Research Seminar

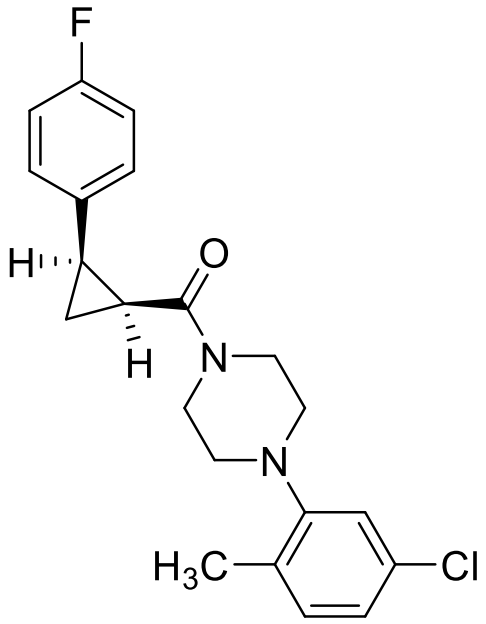
Prasanth Reddy Nyalapatla
Prof. Wipf Research Group
University of Pittsburgh
June 23, 2018

1. Gram scale synthesis of highly active molecule for the treatment of castration-resistant prostate cancer (CRPC)

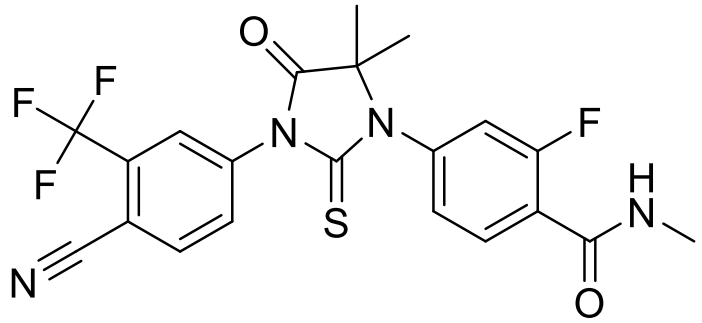
- Androgens required for prostate
- Androgens binding to and activate the AR
- ADT is primary treatment
- CRPC (hormone-refractory prostate cancer)
- Death of ~30,000 patients in the U.S

Johnson, J. K. et al. *ACS Med. Chem. Lett*. **2016**, *7*, 785-790.

- AR plays a key role in the progression of CRPC
- Enzalutamide & bicalutamide are AR antagonists



EC_{50} = 2.7 M

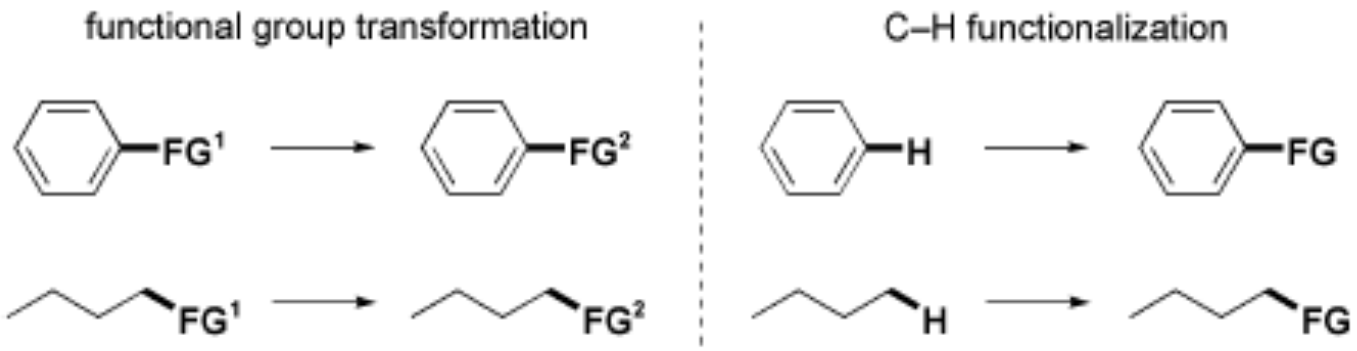


Enzalutamide

EC_{50} = 1.1 M

Johnson, J. K. et al. *ACS Med. Chem. Lett*. **2016**, *7*, 785-790.

Functional group transformation vs C-H functionalization



Why focus on C-H functionalization?

1. C-H bonds are common / could provide new disconnection
2. Atom economical
3. Cost effective

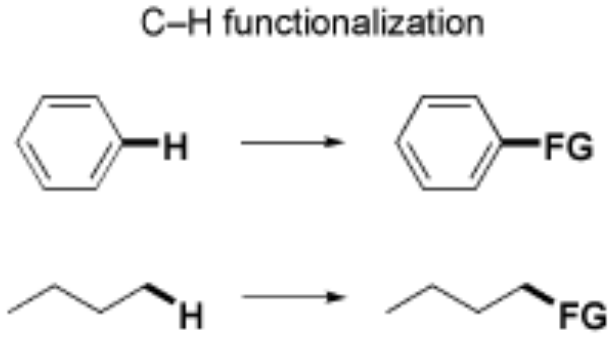
Jazzar, R. et al. *Chem. Eur. J.* **2010**, *16*, 2654-2672.

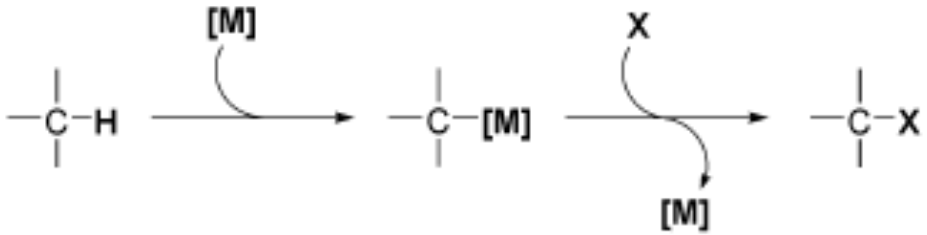
Challenges to C-H functionalization

1. Intrinsic low reactivity

2. Chemoselectivity

3. Regioselectivity

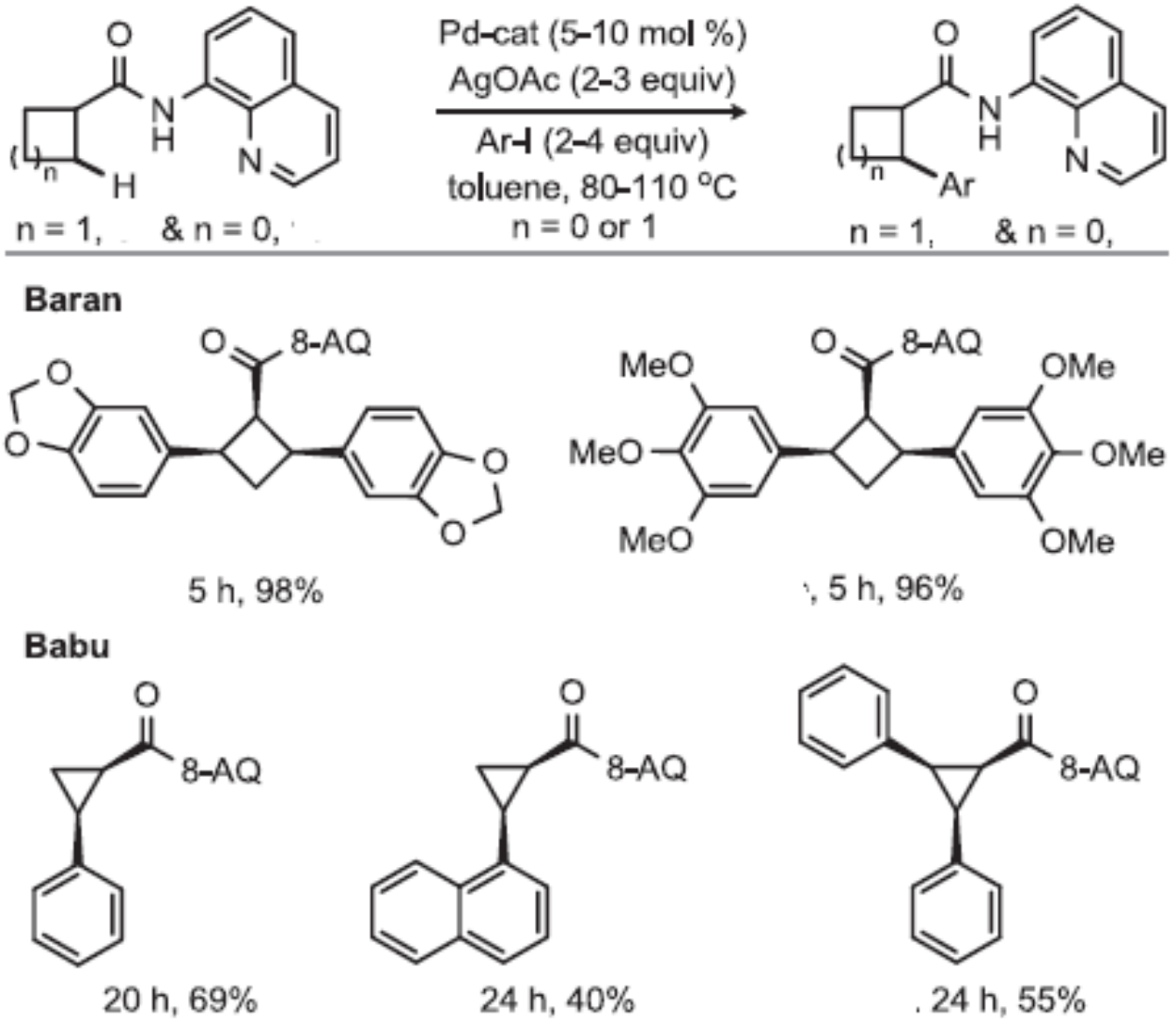




C-H activation: The formation of a carbon-metal bond by cleavage of a carbon-hydrogen bond

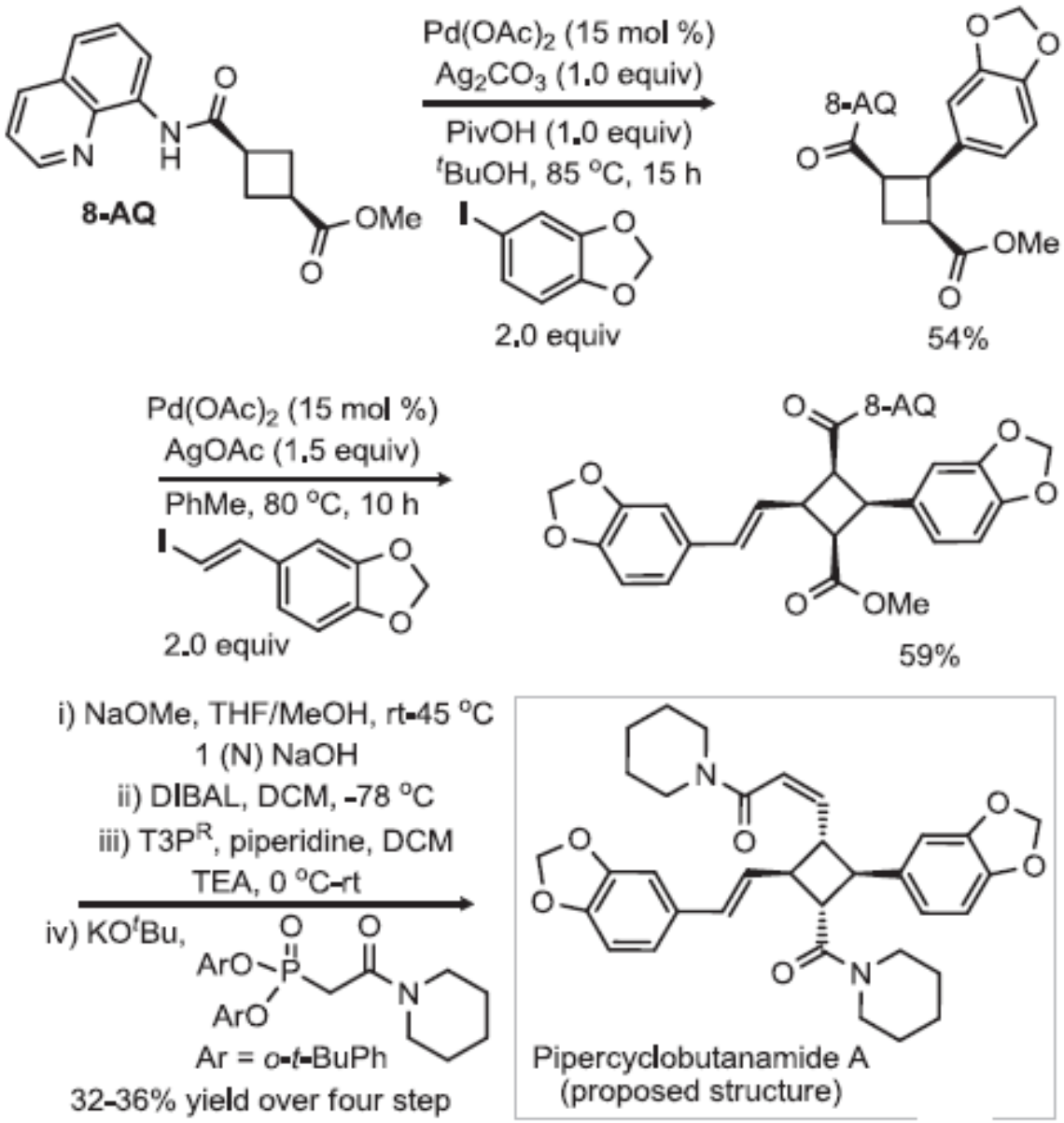
Jazzar, R. et al. *Chem. Eur. J.* **2010**, *16*, 2654-2672.
Labinger, J. A. et al. *Nature* **2002**, *417*, 507-514.
Jazzar, R. et al. *Chem. Eur. J.* **2010**, *16*, 2654-2672.

8-AQ directed arylation of small carbocycles



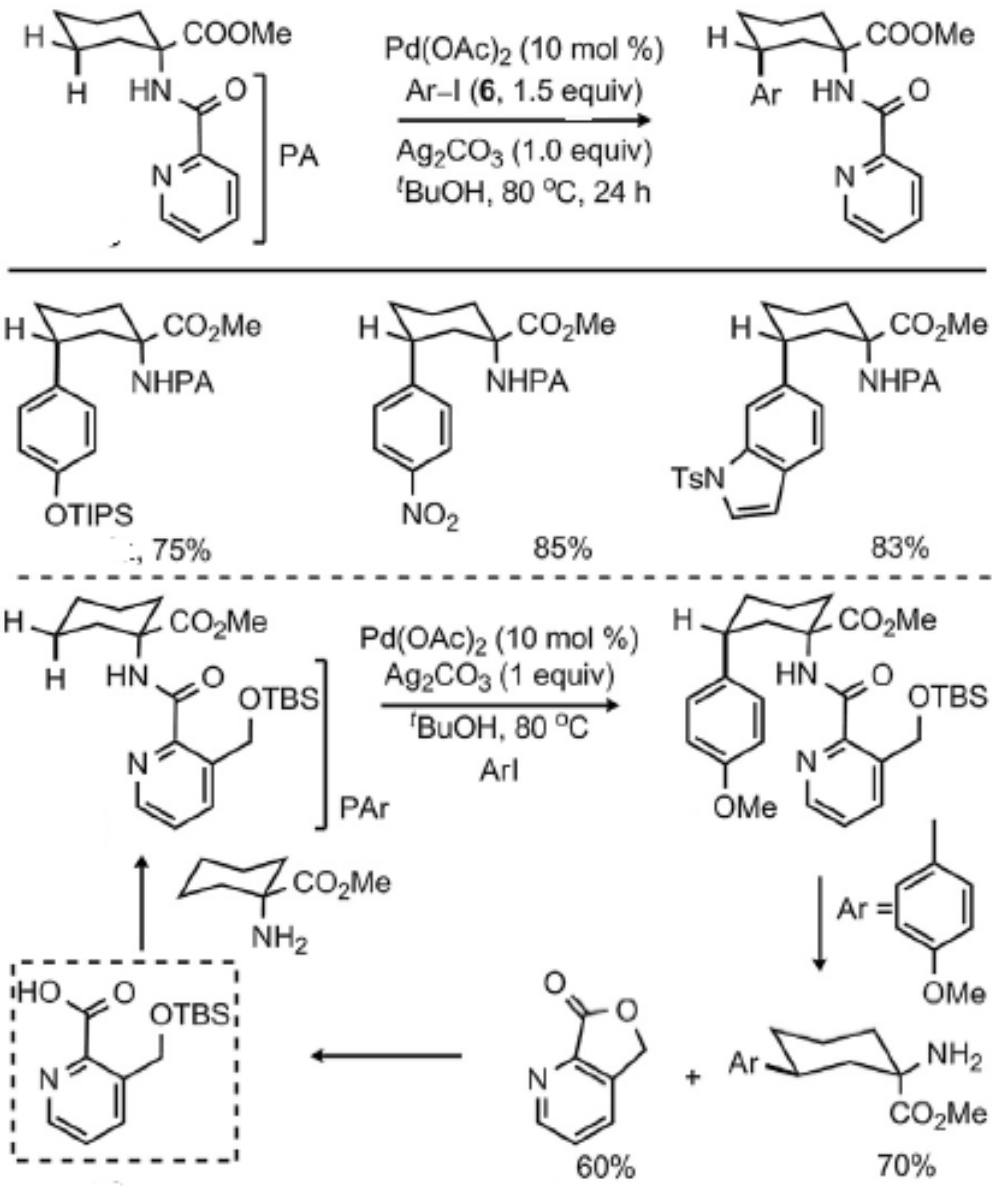
Rit, R. K. et al. *Tetrahedron* **2015**, *71*, 4450-4459.

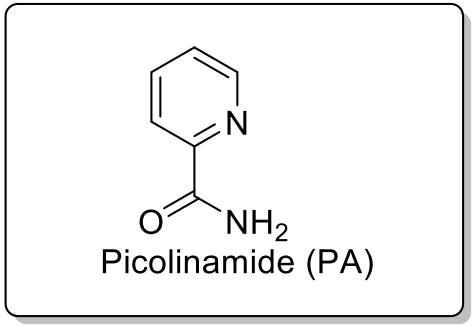
Total synthesis of pipercyclobutanamide A



Rit, R. K. et al. *Tetrahedron* **2015**, *71*, 4450-4459.

Picolinamide (PA)-DG-C(sp^3)-H arylation

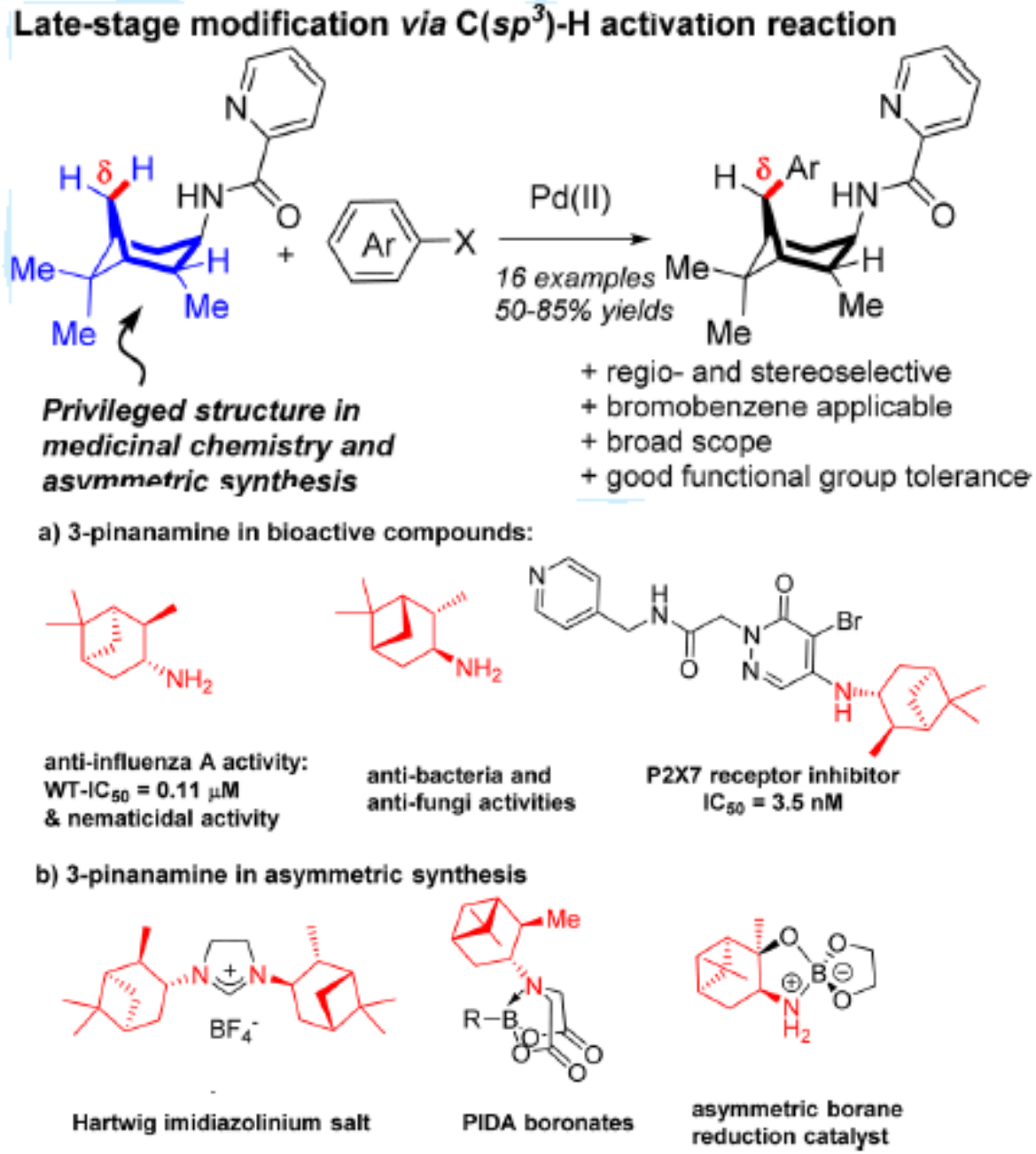




He, G. et al. *Angew. Chem. Int. Ed.* **2011**, *50*, 5192-5196.

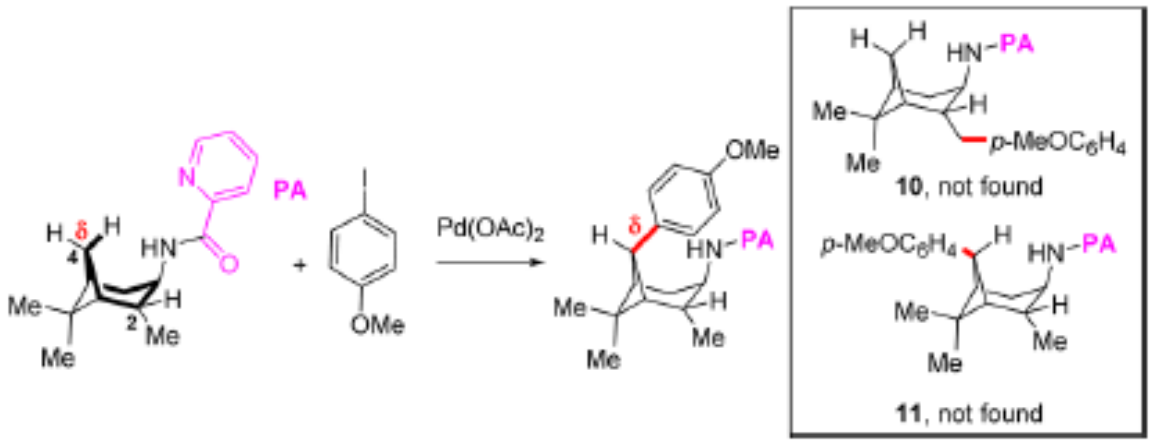
Rit, R. K. et al. *Tetrahedron* **2015**, *71*, 4450-4459.

Palladium catalyzed remote C(sp^3)-H arylation of 3-pinanamine



Cui. W. et al. *Org. Lett.* . **2014**, *16*, 4288-4291.

Reaction optimization

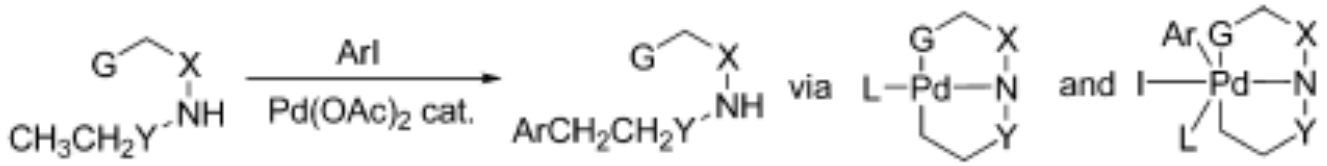


entry	8a (*x* equiv)	solvent	temp (°C)	base (1 equiv)	yield (%)
1	1.5	decalin	130	Ag_2CO_3	<5
2	1.5	toluene	130	Ag_2CO_3	76
3	1.5	mesitylene	130	Ag_2CO_3	65
4	1.5	*o*-DCB[b]	130	Ag_2CO_3	65
5	1.5	PhCN	130	Ag_2CO_3	33
6	1.5	$PhCF_3$	130	Ag_2CO_3	70
7	1.5	toluene	130	AgOAc[c]	9
8	1.5	toluene	130	K_2CO_3[c]	<5
9	1.5	toluene	130	NaOAc[c]	<5
10	1.5	toluene	130	$NaHCO_3$[c]	<5
11	1.5	toluene	100	Ag_2CO_3	10
12	**1.1**	**toluene**	**130**	**Ag_2CO_3**	**75**

[a]7 (0.2 mmol), $Pd(OAc)_2$ (10 mol %), solvent (2 mL), 24 h, isolated yields. [b]*o*-DCB = *ortho*-dichlorobenzene. [c]2.0 equiv of base were used.

Cui. W. et al. *Org. Lett.* . **2014**, *16*, 4288-4291.

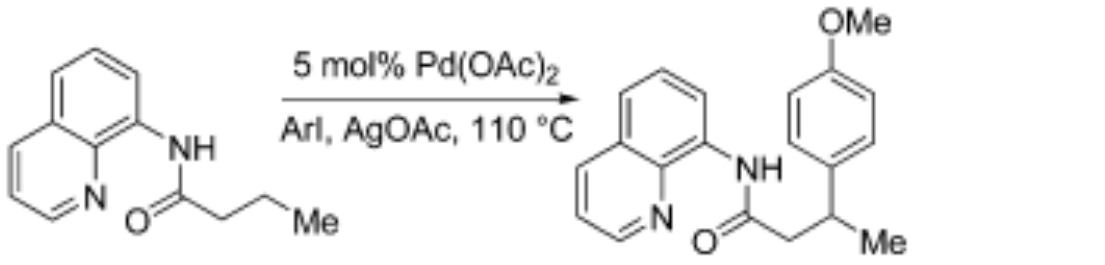
Auxiliary-assisted palladium catalyzed arylation

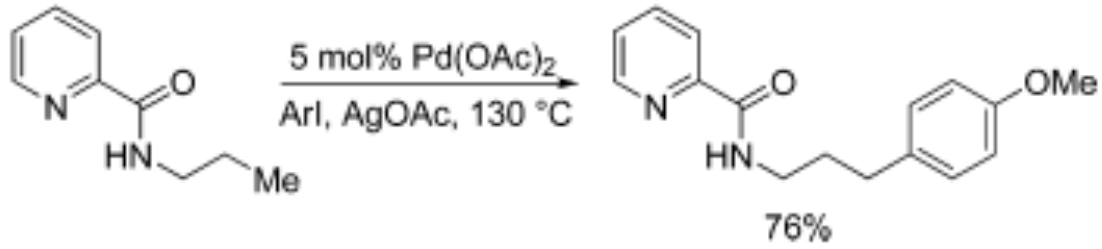


X = CH_2, C=O, aromatic tether

Y = C=O, carboxylic acid β–arylation
Y = CH_2, amine γ–arylation

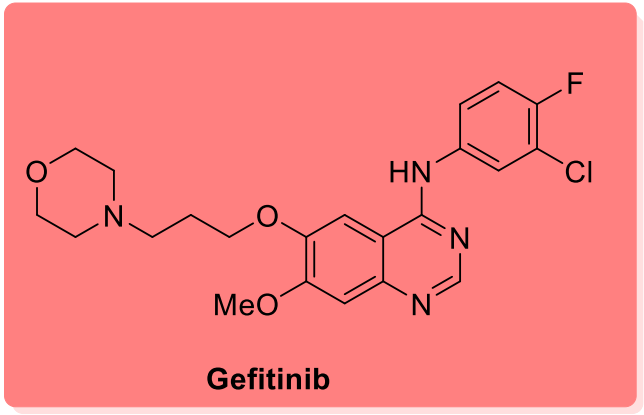
G = chelating group such as NR_2, SR





Shabashov. D. et al. *J. Am. Chem. Soc.* . **2010**, *132*, 3965-3972.

3. Route optimization of Gefitinib

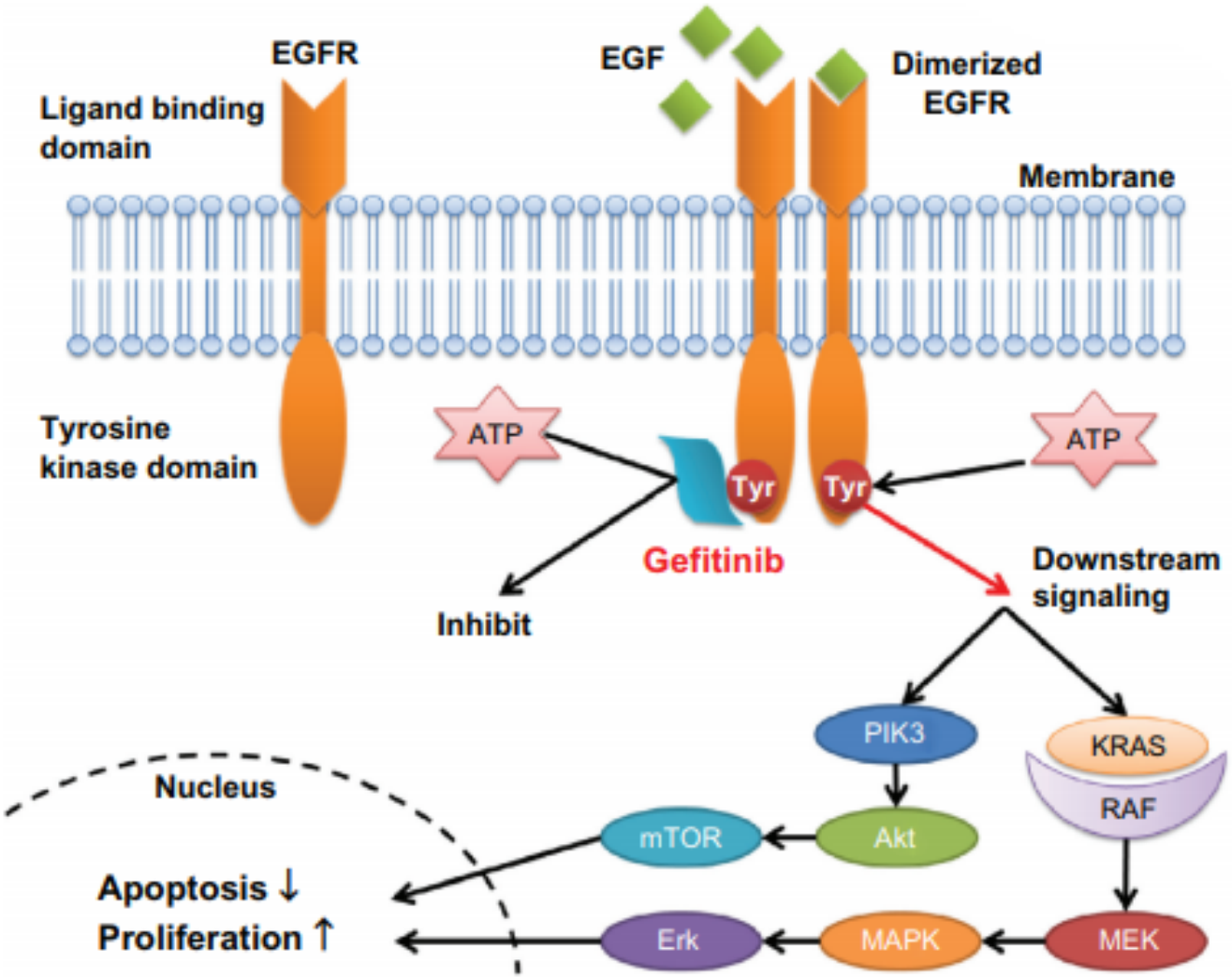


Gefitinib

- Brand name Iressa
- EGFR inhibitor
- AstraZeneca
- Approved in 2003, 2015 for NSCLC
- Price: 250 mg tablets (Qty:30) ~$7500-8500

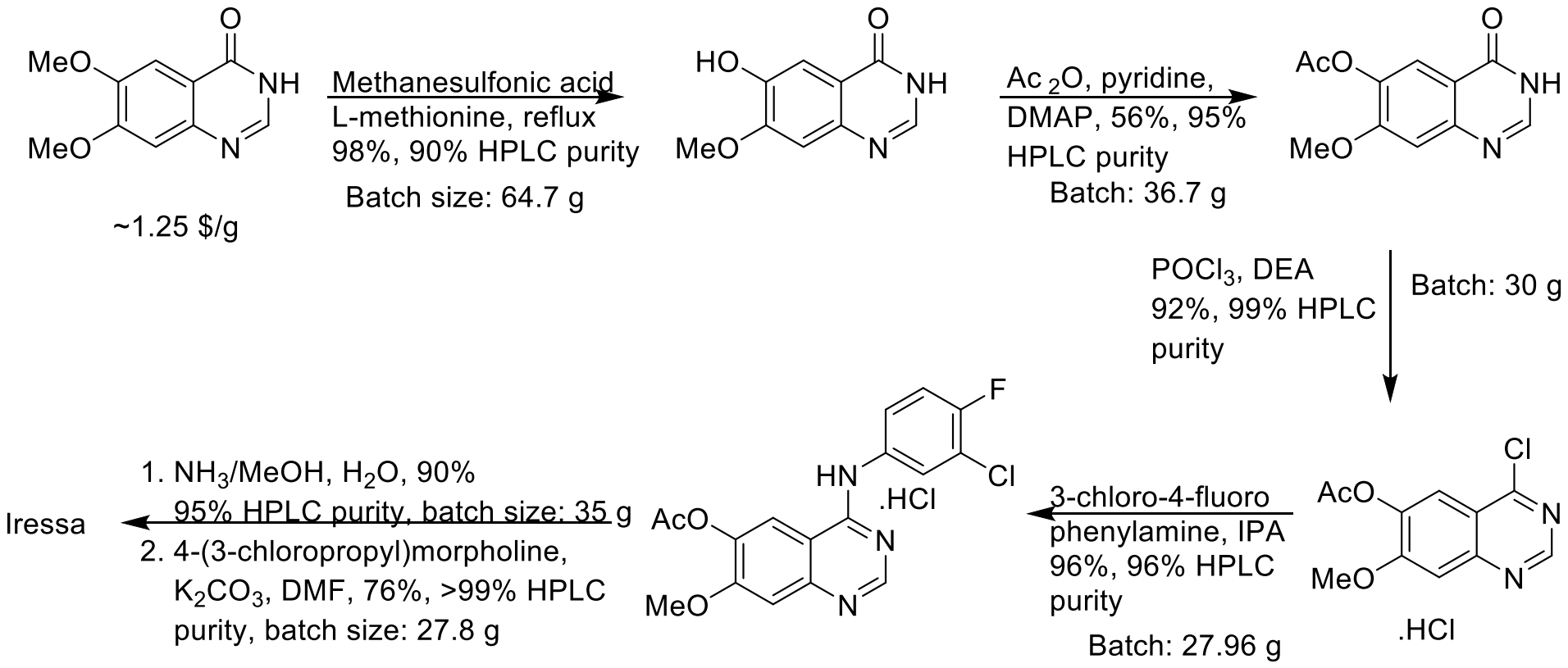
Mechanism of EGFR-tyrosine kinase inhibitors

- EGFR is highly expressed, Activation of EGFR shown tumor cell-proliferation



Araki. T. et al. *Clin Med Insights Oncol.* **2012**; *6:407–421.*

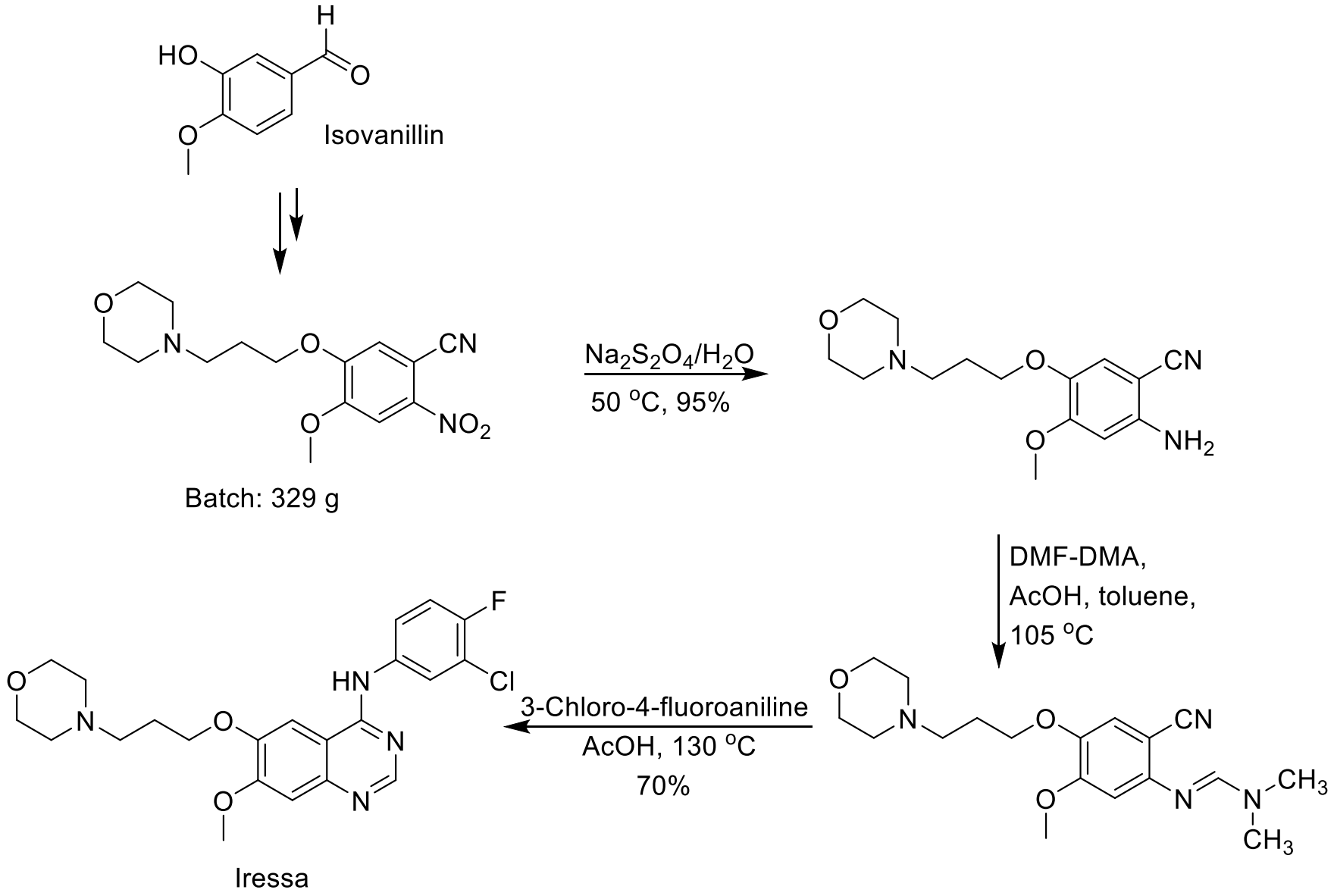
Improved synthesis of substituted 6,7-dihydroxy-4-quinazolineamines: tandutinib, erlotinib and gefitinib



- 6 steps and
  33% overall yield

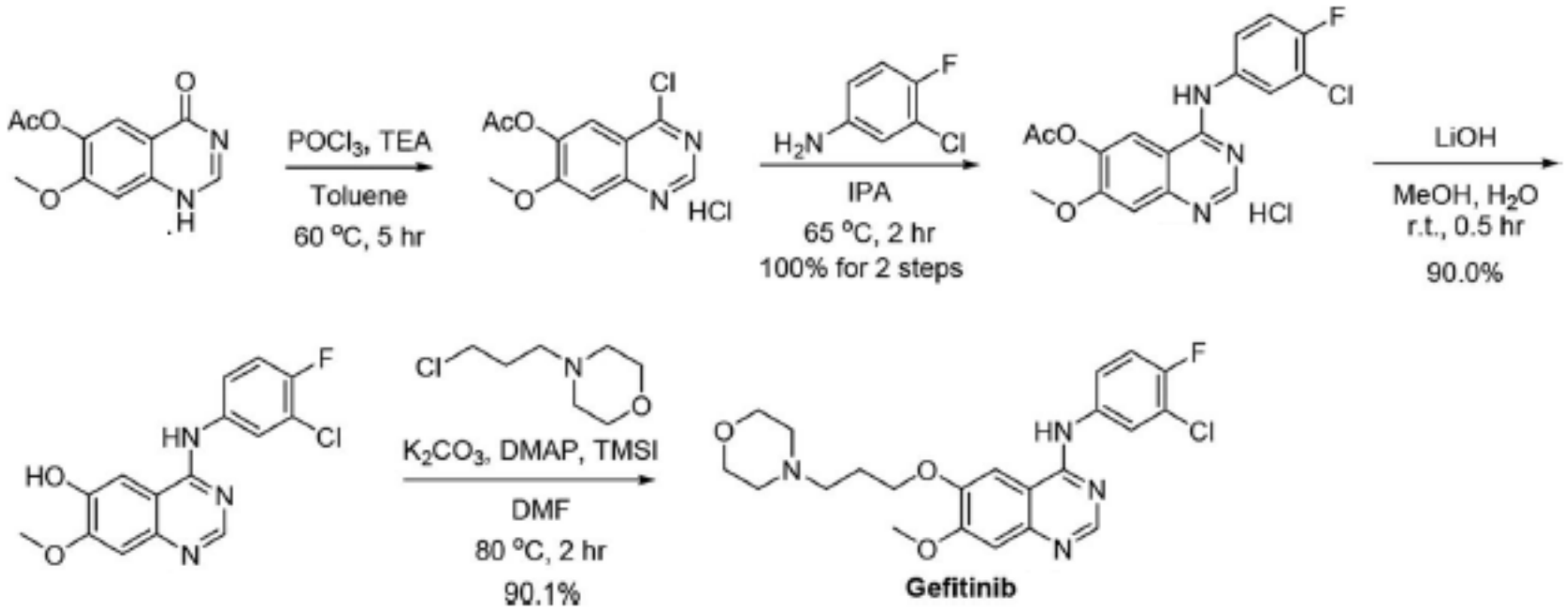
Knesl, P. et al *Molecules*. **2006**, *11,* 286-297.

Convergent approach for commercial synthesis of gefitinib and erlotinib



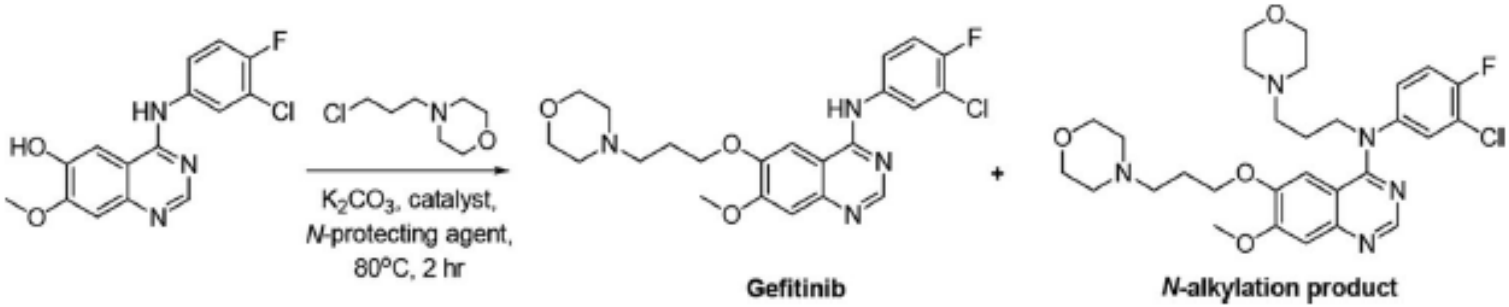
Chandregowda, G. et al *Org. Proc. Res. Dev.* **2007**, *11,* 813-816.

Practical and efficient synthesis of gefitinib through selective O-alkylation: A novel concept for a transient protection group



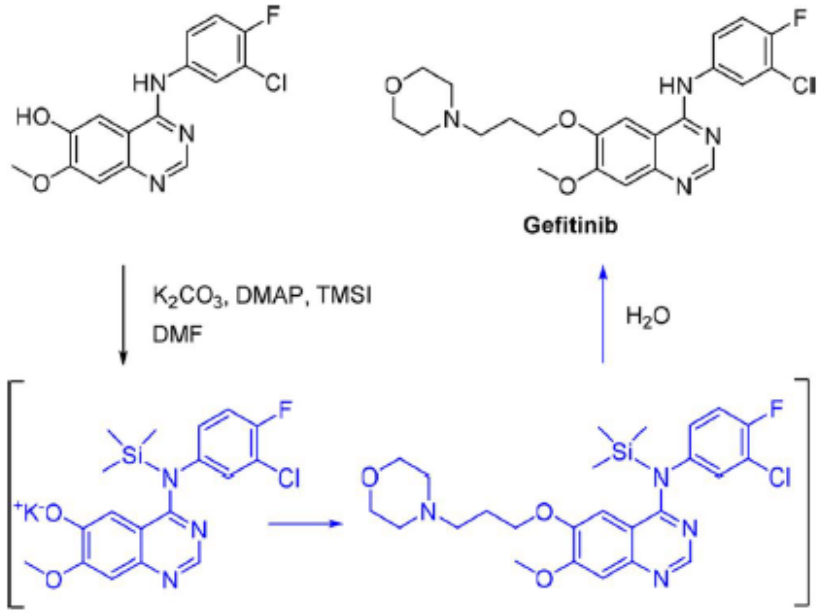
- 4 steps (SM: $13/g) and 81.1% overall yield

Kang, S. K. et al *Synth. Commun*. **2017**, *47,* 1990-1998.



Entry	*N*-Protecting agent	Catalyst	*N*-Alkylation products before purification[a] (%)	*N*-Alkylation products after purification[b] (%)	Yield[c] (%)
1	HCl	—	13.5	1.2	64.5
2	—	DMAP (0.1 eq.)	10.0	1.0	61.6
3	—	KI (0.1 eq.)	20.0	1.3	63.9
4	TMSI	—	2.2	0.2	78.5
5	TMSI	DMAP(0.1 eq.)	0.3	ND	90.1

[a]Determined by HPLC after completion of reaction.
[b]Determined by HPLC after purification.
[c]Isolated yield after purification.

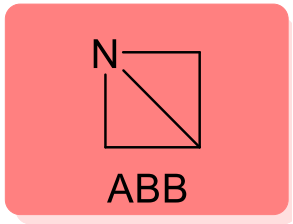


Kang, S. K. et al *Synth. Commun*. **2017**, *47,* 1990-1998.

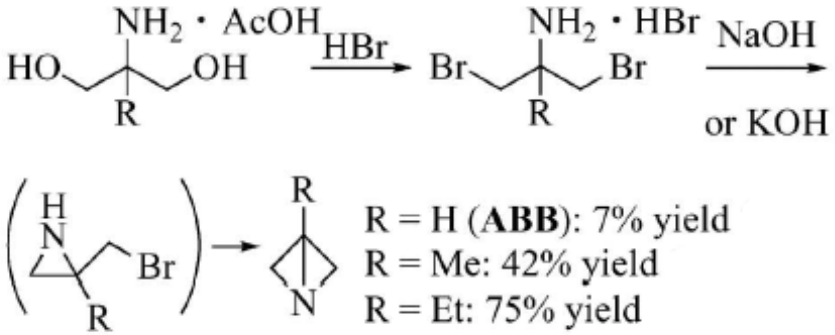
Process guidelines: limits

- Temperature range -15 ^{o}C/120 ^{o}C
- Pressure -1/+0.49 bar
- No use of products classified H350
- No use of prohibited solvents and reagents
- Limited use of dichloromethane
- Chromatography column must be avoided

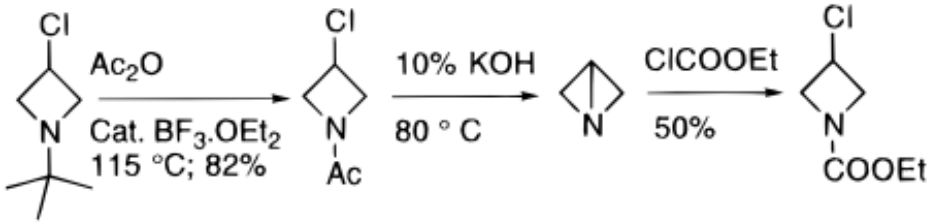
Synthesis of ABB



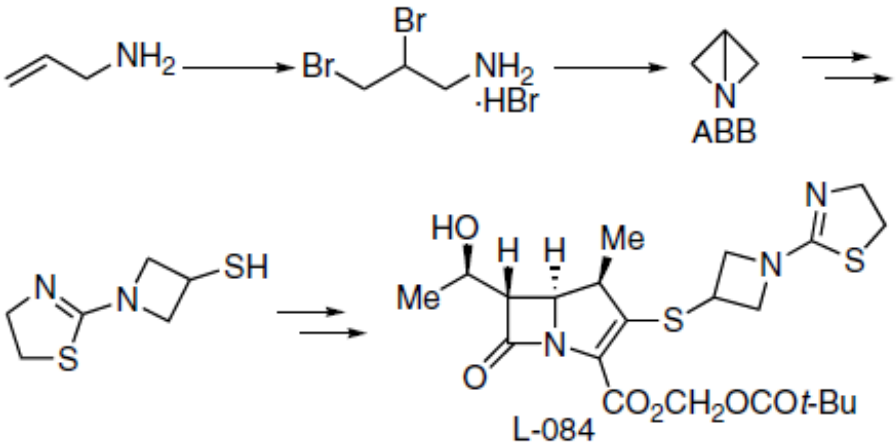
Funke's method



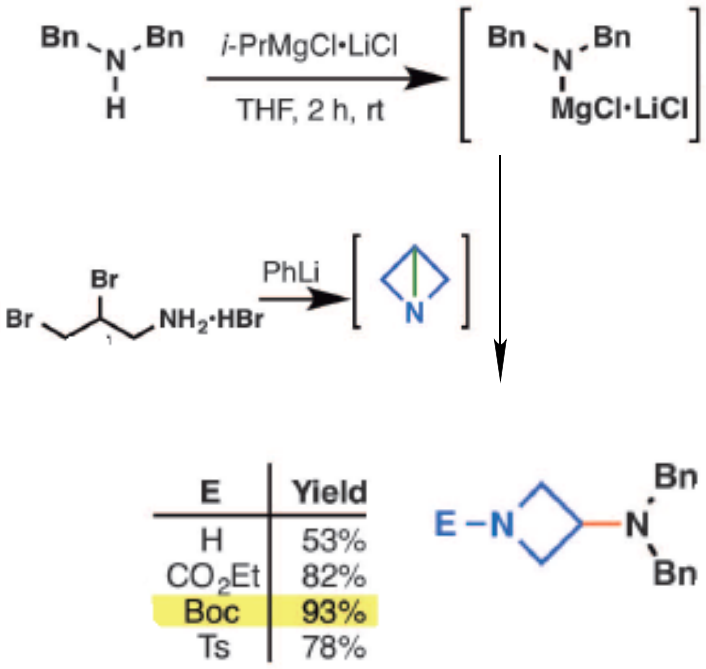
Dave's method



Nagao's method



Baran's method



Hayashi. K. *Yakugaku Zasshi* **2010**, *130*, 1339-1346.

Ikee, Y. et al *Bioorg. Med. Chem. Lett.* **2007**, *17, 942-945*.

Gianatassio, Ryan. et al. *Science* **2016**, *351*, 241.

Thank you
Prof. Peter Wipf

Thanks to Prof. Wipf Research Group