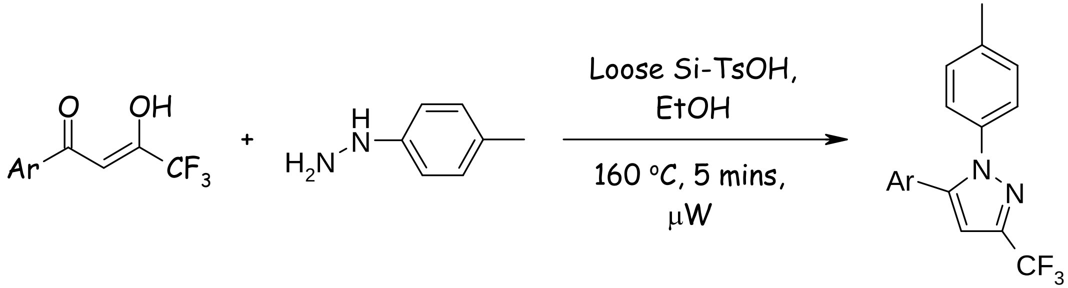
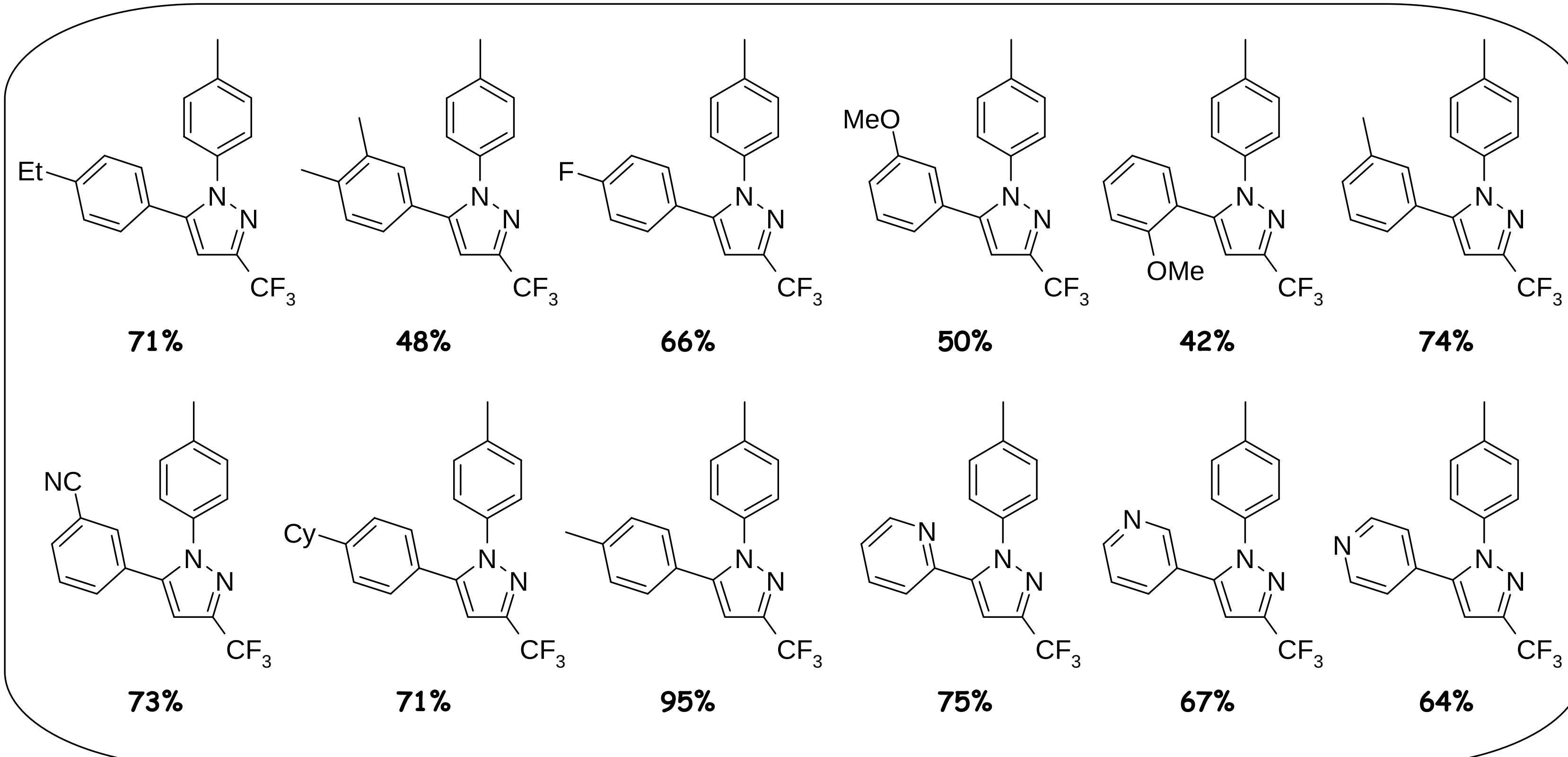
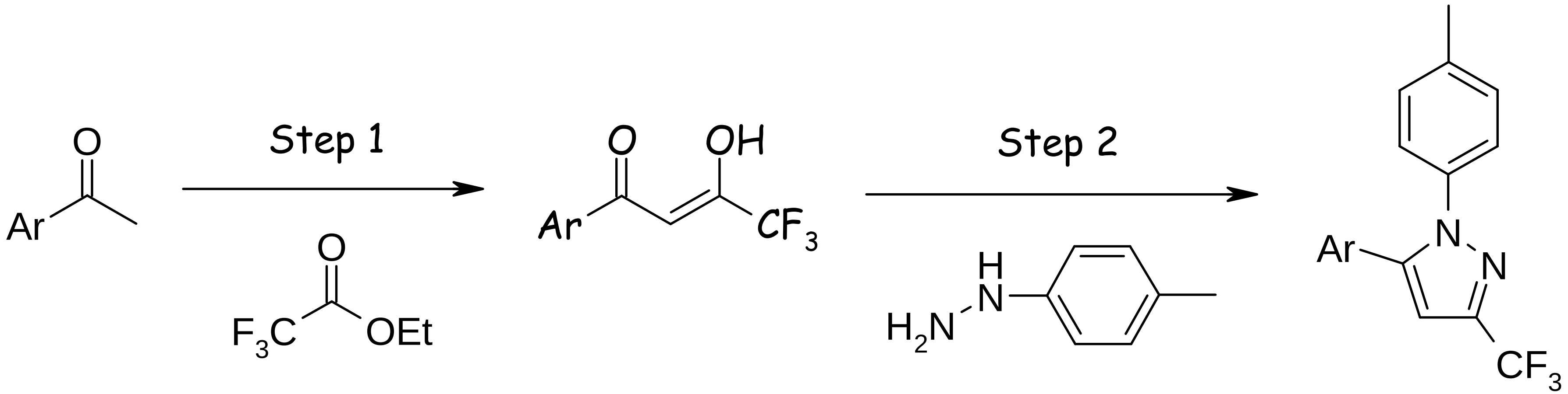
Parallel Cyclization Reactions





Conclusion



	Microwave Assisted Synthesis			Conventional Synthesis		
	Temp (°C)	Time	Yield (%)	Temp (°C)	Time	Yield (%)
Step 1	160	10 min	95	100	2 hrs	60
Step 2 (Loose Si-TsOH)	160	5 min	95	100	7 hrs	84
Total	**----**	**15 min**	**90**	**----**	**9 hrs**	**50**

Humphries, P. S. *et al.* *Tet. Lett.* **2006**, *47*, 2443.

Introduction to Encapsulated Pd

Encapsulated Pd:-

- Use of microencapsulation technology to immobilize Pd, optionally with activating ligands, within a highly crosslinked polyurea matrix. The catalytic activity of Pd is accessed through the porous matrix, thereby leaving the Pd captured within it.

Key Advantages of Encapsulated Pd:-

- Low residual metal levels in final crude product (typically < 10ppm before purification).
- Easy recovery of catalysts by filtration and catalyst recycle.
- Safer and easier to handle than Pd/C for hydrogenation reactions.
- Compatibility with a wide range of process technology options, *e.g.*, fixed bed, fluidized bed, trickle bed, and microwave reactors.

Ley, S. V. *et al. Chem. Commun.* **2002**, 1132.
Pears, D. A.; Smith, S. C. *Aldrich. Acta*, **2005**, 38, 23.

Encapsulated Pd Products

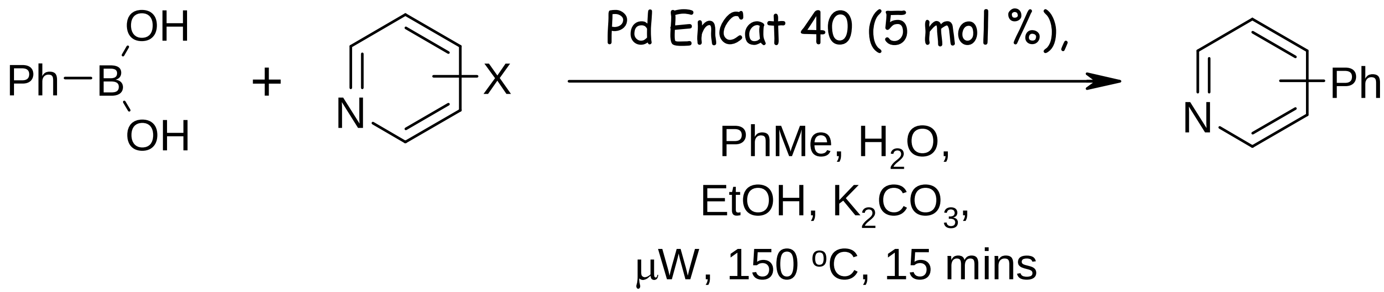
Pd EnCat 40: (0.4 mmol/g) palladium acetate, microencapsulated in polyurea matrix.

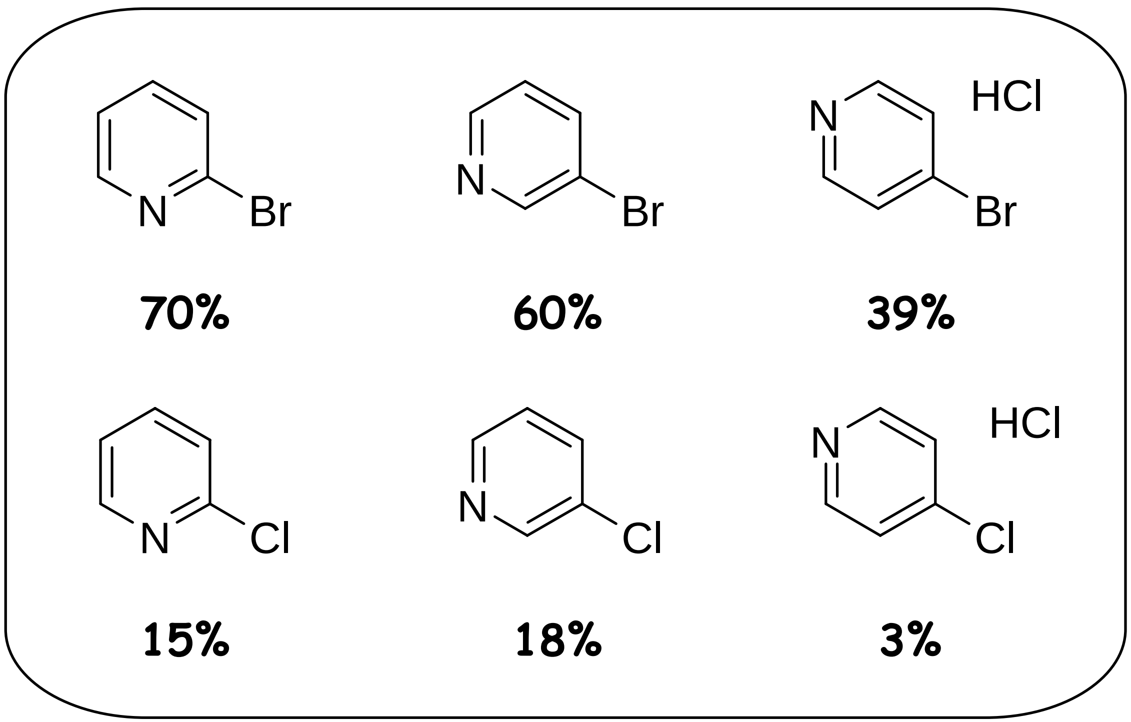
Pd EnCat 30: (0.4 mmol/g) palladium acetate, microencapsulated in polyurea matrix. More porous version of Pd EnCat™ 40 with improved accessibility for substrates.

Pd EnCat TPP30: (0.4 mmol/g) palladium acetate & triphenyl phosphine, microencapsulated in polyurea matrix at 1/0.8 Pd/TPP.

Pd EnCat TOTP30: (0.4 mmol/g) palladium acetate & tri-*o*-tolylphosphine, microencapsulated in polyurea matrix at 1/0.5 Pd/TOTP.

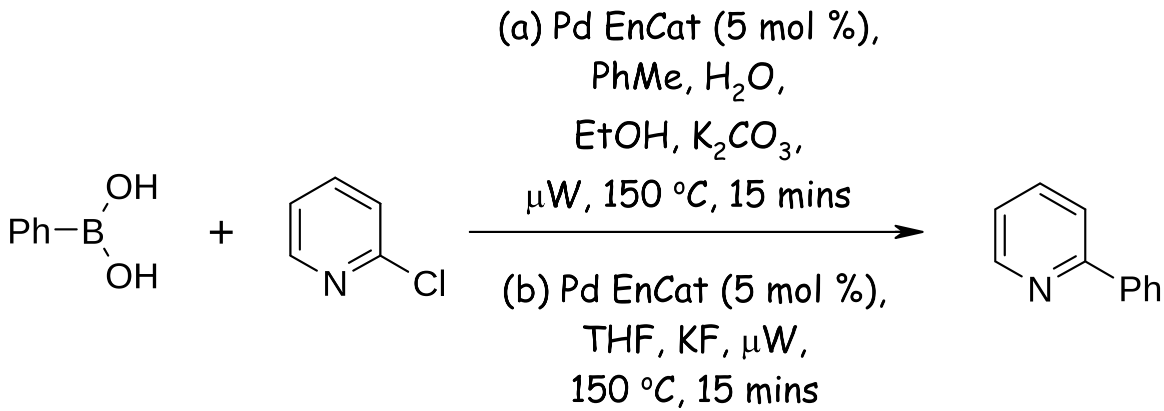
Initial Suzuki Couplings





Ley, S. V. *et al. Chem. Commun.* **2002**, 1132.

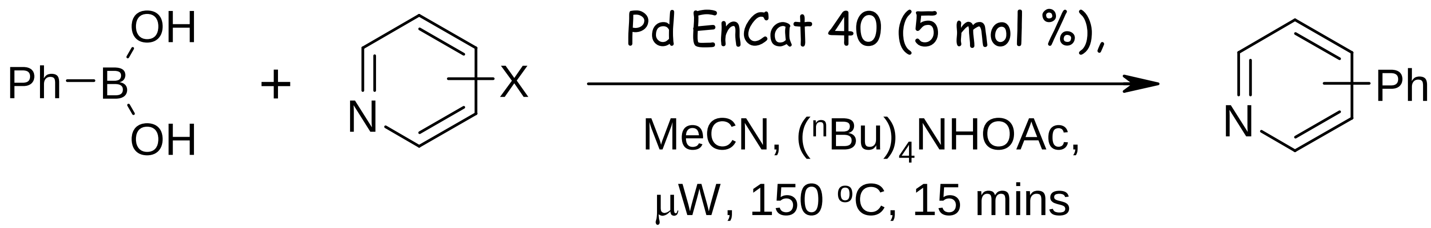
Exploration of EnCats & Ligands

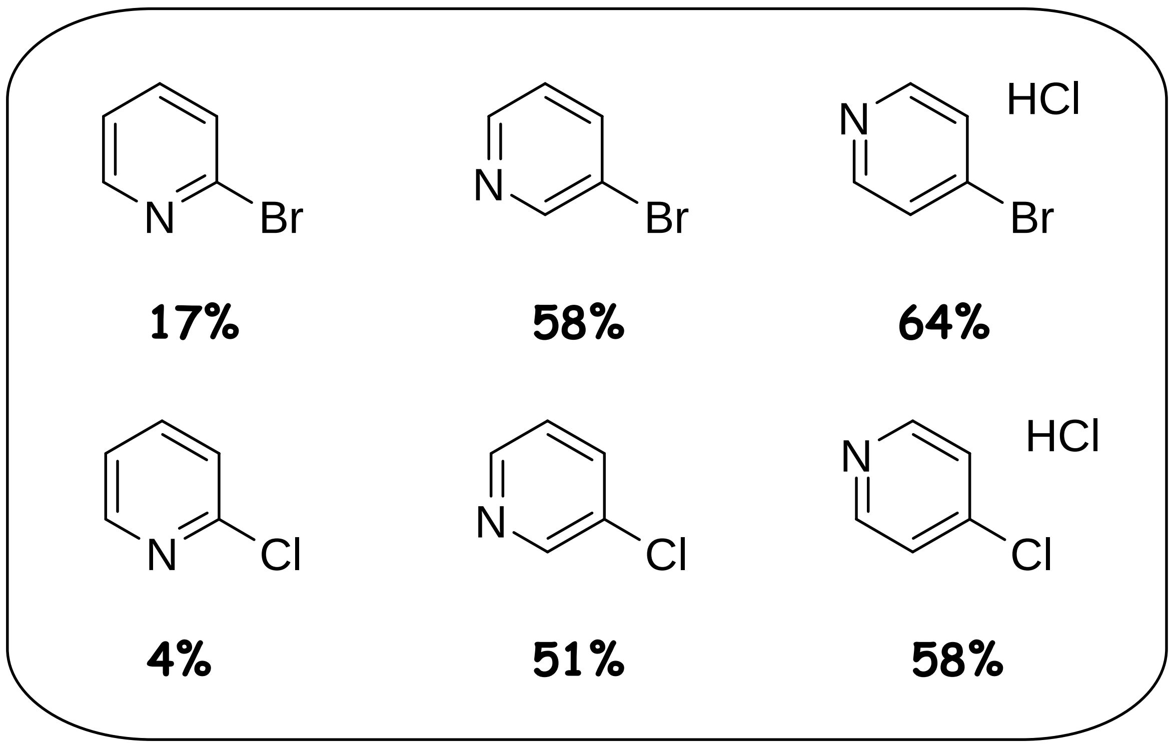


Reaction Conditions	Catalyst	Yield (%)
a	Pd EnCat 40	12
a	Pd EnCat 30	8
a	Pd EnCat TPP30	12
a	Pd EnCat TOTP30	7
b*	Pd EnCat 40 + $[(^tBu)_3PH]BF_4$	8
b*	Pd EnCat 30 + $[(^tBu)_3PH]BF_4$	11

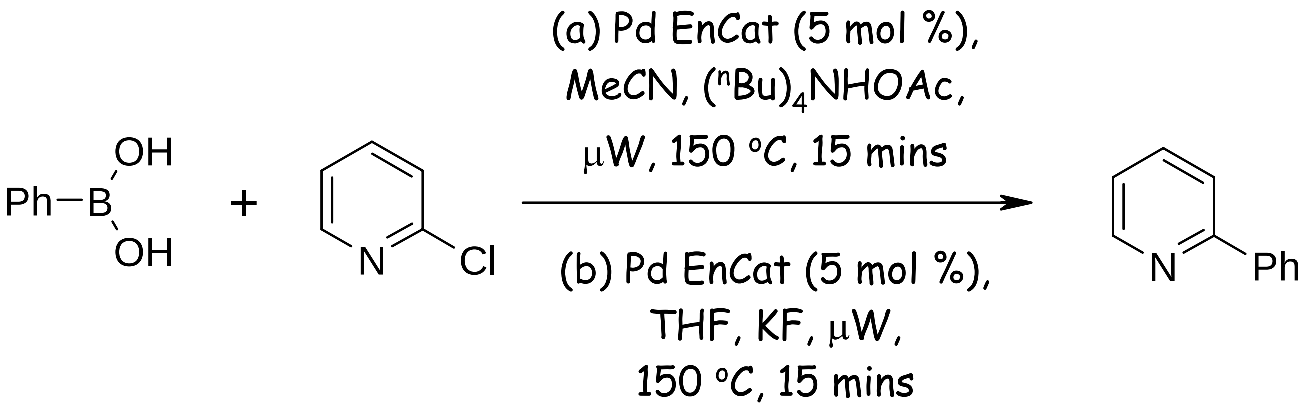
*Fu, G. C. *et al. Org. Lett.* **2001**, 3, 4295.

Improved Conditions?





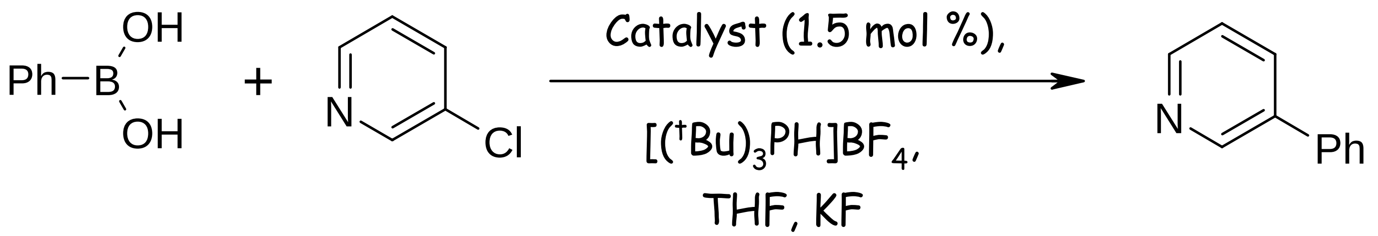
Further Exploration of EnCats & Ligands



Reaction Conditions	Catalyst	Yield (%)
a	**Pd EnCat 40**	**51**
a	Pd EnCat 30	20
a	Pd EnCat TPP30	29
a	Pd EnCat TOTP30	6
b*	Pd EnCat 40 + [(^{t}Bu)$_3$PH]BF$_4$	26
b*	Pd EnCat 30 + [(^{t}Bu)$_3$PH]BF$_4$	32

*Fu, G. C. *et al. Org. Lett.* **2001**, 3, 4295.

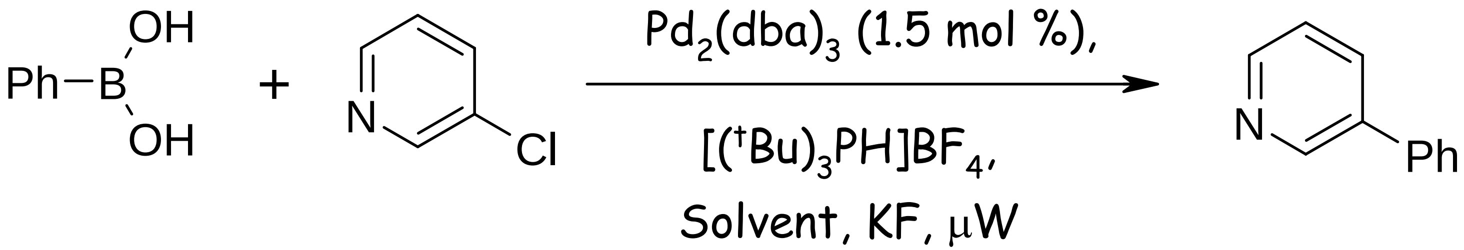
Pd EnCat vs Conventional Pd Catalysts



Temp (°C)	Catalyst	Time (hrs)	Yield (%)
50	$Pd_2(dba)_3$	70	68
50 -> 75	Pd EnCat 40	94	29

Fu, *G. C. et al. Org. Lett.* **2001**, 3, 4295.

Microwave Irradiation Improvements



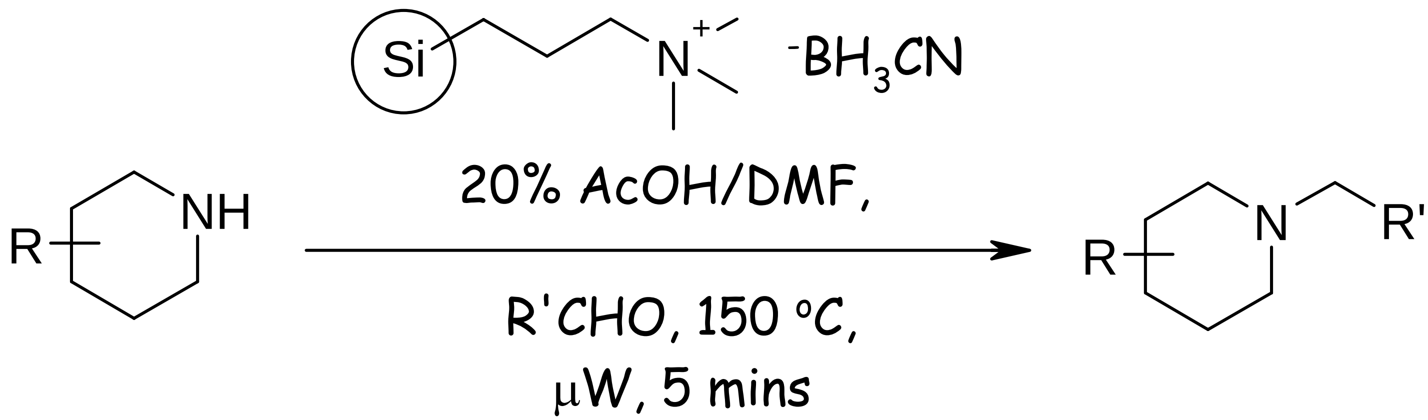
Temp (°C)	Solvent	Time (mins)	Yield (%)
100	**THF**	**15**	**100**
150	THF	5	51
150	MeCN	15	91
150	**MeCN**	**5**	**100**

Fu, *G. C. et al. Org. Lett.* **2001**, 3, 4295.

Conclusion

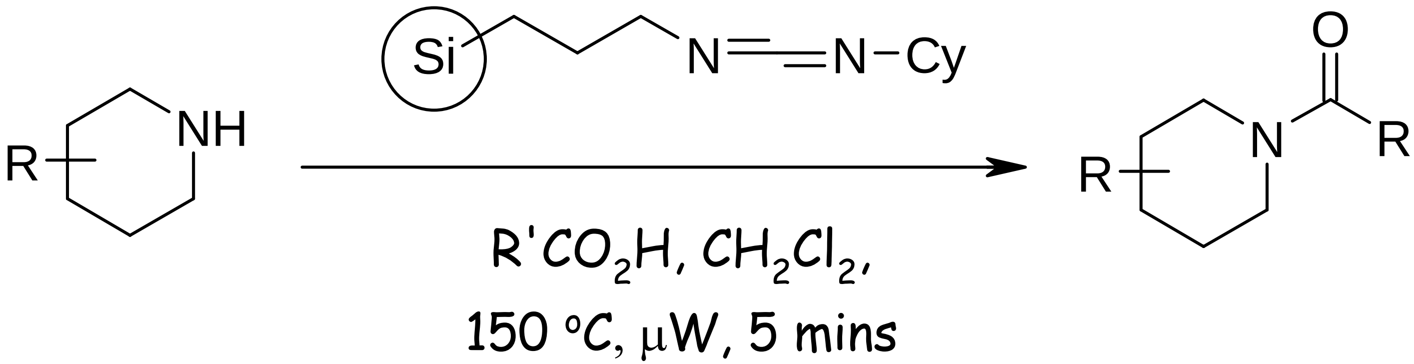
- Heterocyclic Suzuki, Heck & Sonogashira (results not shown) couplings using Pd EnCat catalysts occurred with significantly reduced yields when compared to traditional catalysts.
- Application of microwave irradiation using $Pd_2(dba)_3$ + $[(^tBu)_3PH]BF_4$ (Fu's Salt) significantly reduced reaction time (70h $\rightarrow$ 5 min) of the Suzuki coupling reaction.

Silica-bound cyanoborohydride-mediated reductive aminations



- Performed small array of analogues utilizing robot handler on Biotage Initiator 60.
- Utilized pre-weighed (from ASDI) aldehydes, supplied directly in μW vial.
- Dispensed template & solvent utilizing Tecan automated liquid handler.
- SPE "catch & release" treatment (utilizing SCX cartridges) of crude mixtures allowed for enhanced purification success & avoided LLE.

Silica-bound carbodiimide-mediated amide bond formations



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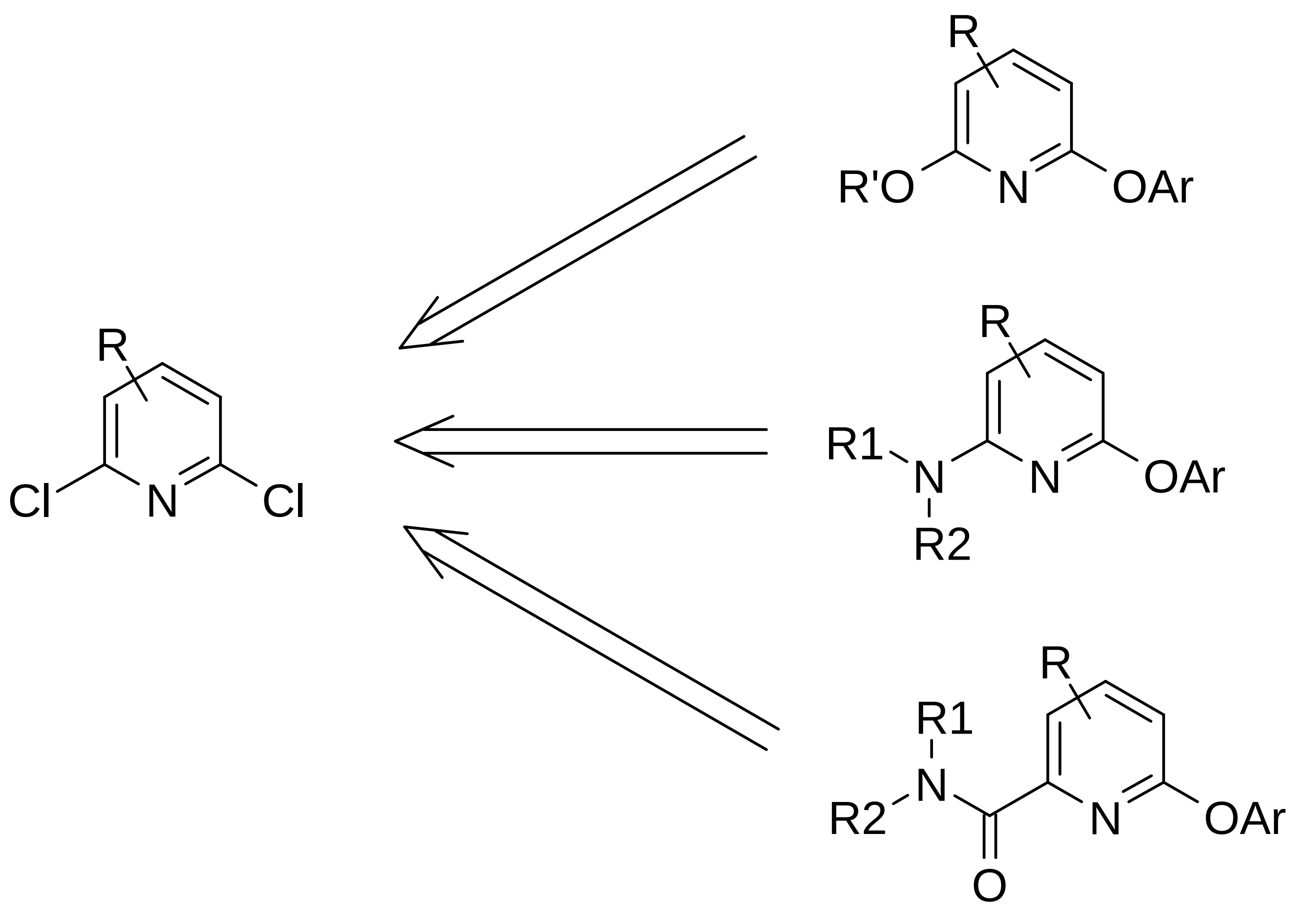
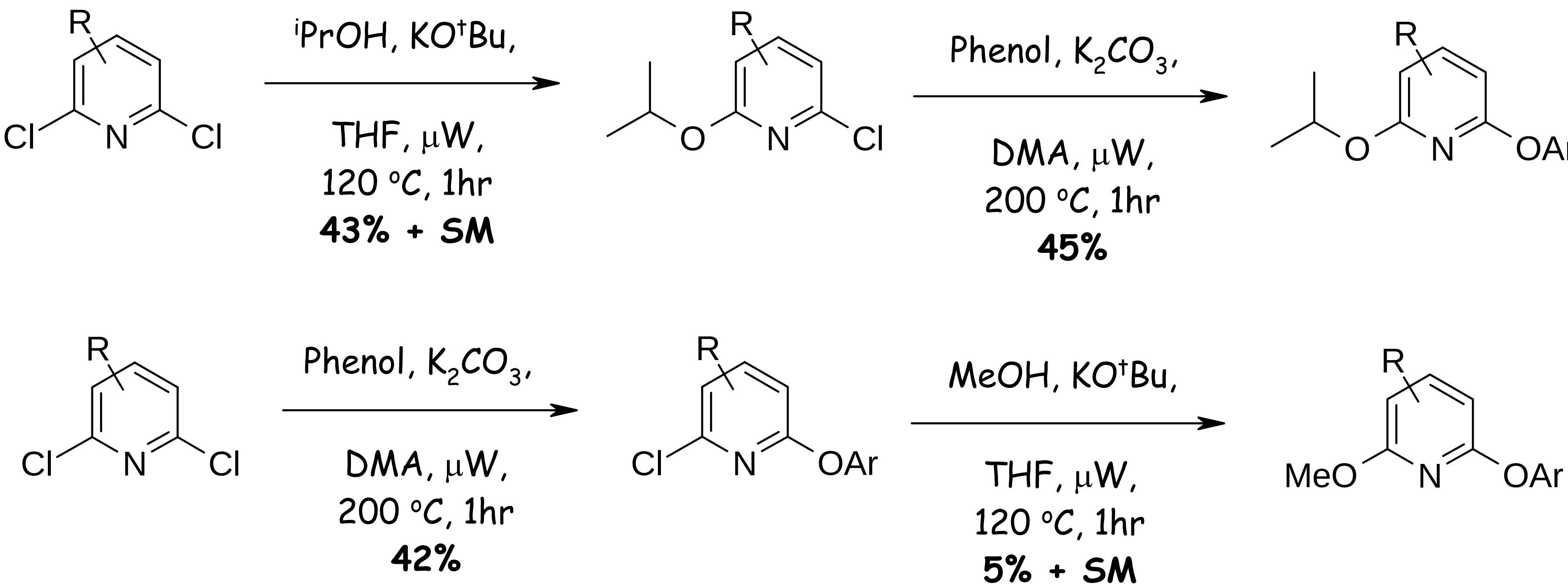
Elaboration of 2-Chloropyridines

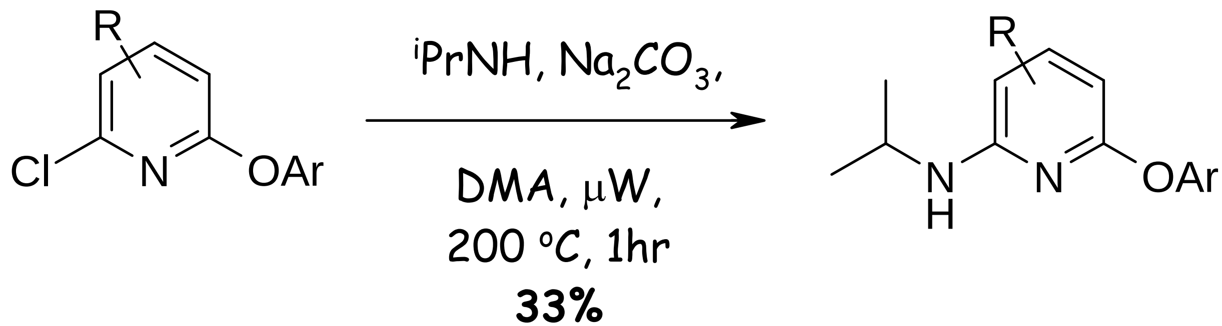


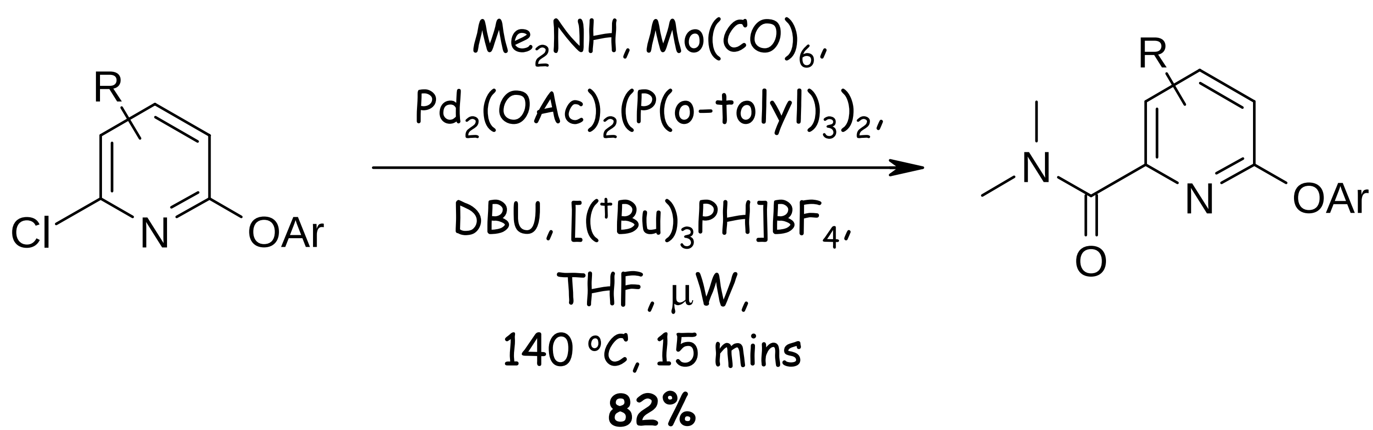
2-Alkoxy-6-Aryloxypyridines



- **Late stage diversification of aryloxy moiety performs better than that of alkoxy, due to deactivation of resulting 2-chloropyridine intermediate.**

2-Alkoxy-6-Amino & 6-Carboxamidopyridines





- **Aminocarbonylation reaction performed better with '05 published conditions vs original conditions published in '03.**

Genin, M. J. *et al.* *J. Med. Chem.* **1996**, *39*, 5267.
Kappe, C. O. *et al.* *J. Comb. Chem.* **2005**, *7*, 574.

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(Biotage – Pd EnCat)
Pino Pilotti
(Biotage – Pd EnCat)