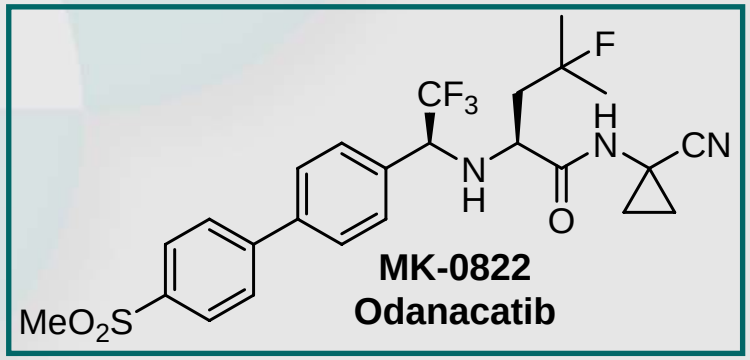
The Discovery & Development of Odanacatib

A Selective Inhibitor of Cathepsin K for the Treatment of Osteoporosis



MK-0822
Odanacatib

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25th Process Development Symposium
Churchill College, Cambridge, UK
March 13, 2007

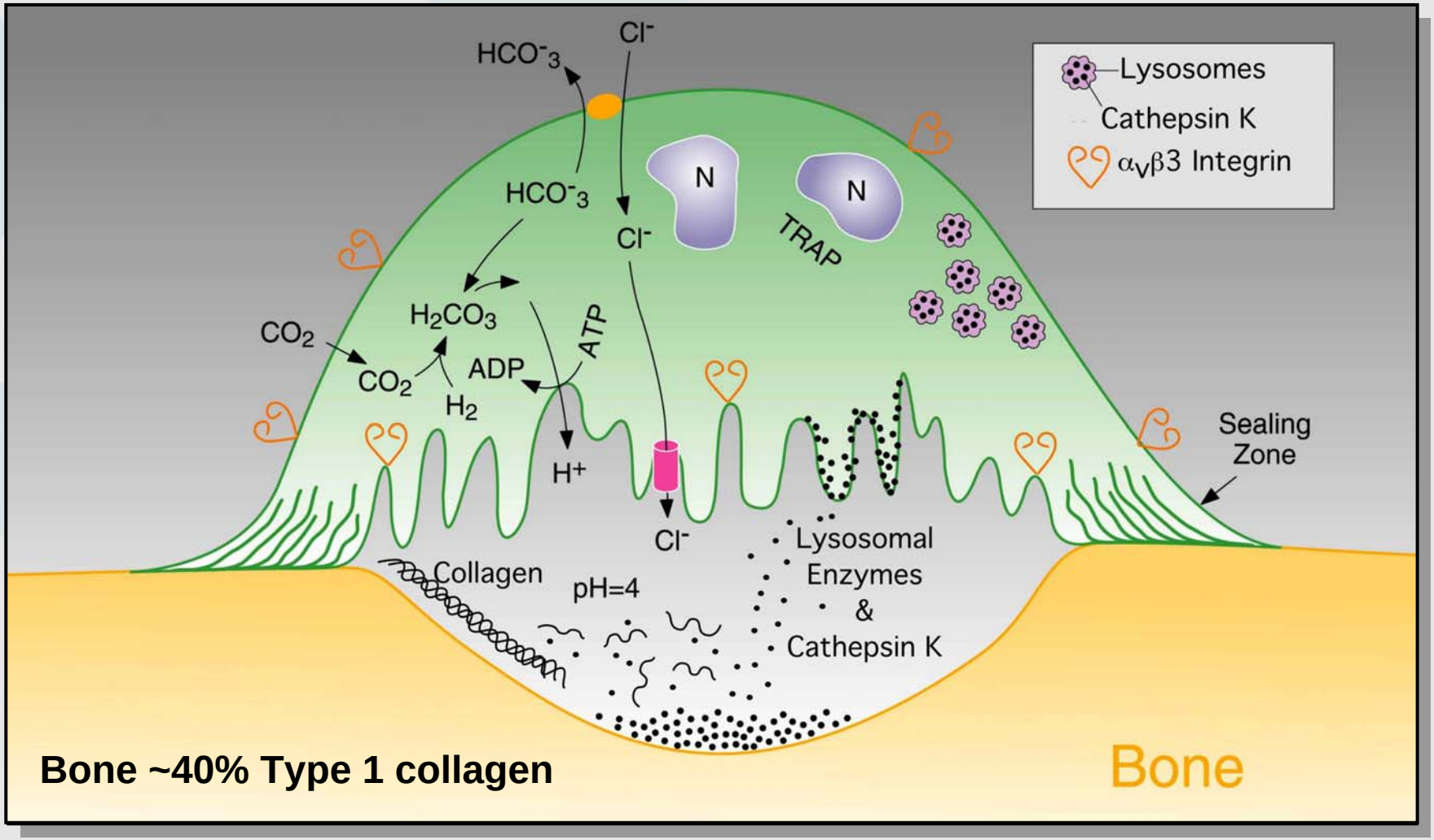
Outline

- Background
  - Justification for pursuing new Osteoporosis mechanisms
  - Biological Rationale for pursuing a Cathepsin K inhibitor
  - Medicinal Chemistry Summary
    - SAR development
    - Metabolism issues
  - Synthetic Approaches to L-873724 & MK-0822
- Chemistry used in the 1st GMP Delivery of MK-0822
- Development of a Manufacturing Route for MK-0822

Osteoporosis

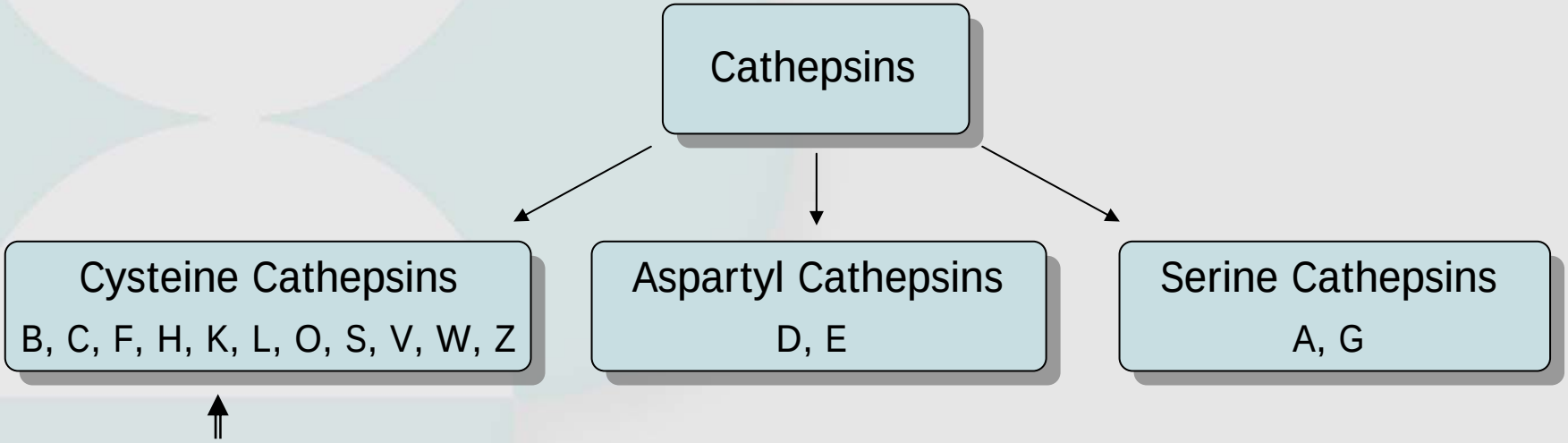
- Decreased bone density and mass. Increased fracture risk.
- Estimated 200 million osteoporosis sufferers worldwide. Strikes ~1 in 4 women and 1 in 8 men over 50 ys.
- 650,000 hip fractures/yr in US-Europe. Majority caused by osteoporosis. 20% will die from fracture & 50% will be disabled.
- Cost of hospitalization in US-Europe : Currently ~ $22 b/year.
- Need exists for improved therapies

Osteoclastic Bone Resorption



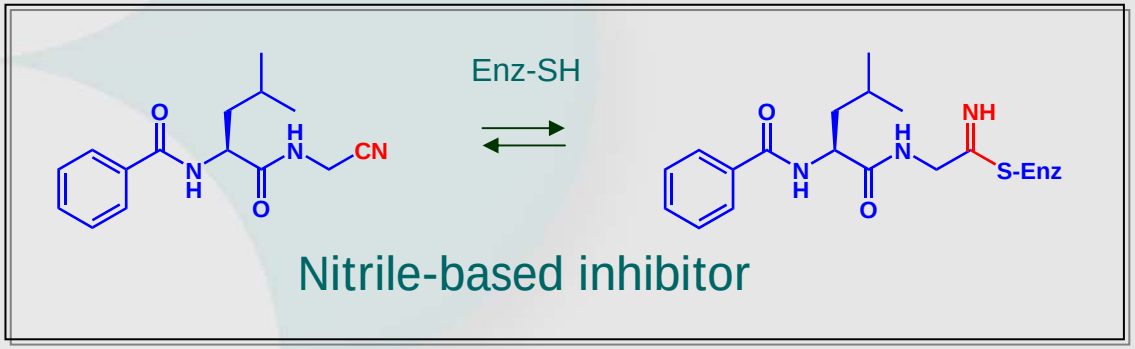
Bone resorption by osteoclasts is the initial step in remodeling

Cathepsins: Lysosomal Proteases

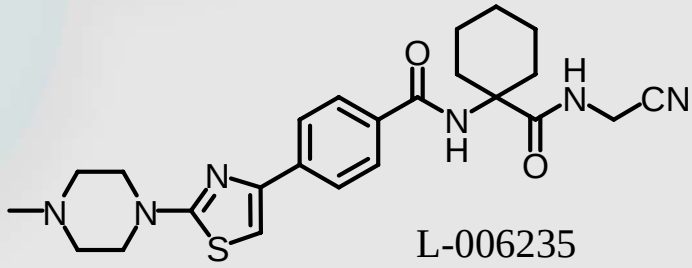


- Cathepsins have optimal activity at acidic pH found in lysosomes
- Cathepsin K is a cysteine protease highly expressed in osteoclasts
  - Efficiently degrades bone collagen
  - Cat K null mice have osteopetrotic phenotype, but otherwise healthy
- Cat K represents a promising target for the treatment of osteoporosis

Reversible Cat K Inhibitors



Optimization

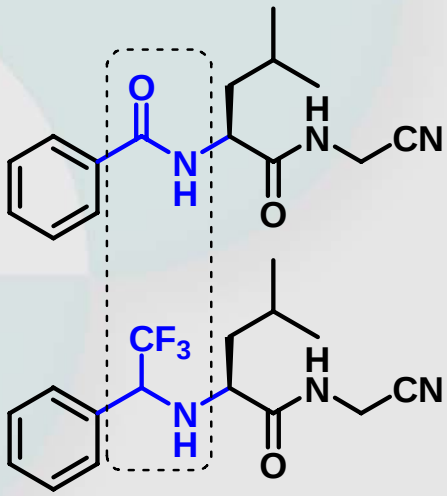


L-006235

J. Med. Chem. **48** 7520 (2005)

- 0.2 nM vs Cat K; 5 nM in osteoclast bone resorption assay
- >5000-fold selective over related cathepsins in purified enzyme assays
- Efficacious in monkey model of osteoporosis at 3 mg/kg/day
- Selectivity is lost in whole cell assays

Amide Replacement: Trifluoroethylamine



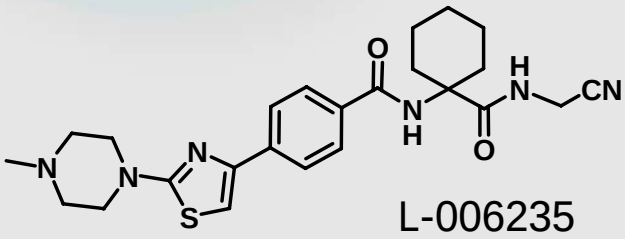
Cat K IC_{50} (nM)
51
4

- Non-basic amine (pKa = 1.5) that it is not protonated at physiological pH
- Retains the H-bond donating properties of an amide bond

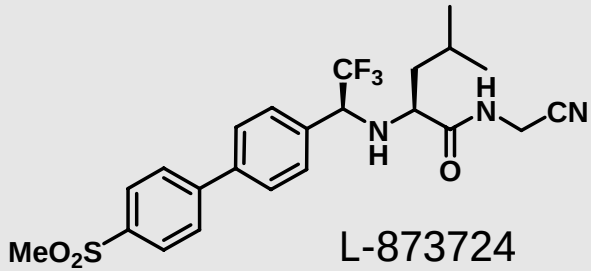
Bioorg. Med. Chem. Lett. **15** 4741 (2005)

L-873724 has Similar Potency in Whole Cells and Purified Cathepsins

	Inhibition of Cathepsins, IC_{50} (nM)					
	Cathepsin B		Cathepsin L		Cathepsin S	
	Enzyme	Cell	Enzyme	Cell	Enzyme	Cell
L-006235	1100	17	6300	340	47000	790
L-873724	5240	4800	264	1220	178	94



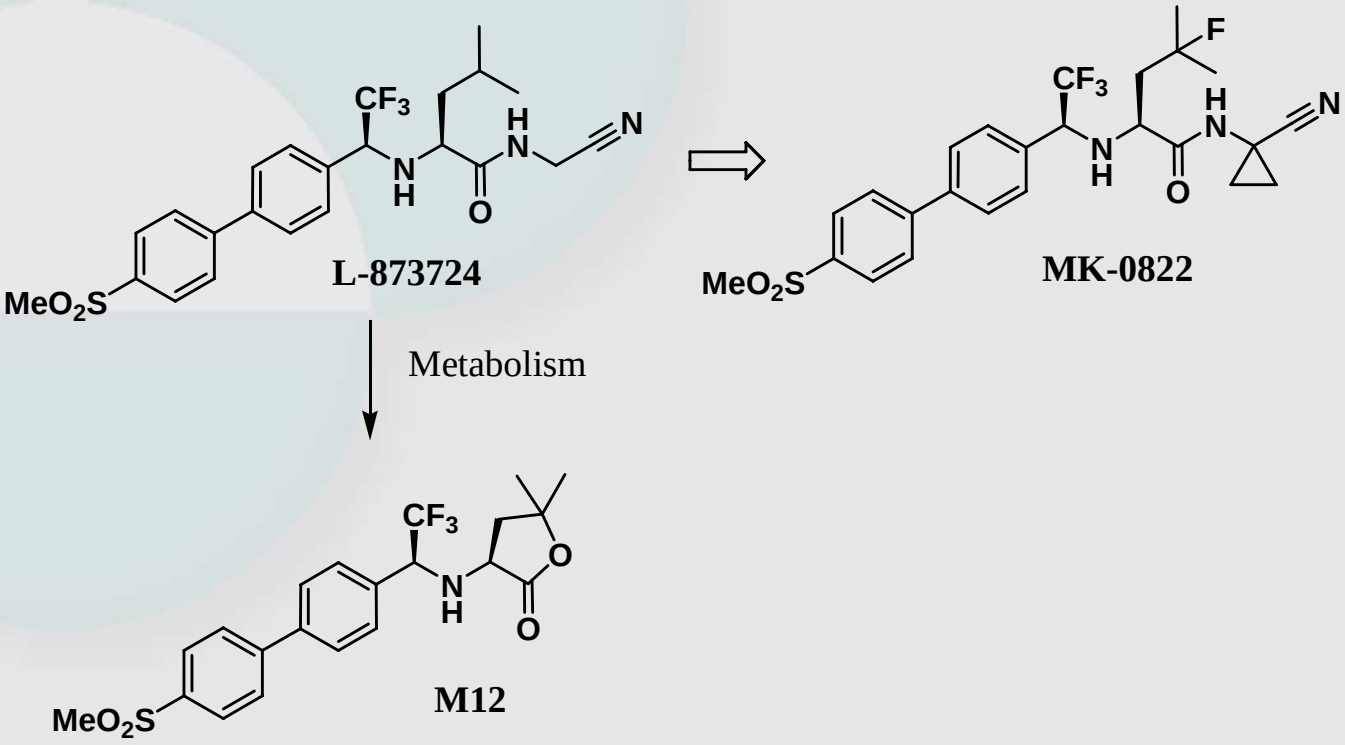
L-006235



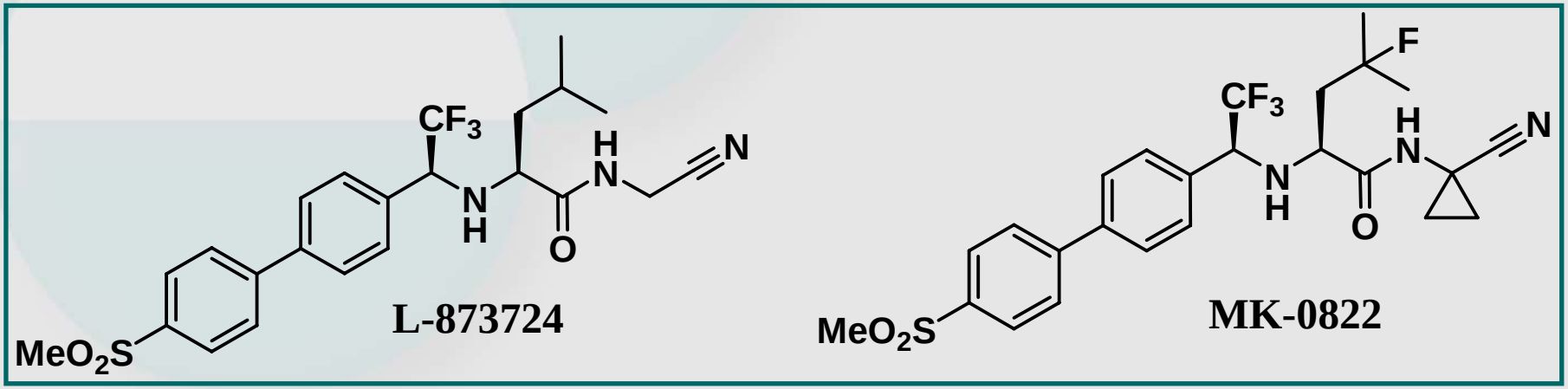
L-873724

- Selectivity profile of L-873724 is maintained in whole cell assays

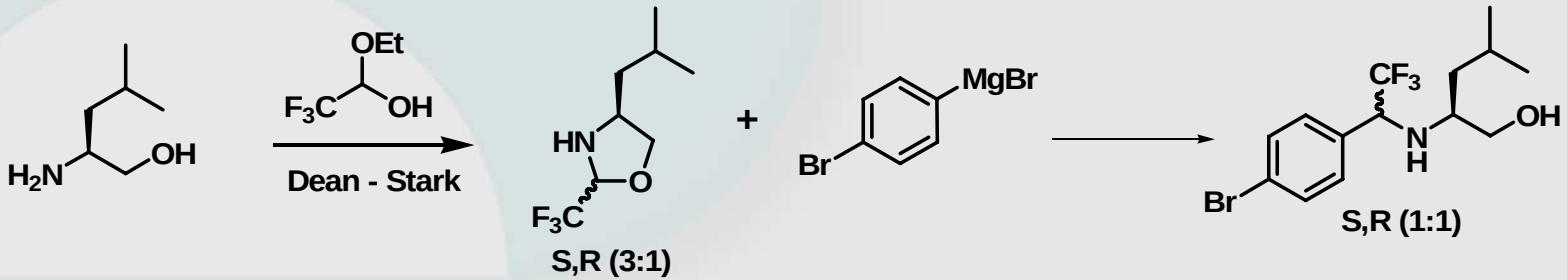
Fixing Metabolic Liabilities

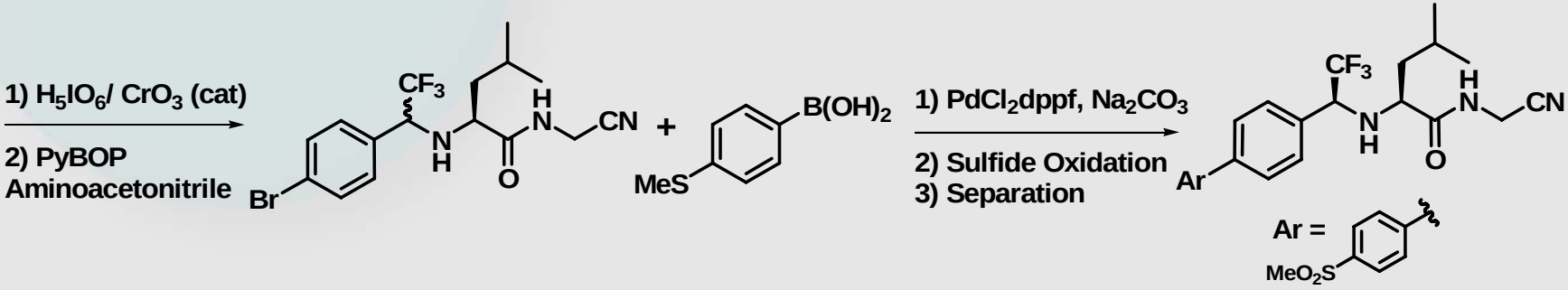


Medicinal Chemistry Synthesis of L-873724 & Odanacatib

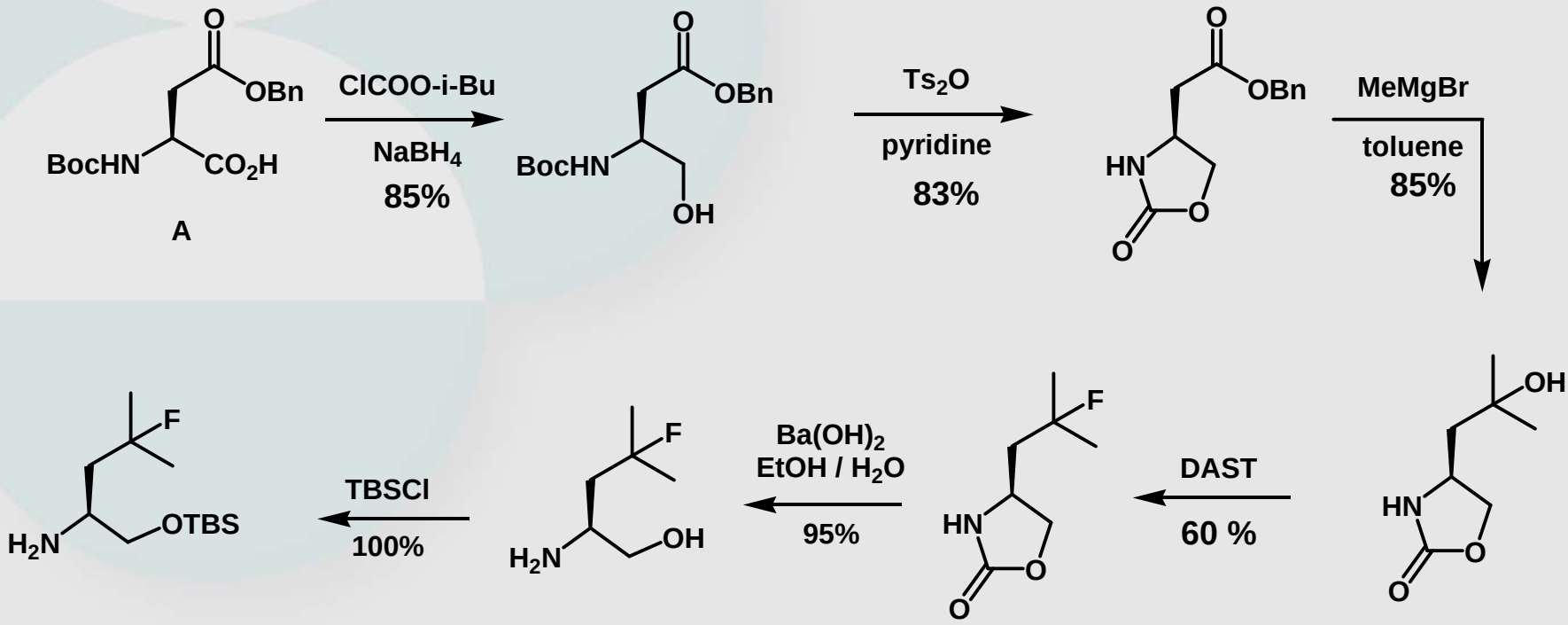


Medicinal Chemistry Approach to L-837724





Medicinal Chemistry Approach to Fluoroleucinol

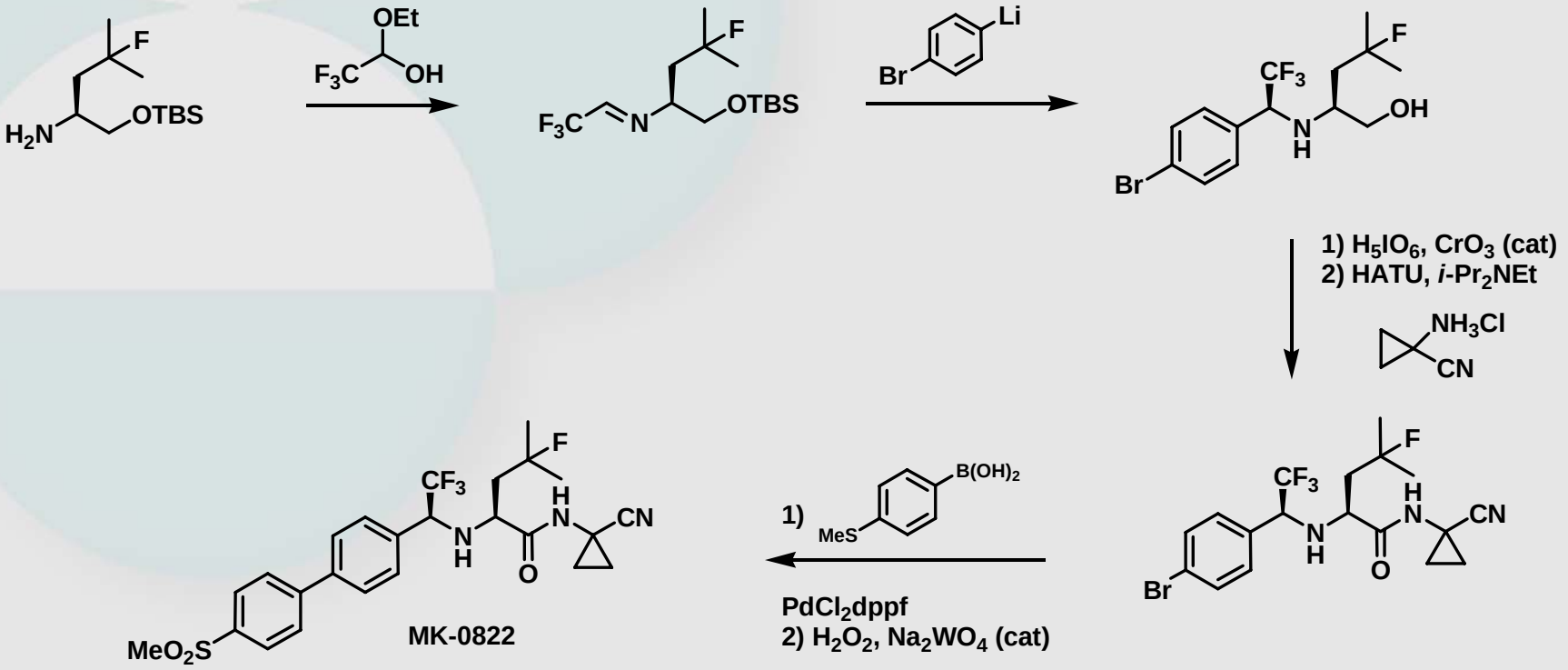


Scale-up Issues:

- **A** is expensive
- Formaiton & work up of 3° alcohol is tedious and irreproducible
- DAST is not a process friendly reagent
- Isolation of Fl-leucinol requires continuous extraction (1 wk)

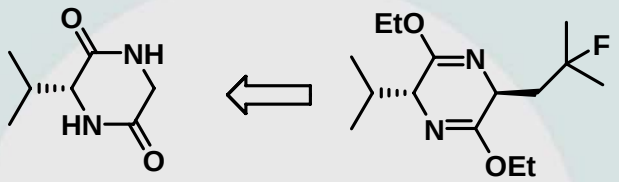
Synthesis of MK-0822

Aryl lithium addition to CF_3-imine

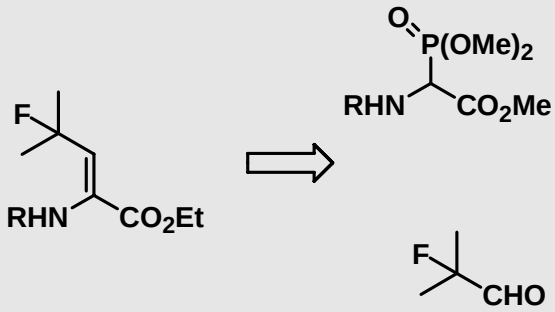


- 40 g of MK-0822 prepared to support characterization
- Oxidation state issues
- Protecting group manipulations
- Pd in final step
- HATU

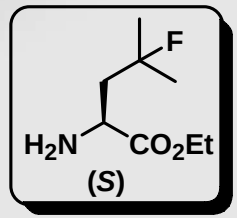
Fluoroleucine-Retrosynthesis

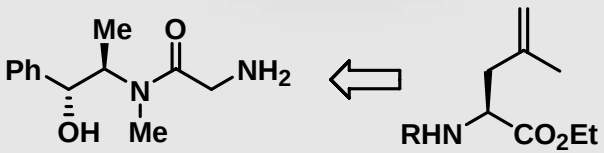


Schoellkopf Alkylation

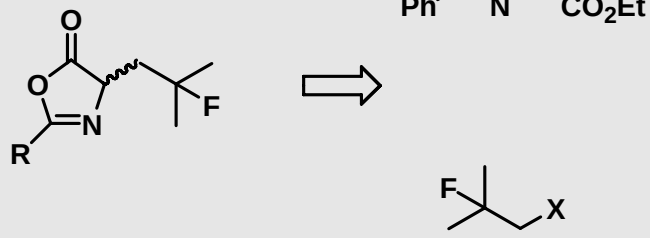


Enamide Hydrogenation



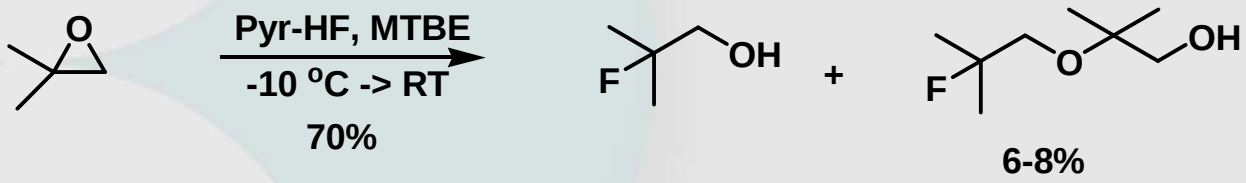


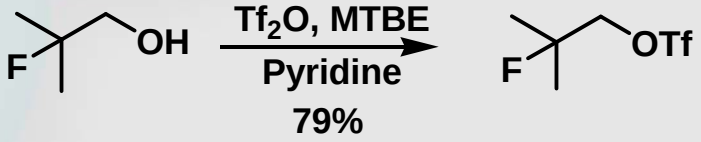
Alkylation/Hydrofluorination



Oxazolinone Resolution

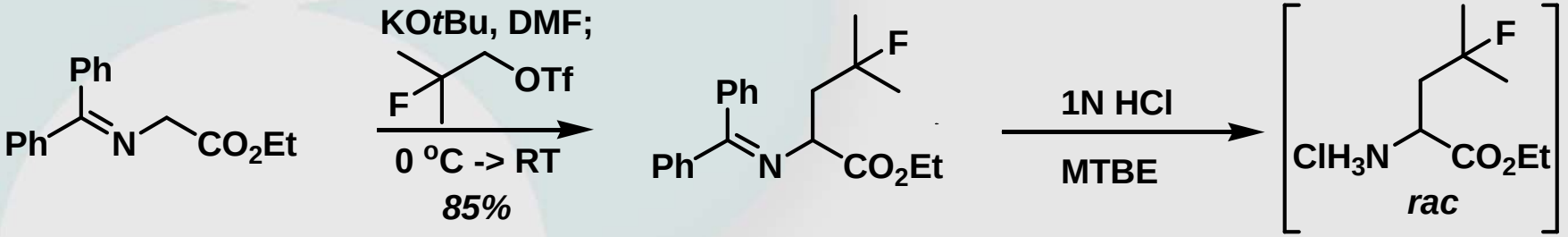
Synthesis of F-Containing Electrophiles

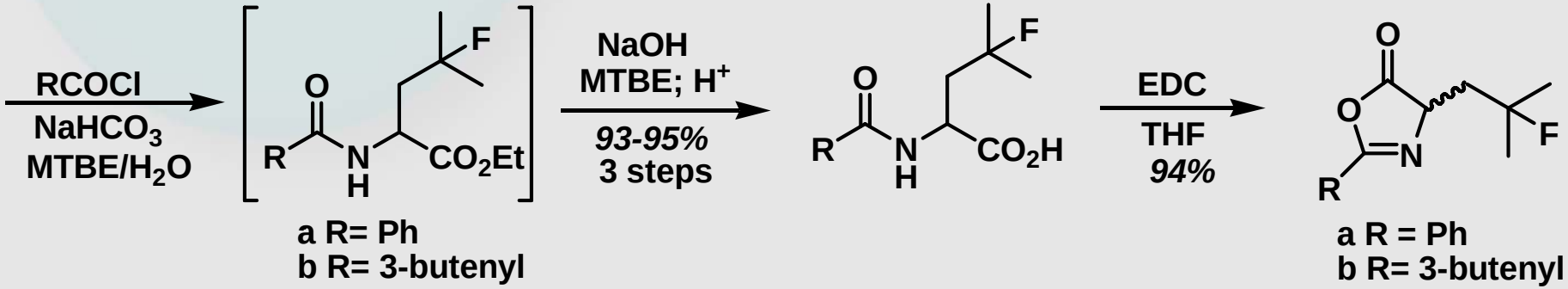




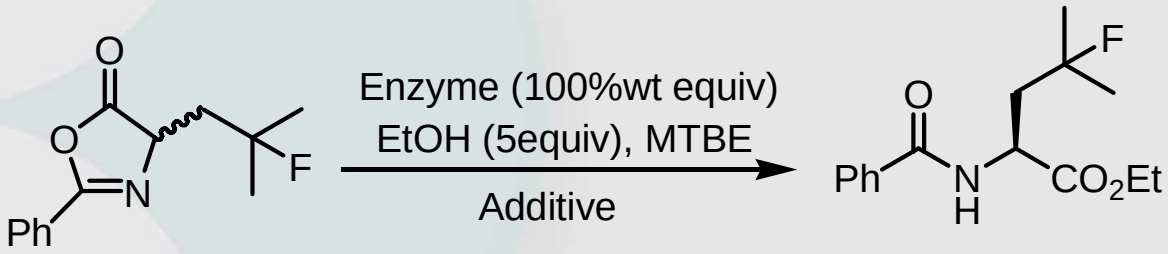
- OTs, I and Br analogues were insufficiently reactive electrophiles

Synthesis of Oxazolinones

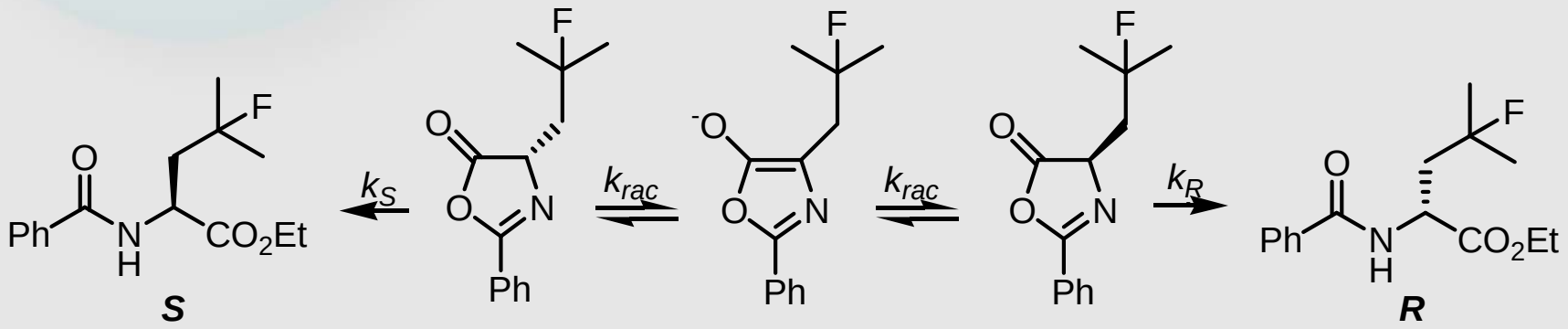




Dynamic Kinetic Resolution of Oxazolinones



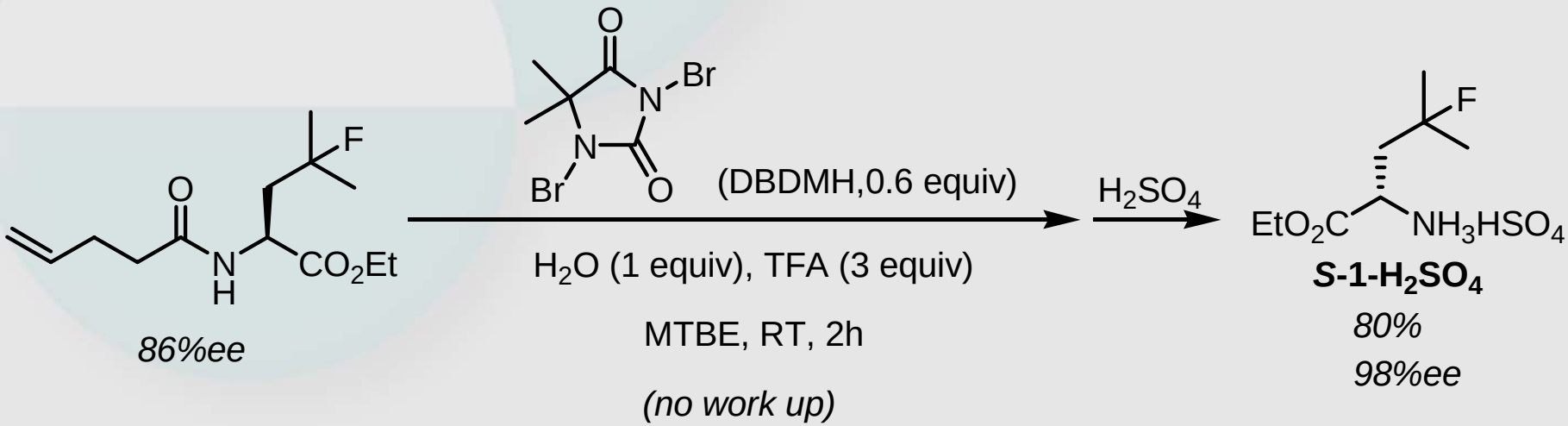
Enzymes	Additive	Temp (^oC)	Time (h)	Results	
				ee (%)	Yield (%)
none	none	50	48		<2
Immobilized Lipase CAL B (*Novozyme-435*)	none	50	12	70	
	none	37	16	84	
	Et_3N (20mol%)	37	4	94	73
	Et_3N (20mol%)	**25**	**4**	**95**	**80**



$k_{rac}>>>k_S>>k_R$

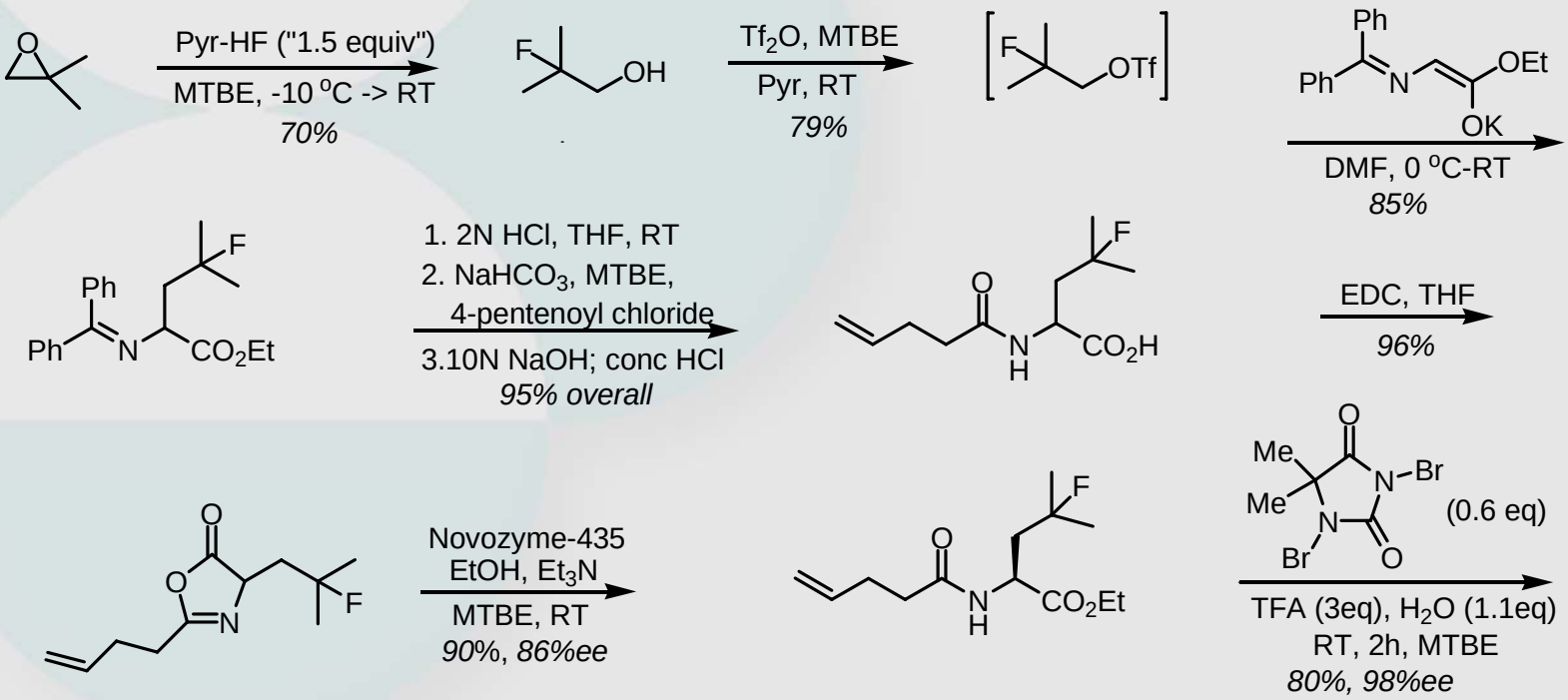
Limanto, J.; Shafiee, A.; Devine, P.N.; Upadhyay, V.; Desmond, R.A.; Foster, B.S; Gauthier, D.; Reamer, R.A. Volante, R.P. *J. Org. Chem*. **2005**, *70*, 2372

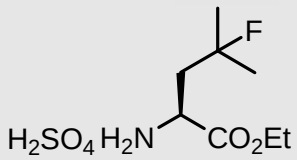
Deprotection of N-Pentenamide F-Leucine Ester



Limanto, J.; Shafiee, A.; Devine, P.N.; Upadhyay, V.; Desmond, R.A.; Foster, B.S; Gauthier, D.; Reamer, R.A. Volante, R.P. *J. Org. Chem*. **2005**, *70*, 2372

Fluoroleucine Synthetic Sequence



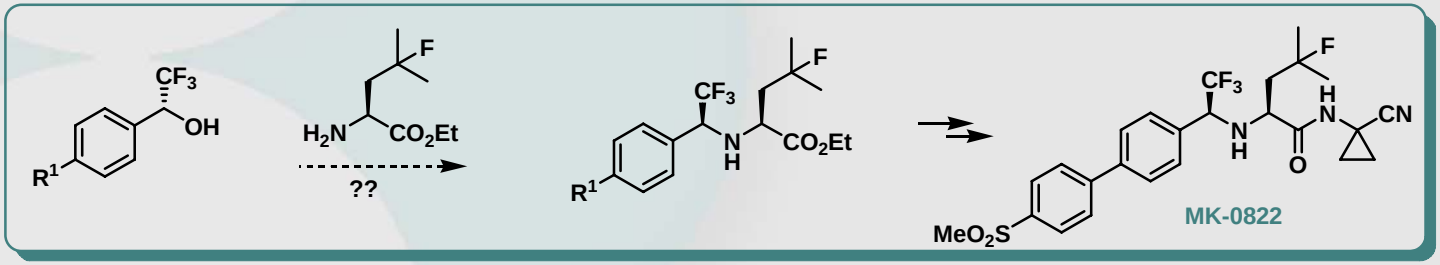


1 Isolation, 33% overall yield
>250 kg prepared

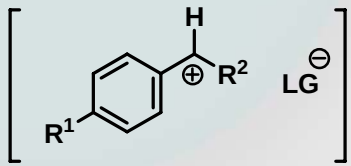
Limanto, J.; Shafiee, A.; Devine, P.N.; Upadhyay, V.; Desmond, R.A.; Foster, B.S; Gauthier, D.; Reamer, R.A. Volante, R.P. *J. Org. Chem.* **2005**, *70*, 2372

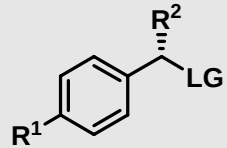
Nucleophilic Displacement Route

"Two wrongs makes a right"

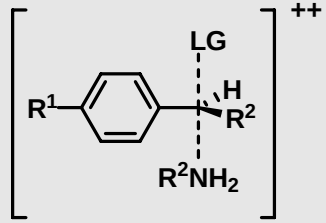


S_N1 Displacement:

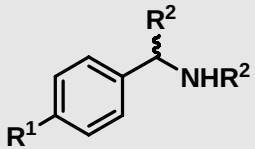




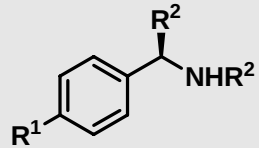
RNH_2



RNH_2



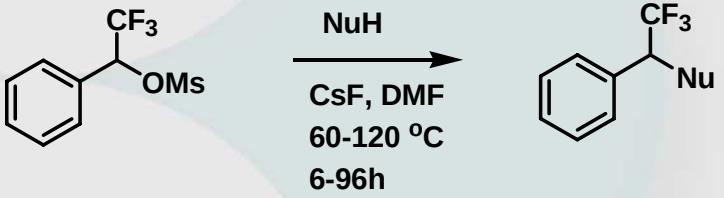
-Racemization



-Inversion

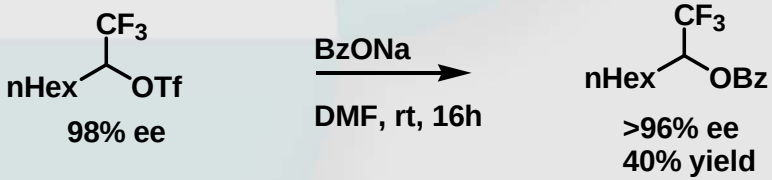
S_N2 Displacement:

S_N2 Displacement Approach

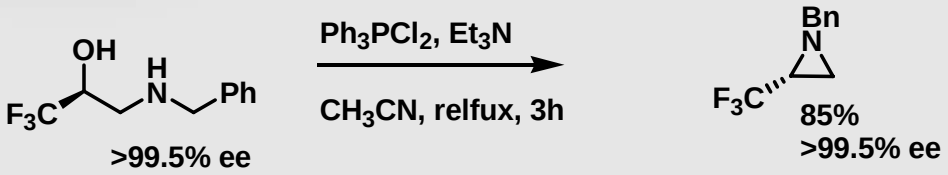


Nu	%Yield
BzO^-	61
PhS^-	71
$PhthN^-$	11

Hagiwara, T.; Tanaka, K.; Fuchikami, T. *Tetrahedron Lett.* **1996** , *37*, 8187.



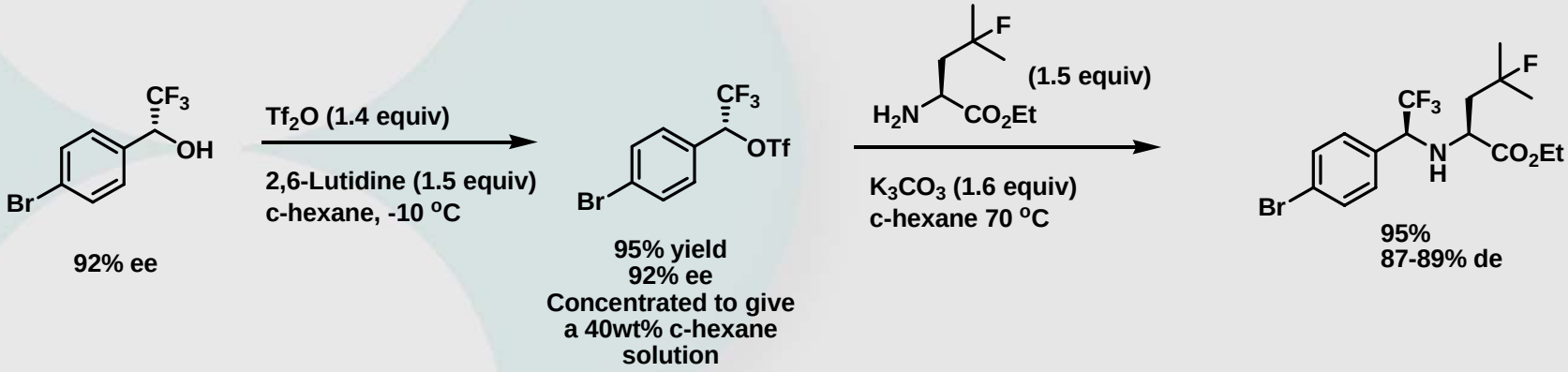
Hagiwara, T.; Ishizuka, M.; Fuchikami, T. *Nippon Kagaku Kaishi* **1998**, *11*, 750.



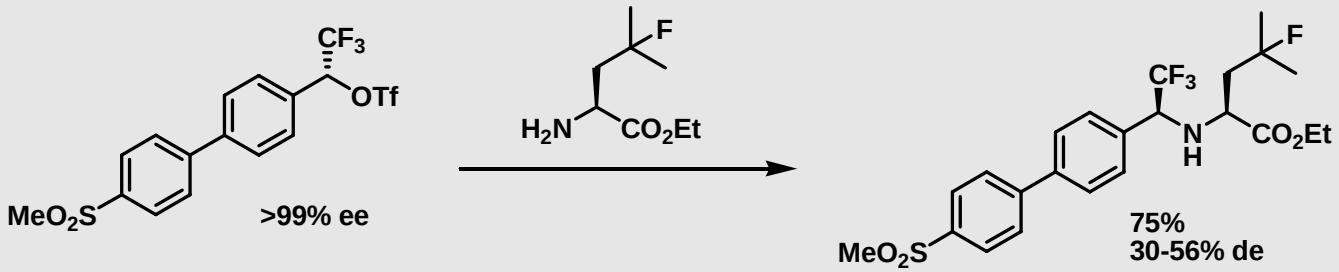
Katagiri, T.; Ihara, H.; Takahashi, M.; Kashino, S.; Furuhashi, K.; Uneyama, K. *Tetrahedron: Asymmetry*, **1997**, *8*, 2933.

S_N2 Displacement Approach

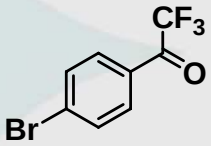
Ideal Displacement Condition



- **Erosion of Stereochemistry is minimized by:**
  - **lower temperatures**
  - **non-polar solvents**
  - **insoluble triflate salt**
  - **concentrated reactions**
  - **electron deficient substrates**

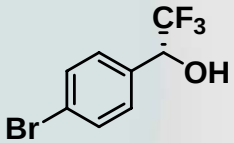


Kg Scale Delivery - Displacement Approach



CatBH

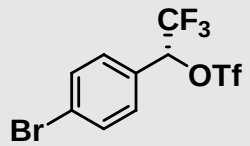
(*S*)-*n*-Bu-OAB (2.5 mol%)
Toluene, -70 to -30 °C, 21h



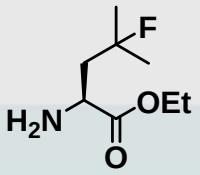
97%
92% ee

Tf_2O

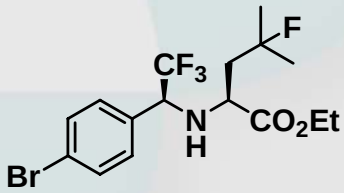
2,6-Lutidine
c-Hexane, -15 °C



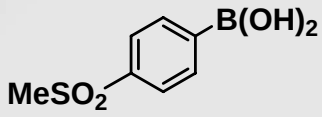
94%
92% ee



K_2CO_3
c-Hexane, 75 °C, 18h

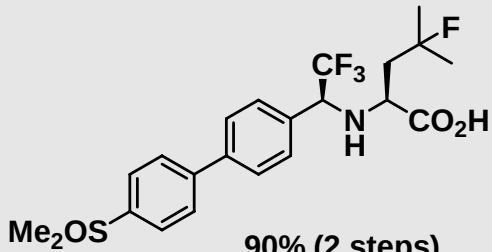


92%
dr = 13 : 1
(~3% erosion at
the benzylic center)

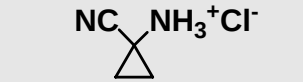
1) 

$Pd(OAc)_2$ (0.5 mol%)
$(o\text{-tol})_3P$ (1.25 mol%)
Na_2CO_3, THF/H_2O, reflux, 2h

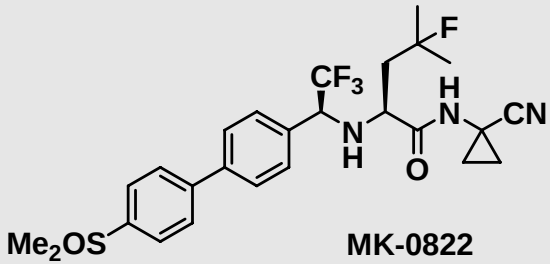
2) NaOH



90% (2 steps)
dr = 12.2 : 1



HATU, DIEA, DMAc



MK-0822

THF/H_2O

Recrystallization

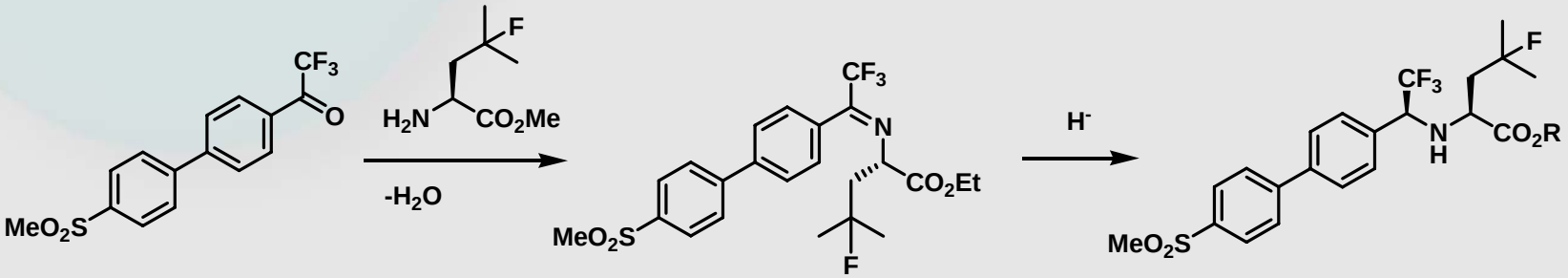
2.1 kg prepared

S_N2 Displacement Approach

Issues with the Synthesis

To be Addressed in Long Term Route

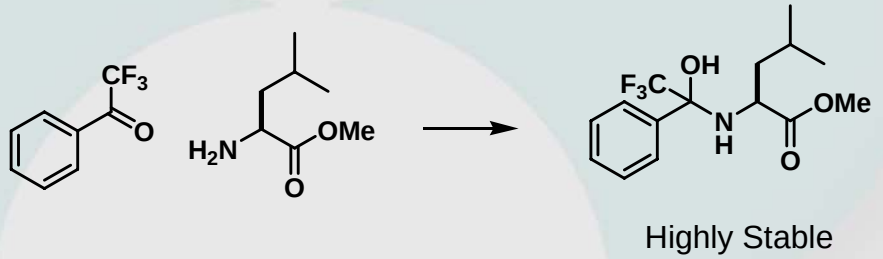
- Creates a stereocenter, then tries hard to retain it
- Not optimally convergent as the Suzuki coupling can not be performed off-line
- Fl-leucine salt break
- These problem could both be addressed with a reductive amination approach:



Barriers to Reductive Amination with 2,2,2-Trifluoroacetophenones

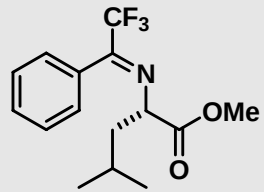
Issues:

A. Dehydration of tetrahedral aminal intermediates.



Highly Stable

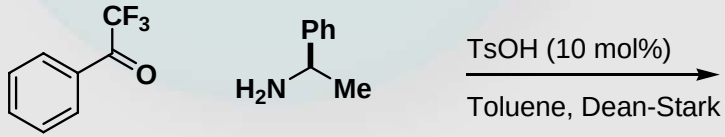
$TiCl_4$ or TsOH/Toluene (reflux)



<30% Yield, extensive decomposition

C.L. Barney, E.W. Huber, J.R. McCarthy, *Tetrahedron Lett.* **1990**, *31*, 5547

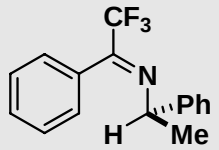
B. Facial selectivity of the reductions.



TsOH (10 mol%)

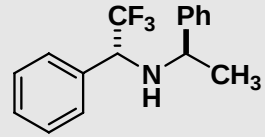
Toluene, Dean-Stark

-Pirkle, W.H.; Hauske J.R. *J. Org. Chem.* **1977**, *42*, 2436

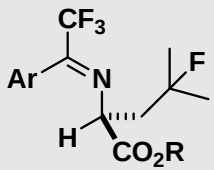


Red-Al

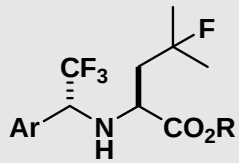
THF, -78°C



95%
dr = 9 : 1

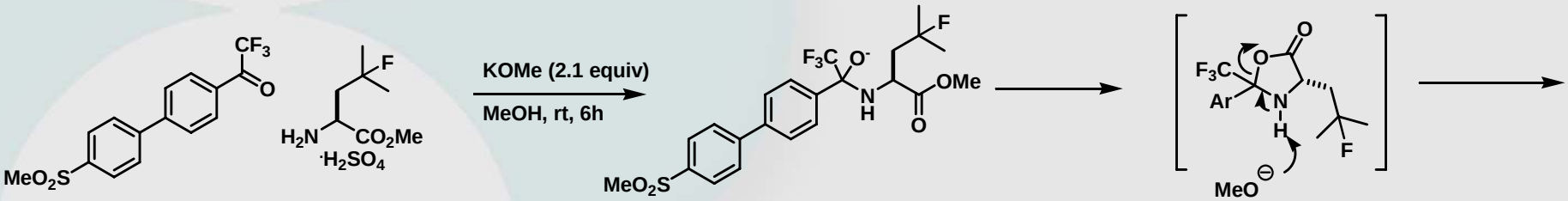


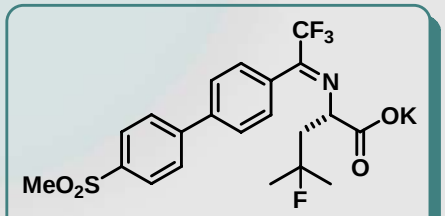
$H^{\ominus}$



Reductive Amination Approach

Base Mediated Imine Formation



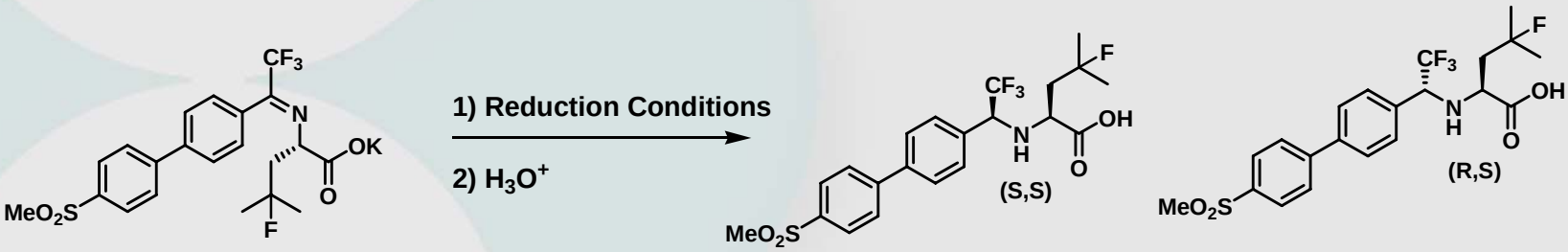


- **Single imine isomer**
- ***E* geometry confimed by nOe between ^{i}Bu and o-protons**

Hughes, G., Devine, P. N.; Naber, J. R.; O'Shea, P. D.; Foster, B. S.; McKay, D.; Volante, R. P., *Angew. Chem., Int. Ed*. **2007**, *45*, 1839.

Reductive Amination Approach

Develepment of an (*S*,*S*) Selective Reduction



Entry	Reduction Conditions	%Conv(%Yield)	(*S*,*S*) : (*R*,*S*)*
1	H_2 (1 atm), $Pd(OH)_2$/C, MeOH, rt	60	1 : 2
2	CatB-H, *S*-CBS (10 mol%), rt	100	1 : 5
3	Red-Al, THF, 0^{o}C	100(40)	1 : 26
4	$NaBH_4$, THF/ H_20, rt	100(86)	1 : 25
5	$Zn(OTf)_2$, CatB-H, THF, rt	100(80)	3 : 1
6	$NaBH_4$, $ZnCl_2$, THF, rt	100	2 : 1

* Determined by ^{19}F NMR

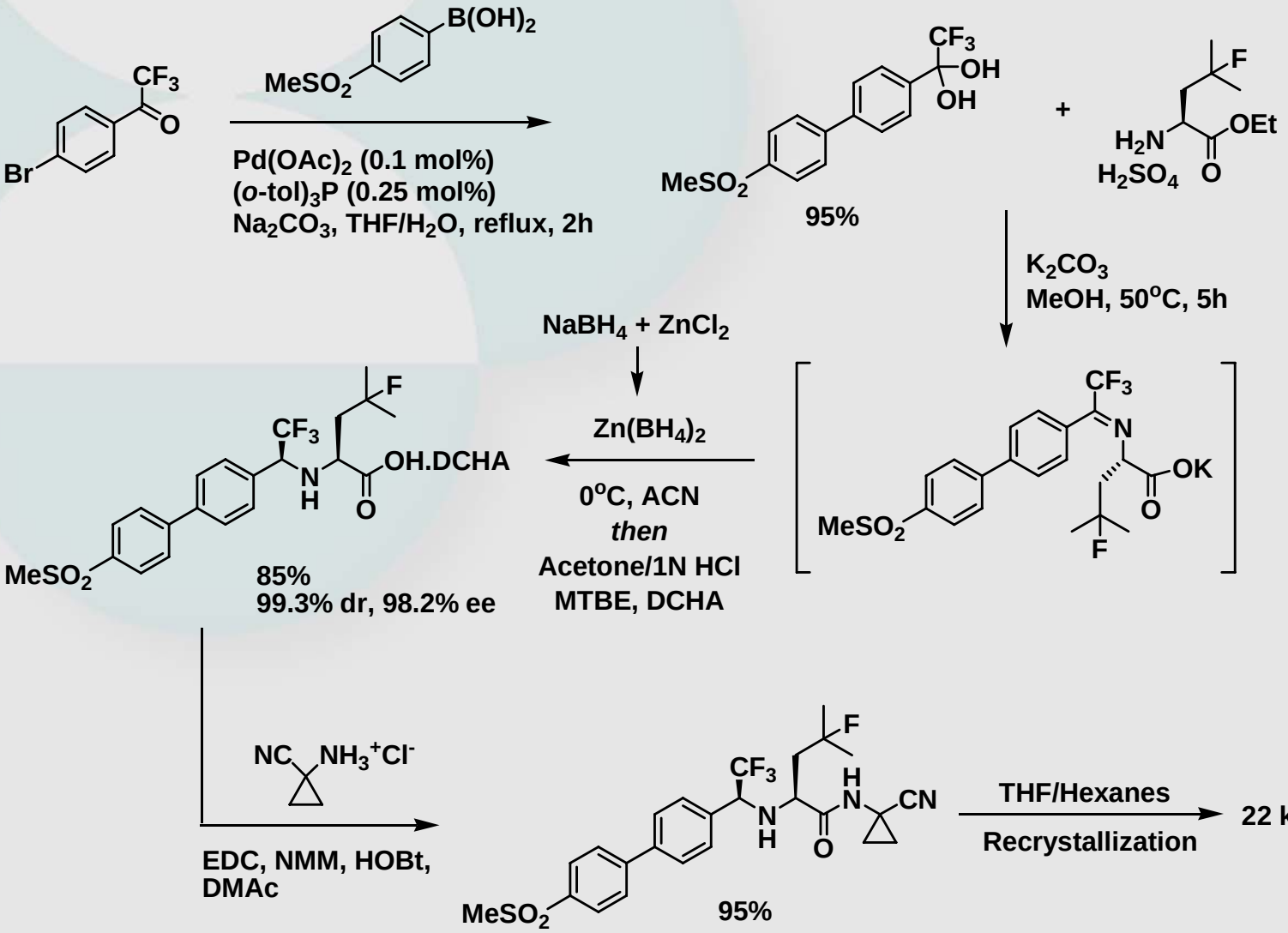
Reductive Amination Approach

Develepment of an (*S*,*S*) Selective Reduction

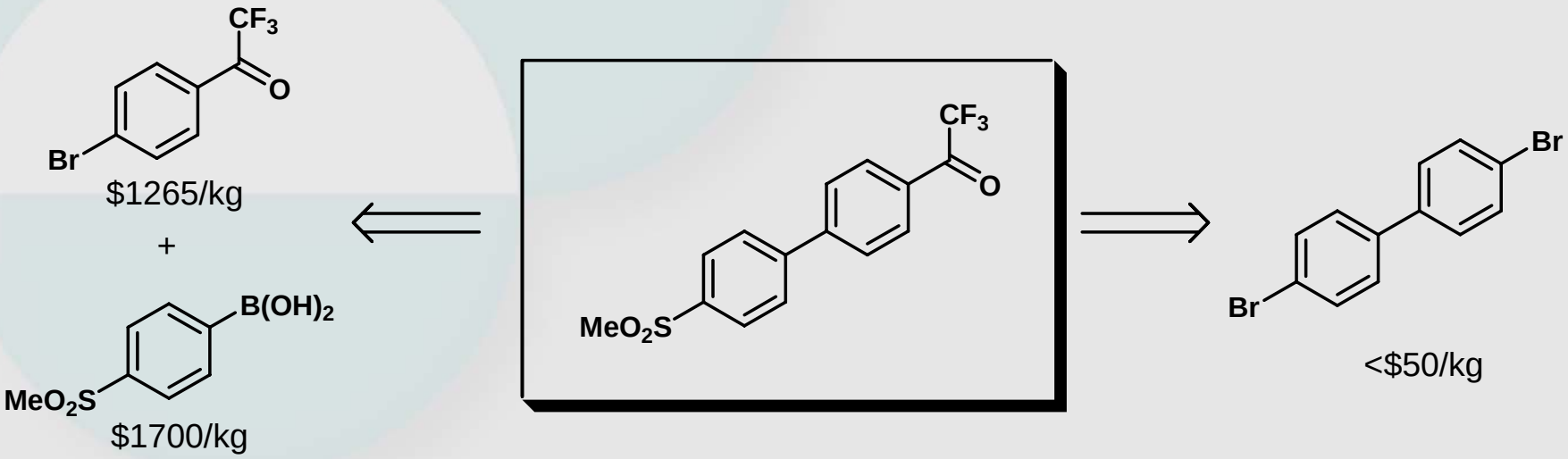
Entry	Solvent	Temp (^{o}C)	Yield	(*S*,*S*) : (*R*,*S*)*
1	Toluene	23	90	1 : 1
2	MTBE	23	90	1.6 : 1
3	THF	23	90	2 : 1
4	MeOH	23	50	1 : 3
5	CH_3CN	23	90	8 : 1
6	CH_3CN	-10	95	17 : 1

* Measured by ^{19}F NMR analysis

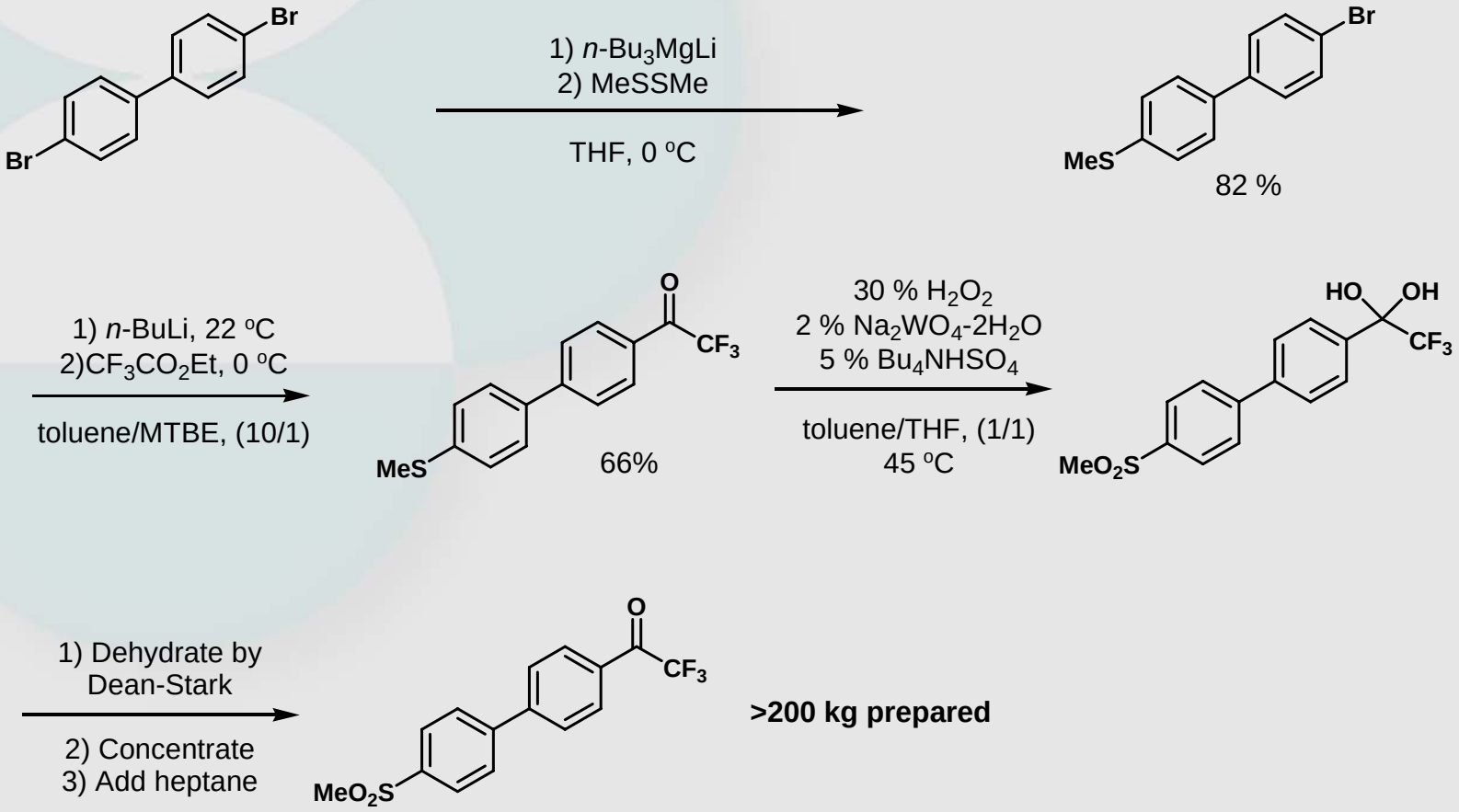
Kg Scale Delivery – Reductive Amination Approach



Cost of Biaryl Fragment

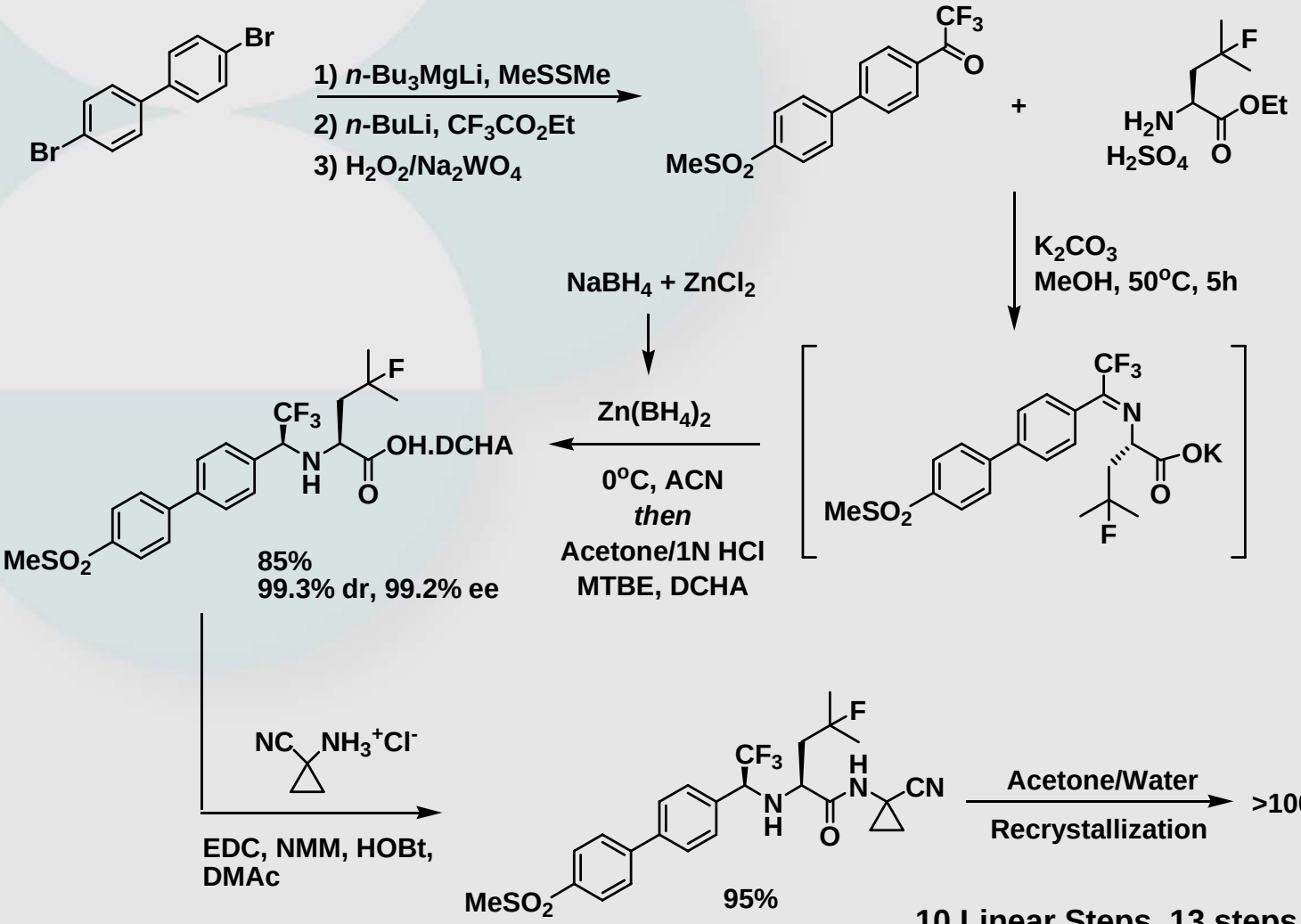


Biaryl Synthesis



Dolman, S.J.; Gosselin, F.; O'Shea, P.D.; Davies, I.W. *Tetrahedron* **2006**, *62*, 5092

Optimized Route



10 Linear Steps, 13 steps total
25%overall yield from isobutylene oxide

Conclusions

- Diastereoselective organometallic addition to trifluoroethyl imines generated from oxazolidines was developed.
- An asymmetric synthesis of fluoroleucine was developed using an enzyme mediated aza-lactone ring opening.
  - > 250 kg have been prepared.
- A first generation synthesis featuring an unprecedented S_N2 displacement of a chiral benzyltrifluoromethyl alcohol with an amino ester was developed.
  - 2.1 kg of Odanacatib prepared.
- A second generation synthesis featuring a new $Zn(BH_4)_2$ mediated *syn* selective reduction of a trifluoromethyl imine was developed.
  - >120 kg of Odanacatib prepared.

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