Research Topic Seminar

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9/24/2016

Outline

- Ph. D. work

  1. Deoxyfluorination of Catechols

  2. Fluorination-Rearrangement

     One-pot Reaction

  3. Synthesis of Fluorinated Bioactive compounds

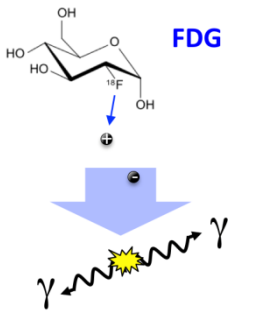
- Current work

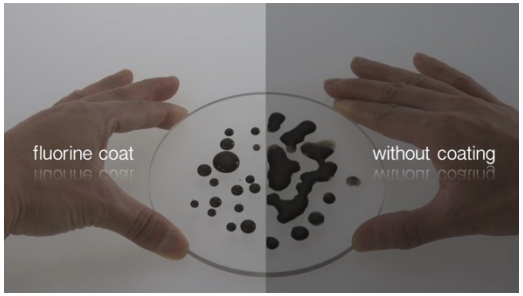
  Discovery for Antagonists of the Nuclear Androgen Receptor

Fluorine in Human Life

F

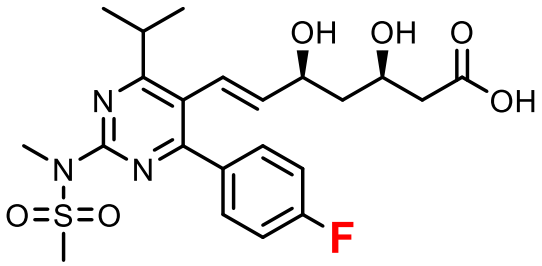
Positron Emission Tomography



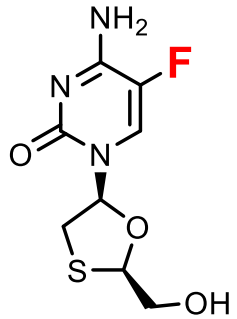


Fluorine in Pharmaceuticals

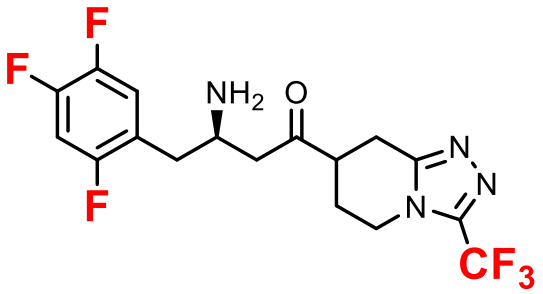
- Potency ↑
- pK_a ↓
- Permeability ↑
- Clearance ↓
- Conformational constraint
- PET



rosuvastatin
(HMG-CoA reductase inhibitor)
treatment of hypercholesterolemia



emtricitabine
nucleoside and non-nucleoside inhibitor
of HIV type 1 reverse transcriptase



Sitagliptin
inhibitors of dipeptidyl peptidase 4 (DPP-4)
antidiabetic drug

J. Med. Chem. **2015**, *58*, 8315−8359

Fluorine in Pharmaceuticals

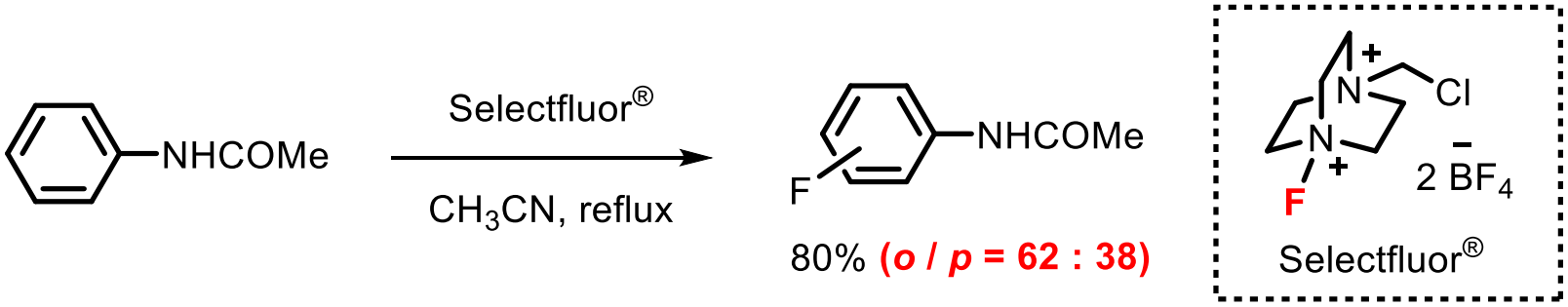
◆ Structural Classification of Fluorine-containing medicines

structure	number	%
Ar-**F**	**113**	**43.5**
Ar-**CF_3**	41	15.8
Ar(het)-**F**	14	5.4
Ar(het)-**CF_3**	5	1.9
Alkyl-**F**	64	24.6
others	23	8.8
Total	260	100

Farumashia **2014**, *1*, 14-18.

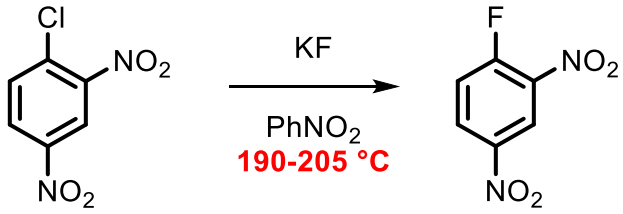
Conventional Aromatic Fluorination

Electrophilic fluorination



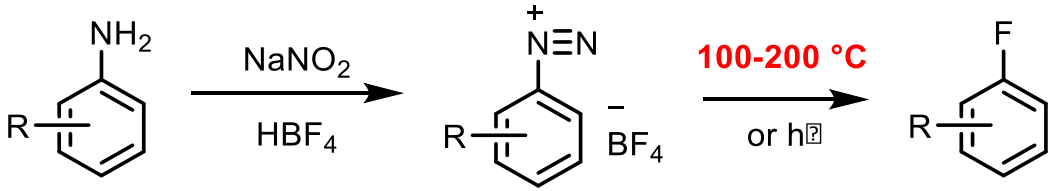
R. E. Banks, S. N. Mohialdin-Khaffaf, G. S. Lal, I. Sharifa, R. G. Syvretb
J. Chem. Soc., chem. comm. **1992**, 595–596.

Halex reaction



G. C. Finger, C. W. Kruse
J. Am. Chem. Soc., **1956**, *78*, 6034–6037.

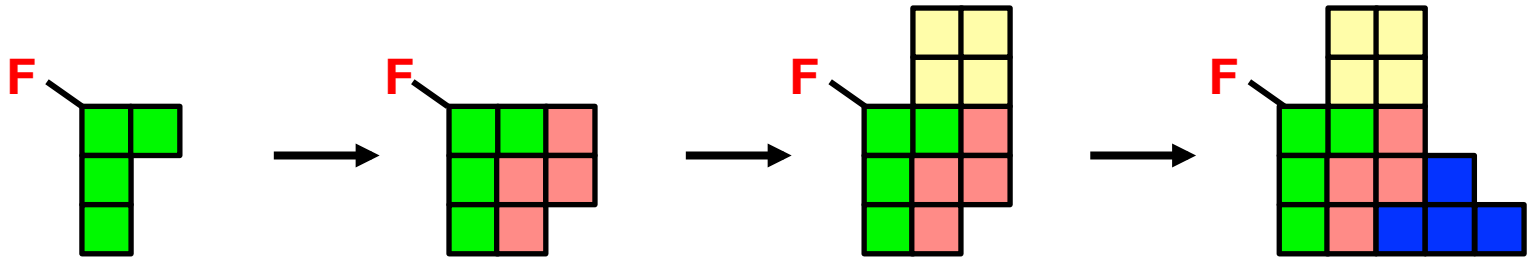
Balz-Schiemann reaction



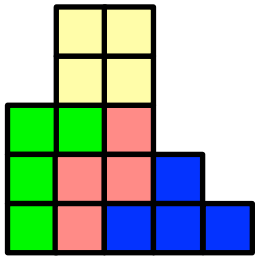
G. Balz, G. Schiemann,
Ber. Dtsch. Chem. Ges. **1927**, *60*, 1186 – 1190

Late-stage Fluorination

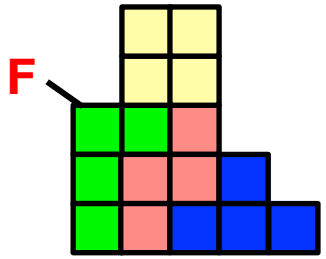
Building Block Approach (Classical approach)



Late-Stage Fluorination (Current approach)

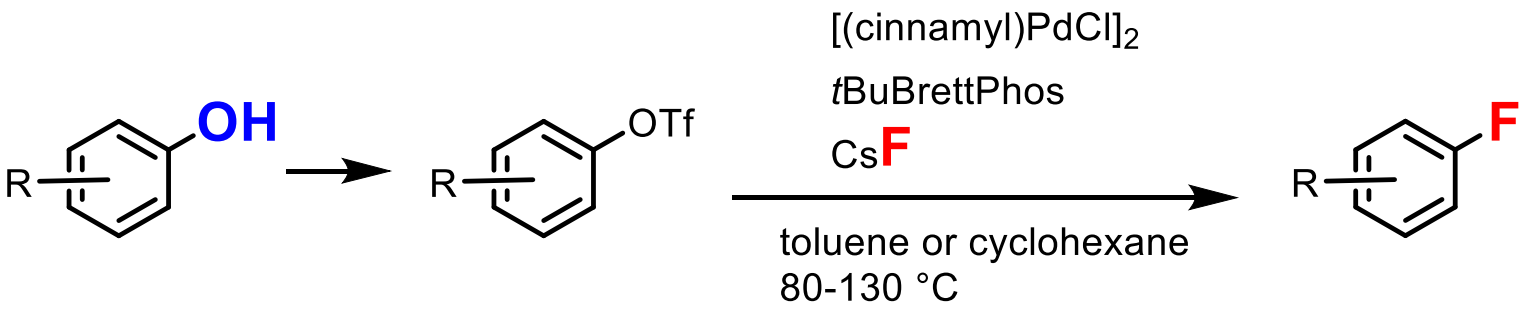


Easily access to various fluorinated analogs !



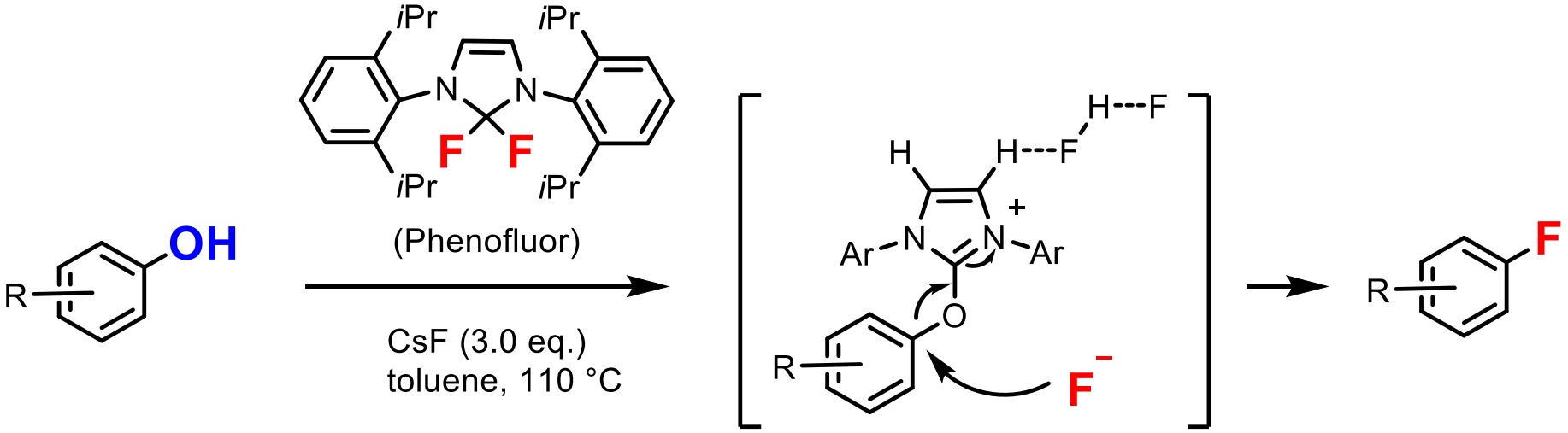
✓ Chemo- and stereoselective fluorination of complex molecules

Deoxyfluorination of Phenols



(R = carbonyl, ester, amino, nitro group, etc.)

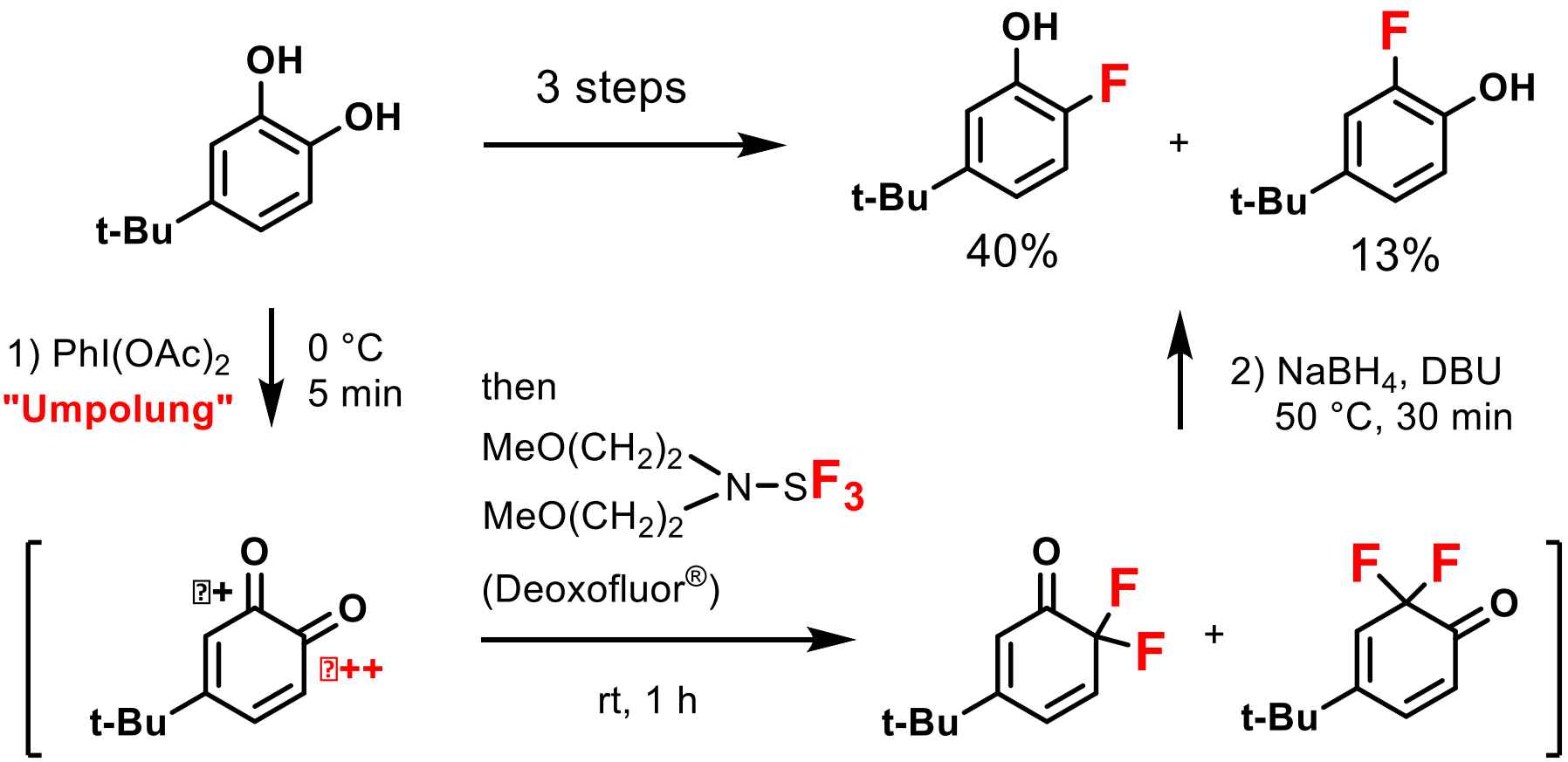
Buchwald, S. L. et al. *Science*, **2009**; *J. Am. Chem. Soc.* **2014**



(R = nitro, ester, carbonyl, halo, amino group, etc.)

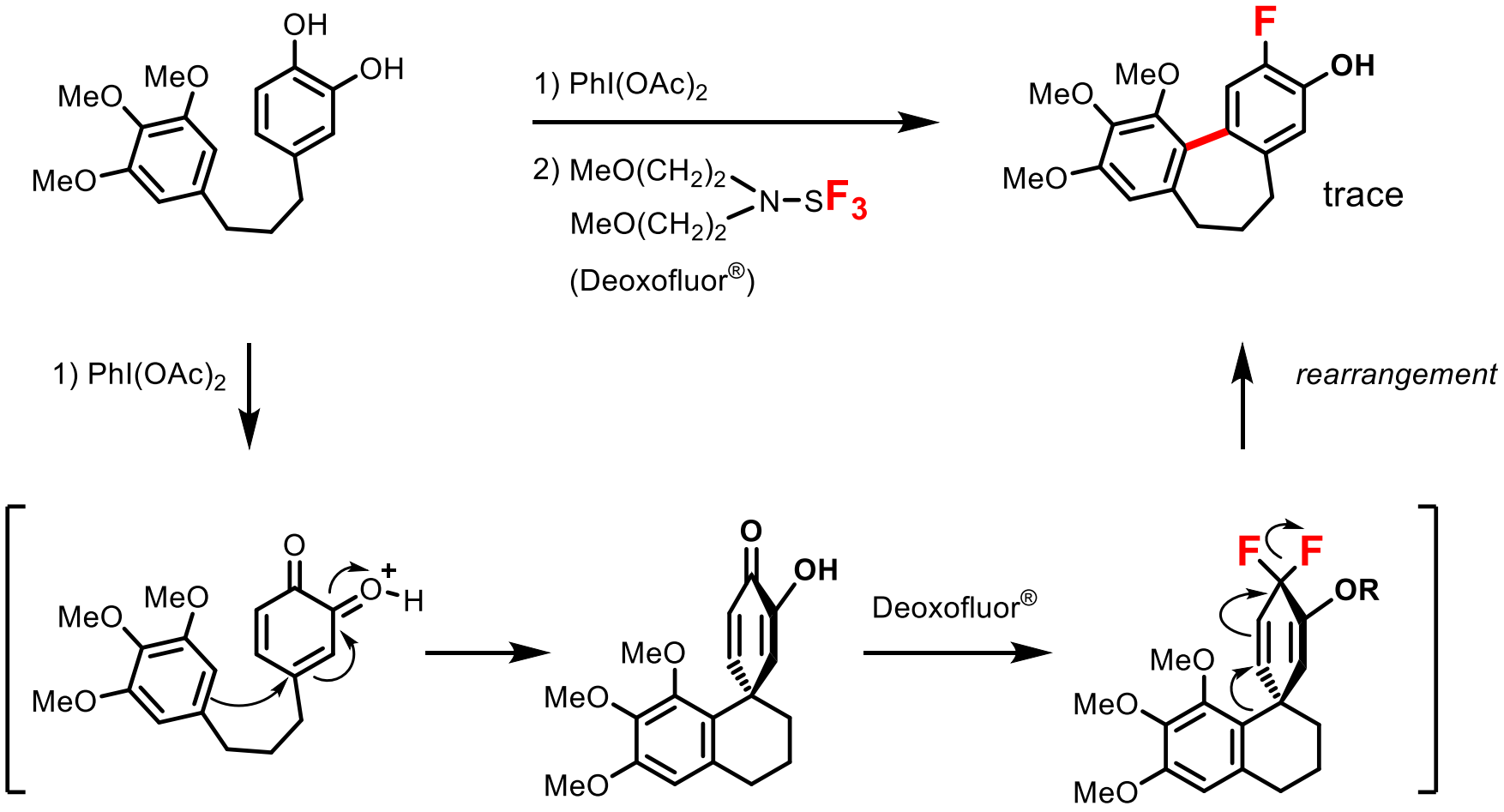
Ritter, T. et al. *J. Am. Chem. Soc.* **2011**, *133*, 11482.; *Org. Proc. Res. Develop.* **2014** , *18*, 1041.

Deoxyfluorination of Catechols



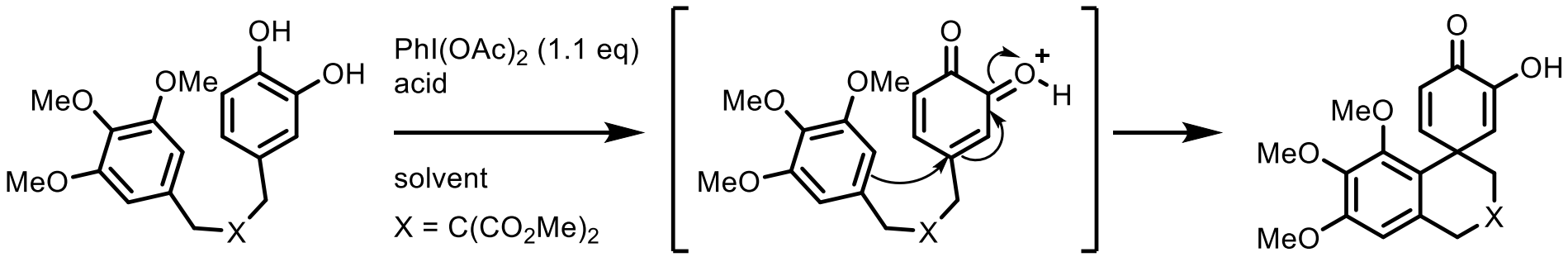
Org. Lett. **2011**, *13*, 2714-2717.

One-pot Fluorination-Rearrangement Reaction



Synlett **2012**, *23*, 1978-1984.

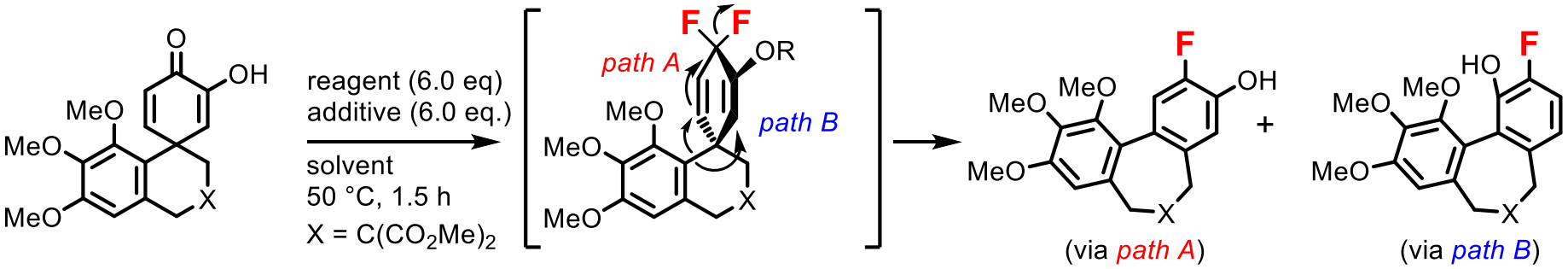
Oxidative Cyclization



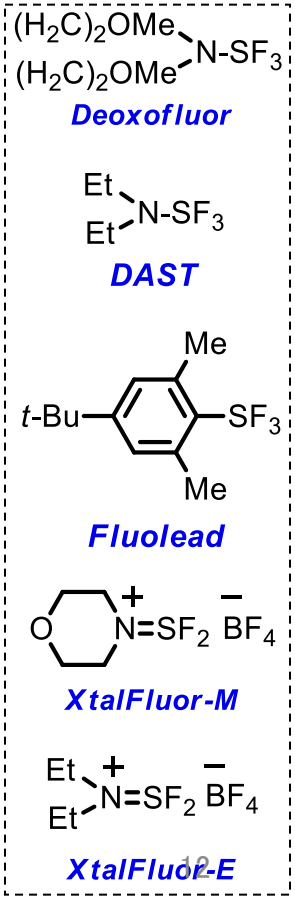
Entry	Solvent	Acid (eq)	Temp (°C)	Time (h)	Yield (%)
1	DME	–	5	48	trace
2	DME	AcOH (5)	5	48	trace
3	DME	TFA (5)	5	48	35
4	DME	TfOH (0.1)	0	1	58
5	**DME**	**MsOH (1)**	**5**	**24**	**95**
6	THF	MsOH (1)	5	24	85
7	dioxane	MsOH (1)	25	24	71
8	Et_2O	MsOH (1)	5	24	66

Synlett **2012**, *23*, 1978-1984.

One-pot Fluorination-Rearrangement Reaction



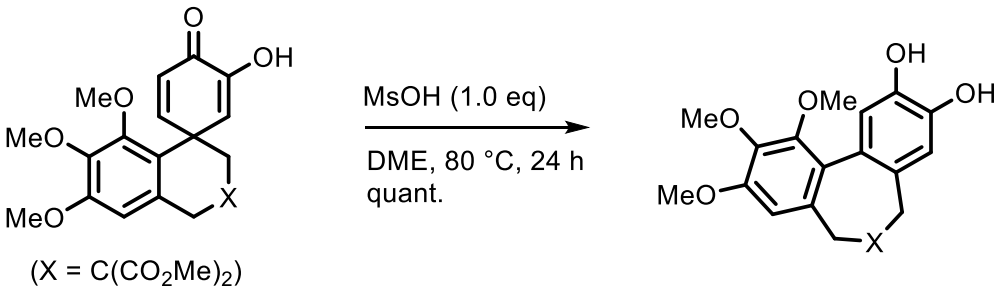
Entry	Reagent	Additive	Solvent	NMR yield (%) [a] Path A	Path B
1	Deoxofluor	–	iPr_2O	40	19
2	DAST	–	iPr_2O	21	15
3	Fluolead	$Et_3N{\cdot}3HF$	iPr_2O	decomposition	
4	XtalFluor-M	$Et_3N{\cdot}3HF$	iPr_2O	decomposition	
5	XtalFluor-E	$Et_3N{\cdot}3HF$	iPr_2O	41	14
6	XtalFluor-E	$Et_3N{\cdot}3HF$	$CHCl_3$	28	5
7	XtalFluor-E	$Et_3N{\cdot}3HF$	$iPr_2O/CHCl_3$ (1:1)	63	16
8	**XtalFluor-E**	**$Et_3N{\cdot}HF$**	**$iPr_2O/CHCl_3$ (1:1)**	**79 (74)[b]**	**21 (18)[b]**



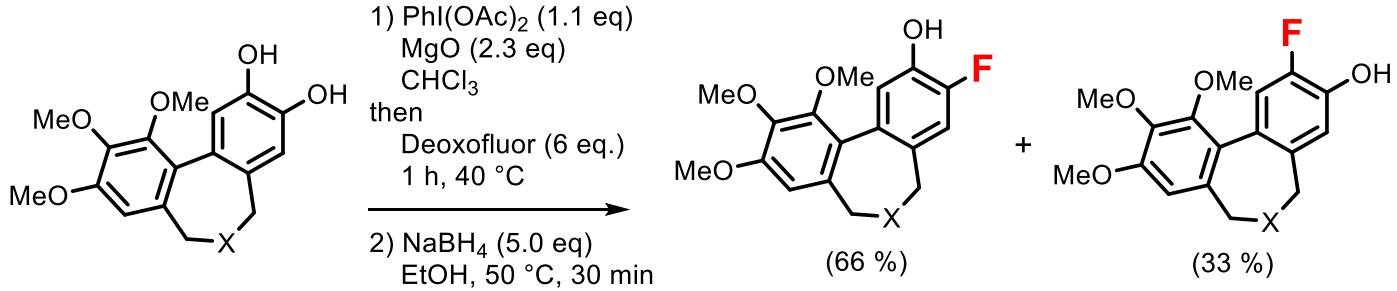
a) The yield was determined by ^1H and ^{19}F NMR using 4-fluorotoluene as the internal standard. b) Isolated yield.

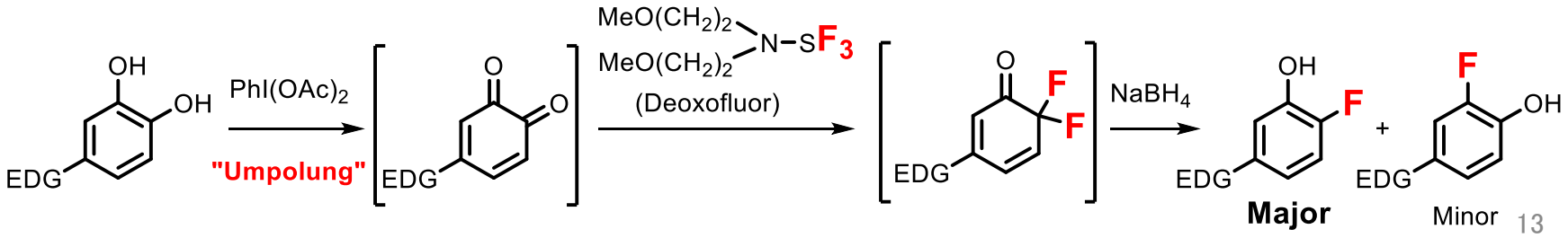
Deoxyfluorination of Catechols

Typical example of substrate synthesis



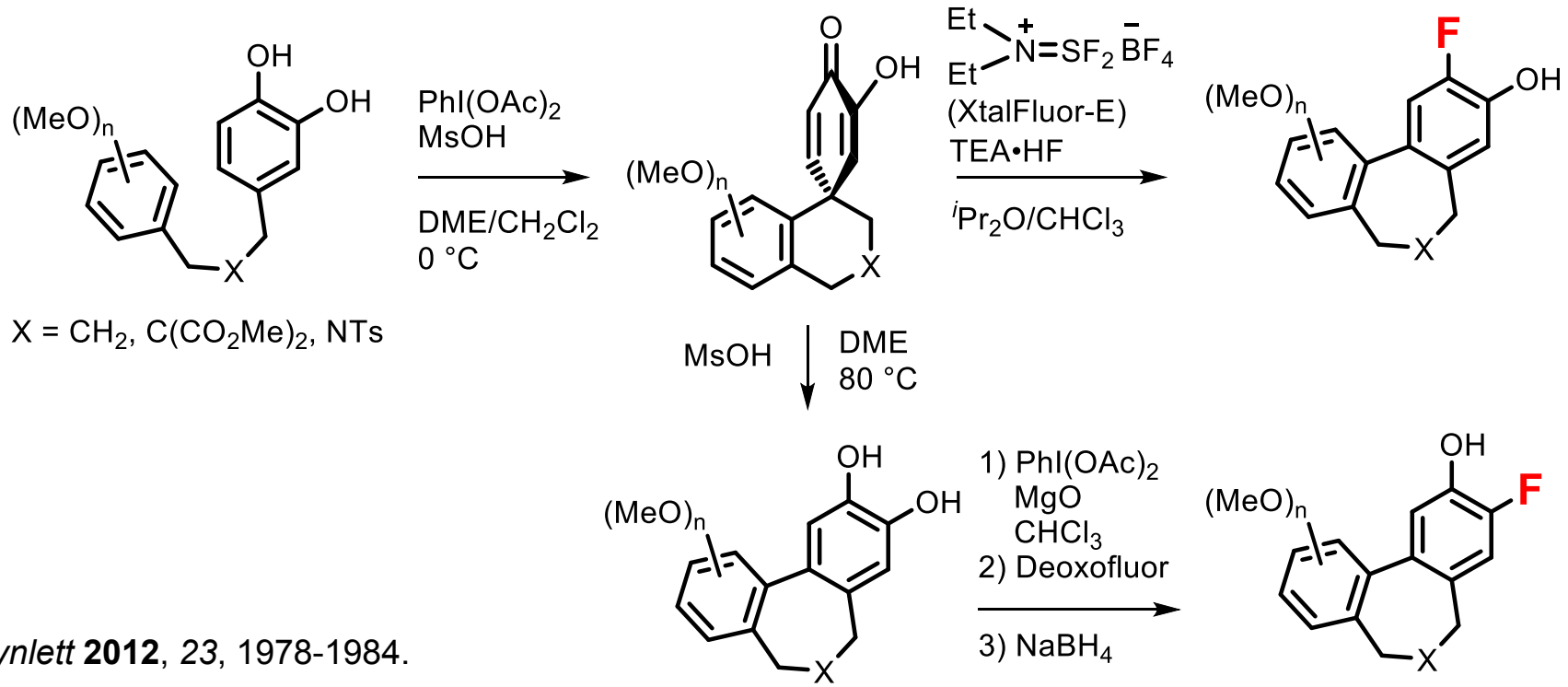
Typical example of fluorination of bridged catechol



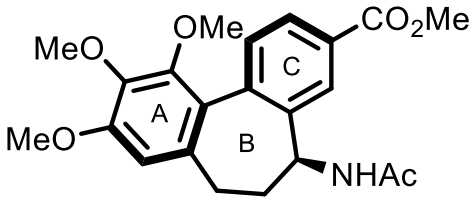


Org Lett. **2011**, *13*, 2714-2717.

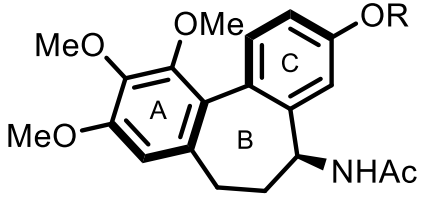
Regiocomplementary Synthesis of Fluorinated Bridged Biphenyls



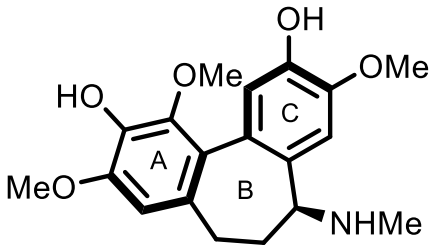
Synlett **2012**, *23*, 1978-1984.



Allocolchicine
（anti-tumor）

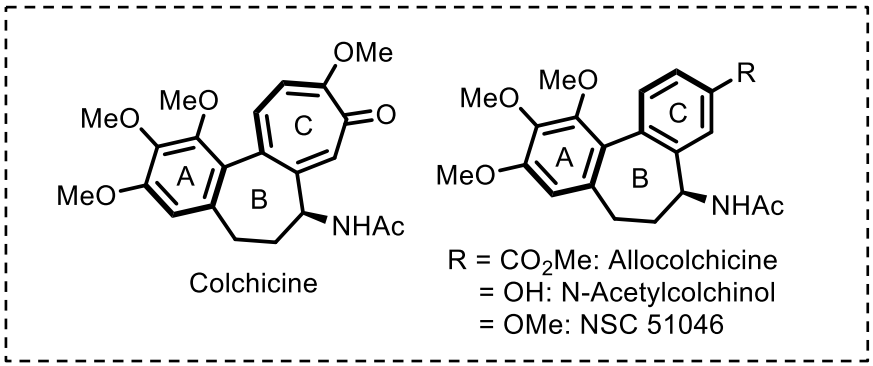


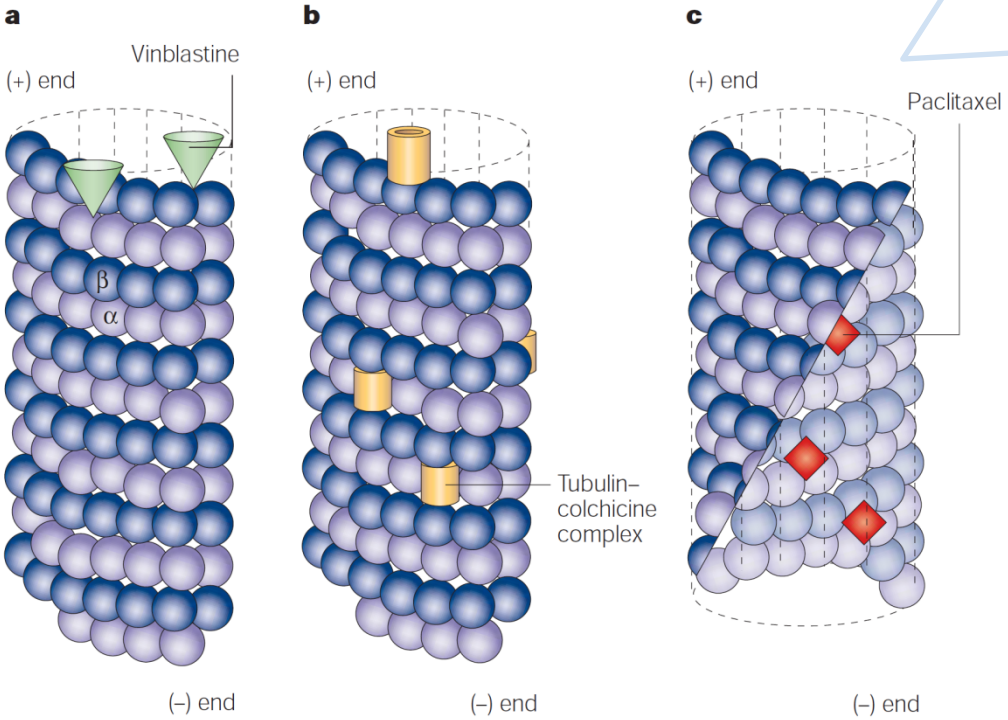
R = H: *N*-acetylcolchinol
= Me: NSC 51046
= $P(O)(OH)_2$: ZD 6126



jerusalemine

Antimitotic drugs

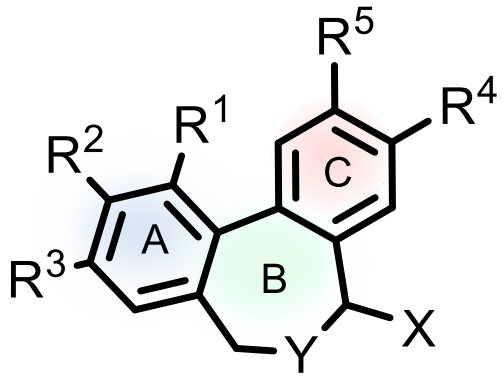




a | A few molecules of vinblastine bound to high-affinity sites at the microtubule plus end suffice to suppress microtubule dynamics.
b | Colchicine forms complexes with tubulin dimers and copolymerizes into the microtubule lattice, suppressing microtubule dynamics.
c | A microtubule cut away to show the interior surface is shown. Paclitaxel binds along the interior surface of the microtubule, suppressing its dynamics.

Nat. Rev. Cancer **2010**, *10*, 194–204

SAR studies of Allocolchicinoids

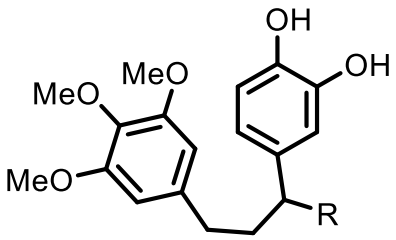


Zone A:
Essential for activities

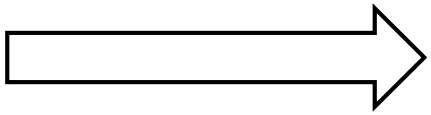
Zone B:
Regulate dihedral angle between A-ring and C-ring

Zone C:
Possible enhancement of the activities

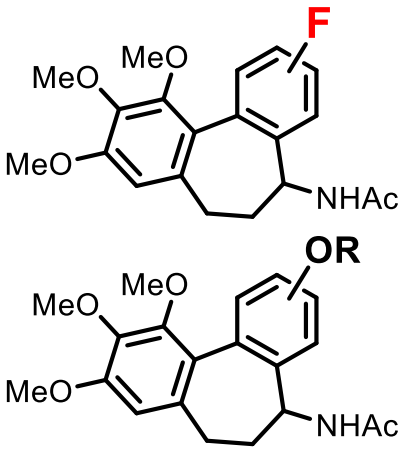
1) *Bioorg. Chem*. **2010**, *38*, 149–158
2) *Bioorg. Med. Chem. Lett*. **2012**, *22*, 3776–3780
3) *J. Med. Chem.* **2015**, *58*, 692–704



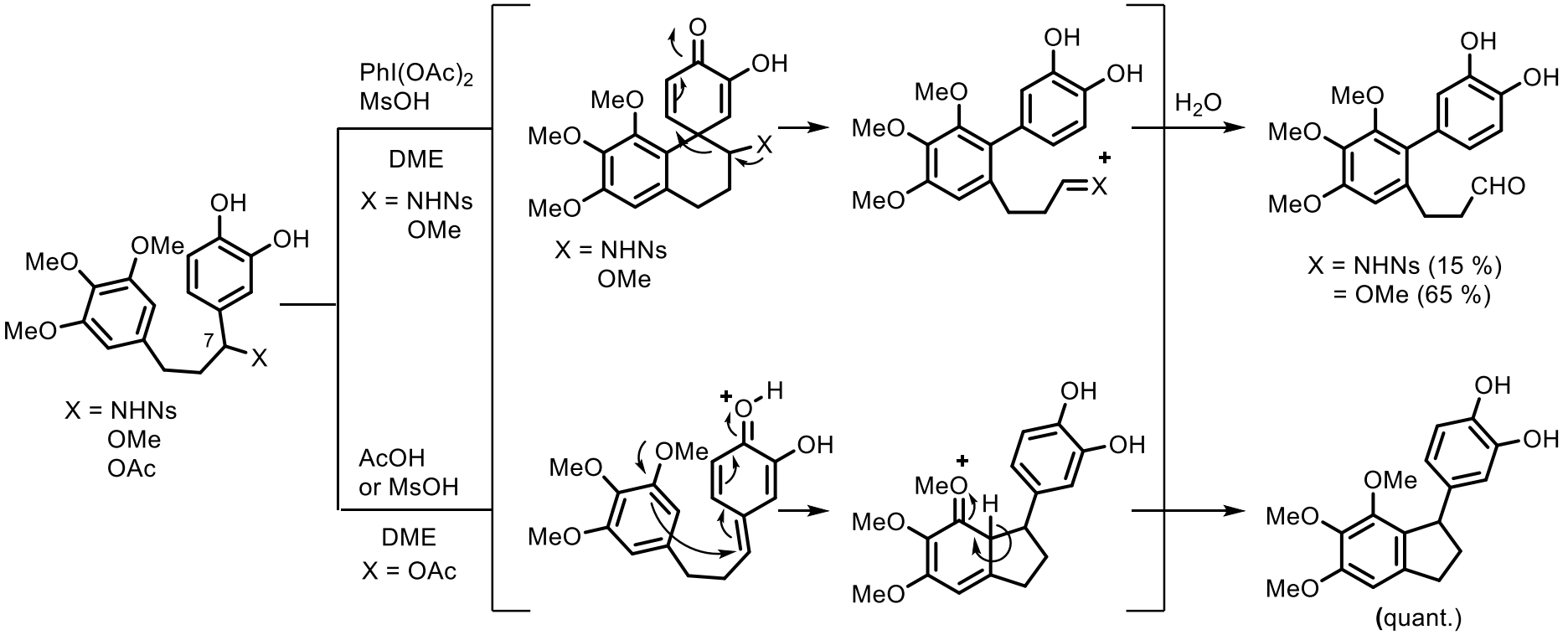
Our fluorination methodology

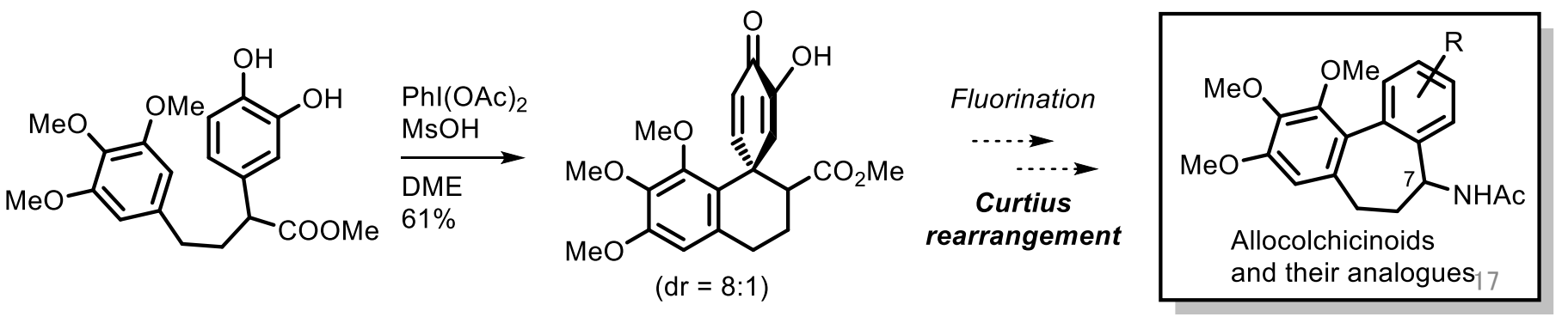


- ✓ Novel fluorinated analogs
- ✓ Known bioactive allocolchicinoids

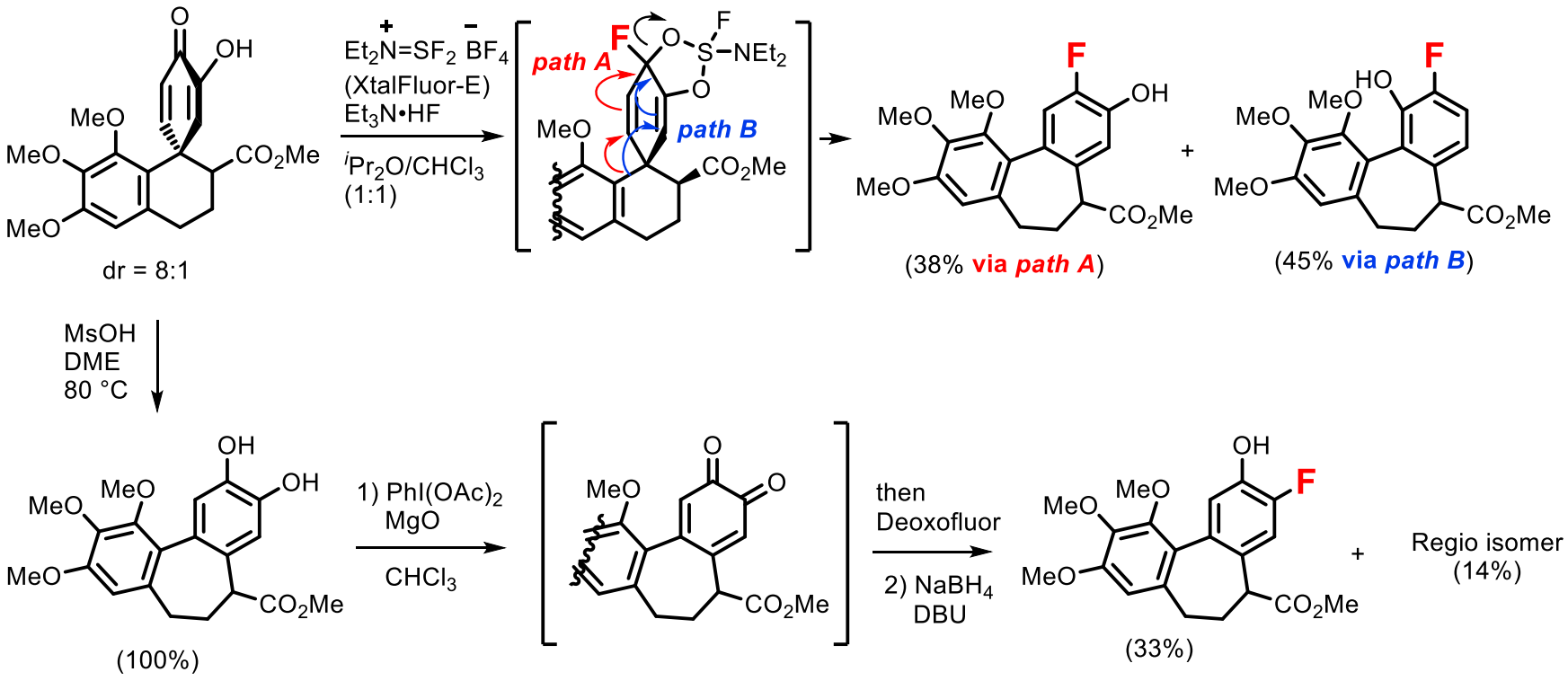


Optimization of Oxidative Cyclization

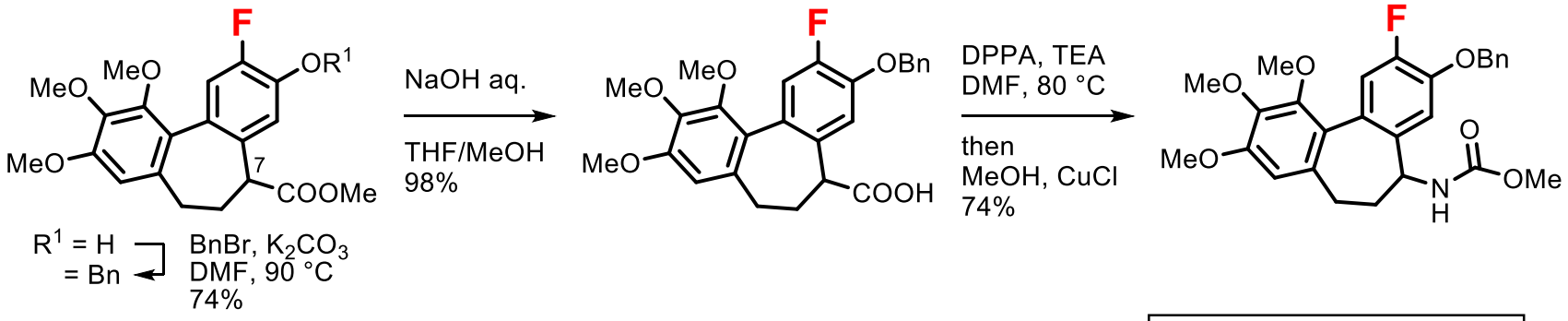




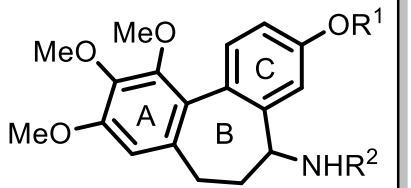
Synthesis of 6-7-6 Tricyclic Compounds Possessing a Fluoro Group



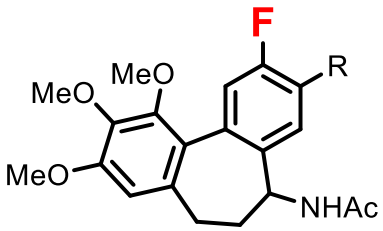
Conversion to Fluorinated Derivatives



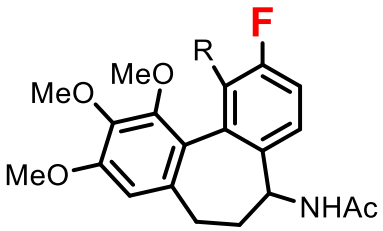
Bioactive allocolchicinoids



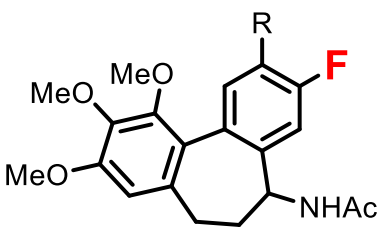
R = Ac: *N*-acetylcolchinol
R = Me: NSC 51046



R = H, OH, OMe

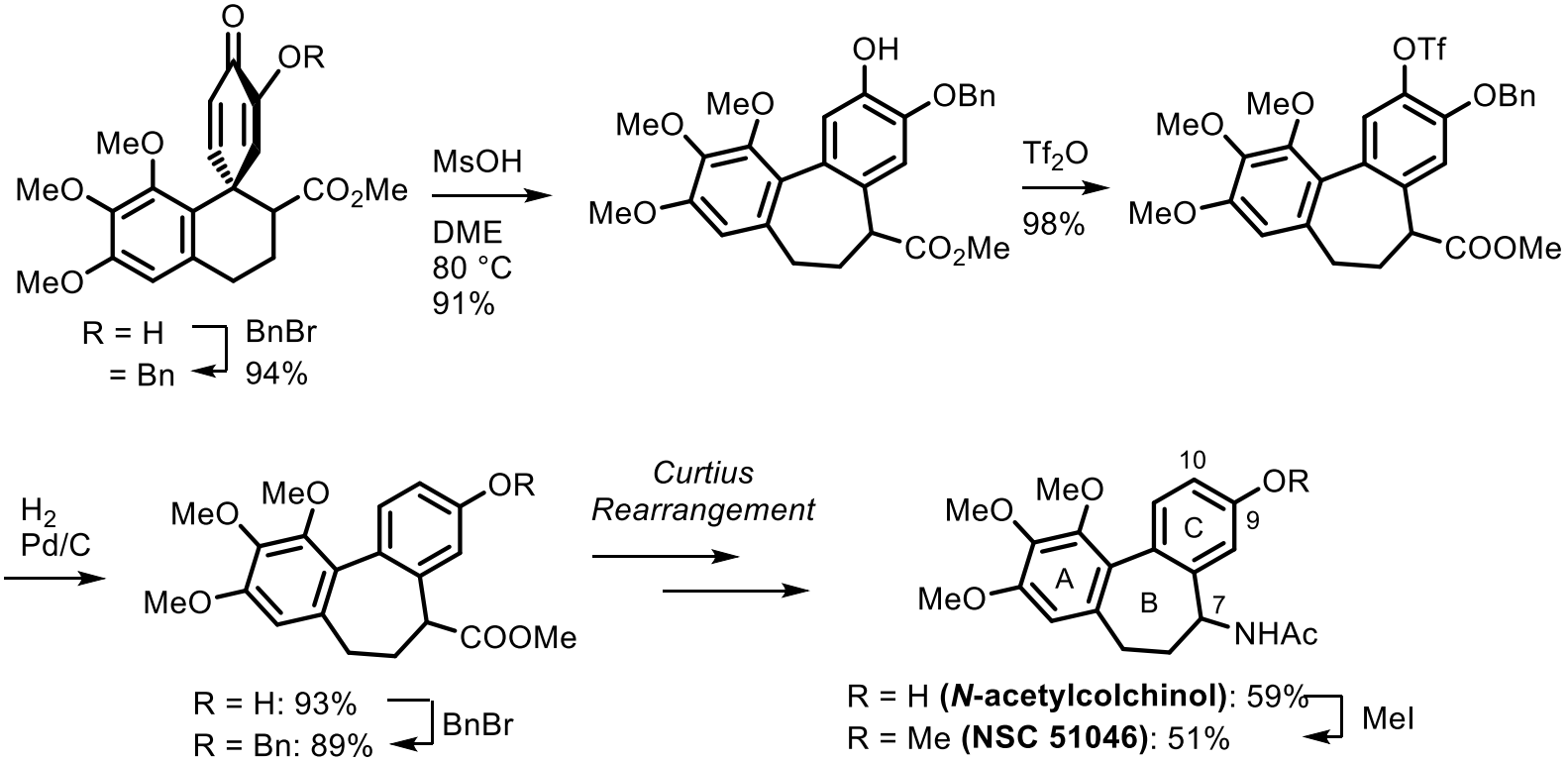


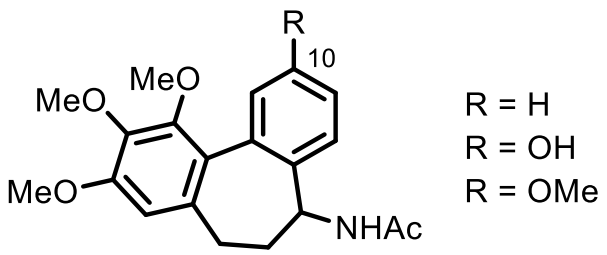
R = OH, OMe



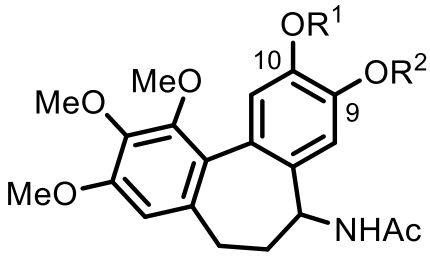
R = H, OH, OMe

Synthesis of *N*-acetylcolchinol, NSC 51046 and Related Oxygen-Substituted Derivatives



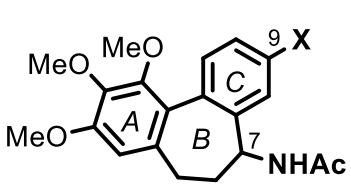
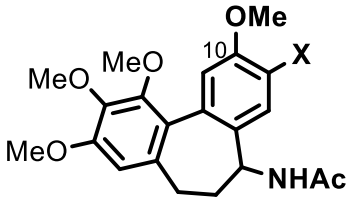
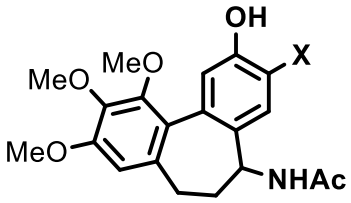
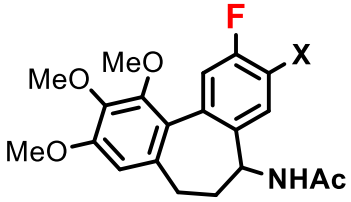
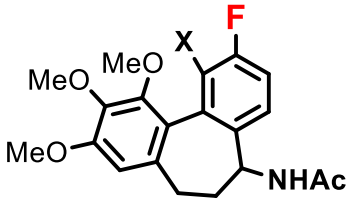


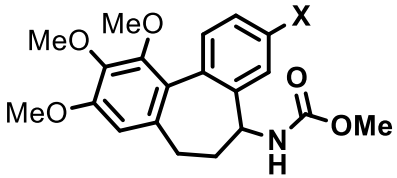
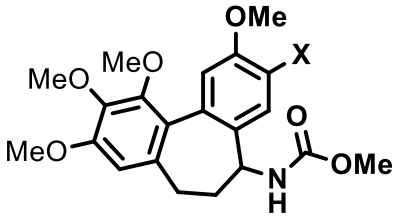
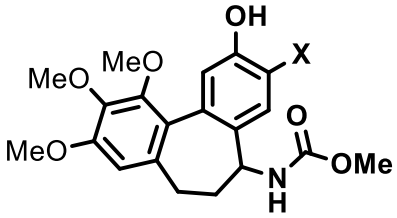
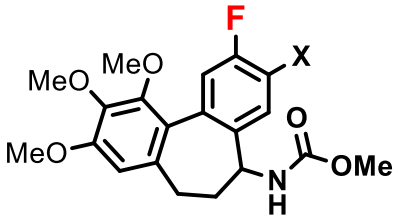
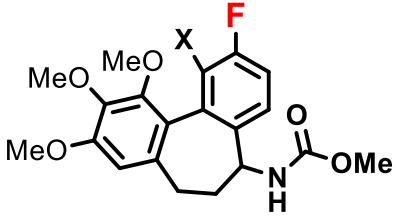
R = H
R = OH
R = OMe



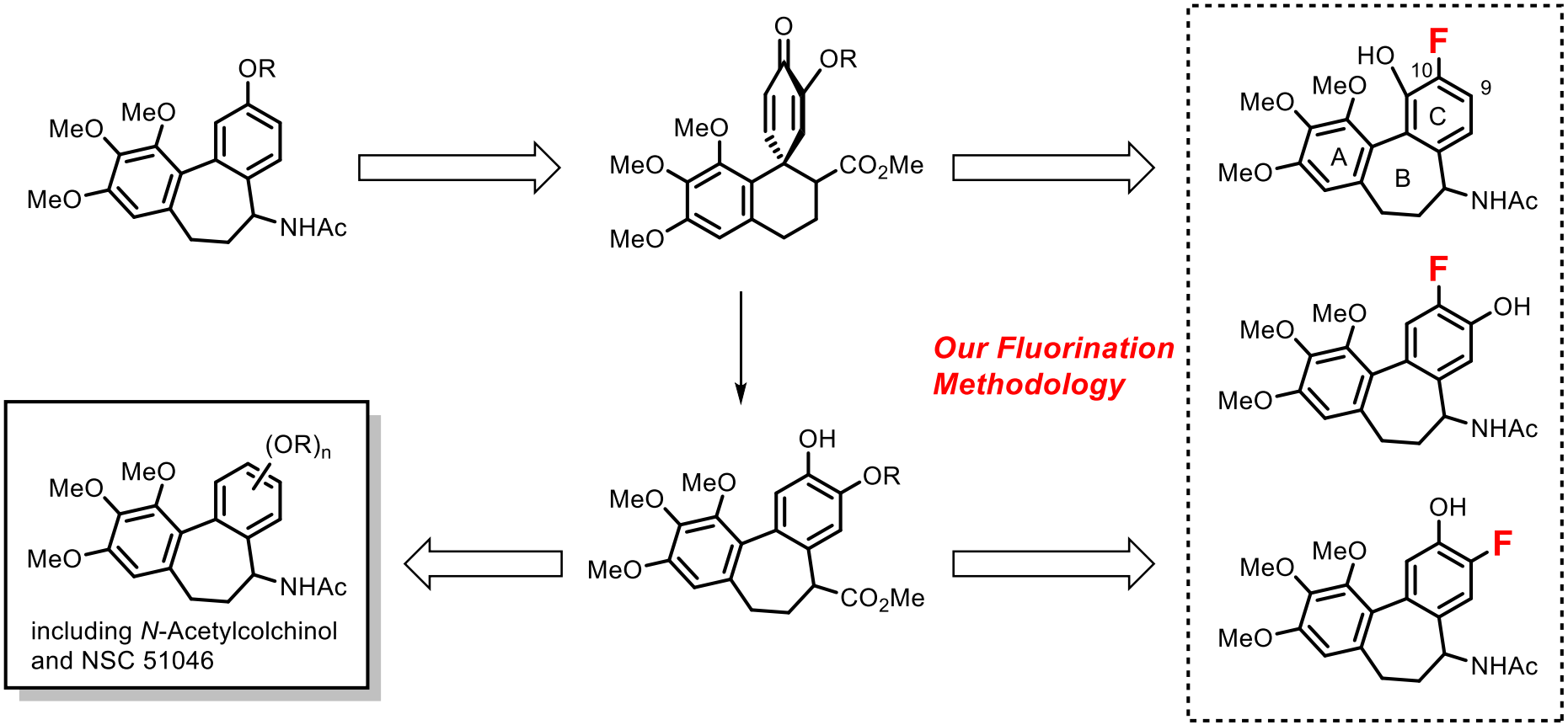
$R^1 = R^2 = H$
$R^1 = Me, R^2 = H$
$R^1 = H, R^2 = Me$
$R^1 = R^2 = Me$

Cytotoxic activities against DU145 and Panc 1 cells

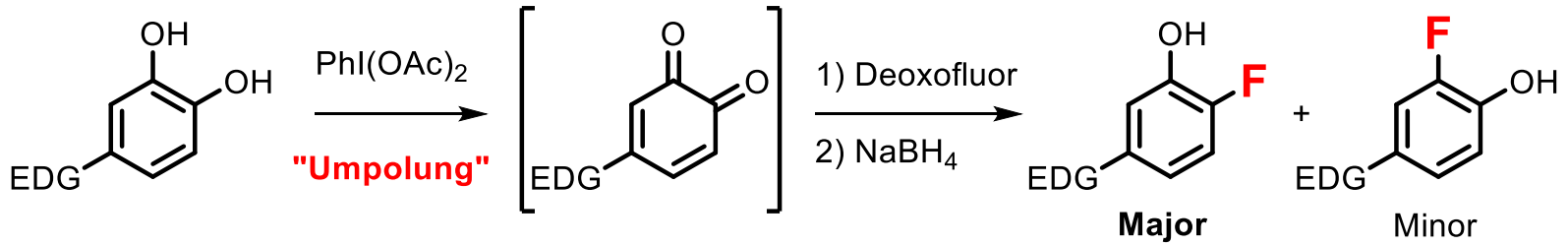
	X =	IC_{50} (μM) DU145	Panc 1
	OH (*N*-acetylcolchinol)	0.72	4.4
	OMe (NSC 51046)	0.78	0.080
	F	0.76	7.9
	H	6.6	>10
	OH	0.83	4.6
	OMe	>10	>10
	F	0.67	1.8
	H	0.54	0.76
	OH	>10	>10
	OMe	>10	>10
	F	9.6	>10
	H	>10	>10
	OH	>10	>10
	OMe	>10	>10
	H	7.0	>10
	OH	>10	>10
	OMe	>10	>10

	X =	IC_{50} (μM) DU145	Panc 1
	OH	0.67	1.0
	OMe	0.088	0.083
	F	1.4	7.0
	H	5.1	7.1
	OH	0.64	6.8
	OMe	6.5	>10
	F	0.76	1.4
	H	0.60	0.94
	OH	5.8	>10
	OMe	>10	>10
	F	>10	>10
	H	>10	>10
	OH	3.7	>10
	OMe	5.0	>10
	H	5.2	>10
	OMe	>10	>10

Conclusion



Synlett **2012**, *23*, 1978-1984., *Eur. J. Org. Chem*. **2016**, 1562-1576.



Org Lett. **2011**, *13*, 2714-2717.

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- Prof. Yoon-Jeong Kim (Office for University-Industry Collabolation)
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University of Shizuoka

- Dr. Hiroyuki Nemoto
- Mr. Takafumi Ide

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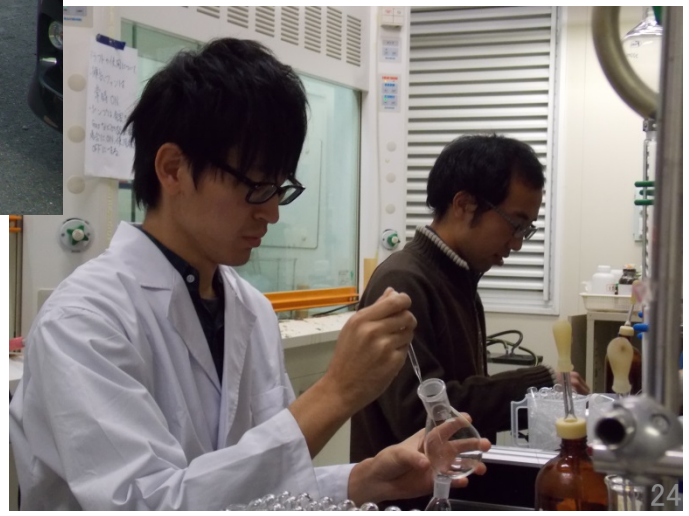
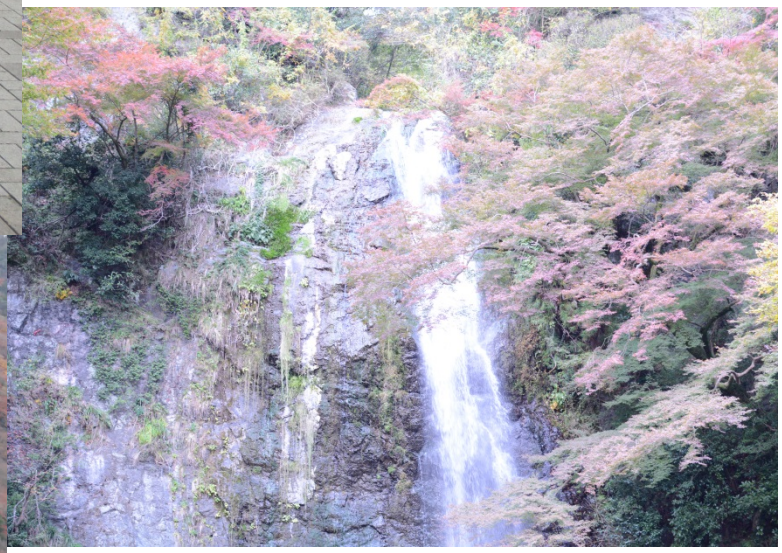
University of Shizuoka

Mt. Fuji (the highest mountain in Japan)
↓↓↓↓↓↓



Acknowledgements

Osaka University



Outline

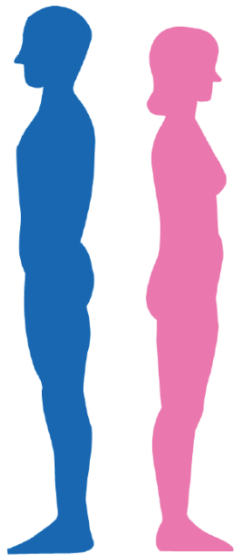
- Ph. D. work

- **Discovery for Antagonists of the Nuclear Androgen Receptor (Current work)**
  - Background
  - Synthesis of JJ-450
  - Synthesis of Analogs
  - Scale-up Synthesis of JJ-450

Prostate Cancer

Estimated Deaths

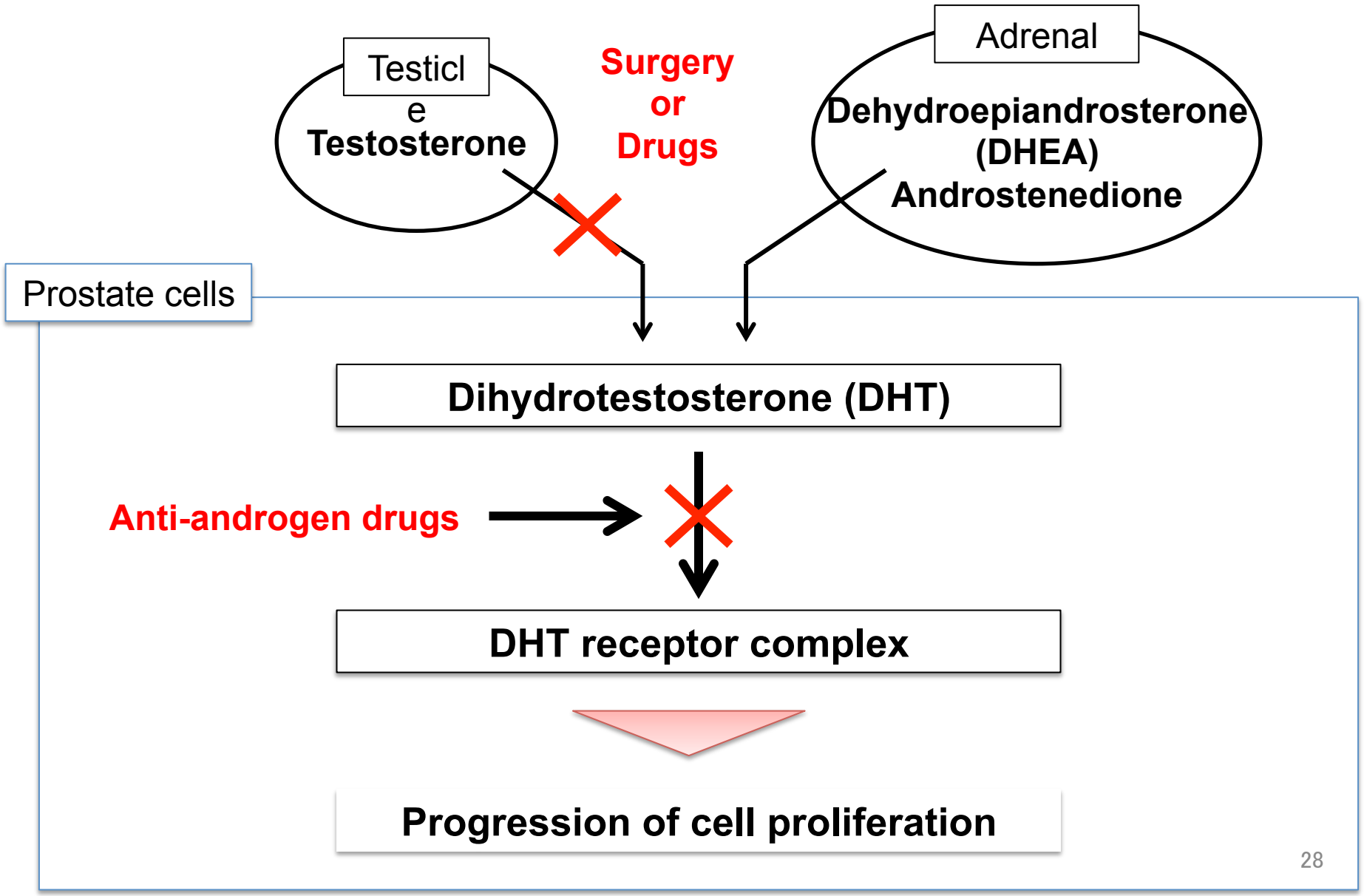
Males			Females		
Lung & bronchus	86,930	28%	Lung & bronchus	72,330	26%
Prostate	29,480	10%	Breast	40,000	15%
Colorectum	26,270	8%	Colorectum	24,040	9%
Pancreas	20,170	7%	Pancreas	19,420	7%
Liver & intrahepatic bile duct	15,870	5%	Ovary	14,270	5%
Leukemia	14,040	5%	Leukemia	10,050	4%
Esophagus	12,450	4%	Uterine corpus	8,590	3%
Urinary bladder	11,170	4%	Non-Hodgkin lymphoma	8,520	3%
Non-Hodgkin lymphoma	10,470	3%	Liver & intrahepatic bile duct	7,130	3%
Kidney & renal pelvis	8,900	3%	Brain & other nervous system	6,230	2%
All Sites	**310,010**	**100%**	**All Sites**	**275,710**	**100%**



- Percent surviving 5 years: **98.9 %** (2006 - 2012)
- **2nd** most deadly cancer type in men in the U.S.
- **30,000** patients are dead each year in the U.S.

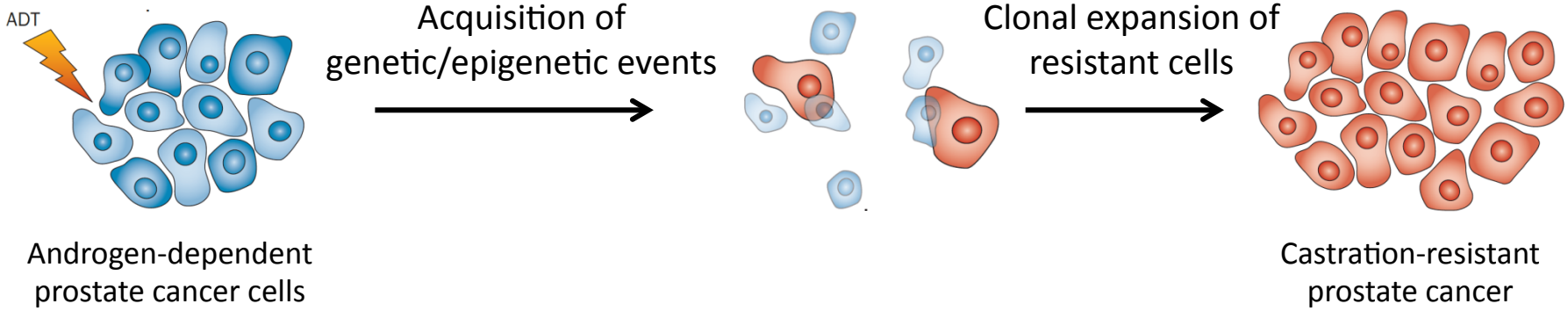
1) Cancer statistics, 2014. Ca Cancer J. Clin. **2014**, *64*, 9−29
2) SEER Stat Fact Sheets: Prostate Cancer. http://seer.cancer.gov/ statfacts/html/prost.html.

Mechanism of Prostate Cancer

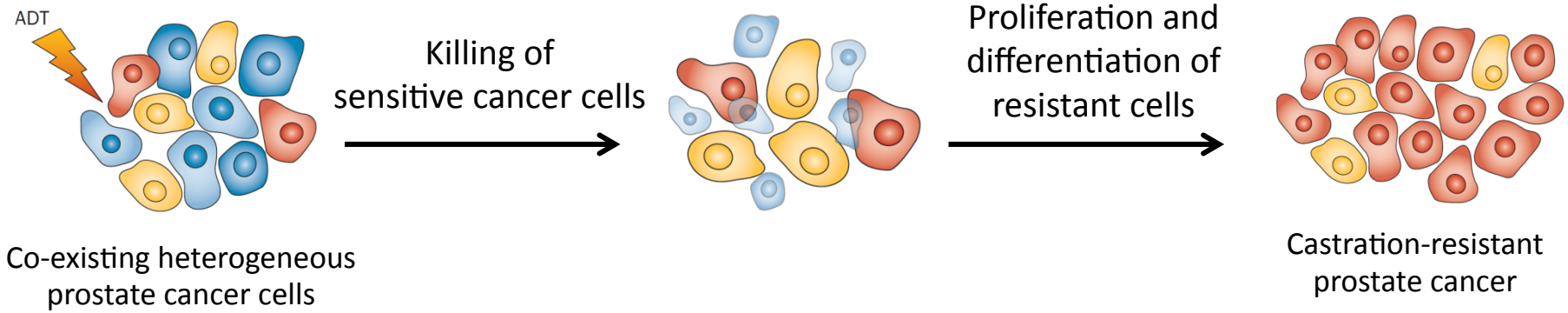


Castration-Resistant Prostate Cancer (CRPC)

◆ Adaptation medel

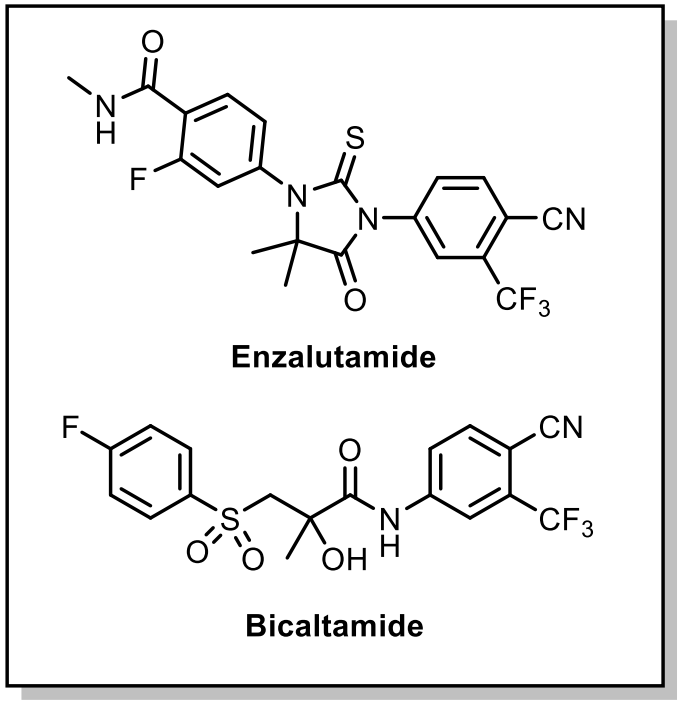


◆ Selection medel



Nature **2013**, *10*, 90-98

Current treatment for CRPC



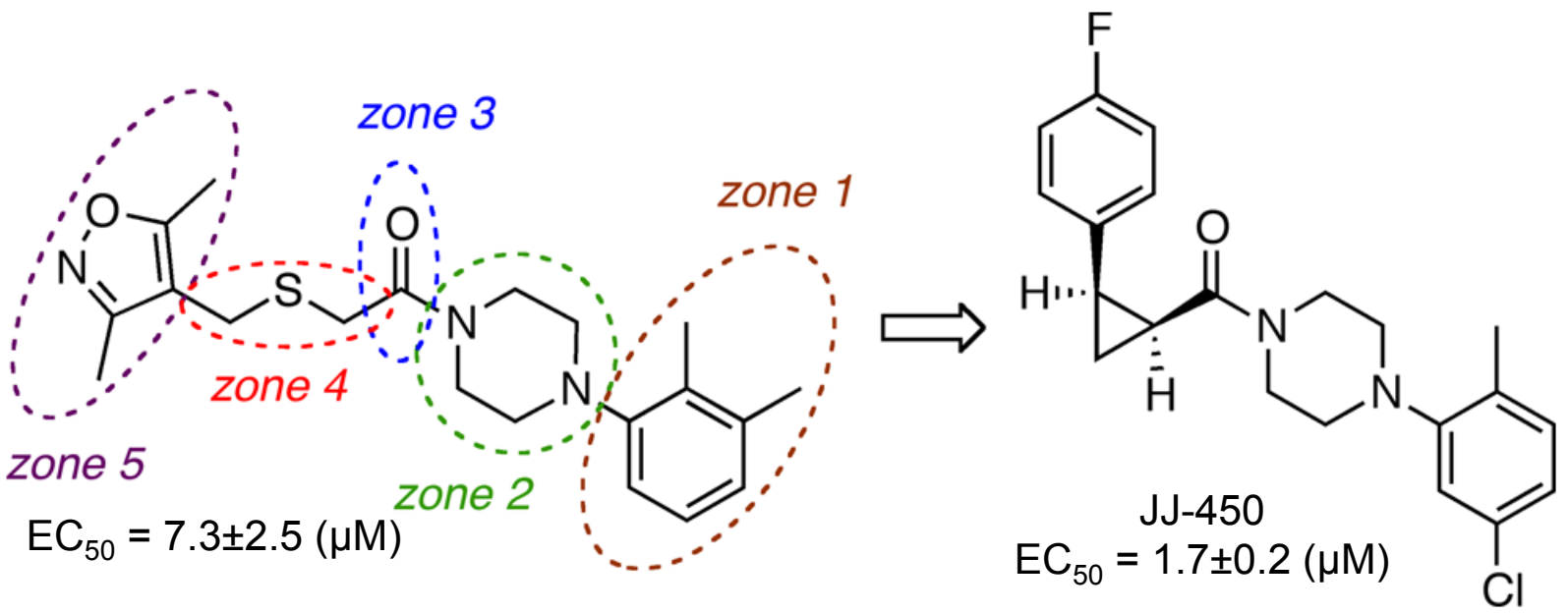
- Enzalutamide (MDV3100) and bicalutamide are androgen receptor (AR) antagonists that are currently used as treatments for CRPC and can extend the lifespan of patients for **only 3−5 months**.
- **There are no known therapies** that decisively inhibit nuclear localized AR in CRPC cells.

Science **2009**, *324*, 787−790.

Our goal is

Discovery of a novel series of small molecules identified by their ability to reduce the nuclear level of AR and, subsequently, AR activity.

Prostate Cancer



Zone 1: The ortho-substituent on the phenyl ring was important for activity.

Zone 2: The sterically encumbered 2,6-dimethylpiperazine proved superior to flexible unsubstituted, and bridged analogues.

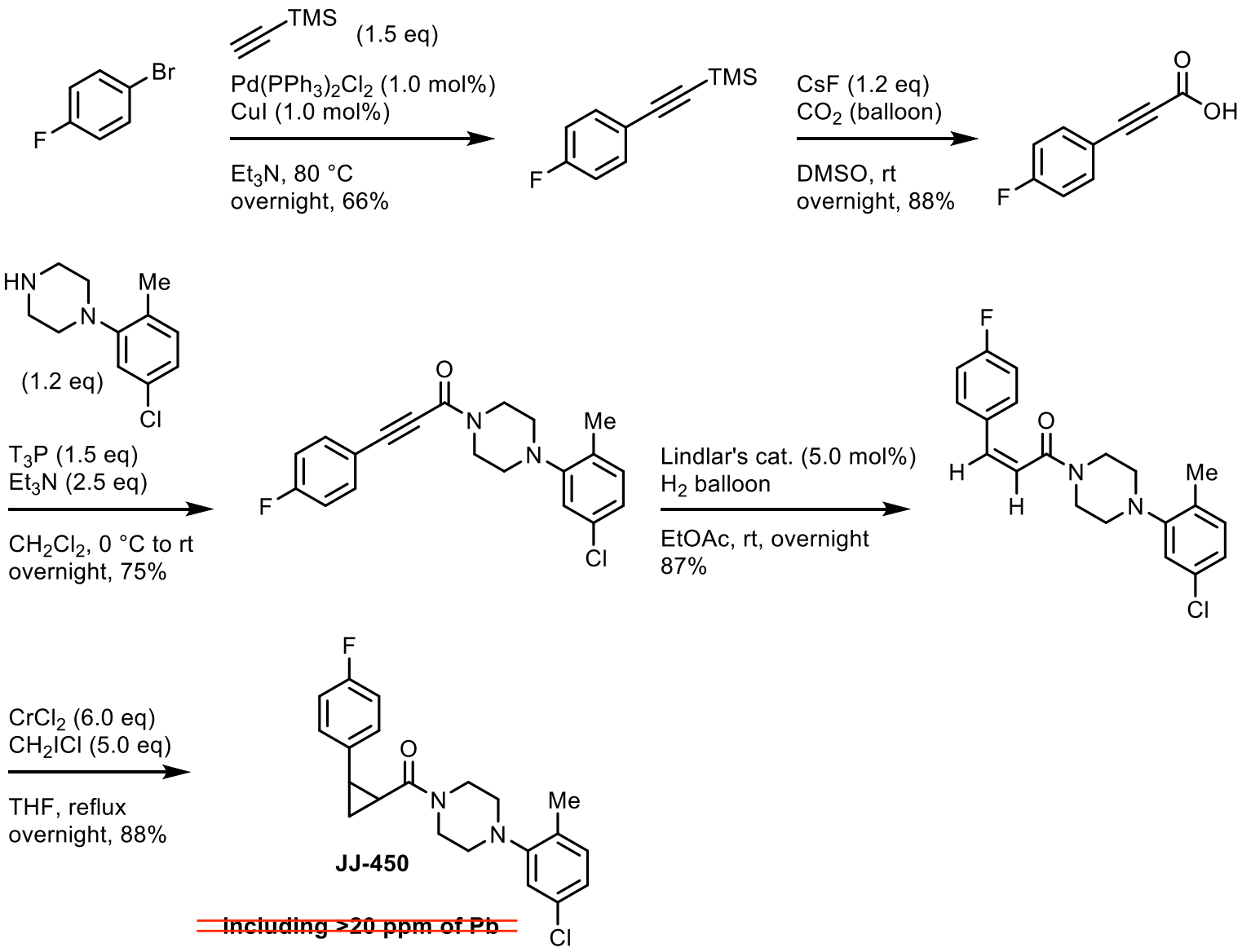
Zone 3: A carbonyl group was not required, and a sulfonamide and even the reduced amine were well tolerated.

Zone 4: Thioether oxidation reduced activity, and only the *cis*-cyclopropane significantly improved the EC50.

Zone 5: Limited substitutions were performed.

ACS Med. Chem. Lett. **2016**, *7*, 785−790

Synthesis of JJ-450



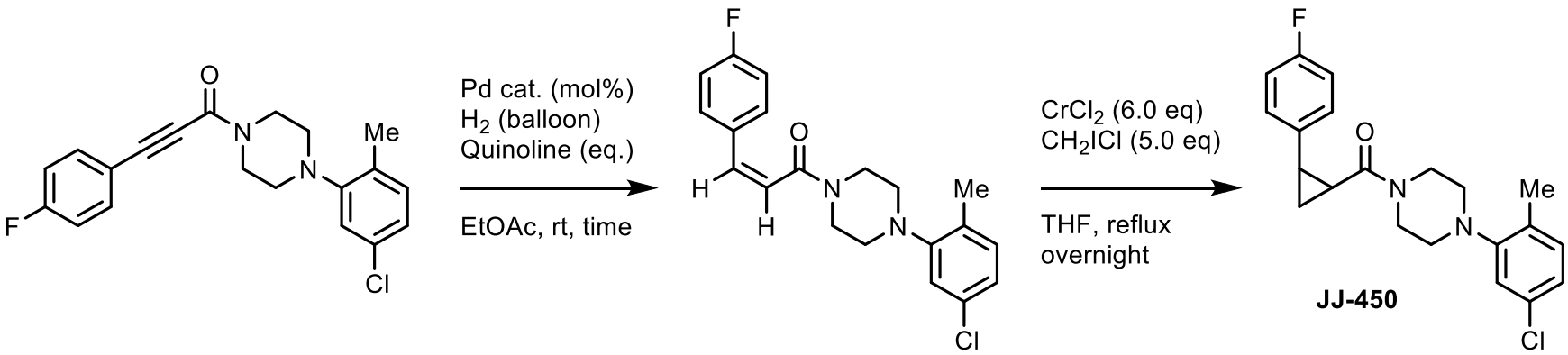
Permitted Concentrations of Elemental Impurities for Option 1

Option 1: Common permitted concentration limits of elements across drug product components for drug products with daily intakes of not more than 10 grams

Element	Class	Oral Concentration µg/g	Parenteral Concentration µg/g	Inhalation Concentration µg/g
Cd	1	0.5	0.2	0.2
Pb	1	0.5	0.5	0.5
As	1	1.5	1.5	0.2
Hg	1	3	0.3	0.1
Co	2A	5	0.5	0.3
V	2A	10	1	0.1
Ni	2A	20	2	0.5
Tl	2B	0.8	0.8	0.8
Au	2B	10	10	0.1
Pd	2B	10	1	0.1
Ir	2B	10	1	0.1
Os	2B	10	1	0.1
Rh	2B	10	1	0.1
Ru	2B	10	1	0.1
Se	2B	15	8	13
Ag	2B	15	1	0.7
Pt	2B	10	1	0.1
Li	3	55	25	2.5
Sb	3	120	9	2
Ba	3	140	70	30
Mo	3	300	150	1
Cu	3	300	30	3
Sn	3	600	60	6
Cr	3	1100	110	0.3

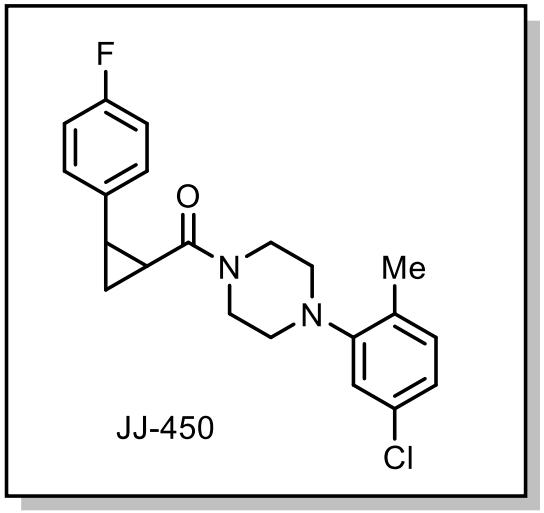
International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human use (ICH) Harmonised Guideline, dated 16 Dec. 2014

Optimization of Hydrogenation



Entry	Pd cat (mol%)	Quinoline (eq.)	time	Yield of (*Z*)-Alkene(%)	Residual lead of JJ-450
1	Lindlar's cat (5.0)	–	o/n	overreducted pdt. (97%)	~~>20 ppm~~ 0 ppm
2	5% Pd/BaSO4 (5.0)	1	2 h	overreducted pdt. (97%)	Not measured
3	5% Pd/BaSO4 (5.0)	5	50 min	desired pdt. : overreducted pdt. = 1 : 1	Not measured
4	**5% Pd/BaSO4 (1.0)**	**5**	**30 min**	**quant.**	~~9 ppm~~ **0 ppm**

Optimization of Recrystallization



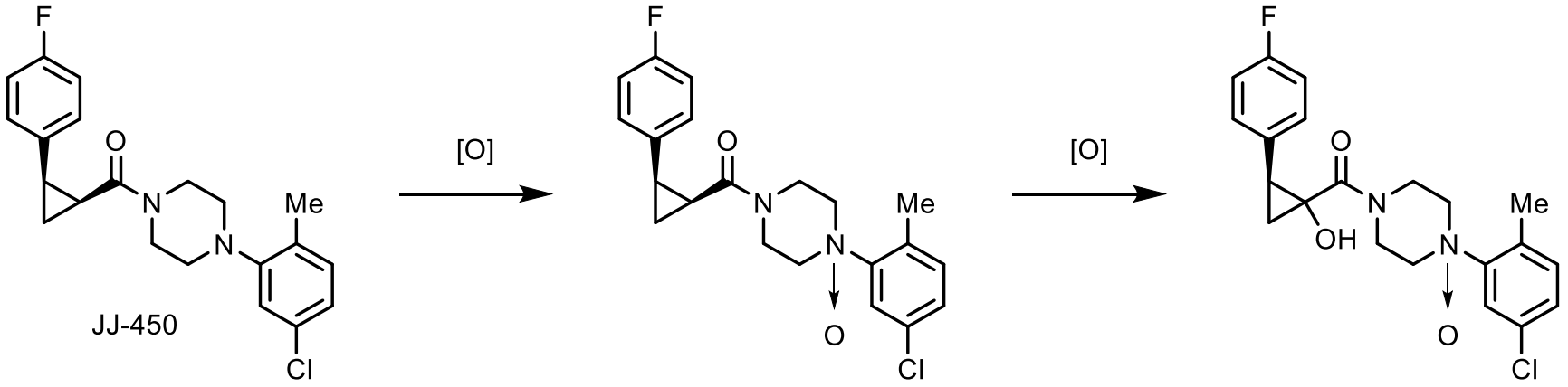
JJ-450

Recrystallization conditions
Hexane (1.88) ... not dissolved
Cyclohexane (2.02) ... dissolved at 70 °C (75% yield)
Toluene (2.38) ... dissolved at RT

Solvent	Dielectric Constant	Bp (°C)	Solvent	Dielectric Constant	Bp (°C)
Hexane	1.88	69	i-PrOH	20.33	82.4
Cyclohexane	2.02	80.7	Acetone	20.7	56.05
Toluene	2.38	110.6	EtOH	24.55	78.5
Ethyl Ether	4.33	34.5	Acetonitrile	37.5	81.65
Chloroform	4.81	61.7	Water	80.1	100
Ethyl Acetate	6.02	77.1			
THF	7.58	65.6			

https://www.organicdivision.org/orig/organic_solvents.html

Metabolism test



Time	Remained JJ-450
0 min	100 %
10 min	91 %
30 min	60 %
60 min	27 %

* The test was conducted by using female mouse liver microsomes

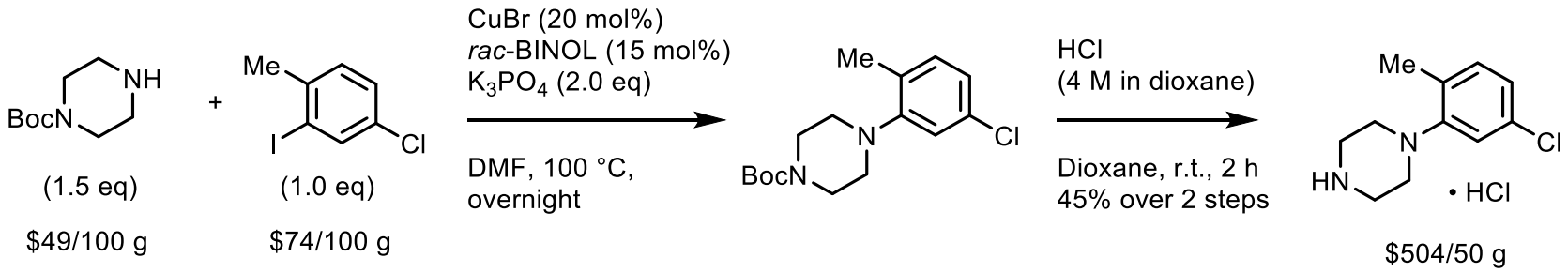
Our goal

- Decrease metabolism

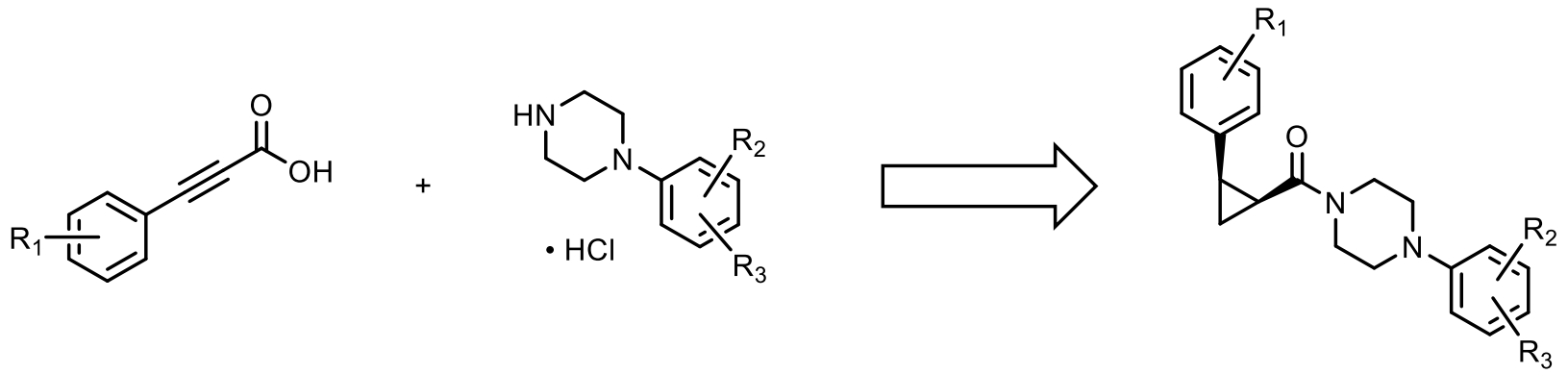
…

- Attach electron withdrowing groups on the benzene rings
- Block sites of metabolism with fluorine substitutions

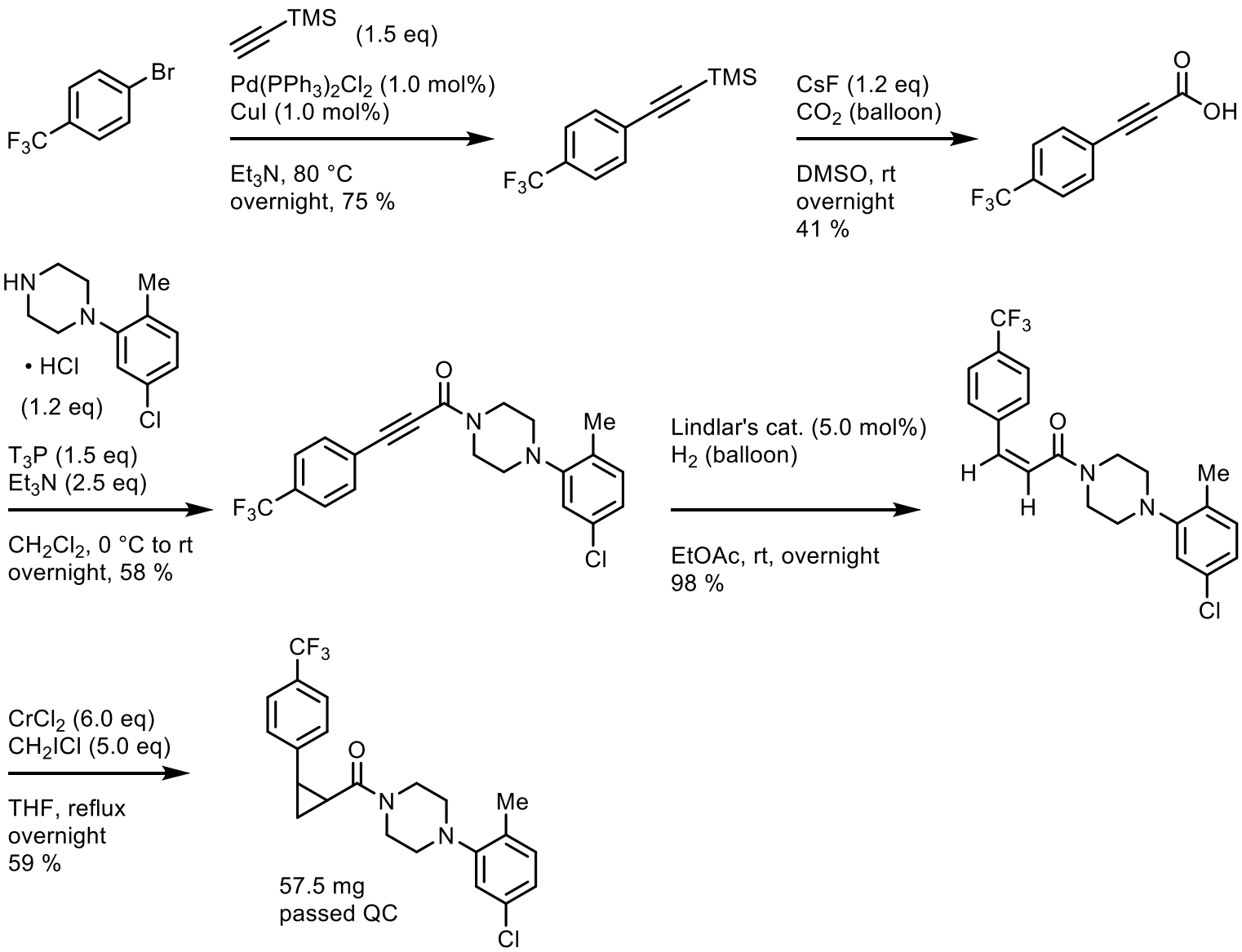
Synthesis of Piperazine derevatives



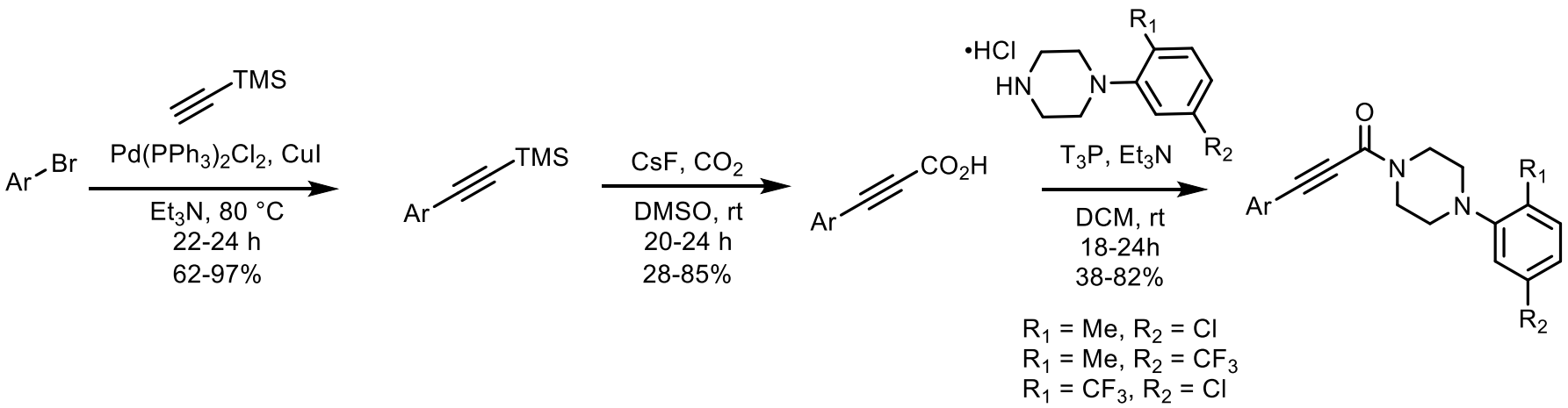
◆ Synthetic strategy for various analogs

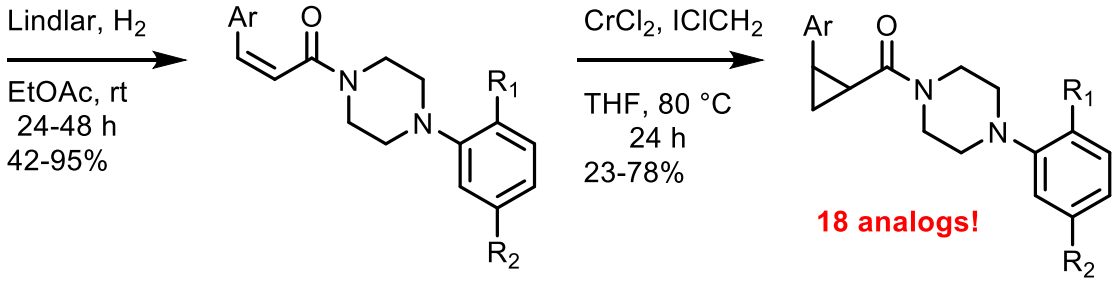


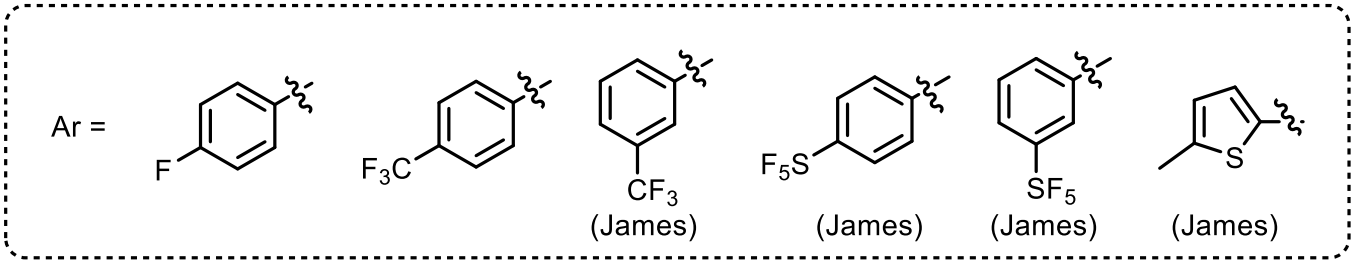
Synthesis of Analogs



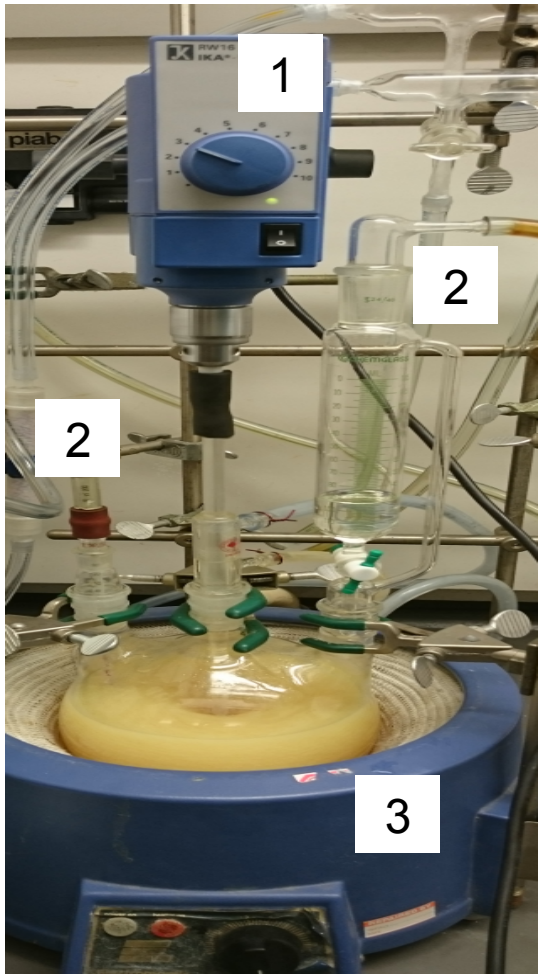
Synthesis of Analogs







Large-scale Synthesis



I. Set up reaction

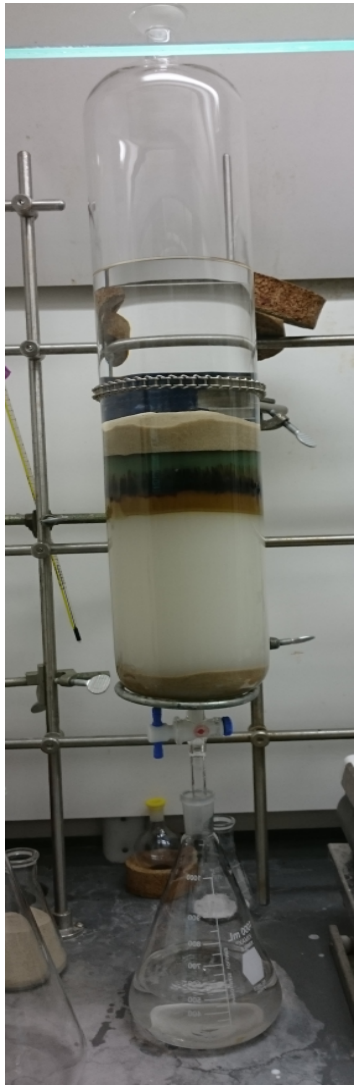
① <u>Magnetic stirrer bar → Overhead stirrer</u>
Magnetic stir bars do not mix large, thick mixtures well, and overhead stirring is more consistent when scaling up from one level to the next.

② <u>Syringe → Equal-dropping funnel</u>
Temperature control is critical for safely performing scale-up reactions.
(Monitor the **Internal** reaction temperature **Carefully**!)

③ <u>Oil (aluminum beads) bat</u>
<u>→ Heating Mantle</u>

https://www.drs.illinois.edu/SafetyLibrary/ScaleUpReactionSafety

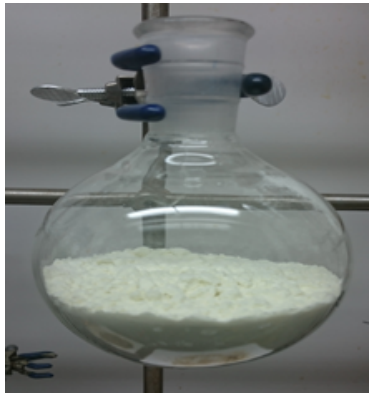
Large-scale Synthesis



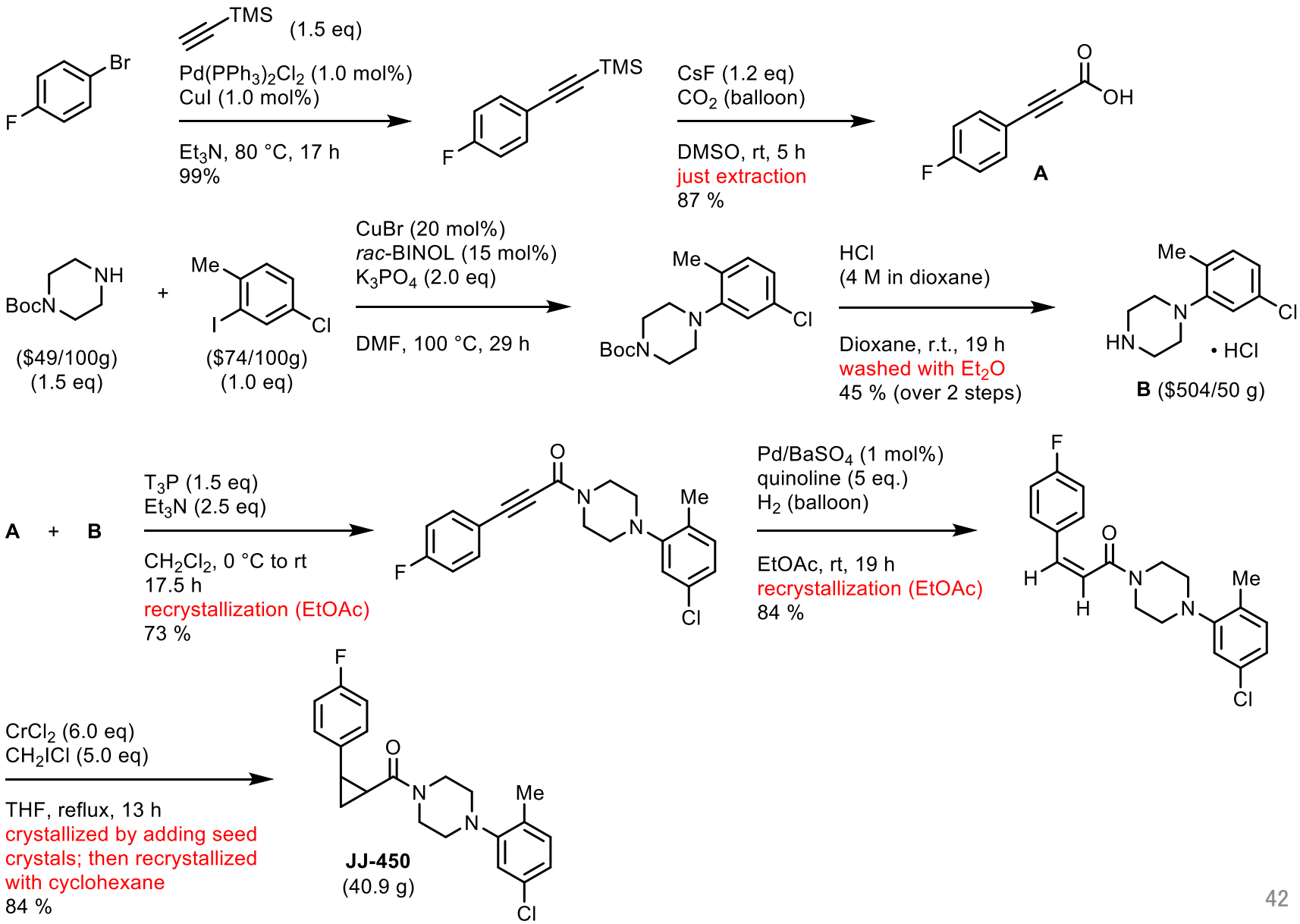
3. Purification
   - Column chromatography
     - ✓ Use quite a bit of solvents (~ 10 L for 200 g of crude product)
     - ✓ Take long time
     - ✓ Use a lot of Silica gel

To avoid the above matters …

- Recrystallization
- Extraction
- Trituration
- Wash

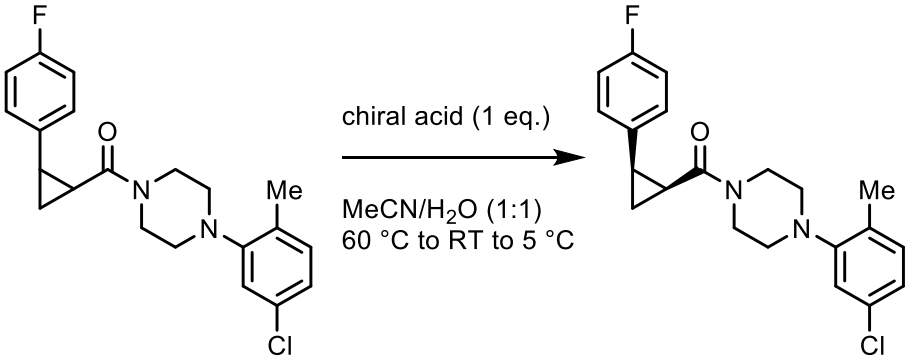


Large-scale Synthesis



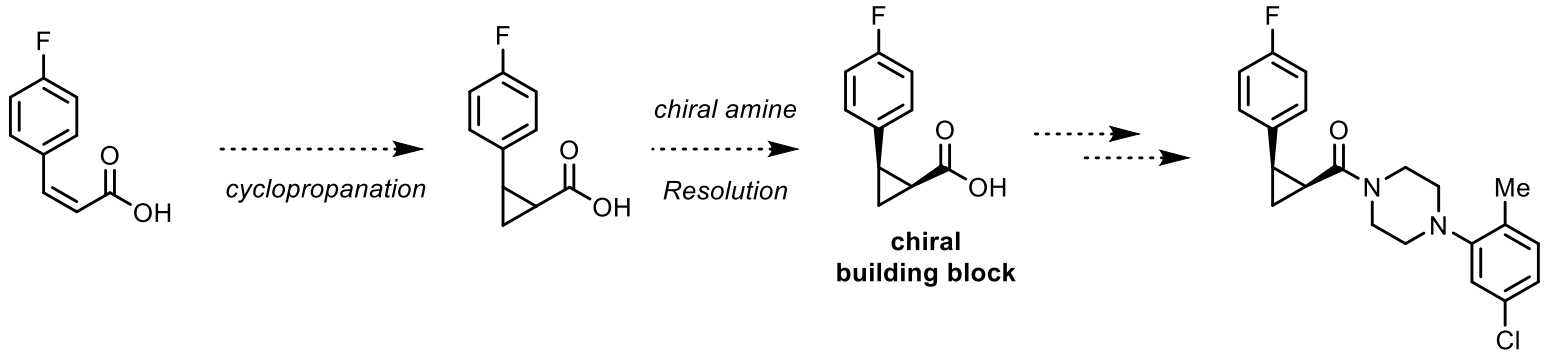
Future works

- Chiral resolution



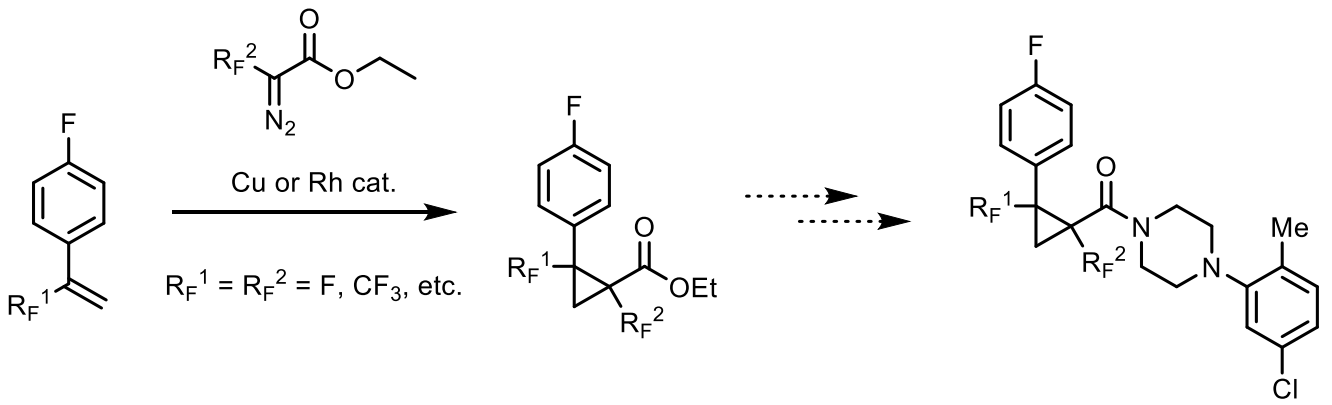
Entry	chiral acid	time	Yield (%)
1	(1R)-(-)-Camphor-10-sulfonic acid	5 days	no cystal
2	(-)-Benzoyl-L-tartaric acid	5 days	no cystal

- Chiral building block approach

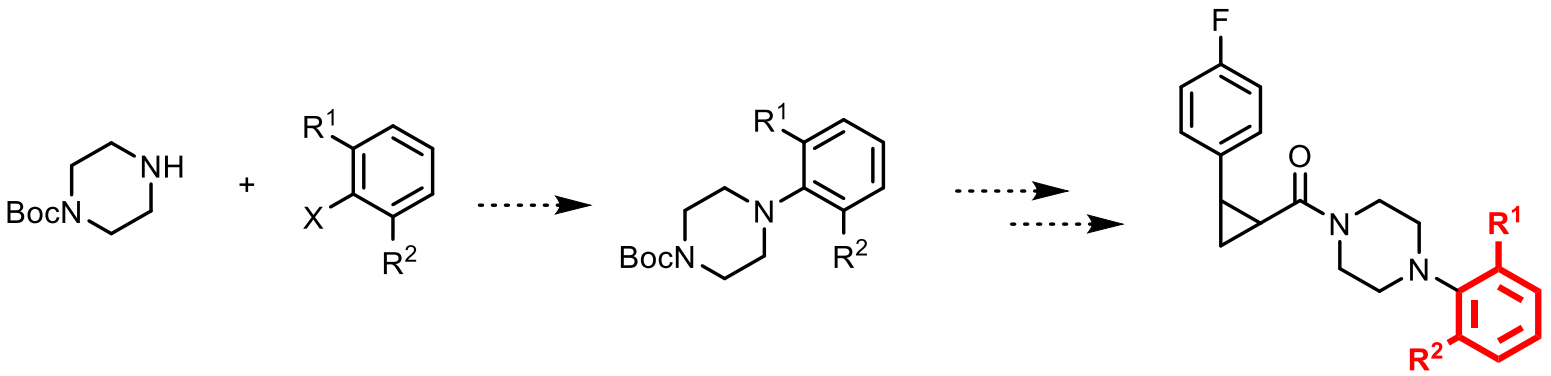


Future works

- Functionalization of the cyclopropane ring (Serene)



- Synthesis of *ortho*-disubstituted analogues



Conclusion

- Improve hydrogenation by not using Lindlar's catalyst
- Development of the recrystallization condition of JJ-450
- Development of the practical approach for the analog synthesis
- Modification of the synthetic protocol for scale-up synthesis

Acknowledgements

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