



"The objectives and beliefs of Boehringer Ingelheim can be summed up in a single phrase: Value through Innovation. This vision has helped us to build on our strengths and make the most of our distinctive character. In a competitive and fast-changing world, the value of products, services and companies is constantly changing. Real customer value today can only be created by constantly developing new solutions and doing what we already do better." <http://www.boehringer-ingelheim.com/>

A Brief Timeline:

1885: Albert Boehringer purchased a small factory in Nieder-Ingelheim to manufacture tartaric acid salts.

1895: Boehringer found that lactic acid can be produced via bacteria.

1912: Laudanum, an analgesic, was launched as the first pharmaceutical.

1939: Albert Boehringer passed away; his sons Albert and Ernst and son-in-law Julius Liebrecht took over the company.

1945: Factory gates were closed as American troops begin occupation of Ingelheim. Work resumes about two months later.

1948: First foreign subsidiary (Bender & Co. GmbH) was founded in Vienna (many others were founded in the following years)

1971: Boehringer Ingelheim Pharmaceuticals, Inc. is founded in Ridgefield, Connecticut.

1985: Centenary of the company. Over 20,000 people are employed by the company at this time.

1986: Biotechnological center in Biberach starts production; it is the largest plant in Europe for production of biopharmaceuticals from cell cultures.

1987: Actilyse (treatment of acute heart attacks) is the first biotech product by Boehringer Ingelheim that is approved

1997: Viramune, an antiretroviral drug designed to fight HIV/AIDS, is introduced.

2010: This year marks the 125th anniversary of the company.

Evolution of the company logo:



1893 - 1905



1924 - 1962

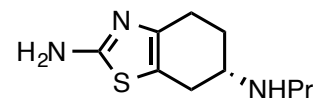


1905 - 1924

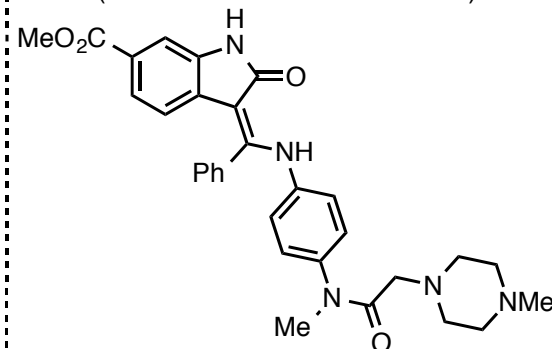


1962 - 1997

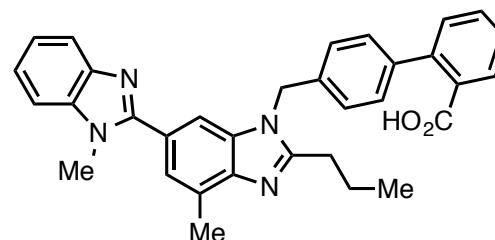
Some current pharmaceuticals (not all-inclusive):



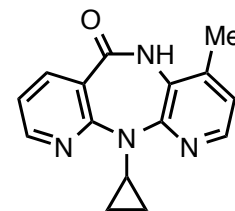
Mirapex®
(Parkinson's Disease treatment)



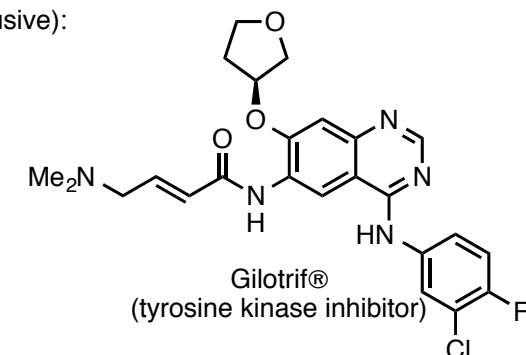
OFEV®
tyrosine kinase inhibitor



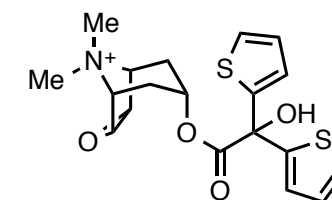
Micardis®
(hypertension treatment)



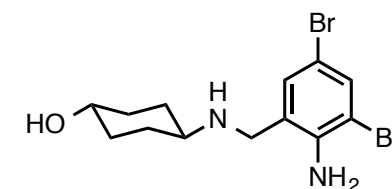
Nevirapine
(non-nucleoside reverse transcriptase inhibitor, synthesis discussed today)



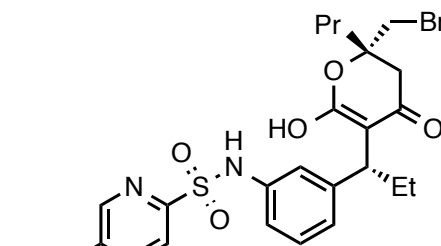
Gilotrif®
(tyrosine kinase inhibitor)



Spiriva®
(muscarinic receptor antagonist)

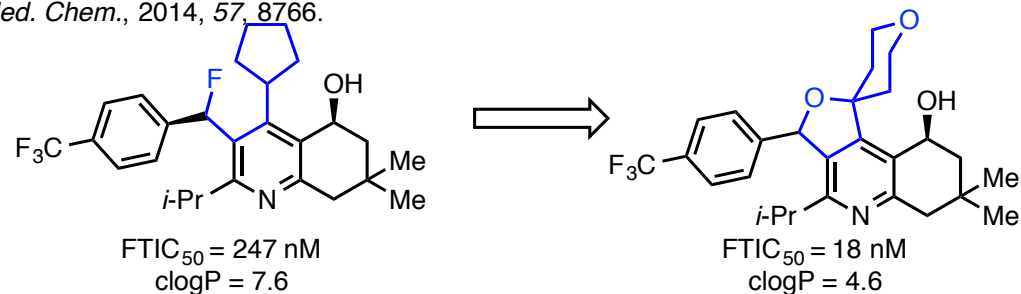


Mucosulvan®
(respiratory disease treatment)

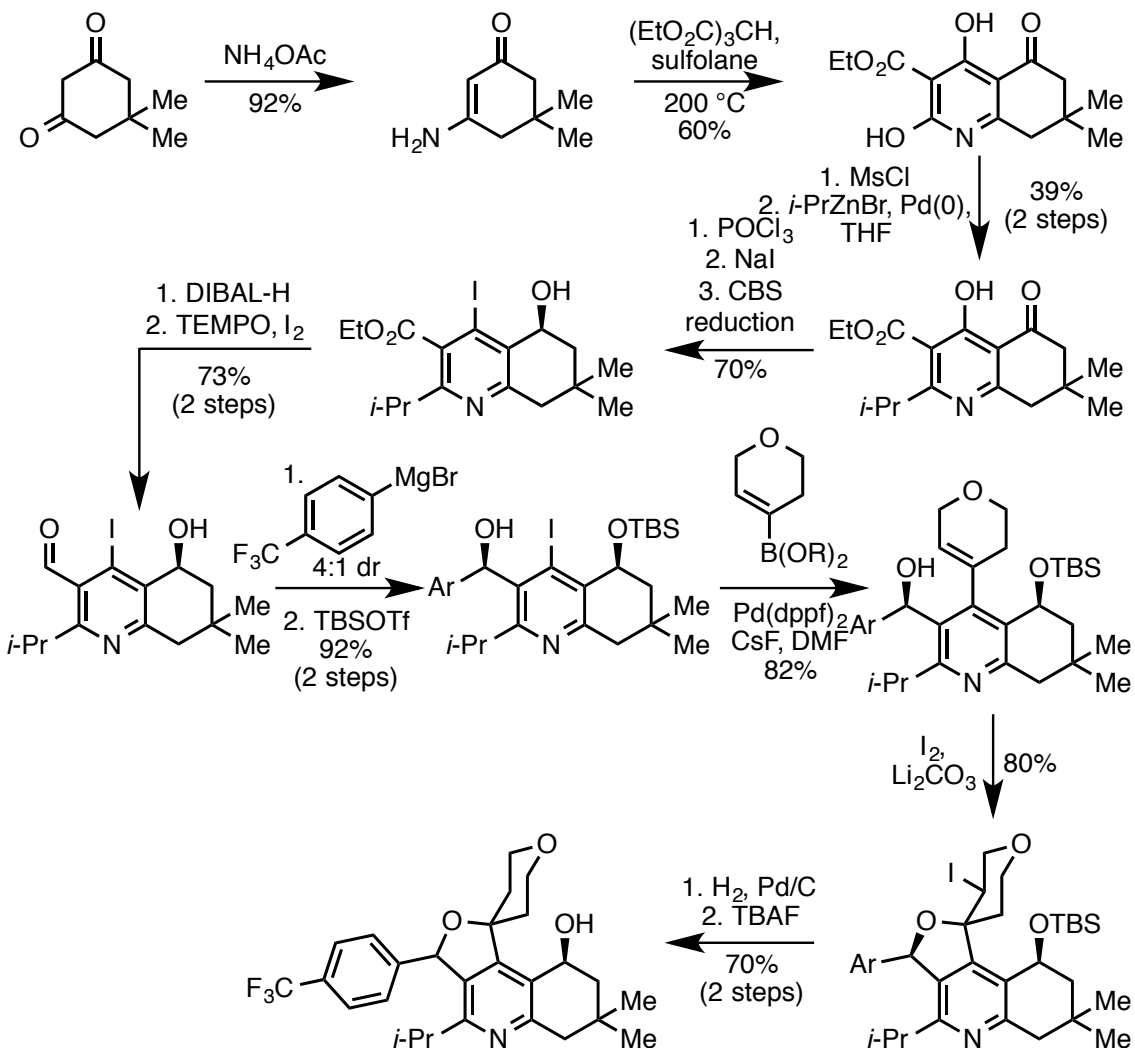


Aptivus®
(protease inhibitor, see Michaudel, Short Stories in Pharmaceutical Discovery, Process, and Isotopic Labeling, 2011)

Potent Cholesteryl Ester Transfer Protein Inhibitors of Reduced Lipophilicity:
1,1'-Spiro-Substituted Hexahydrofuraquinoline Derivatives
J. Med. Chem., 2014, 57, 8766.

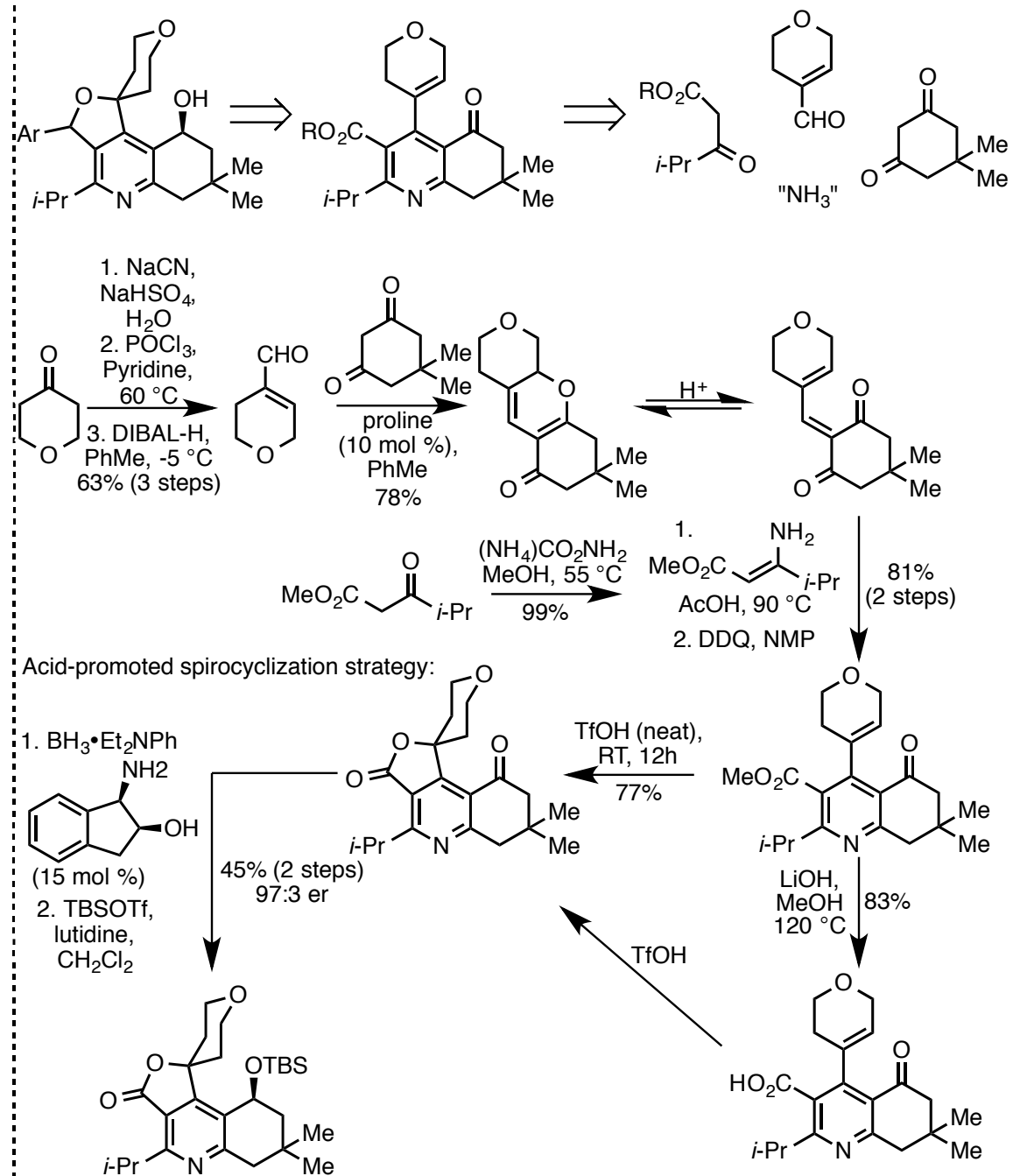


Medicinal chemistry discovery route:

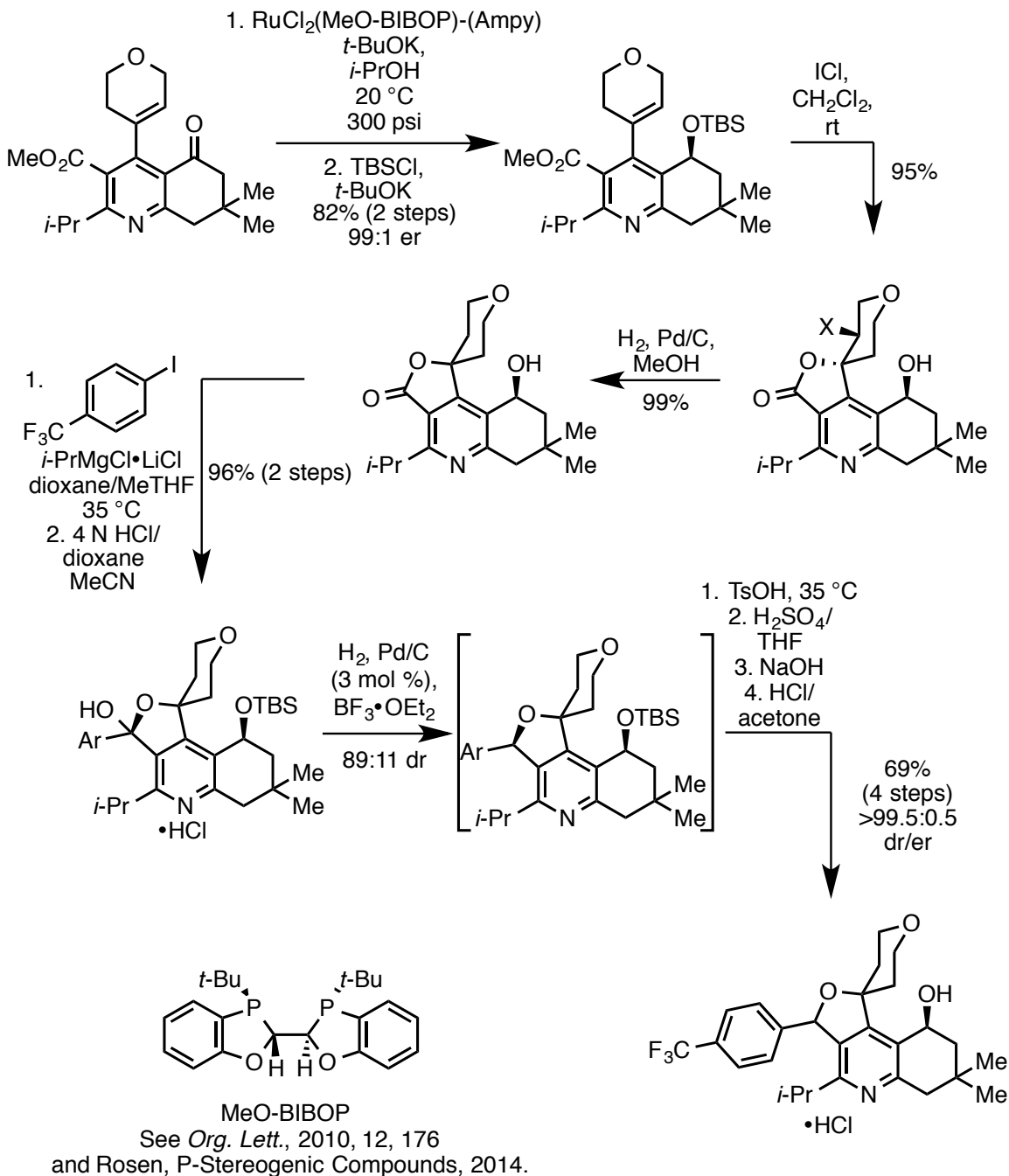
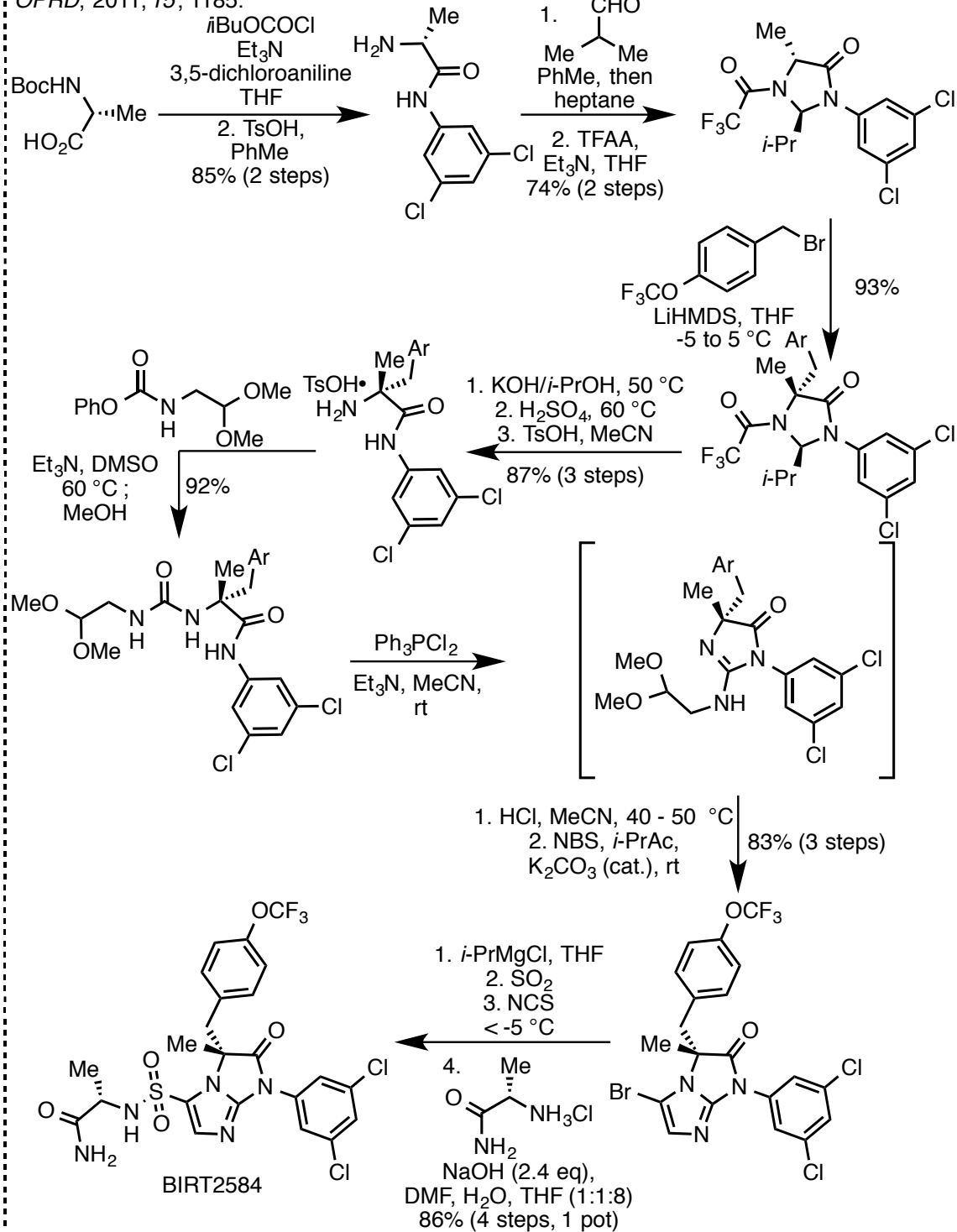


Facile Entry to an Efficient and Practical Enantioselective Synthesis of a Polycyclic
Cholesteryl Ester Transfer Protein Inhibitor
Org. Lett., 2014, 16, 4142.

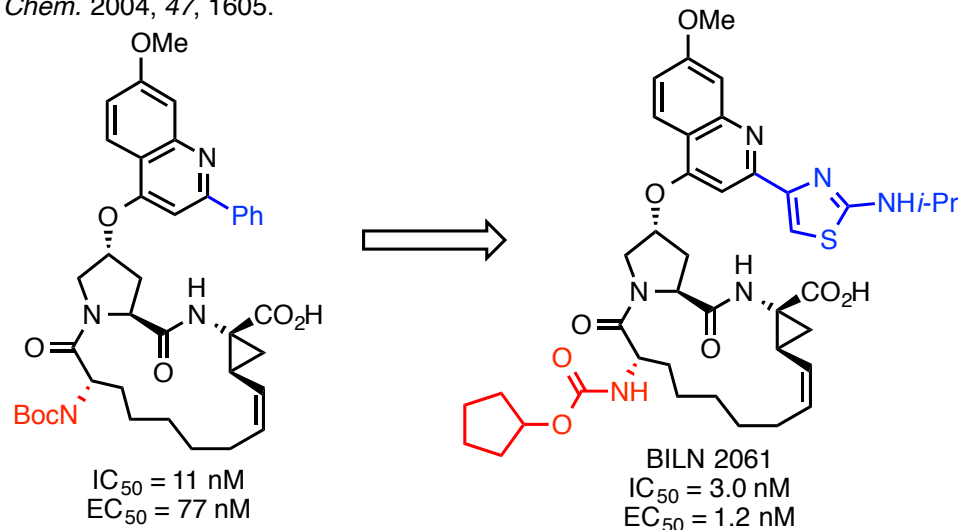
Initial scalable process route to afford suitable material for early clinical development:



To a more efficient process:

Asymmetric Synthesis of LFA-1 Inhibitor BIRT 2584 on Metric Ton Scale
OPRD, 2011, 15, 1185.

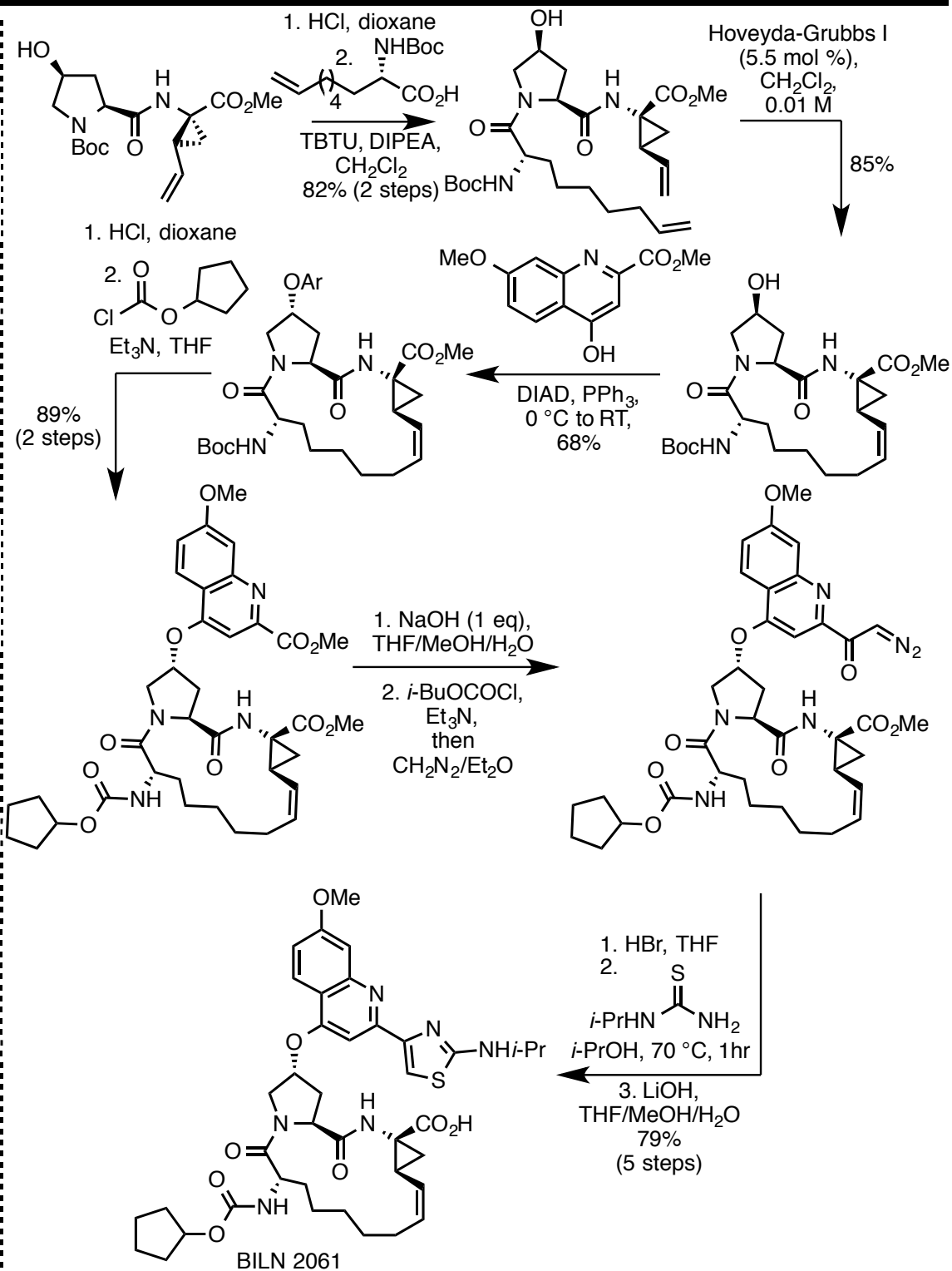
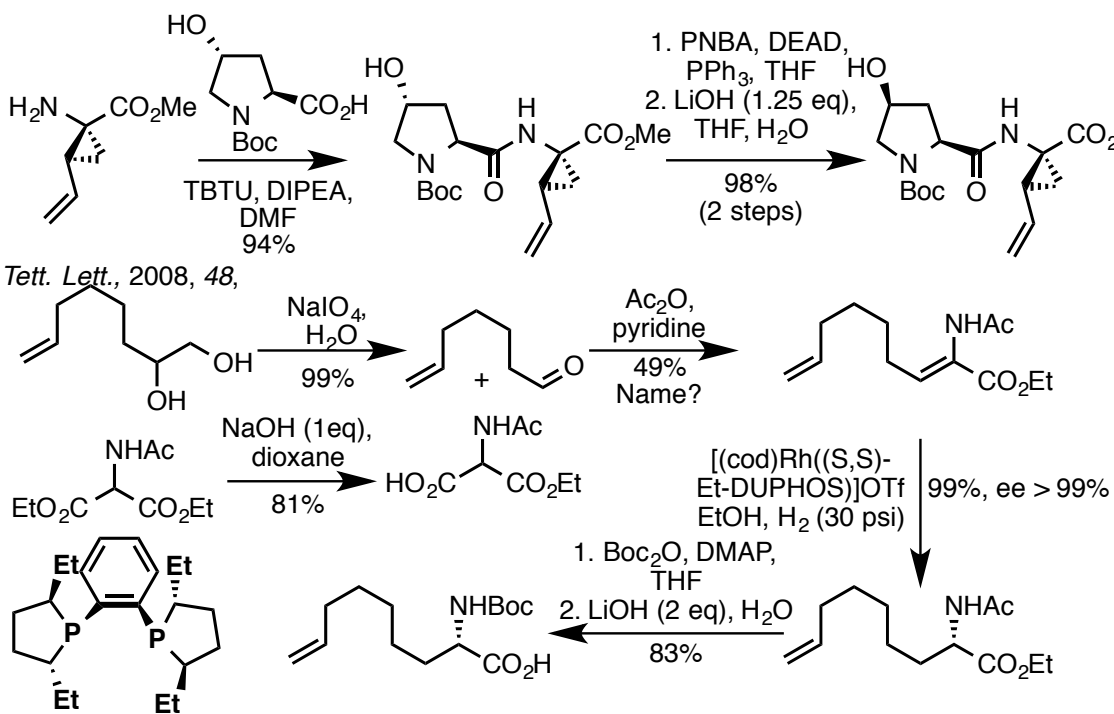
Structure-Activity Study on a Novel Series of Macrocyclic Inhibitors of the Hepatitis C Virus NS3 Protease Leading to the Discovery of BILN 2061
J. Med. Chem. 2004, 47, 1605.



Synthesis of BILN 2061, an HCV NS3 Protease Inhibitor with Proved Antiviral Effect in Humans

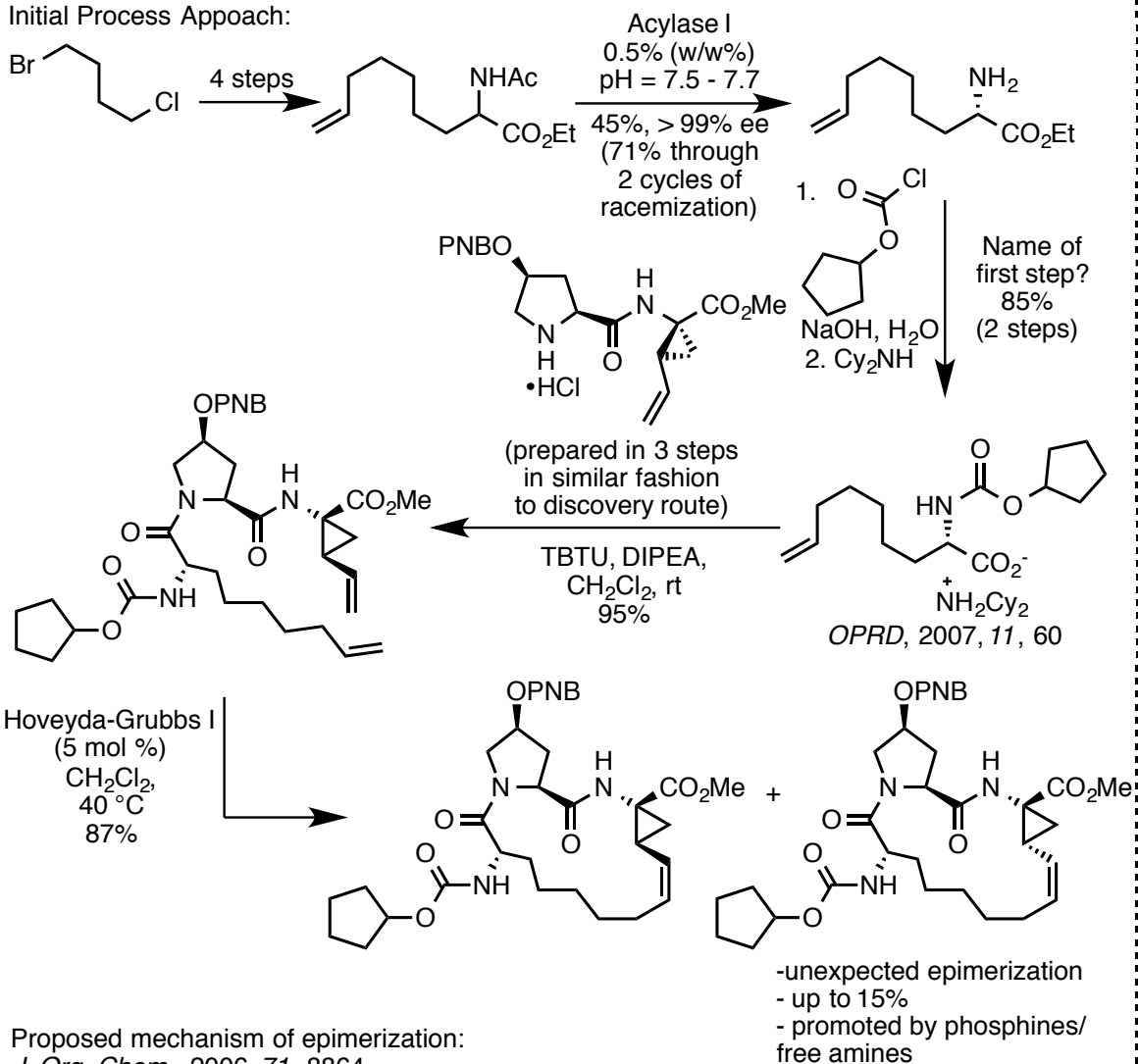
Org. Lett., 2004, 6, 2901.

Discovery route for SAR studies and preclinical pharmacological studies:

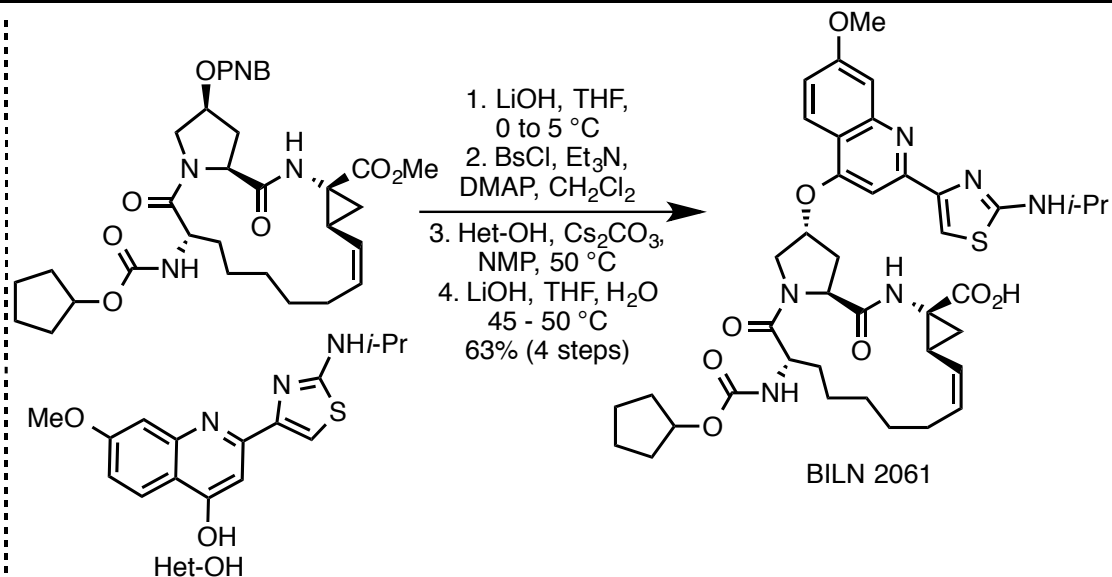
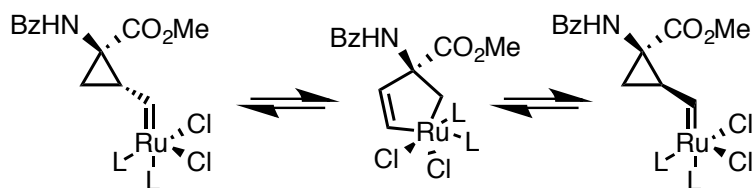


Efficient Large-Scale Synthesis of BILN 2061, a Potent HCV Protease Inhibitor, by a Convergent Approach Based on Ring-Closing Metathesis
J. Org. Chem., 2006, 71, 7133.

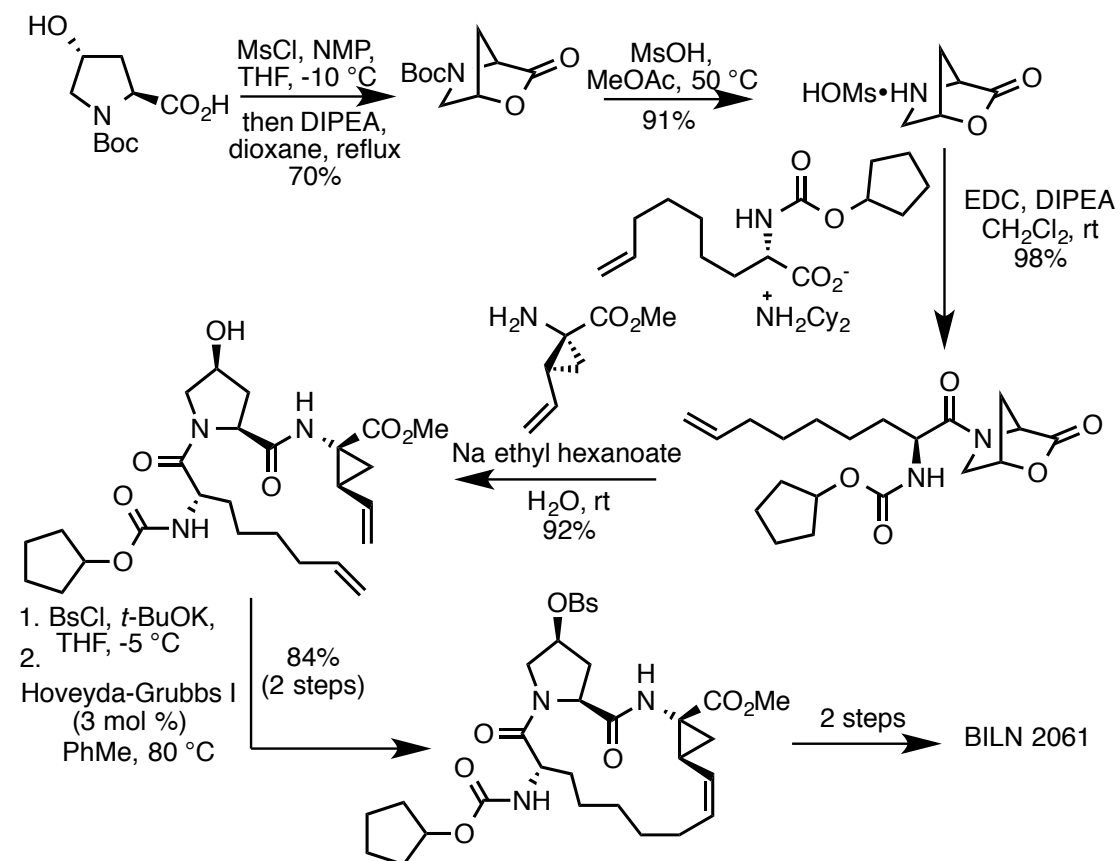
Initial Process Approach:



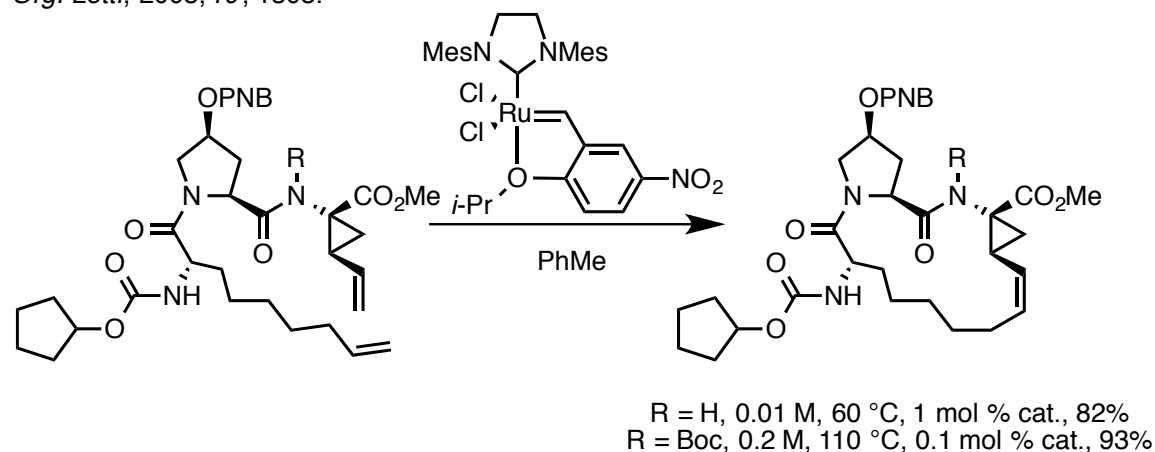
Proposed mechanism of epimerization:
J. Org. Chem., 2006, 71, 8864.



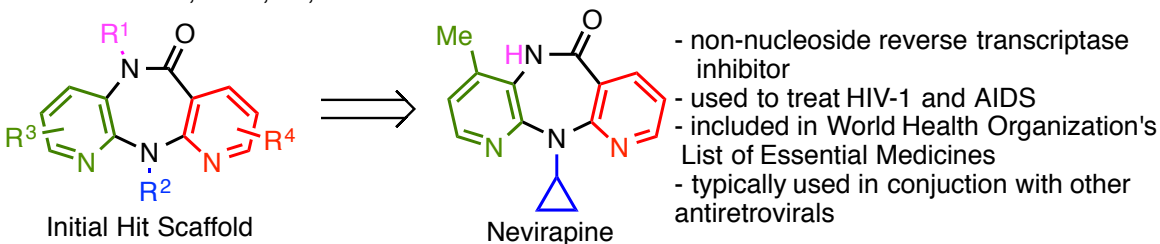
Pilot Synthesis (A Few Modifications):



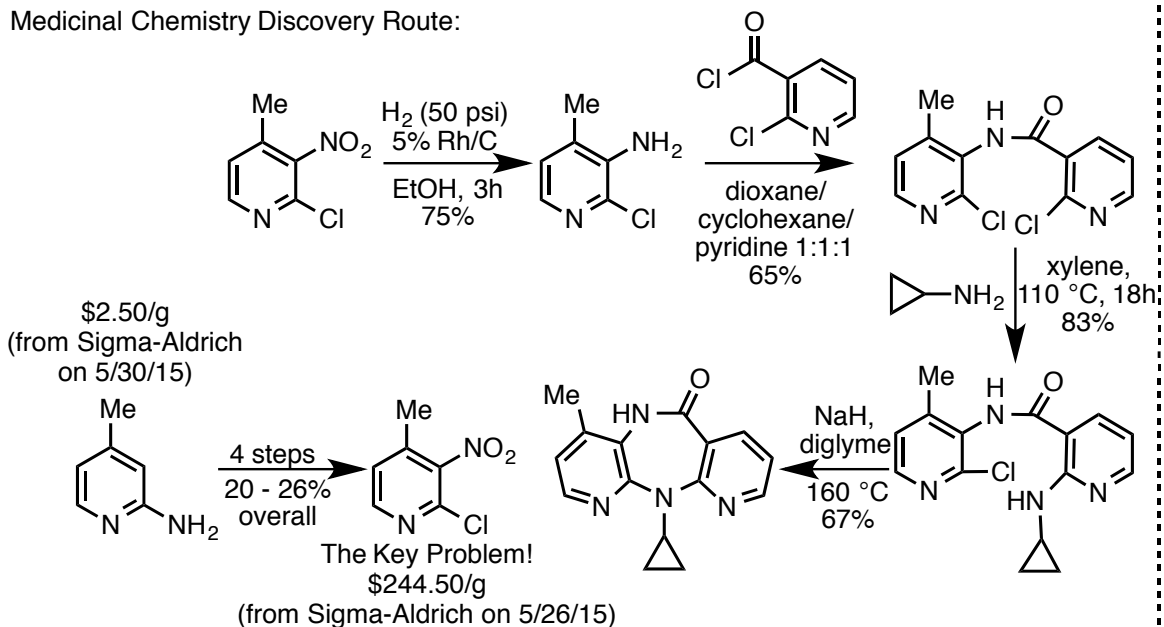
Org. Lett., 2008, 10, 1303.



Novel Non-Nucleoside Inhibitors of HIV-1 Reverse Transcriptase. 1. Tricyclic Pyridobenzo- and Dipyridodiazepinones
J. Med. Chem., 1991, 34, 2231.



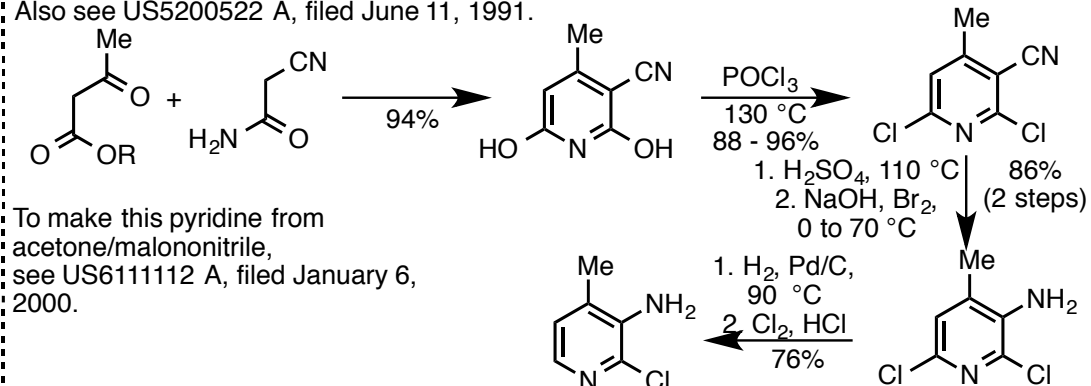
Medicinal Chemistry Discovery Route:



Synthesis of Nevirapine and its Major Metabolite

J. Heterocyclic Chem., 1995, 32, 259.

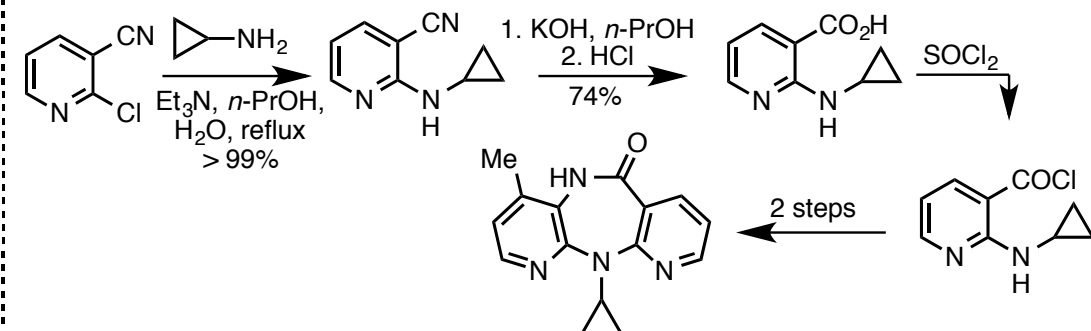
Also see US5200522 A, filed June 11, 1991.



To make this pyridine from acetone/malononitrile, see US611112 A, filed January 6, 2000.

Method for making nevirapine US20040002603 A1

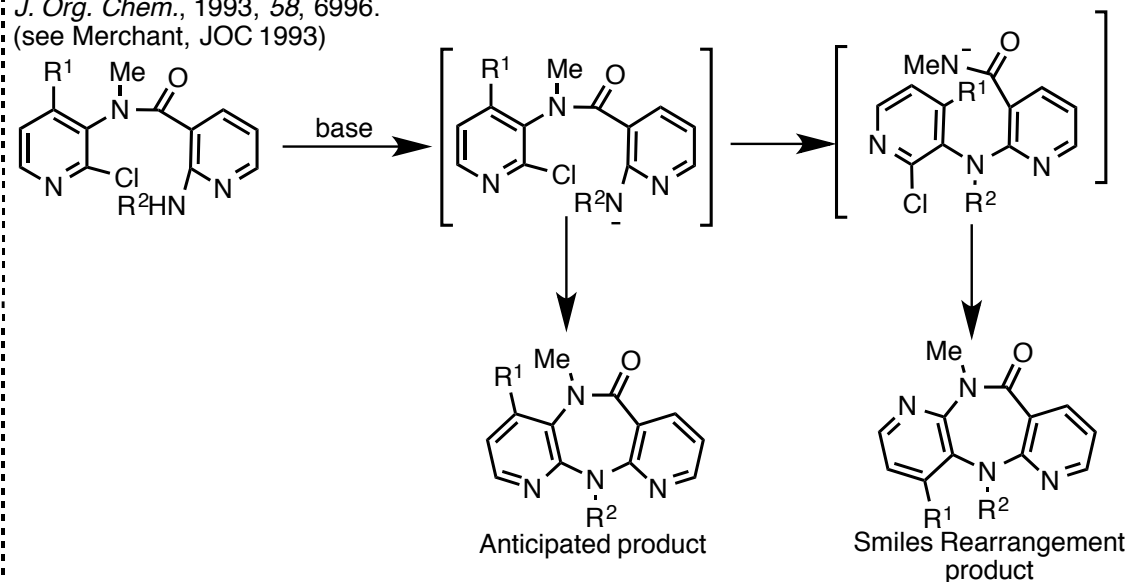
Filed June 5, 2003



A Novel Smiles Rearrangement Gives Access to the A-Ring Pyridine Isomers of the Nevirapine Ring System

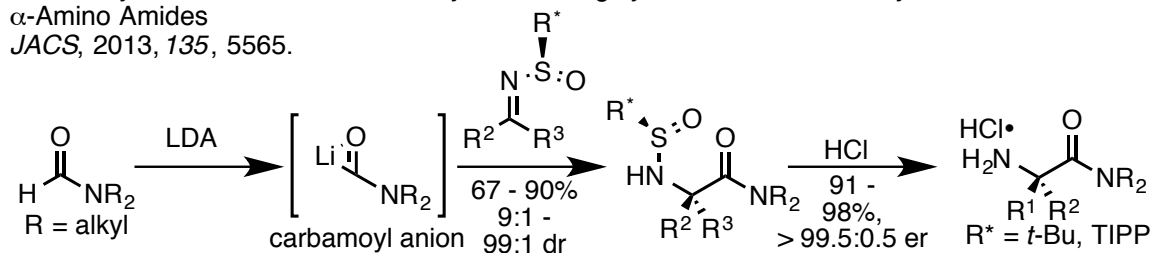
J. Org. Chem., 1993, 58, 6996.

(see Merchant, JOC 1993)



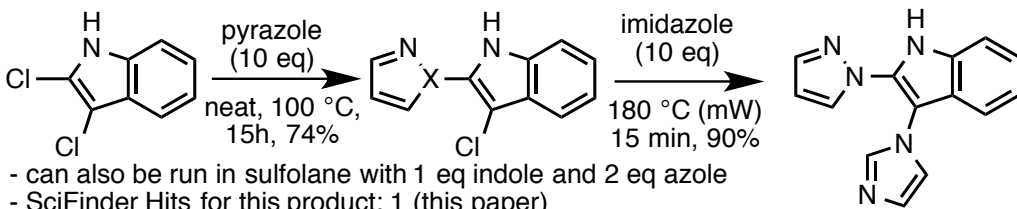
Some interesting methodologies:

Carbamoyl Anion Addition to *N*-Sulfinyl Imines: Highly Diastereoselective Synthesis of α -Amino Amides
JACS, 2013, 135, 5565.

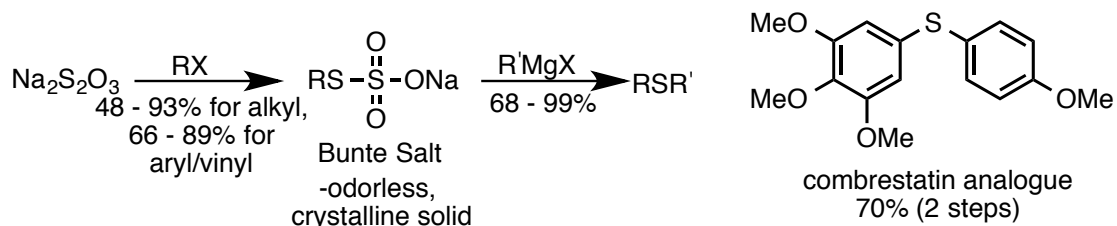


For addition into nitrones, see *J. Org. Chem.*, 2014, 79, 5895.

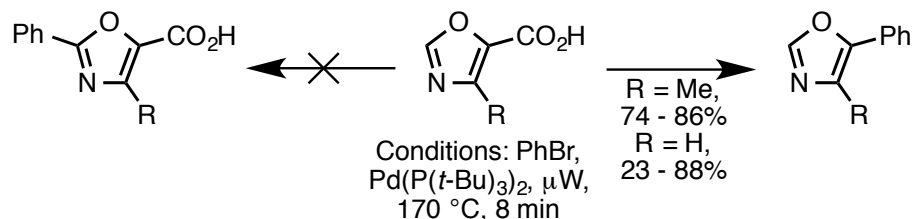
Metal-Free Coupling of Azoles with 2- and 3-Haloindoles Providing Access to Novel 2- and 3-(Azol-1-yl)indole Derivatives
Org. Lett., 2010, 12, 2334.



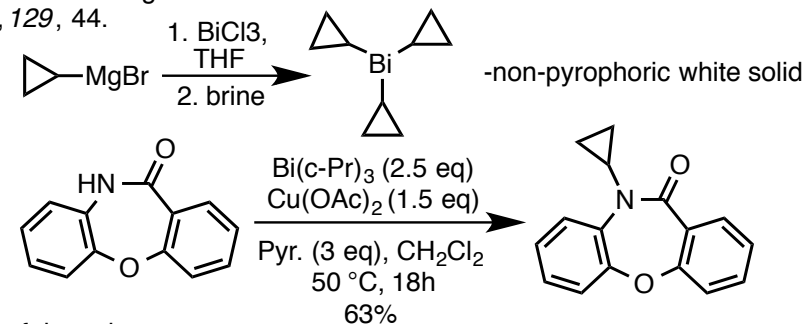
The Reaction of Grignard Reagents with Bunte Salts: A Thiol-Free Synthesis of Sulfides
Org. Lett., 2014, 16, 1196.



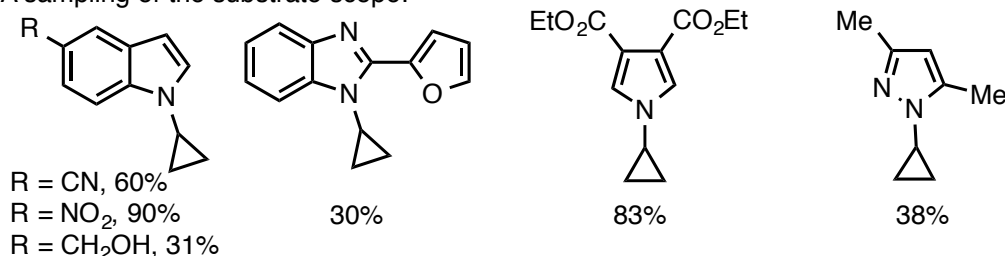
Unexpected Intermolecular Pd-Catalyzed Cross-Coupling Reaction Employing Heteroaromatic Carboxylic Acids as Coupling Partners
JACS, 2006, 128, 11351.



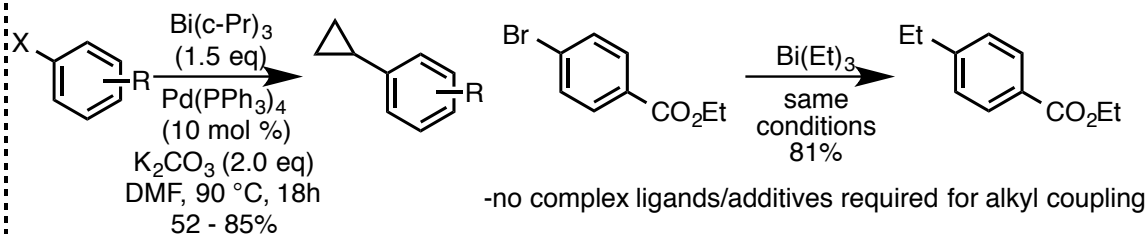
Direct *N*-Cyclopropylation of Cyclic Amides and Azoles Employing a Cyclopropylbismuth Reagent
JACS, 2007, 129, 44.



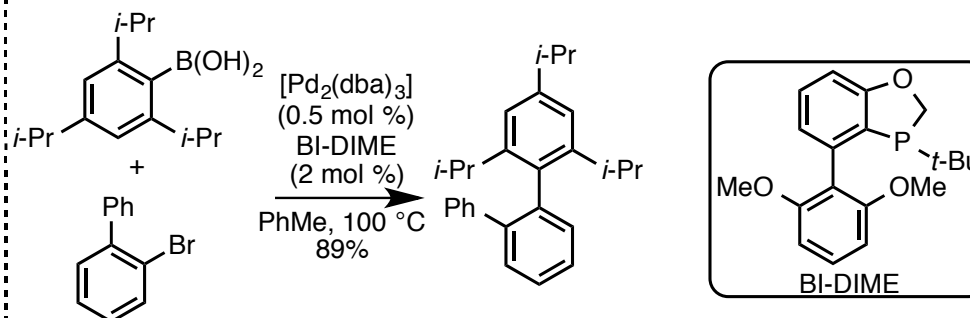
A sampling of the substrate scope:



Palladium-Catalyzed Cross-Coupling Reaction of Tricyclopropylbismuth with Aryl Halides and Triflates
JOC, 2008, 73, 3604.

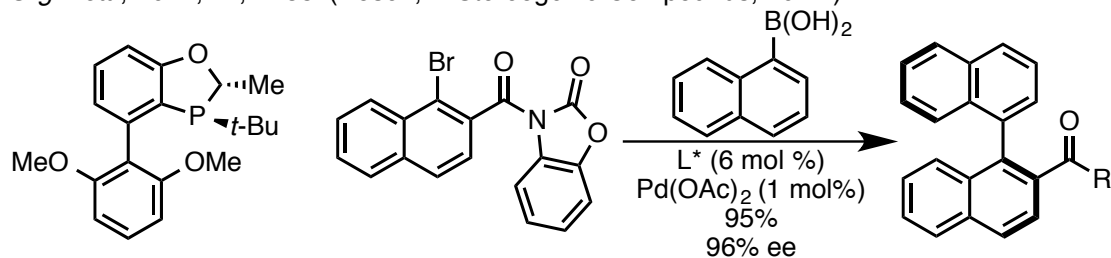


A General and Special Catalyst for Suzuki-Miyaura Coupling Processes
ACIE, 2010, 49, 5879. (also see Rosen, P-Stereogenic Compounds, 2014)

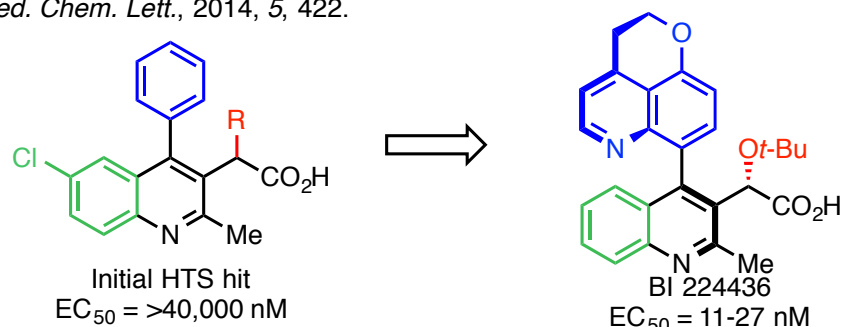


- ligand is air-stable and can be prepared in kilogram quantities
- tolerates free amino groups and heteroaryl substrates
- can use with aryl chlorides, cyclopropaneboronic acid, vinylboronic acid

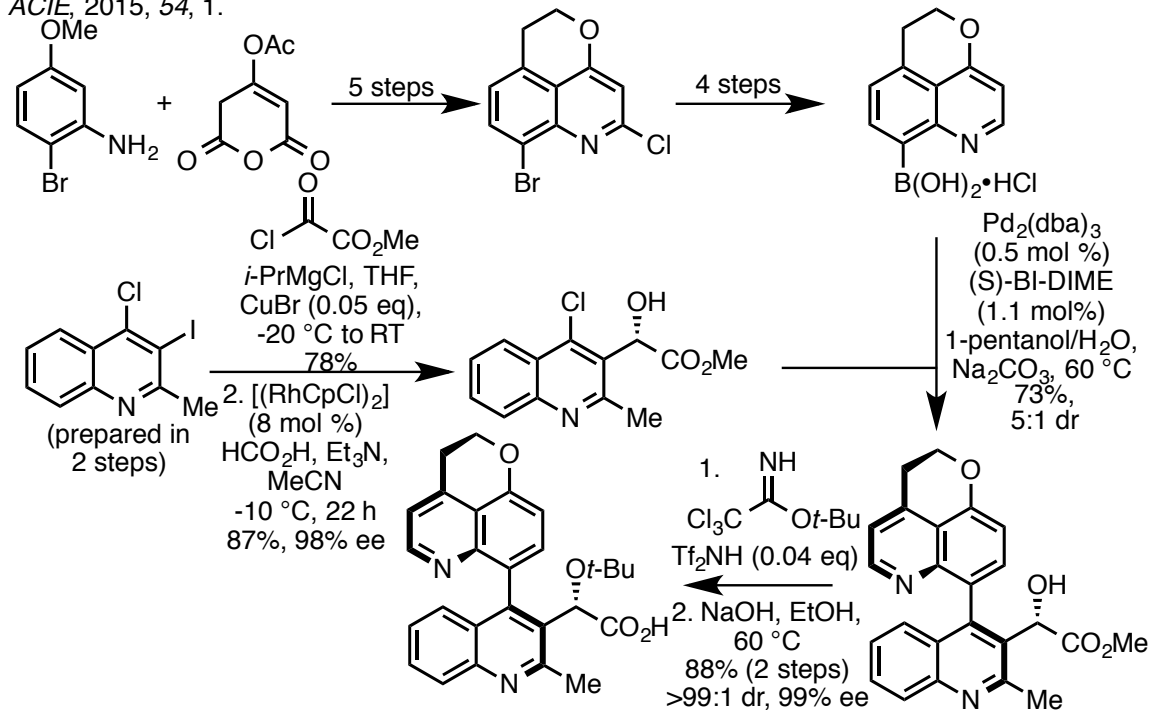
Efficient Chiral Monophosphorus Ligands for Asymmetric Suzuki-Miyaura Coupling Reactions

Org. Lett., 2012, 14, 2258. (Rosen, P-Stereogenic Compounds, 2014.)

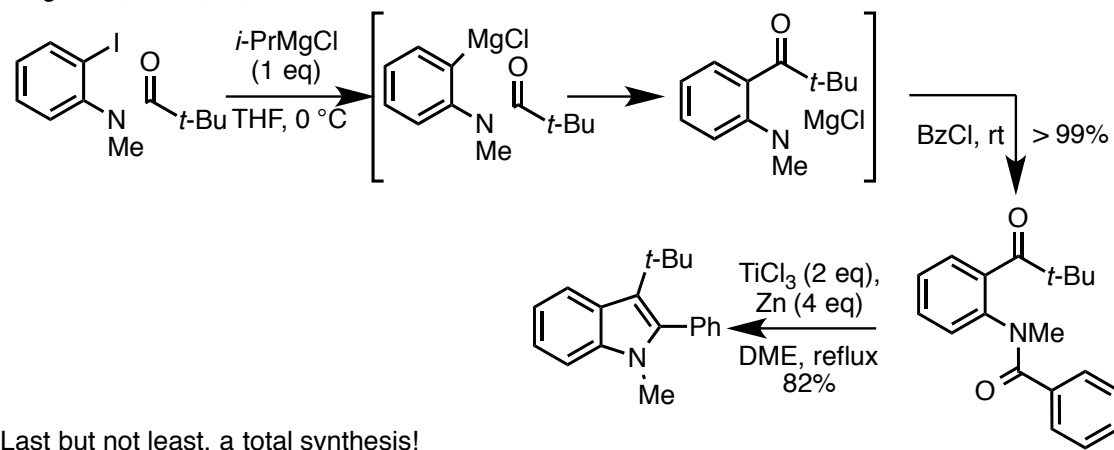
Discovery of BI 224436, a Noncatalytic Site Integrase Inhibitor (NCINI) of HIV-1

ACS Med. Chem. Lett., 2014, 5, 422.

Concise and Practical Asymmetric Synthesis of a Challenging Atropisomeric HIV Integrase Inhibitor

ACIE, 2015, 54, 1.

Anionic N-Fries Rearrangement of N-Alkyl-2-iodo Anilides Induced by Iodine-Magnesium Exchange: Application for Synthesis of Strained 1,2,3-Trisubstituted Indoles

Org. Lett., 2008, 10, 1067.

Last but not least, a total synthesis!

A Concise Synthesis of Butylcycloheptylprodigiosin

Org. Lett., 2007, 9, 1879.