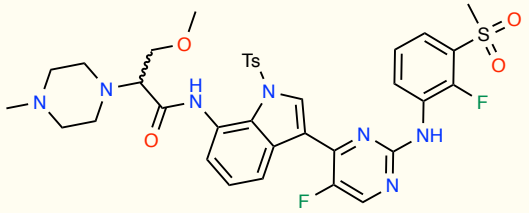
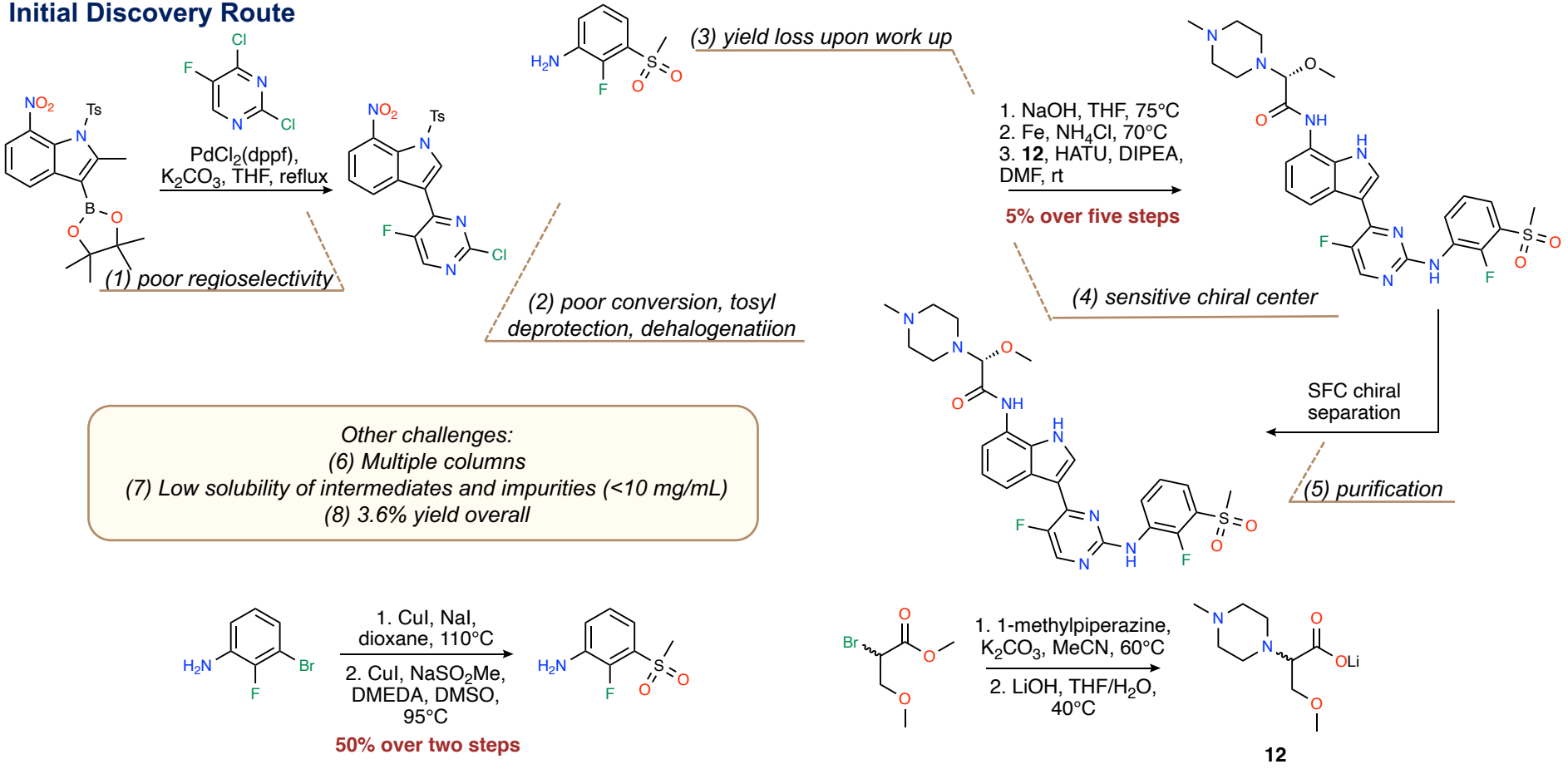
JAK1 Inhibitor: AZD4604

- AZD4604 is a potent JAK1 inhibitor discovered in a lead optimization campaign for treatment of asthma via inhalation at Astrazeneca
- Upon delivery to a ovalbumin-challenge rat model of allergic asthma, reduction of pSTAT3 and pSTAT5 indicated the lung was observed
- The first in human study began in 2022
- To support toxicological pre-studies the included large-scale manufacturing route was developed



Initial Discovery Route



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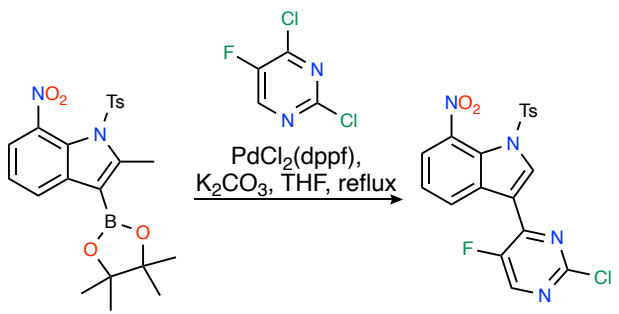
Suzuki Coupling Optimization

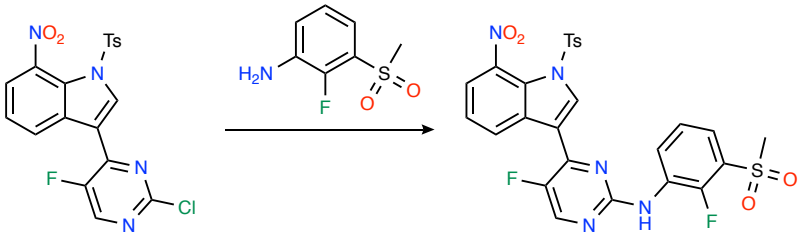


Product precipitates

89% yield, 99% HPLC purity

Entry	Cat.	Eq of Pyrimidine	Temp	Solvent	Conversion to Product
1	$Pd(dppf)Cl_2•CH_2Cl_2$ (5 mol%)	1.3	70	THF	72%
2	$PdCl_2(dtbpf)$ (5 mol%)	1.3	70	THF	56%
3	$Pd(dppf)Cl_2•CH_2Cl_2$ (2.5 mol%)	1.3	70	THF	68%
4	$Pd(dppf)Cl_2•CH_2Cl_2$ (1.5 mol%)	1.3	70	THF	69%
5	$Pd(dppf)Cl_2•CH_2Cl_2$ (5 mol%)	1.2	70	THF	72%
6	$Pd(dppf)Cl_2•CH_2Cl_2$ (2.5 mol%)	1.2	70	MeCN	44%
7	$Pd(dppf)Cl_2•CH_2Cl_2$ (5 mol%)	1.2	70	MeTHF	79%
8	$Pd(dppf)Cl_2•CH_2Cl_2$ (5 mol%)	1.2	22	MeTHF	95%

Attempts Toward S_NAr



Abandoned S_NAr attempt of the two fragments

Entry	Base	Conditions	Result by LCMS
1	-	1,4 dioxane, 150-160°C, Microwave,	Trace product by LCMS
2	Cs_2CO_3 (2 eq)	1,4 dioxane, 150-160°C, Microwave	
4	K_2CO3 (2 eq)	1,4 dioxane, 150-160°C, Microwave	
5	Et_3N (2 eq)	1,4 dioxane, 150-160°C, Microwave	
6	Et_3N (1 eq)	120°C, Microwave in IPA, 1h	
7	-	p-TSA (cat) in IPA, sealed tube, reflux, 1 week	15% of product

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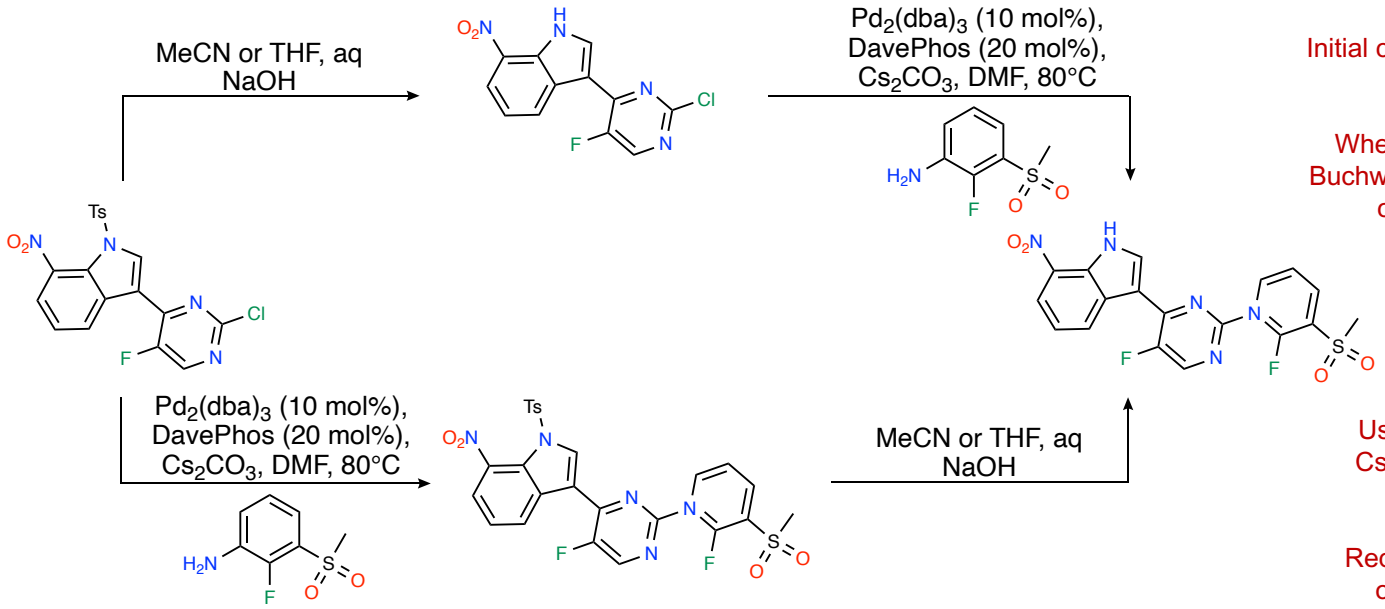
Buchwald Hartwig Amination Optimization

Route A



Initial conditions yielded decomposed product for tosyl deprotection.

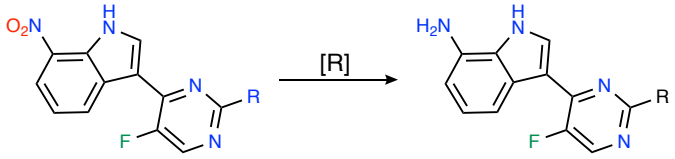
When detosylated product was obtained, Buchwald Hartwig amination failed (poisoned catalyst and solubility challenges)

Used MeTHF and water as solvent with Cs_2CO_3, prevented tosyl deprotection of starting material

Reduction in solvent waste, crystallization occurred without antisolvent addition

Route B

Nitro Reduction Optimization



97% yield, 99% HPLC purity

Entry	Conditions	Conversion to Product	Results
1	Pd-C: 10 mol %, hydrogen: −2 bar, EtOH (30 vol), 25°C	81%	3-8% dehalogenated product
2	Pd-C: 10 mol %, hydrogen: −2 bar, THF/EtOH (20 vol), 25°C	78%	-
3	Pd-C: 10 mol %, HCO_2NH_4 (6 eq), THF/EtOH (20 vol), 65°C	98%	high sublimation
4	Pd-C: 10 mol %, HCO_2NH_4 (6 eq), THF/EtOH (20 vol), 40°C	99%	reduced sublimation

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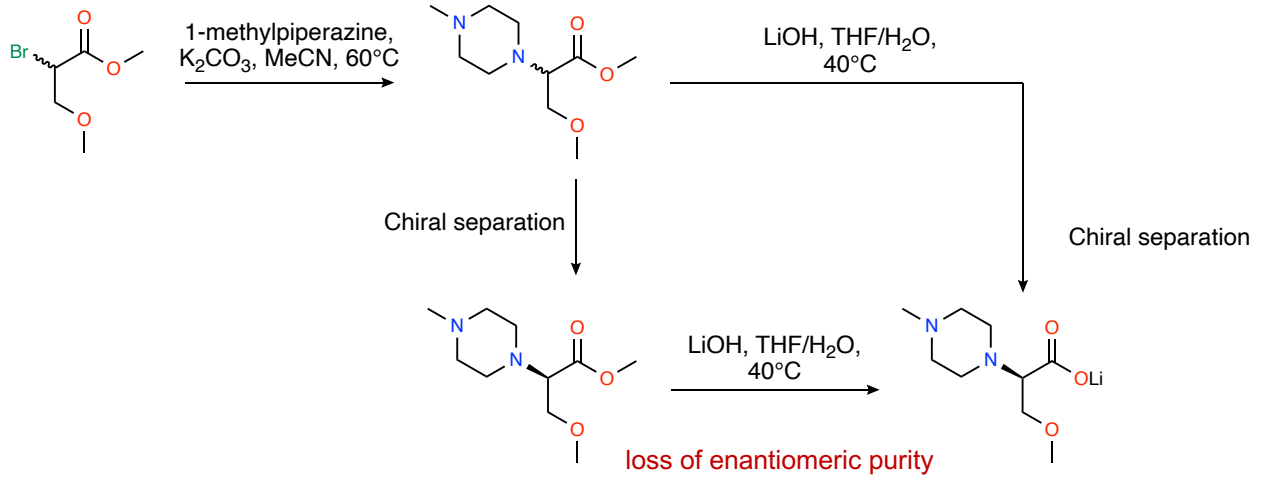
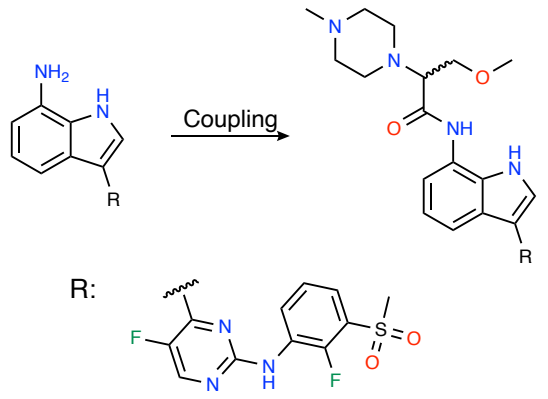
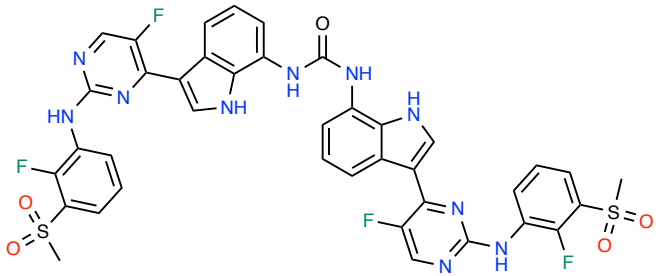
Synthesis of Chiral Acid Salt

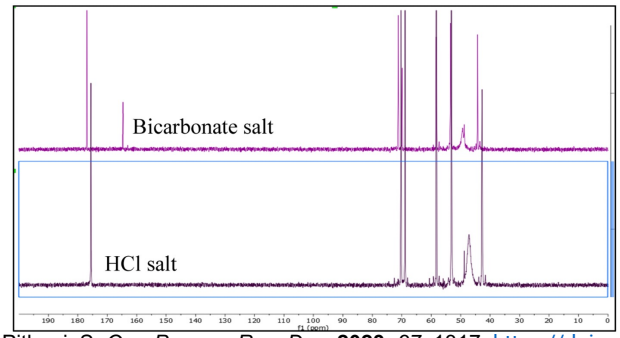


Amide Coupling Optimization



Formation of urea from carbonate salt





Entry	Conditions	Conversion	Observations
1	T3P, carbonate (batch 1), pyridine, EtOAc	91%	
2	T3P, carbonate (batch 2), pyridine, EtOAc	33%	impurities
3	T3P. carbonate salt, pyridine, DMF	68%	
4	T3P carbonate salt, pyridine, THF	50%	degradation
5	T3P, carbonate salt, pyridine, DCM/DMF	76%	tedious work up, low yield
6	T3P, HCl salt, DCM/DMF	97%	tedious work up
7	COMU, HCl salt, pyridine, DMF	42%	low ee, ~80%
8	COMU, HCl salt, Et_3N, DMF	66%	
9	COMU, HCl salt, DIPEA, DMF	82%	

Fine powder precipitates with addition of water, 85% yield and 99.9% ee (450 g scale)

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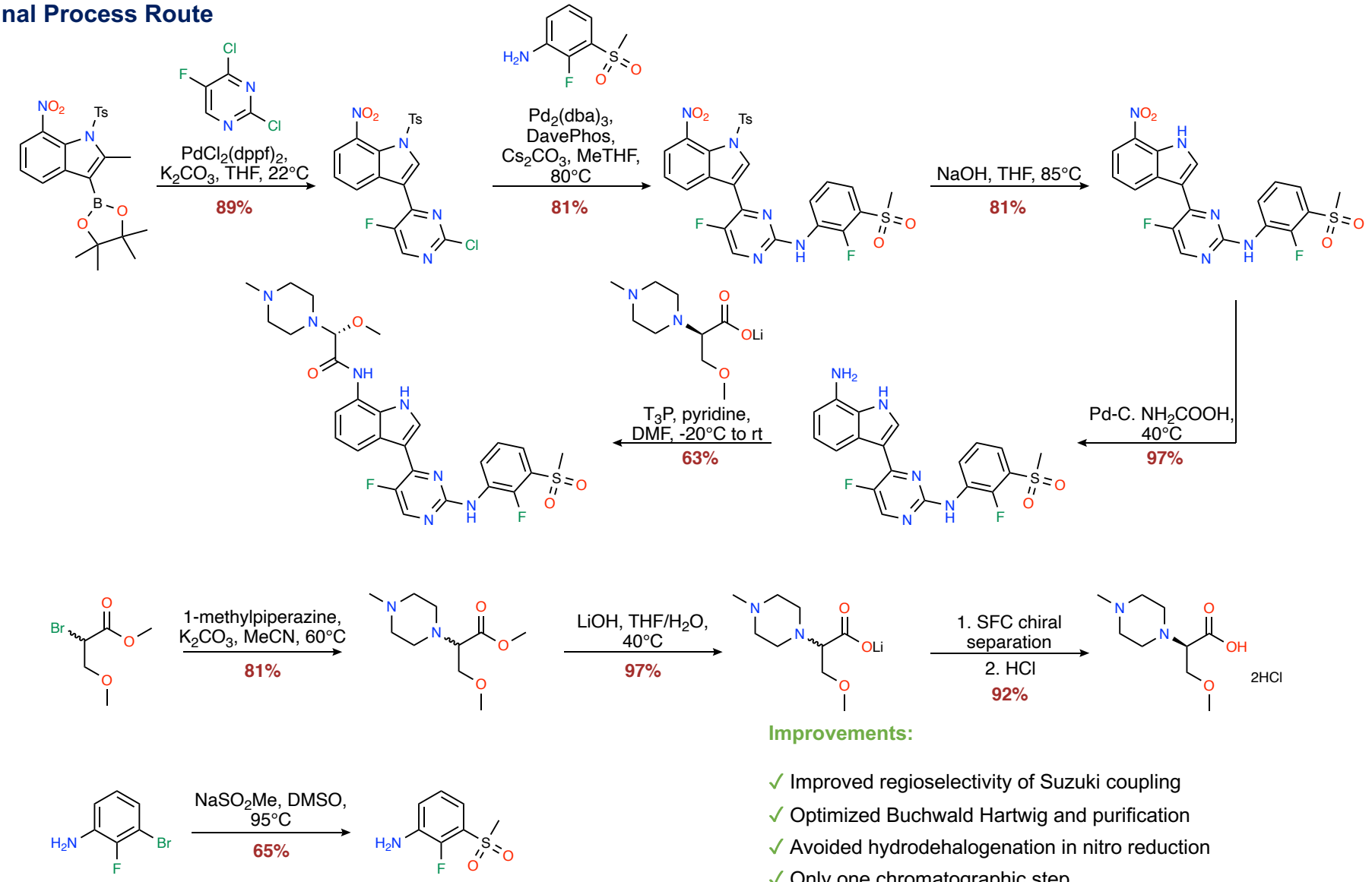
Final Process Route



Improvements:

- ✓ Improved regioselectivity of Suzuki coupling
- ✓ Optimized Buchwald Hartwig and purification
- ✓ Avoided hydrodehalogenation in nitro reduction
- ✓ Only one chromatographic step
- ✓ Overall yield increased to 36% from 3.6%
- ✓ 600 g material produced for preclinical studies

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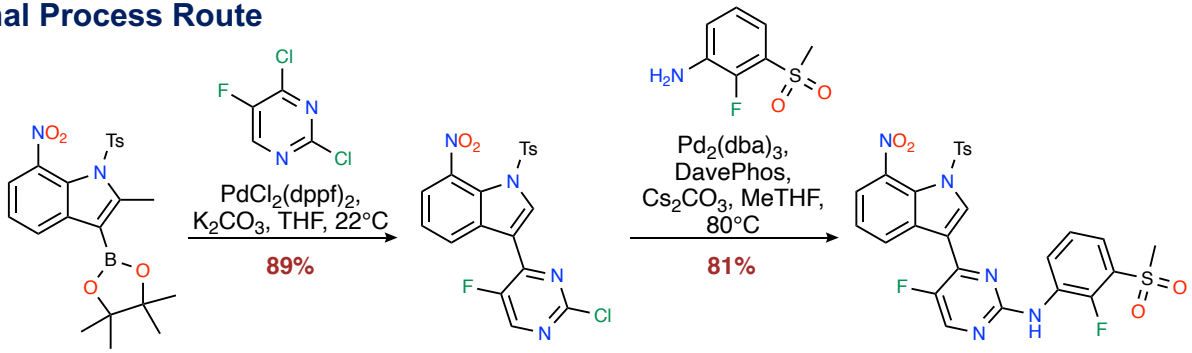

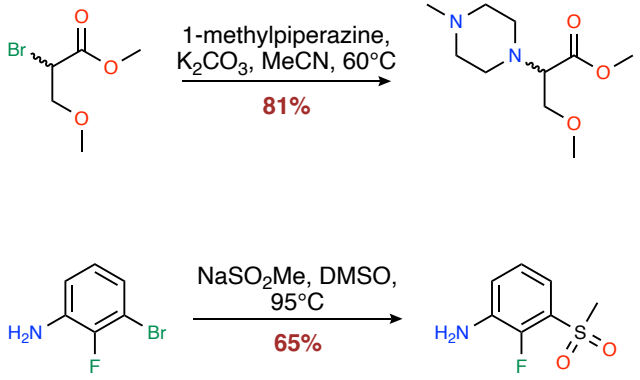

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