Synthesis of the HCV Protease Inhibitor Vaniprevir (MK-7009) Using Ring-Closing Metathesis Strategy

Jongrock Kong*, Cheng-yi Chen*, Jaume Balsells-Padros, Yang Cao, Robert F. Dunn, Sarah J. Dolman, Jacob Janey, Hongmei Li, and Michael J. Zacuto

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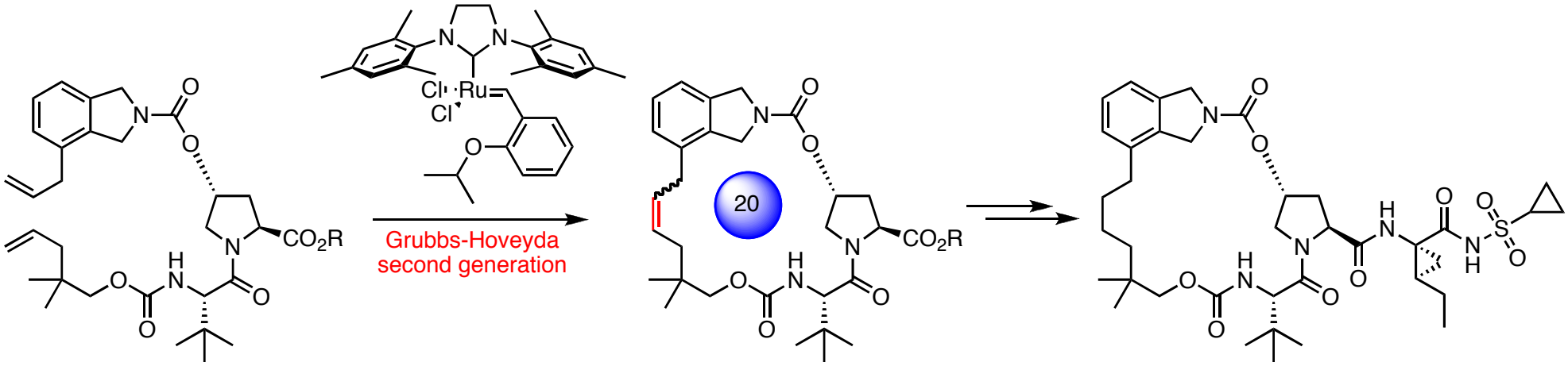
DOI: 10.1021/JO3001595

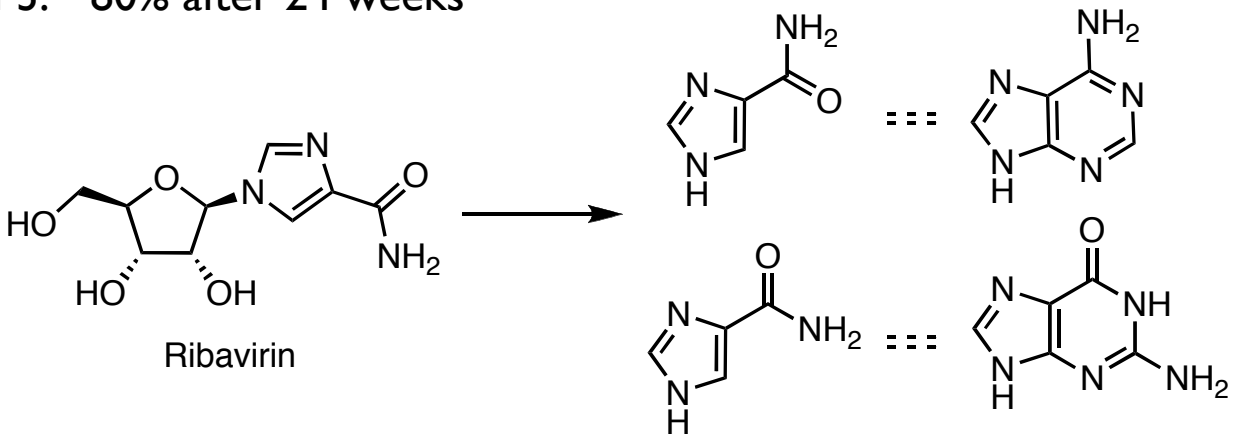


Vaniprevior (MK-7009)
9 steps, 55% overall yield

Christopher Rosenker
Wipf Group - Current Literature
April 28, 2012

Hepatitis C Virus (HCV)

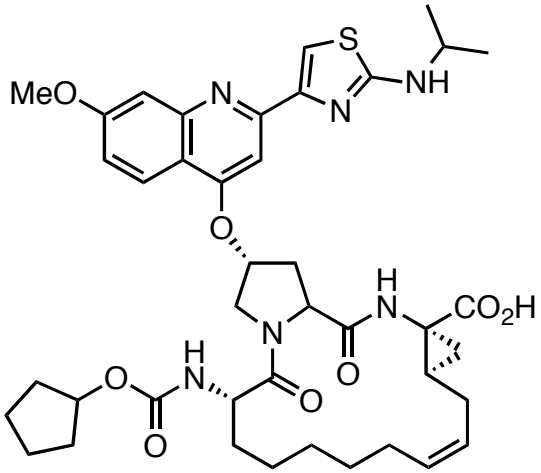
- 130-170 million people worldwide are affected by Hepatitis C virus (HCV)
- Infection commonly leads to liver diseases including cirrhosis and hepatocellular carcinoma
- Leading cause of death in HIV patients
- Current therapy is pegylated interferon-α and ribavirin
  - Weekly injection of interferon; ribavirin orally
  - Serious side effects limit patients eligible for treatment
  - Therapy duration is dependant on HCV genotype
    - genotype 1: ~45% after 48 weeks
    - genotype 2 and 3: ~80% after 24 weeks



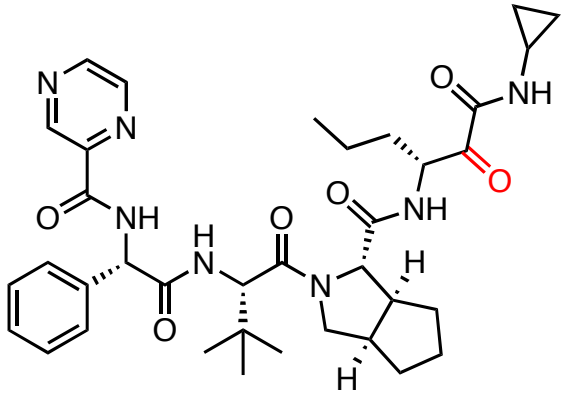
J. Med. Chem. **2010**. *53*. 2443.

Hepatitis C Virus (HCV)

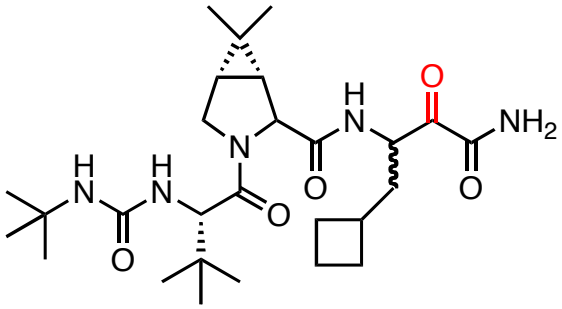
Development of NS3/4a protease inhibitors has led to several clinical drug candidates.



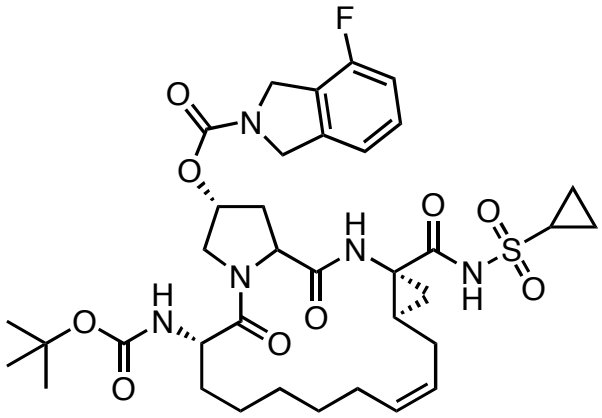
BILN-2061
Boehringer Ingelheim
(rapidly reversible)



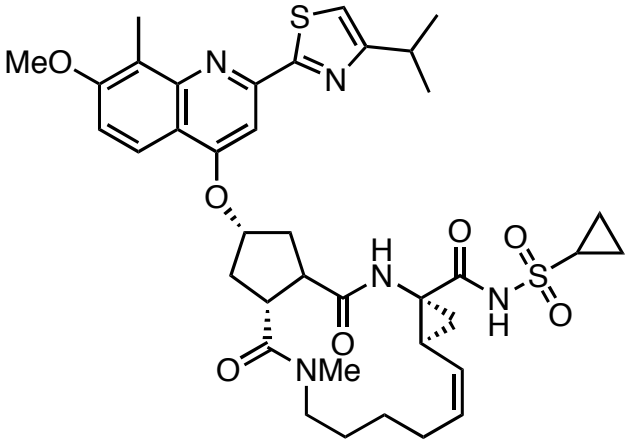
Telaprevir (VX-950)
Vertex
(covalent inhibitor)



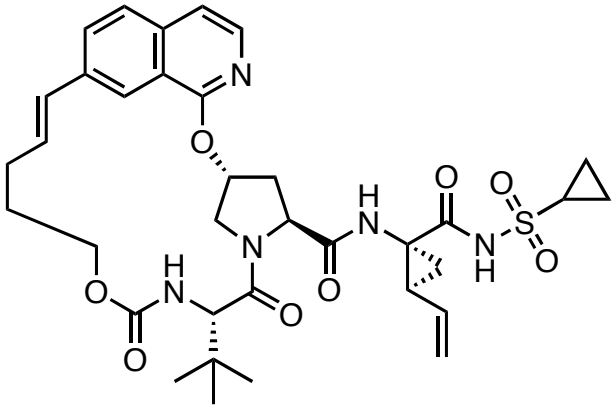
Boceprevir (SCH 503034)
Schering-Plough
(covalent inhibitor)



ITMN-191
InterMune & Array Biopharma
(rapidly reversible)



TMC-435350
Tibotec BVBA & Medivir AB
(rapid reversible)

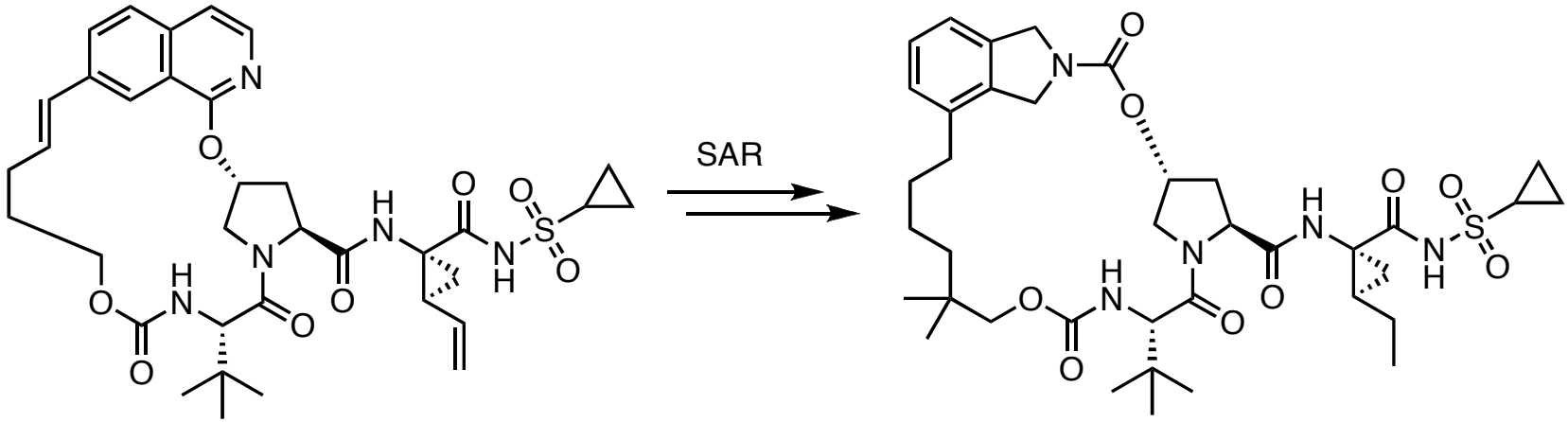


Merck
(initial lead)

J. Med. Chem. **2010**. *53*. 2443.

Discovery of Vaniprevir (MK-7009)

Merck's initial lead was discovered by molecular modeling of therapeutic hits VX-950 (Vertex) and BILN-2061 (BI) bound to Hepatitis C NS3/4A Protease.



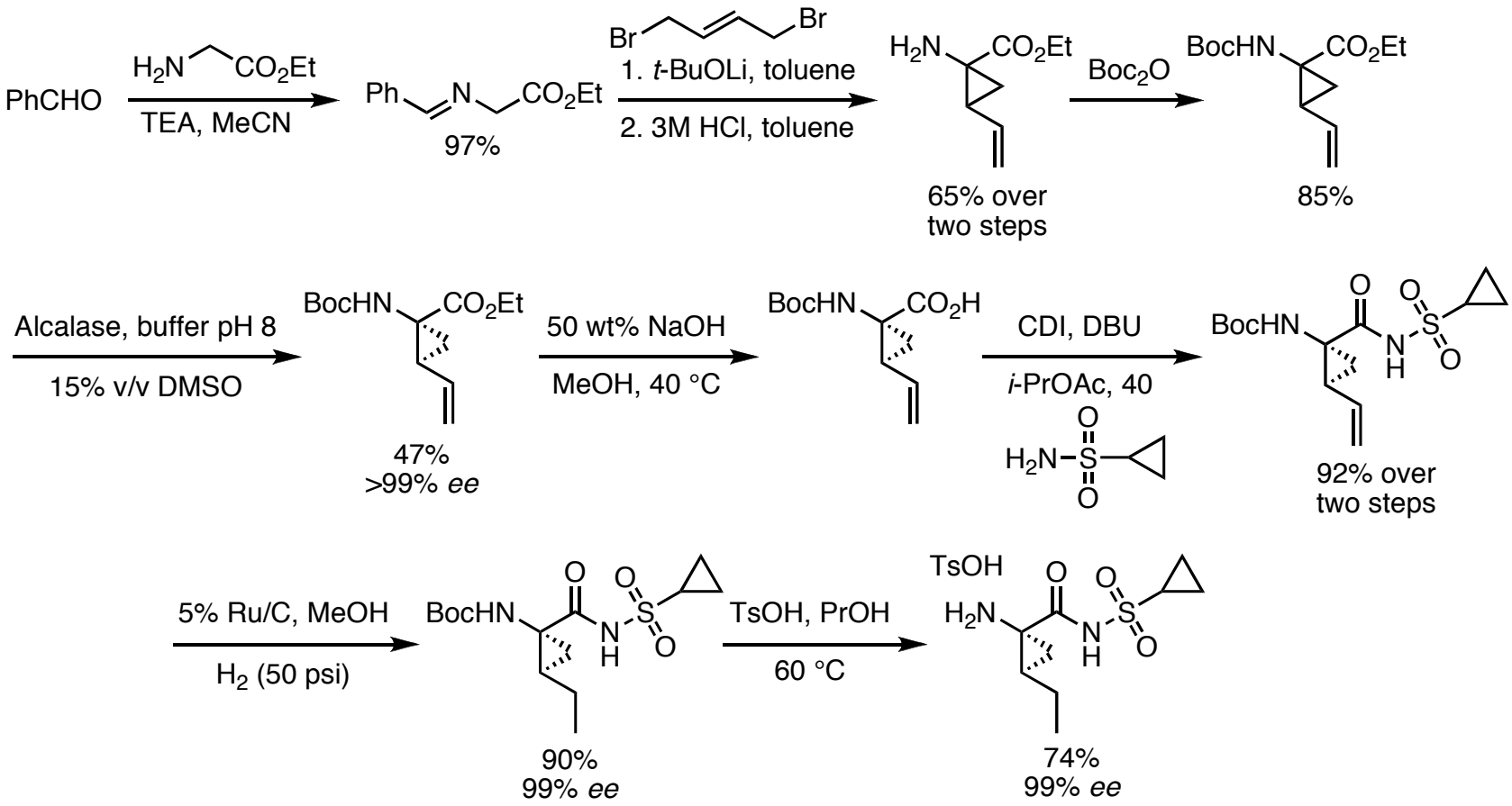
Merck
(initial lead)

Vaniprevir (MK-7009)

J. Am. Chem. Soc. **2008**, *130*, 4607.
J. Med. Chem. **2010**, *53*, 2443.

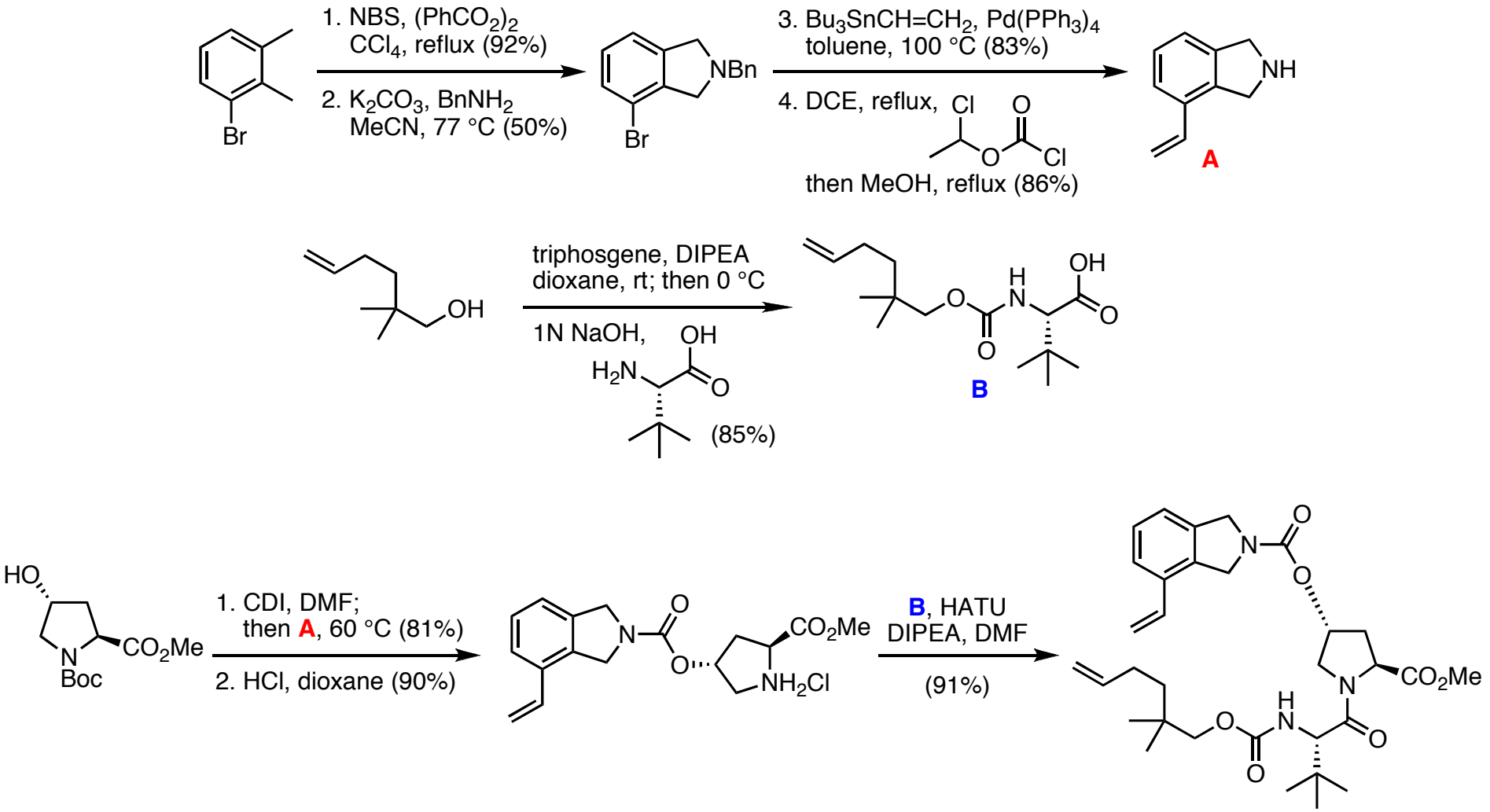
Discovery Synthesis of Vaniprevir (MK-7009)

Side chain synthesis: Reported on multi-kilogram scale, 9 steps, 15% yield



WO 2011/025849
PCT/US2010/046725

Discovery Synthesis of Vaniprevir (MK-7009)



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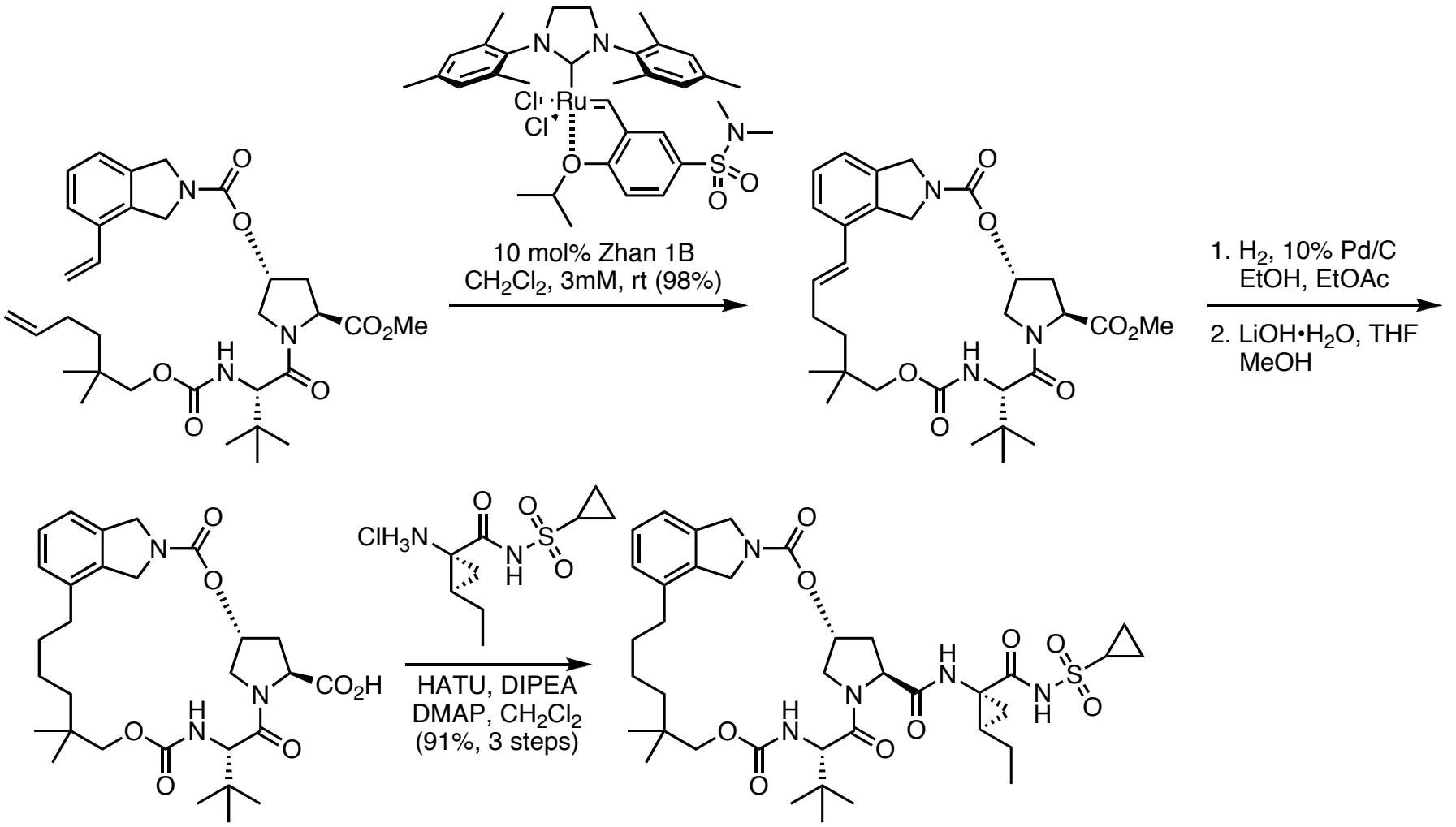
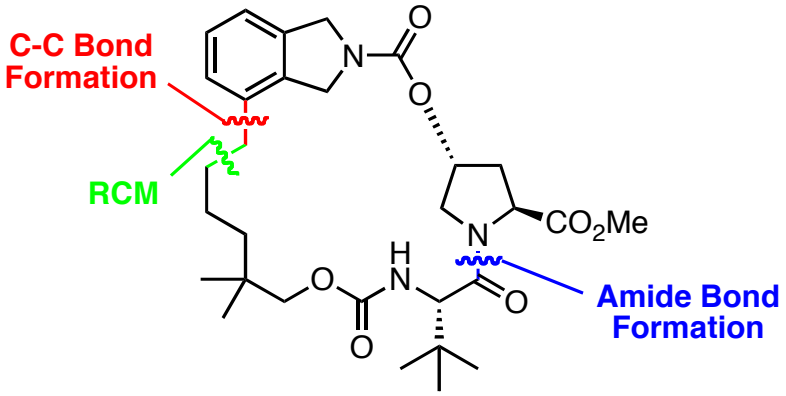
Discovery Synthesis of Vaniprevir (MK-7009)



Vaniprevir (MK-7009)
11 steps LLS, 19% yield

J. Med. Chem. **2010**. *53*. 2443.

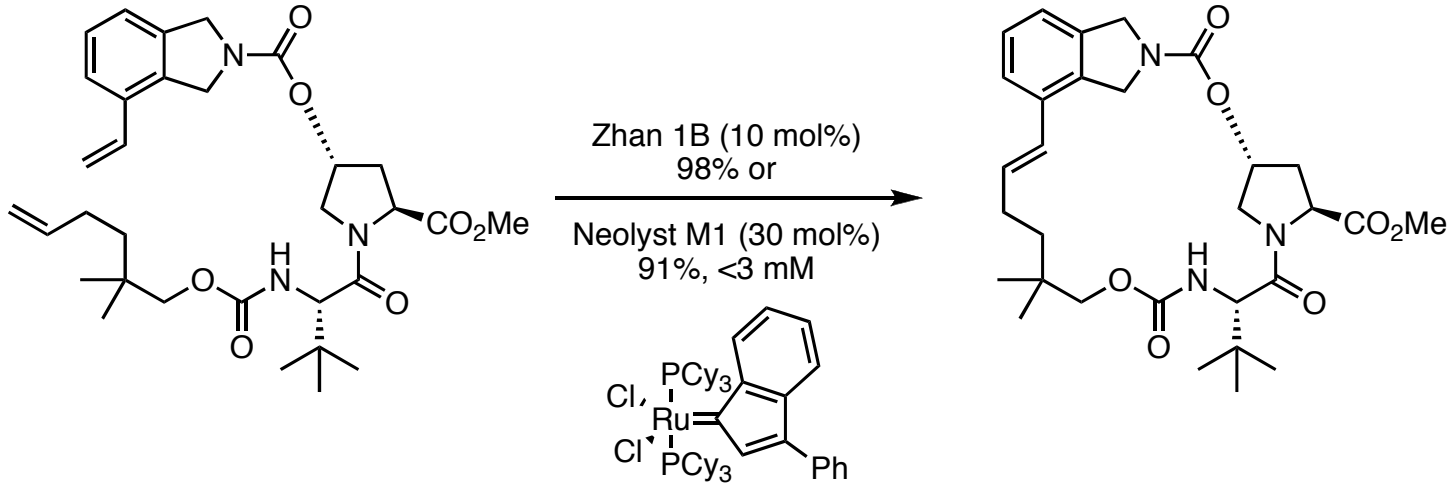
Synthesis of Vaniprevir (MK-7009): Route Improvement



Possible Macrocylization Strategies

- Ring Closing Metathesis
- Metal-mediated C-C
- Amide Bond Formation

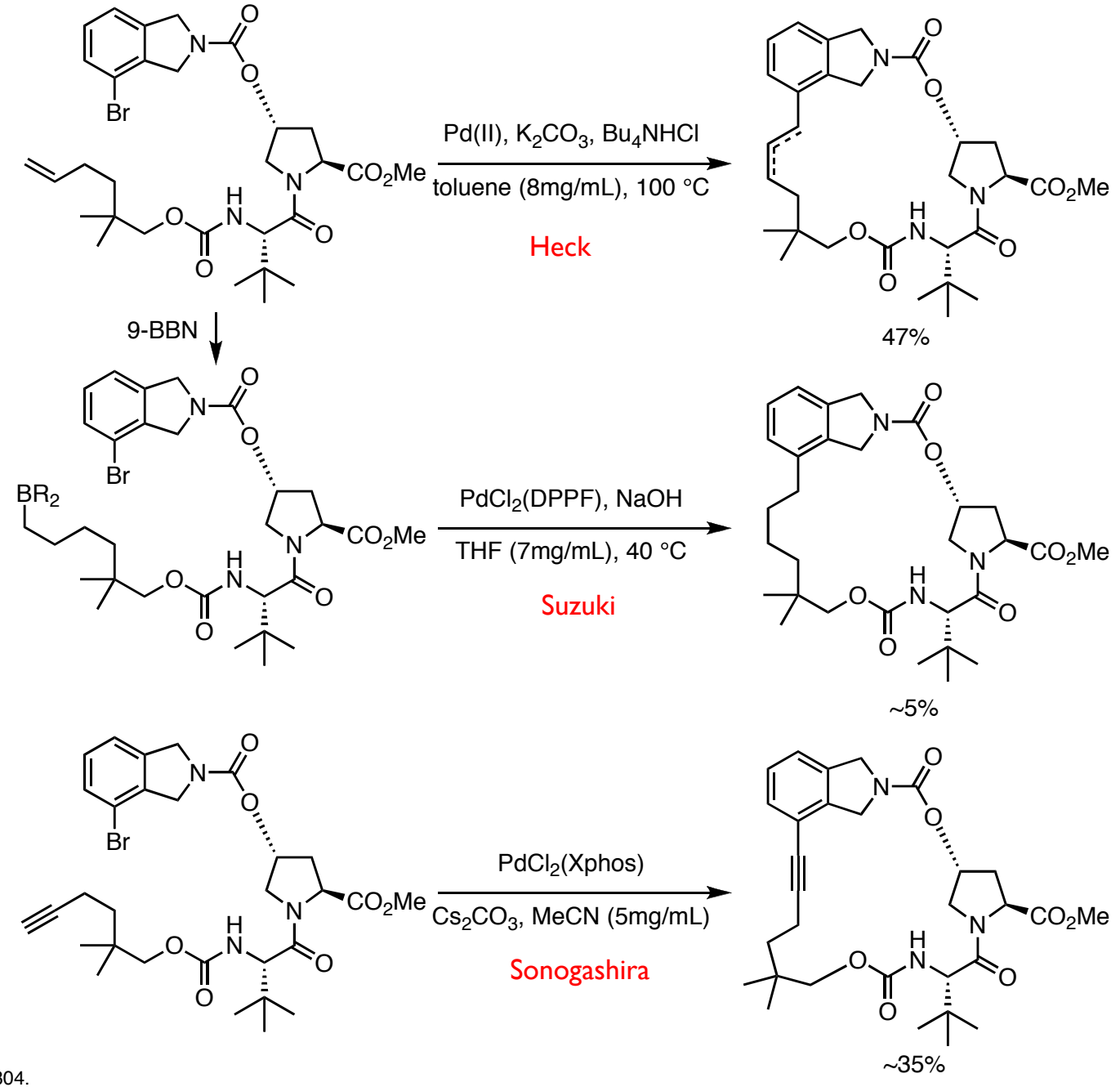
Macrocylization using RCM



- Requires rigorous purification of diene
- High catalyst loading
- High reaction concentration
- Incomplete conversion
- Difficult catalyst removal process
- Catalyst cost

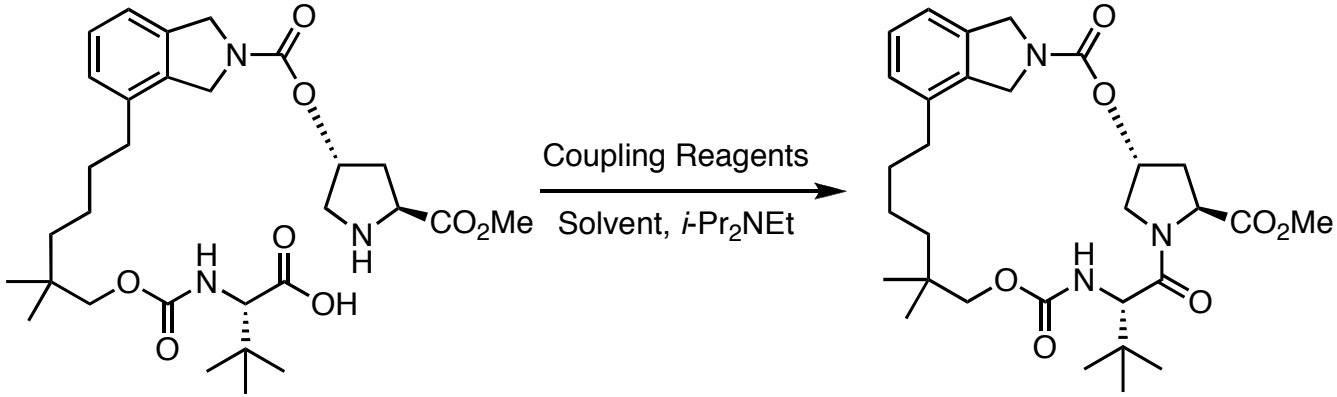
J. Org. Chem. **2011**, *76*, 7804.

Synthesis of Vaniprevir (MK-7009): Metal-mediated C-C

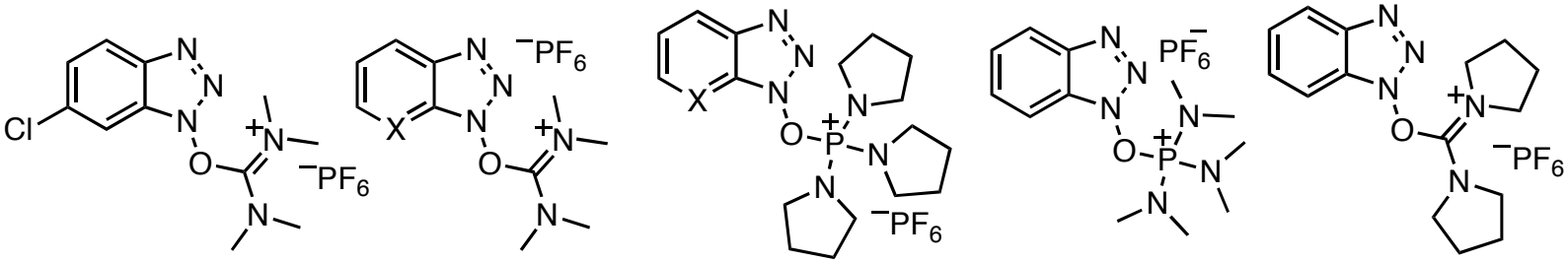


J. Org. Chem. **2011**, *76*, 7804.

Synthesis of Vaniprevir (MK-7009): Amide Bond Formation



Uronium Derived Reagents and Cyclization Yields



HCTU 60%

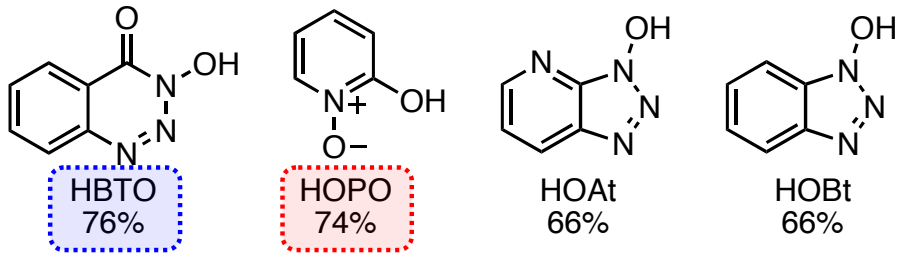
HBTU (X = CH) 60%
HATU (X = N) 75%

pyBOP (X = CH) 64%
pyAOP (X = N) 79%

BOP 62%

HBPYU 50%

EDC + Additive and Yields



HBTO 76%

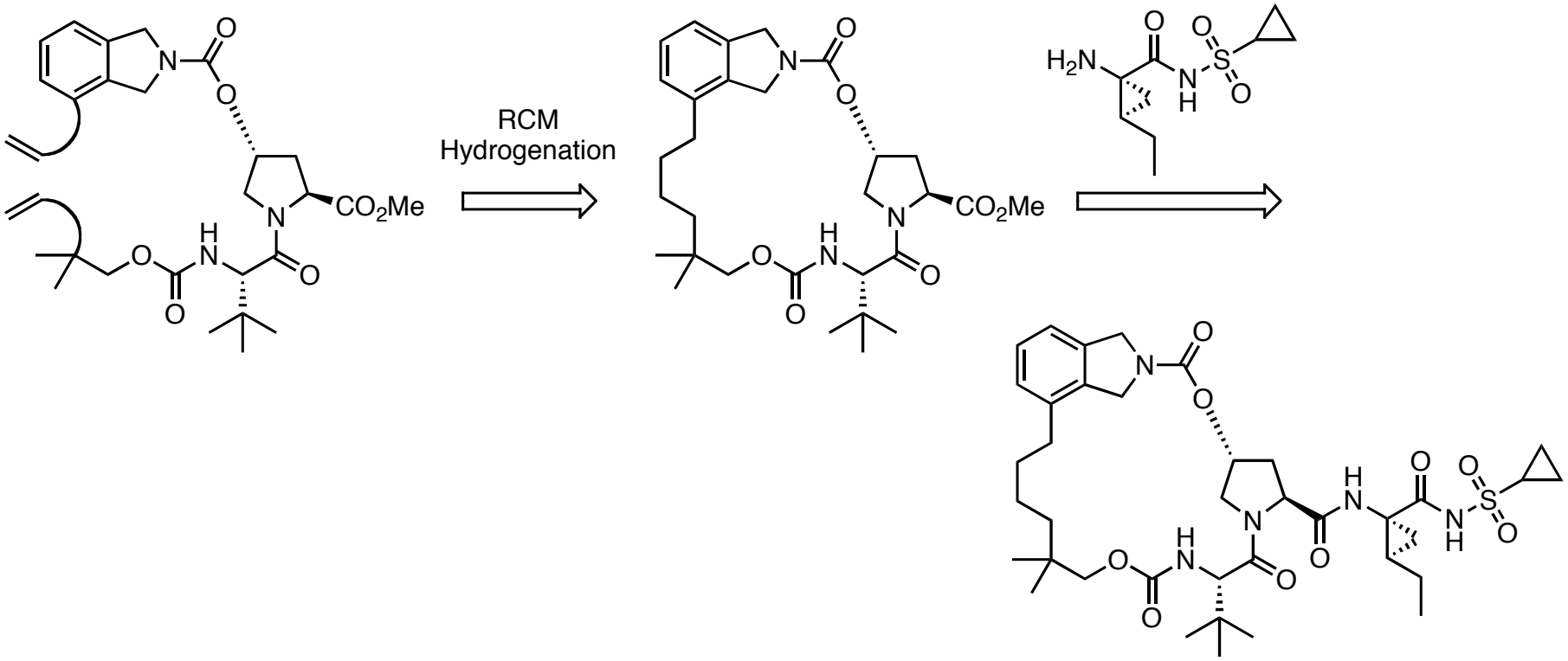
HOPO 74%

HOAt 66%

HOBt 66%

J. Org. Chem. **2011**, *76*, 7804.

Title Paper: Vaniprevir (MK-7009) using RCM



Vaniprevir (MK-7009)

J. Org. Chem. **2012**, *ASAP*. doi: 10.1021/jo3001595

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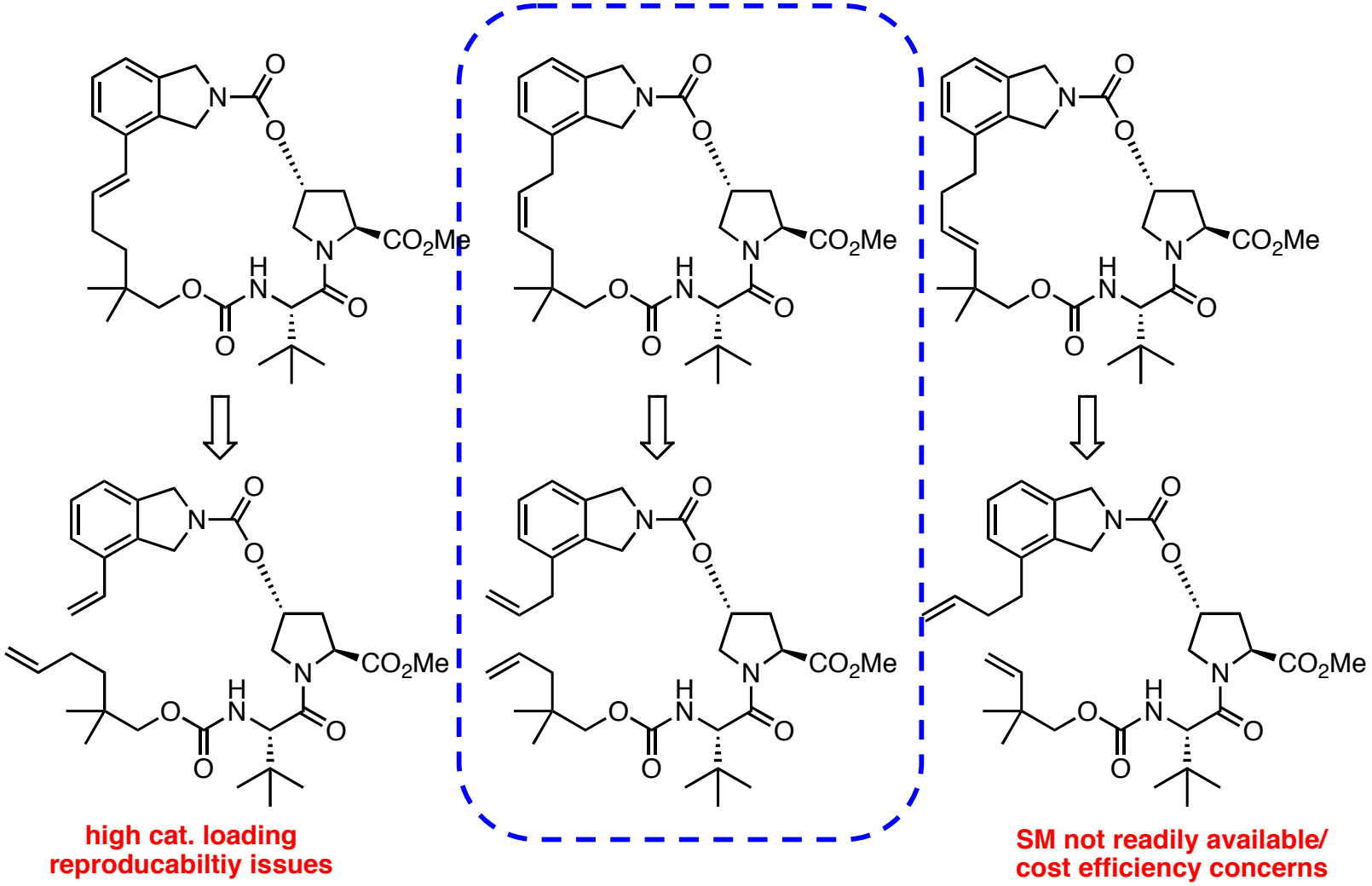

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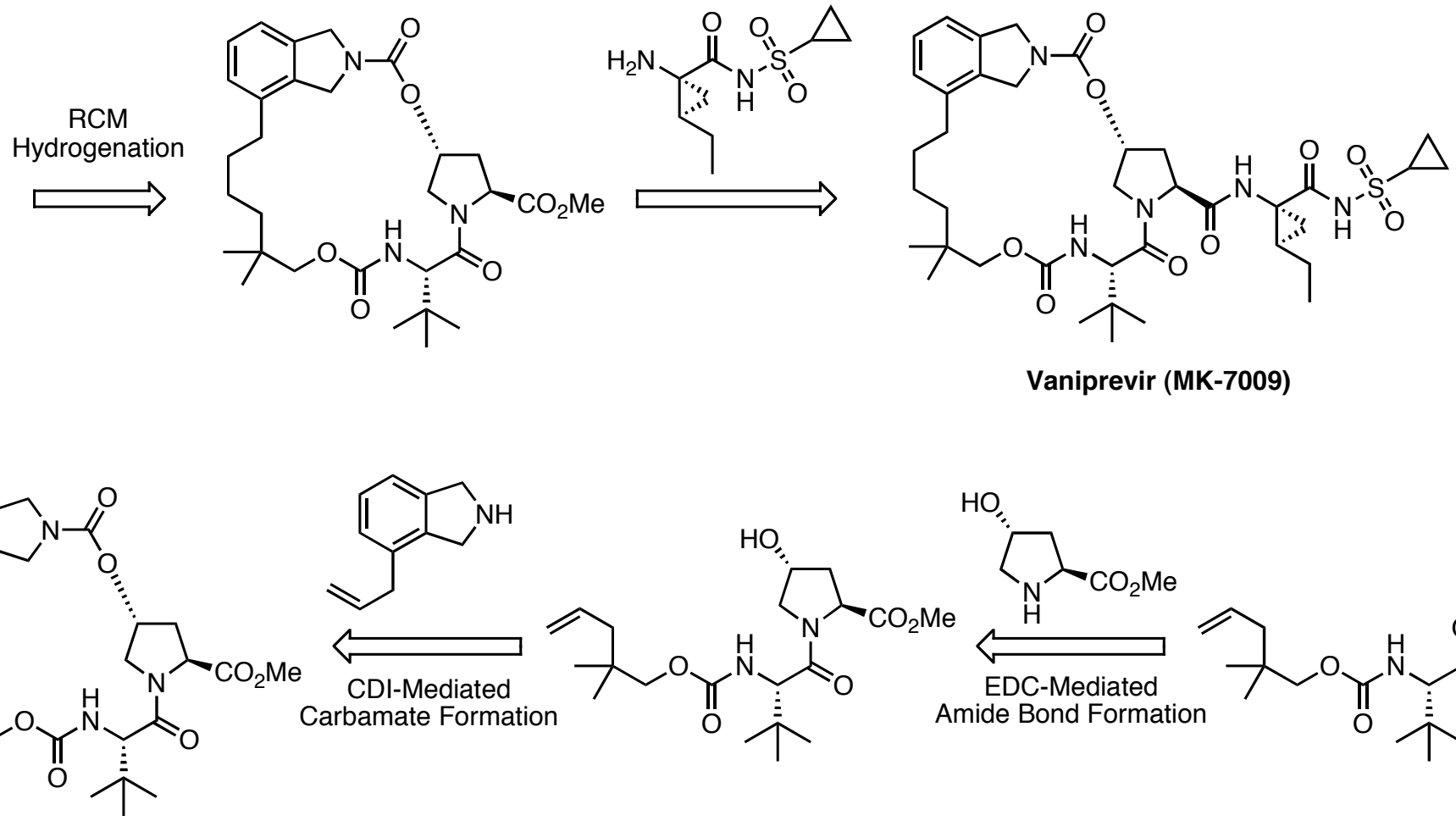
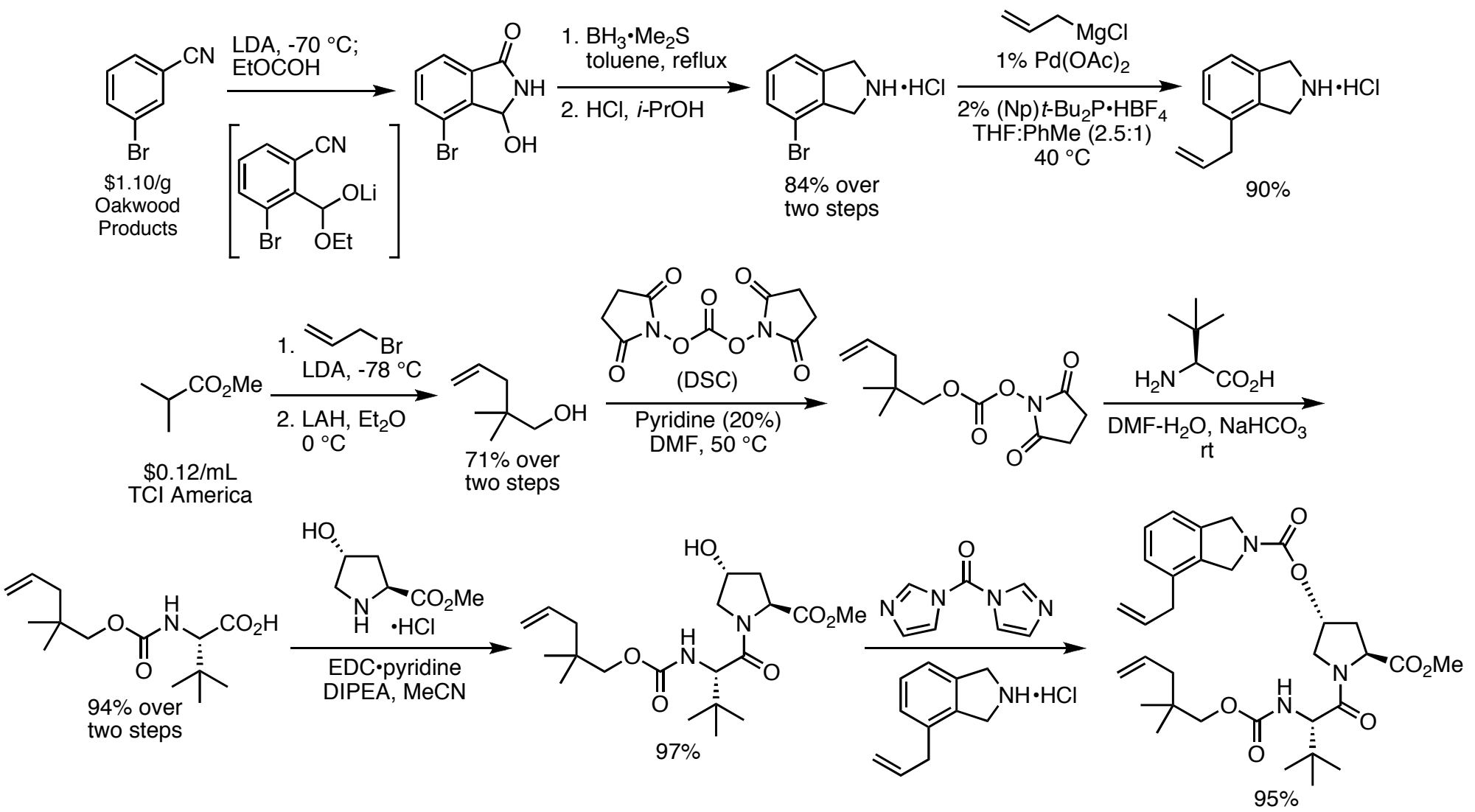


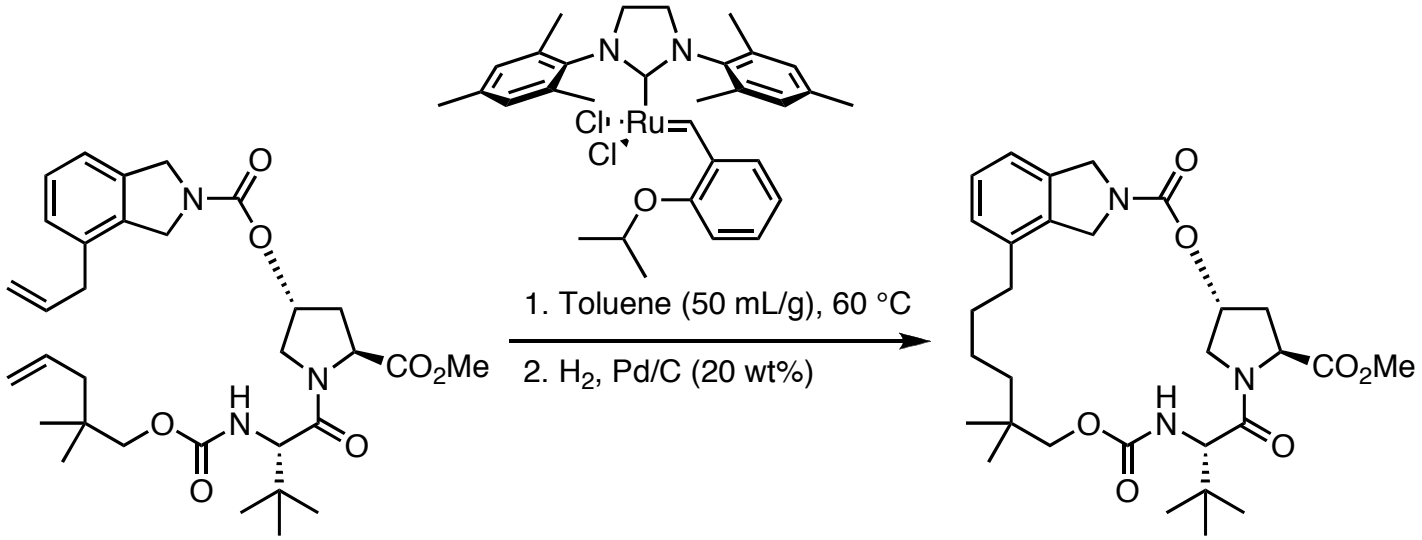
J. Org. Chem. **2012**, *ASAP*. doi: 10.1021/jo3001595

Title Paper: Preparation of Macrocycle Precursor



J. Org. Chem. **2012**, *ASAP*. doi: 10.1021/jo3001595

Title Paper: RCM Optimization



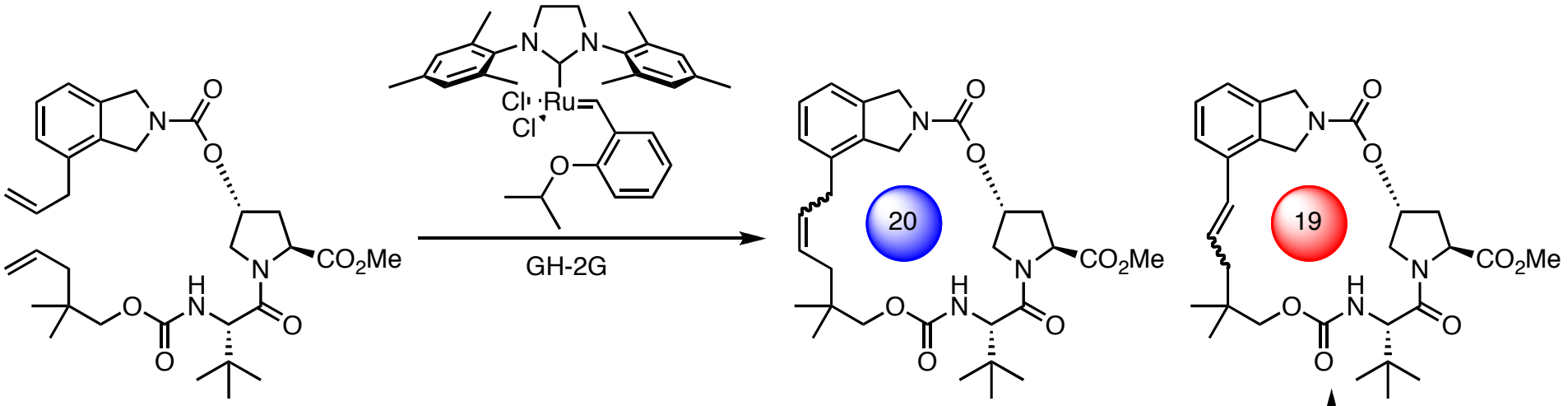
Addition mode	Cat. Loading	Yield
one-pot	1 mol%	57%
one-pot	5 mol%	67%
slow addition of cat.	1 mol%	82%

- Optimization goals are cost motivated: low cat. loading, high concentration, high yield
- Initial test reaction indicated significant optimization required
- Reaction profiling indicated high catalytic activity at the beginning of the reaction
  - Catalyst activity diminished as reaction proceeded
  - Oligomer formation occurred towards the end of the reaction

J. Org. Chem. **2012**, *ASAP*. doi: 10.1021/jo3001595

Title Paper: RCM Optimization

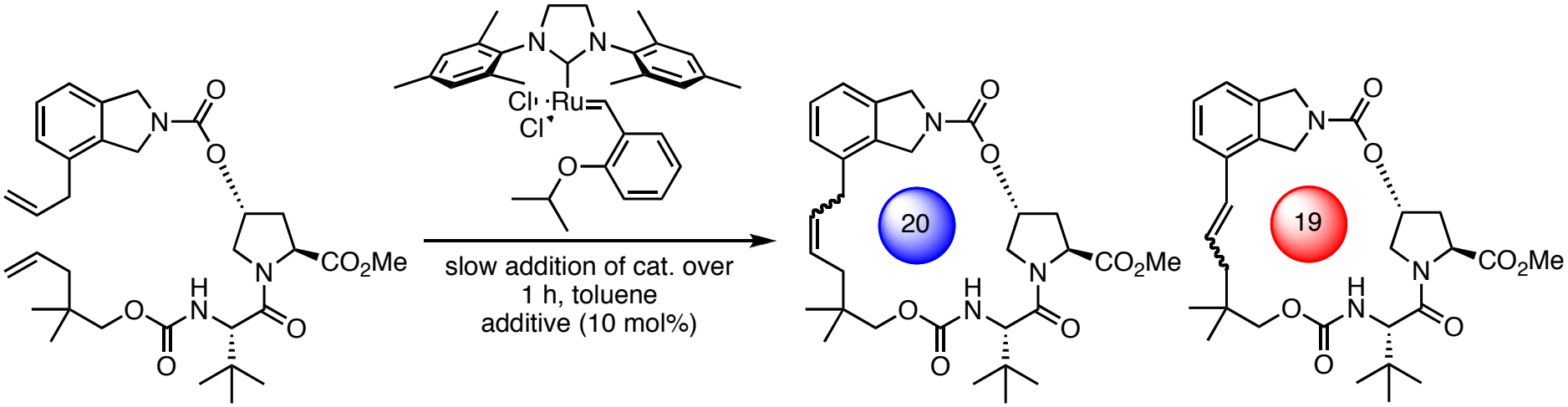
- Attempts to increase concentration of diene led to undesired 19-membered ring
- Ru-H complex generated by decomposition of GH-2G is responsible for isomerization



Rxn Conditions	Volume Ratio (mL/g SM)	Results 20-mac	19-mac
1 mol% Ru slow addition over 1 h, toluene, 60 °C	50	82%	<1%
	30	61%	9%

J. Org. Chem. **2012**, *ASAP*. doi: 10.1021/jo3001595

Title Paper: RCM Optimization



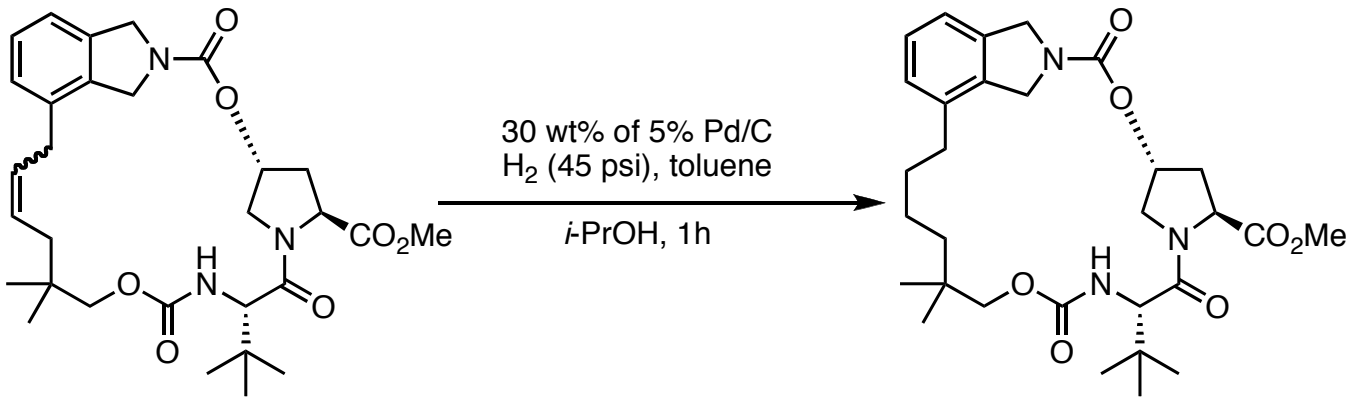
						Results		
Entry	**mol% cat.**	**Temp (°C)**	**Method**	**Additive**	**Conc. (ml/g)**	20-ring	19-ring	dimers/oligomers
1	1	70	A	none	20	62	8	5
2	0.2	70	A	2,6-dichloroquinone	20	72	<1	5
3	0.2	100	A	2,6-dichloroquinone	20	84	1.5	5
4	0.2	100	B	2,6-dichloroquinone	20	88	1.5	5
5	0.2	100	B	2,6-dichloroquinone	13.5	78	2	>15
6	0.2	100	C	2,6-dichloroquinone	13.5	91	2	5

Method A: no additional operation
Method B: subsurface N_2 gas bubbling
Method C: simultaneous addtion of diene substrate

- Ru-H complex mediated isomerization can be suppressed by addition of quinone additives
- Lower cat. loading, higher temperature increased yield
- Removal of ethylene by subsurface N_2 bubbling increased yield slightly
- Simultaneous addition of diene and cat. mimic high dilution allowing increased overall concentration and yield.

J. Org. Chem. **2012**, *ASAP.* doi: 10.1021/jo3001595

Title Paper: Saturated Macrocycle

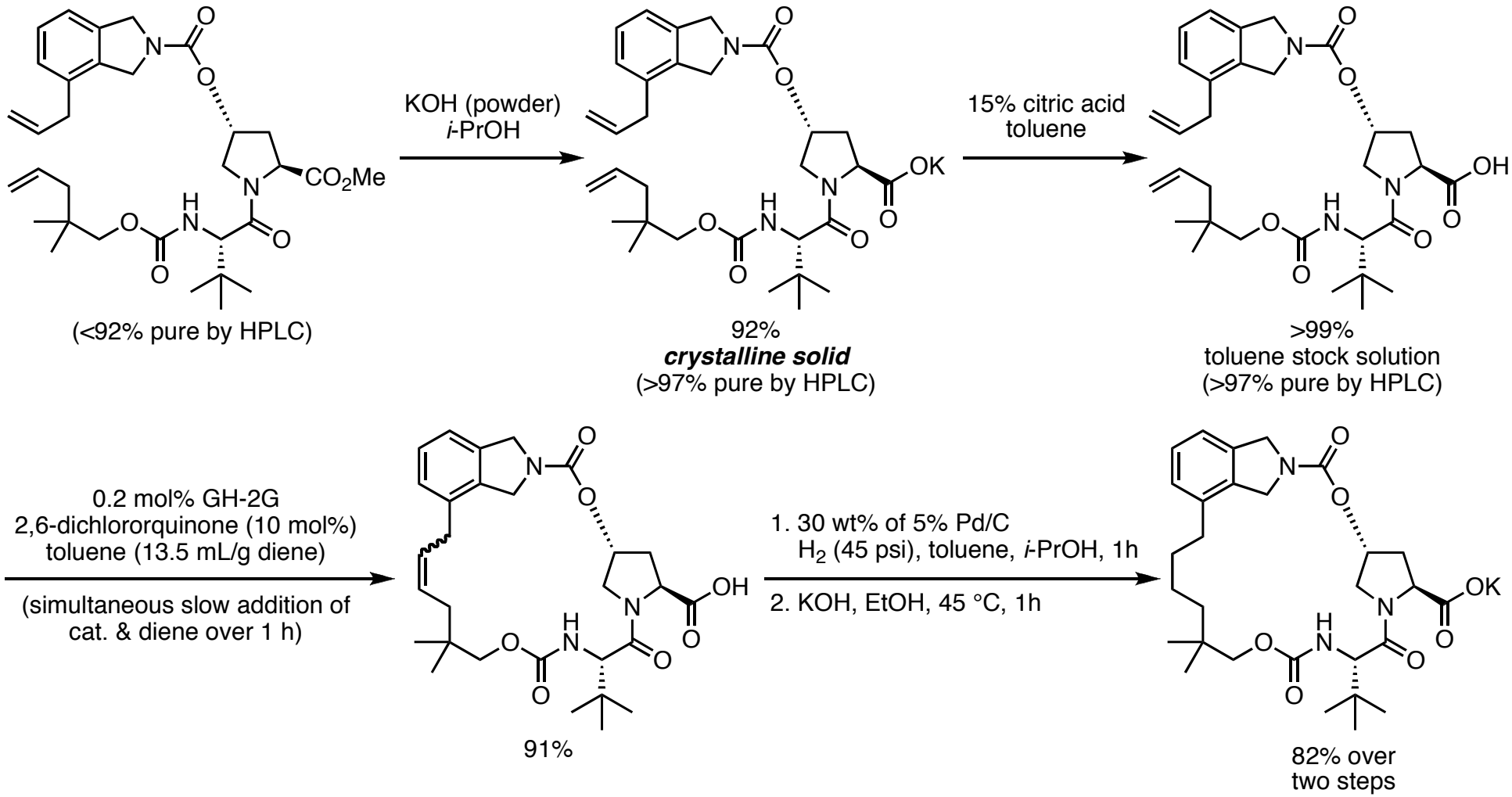


89%
(>99% purity by HPLC)
(1 RXC from *i*-PrOH/water
<10 ppm Ru & Pd)

- Successfully performed preparation of saturated macrocycle on 100 g scale
- Found RCM to be sensitive to impurities, not acceptable for robust manufacturing process
- Oily diene precursor not amenable to crystallization

J. Org. Chem. **2012**, *ASAP.* doi: 10.1021/jo3001595

Title Paper: Second-Generation RCM Strategy



(<92% pure by HPLC)

92%
crystalline solid
(>97% pure by HPLC)

>99%
toluene stock solution
(>97% pure by HPLC)

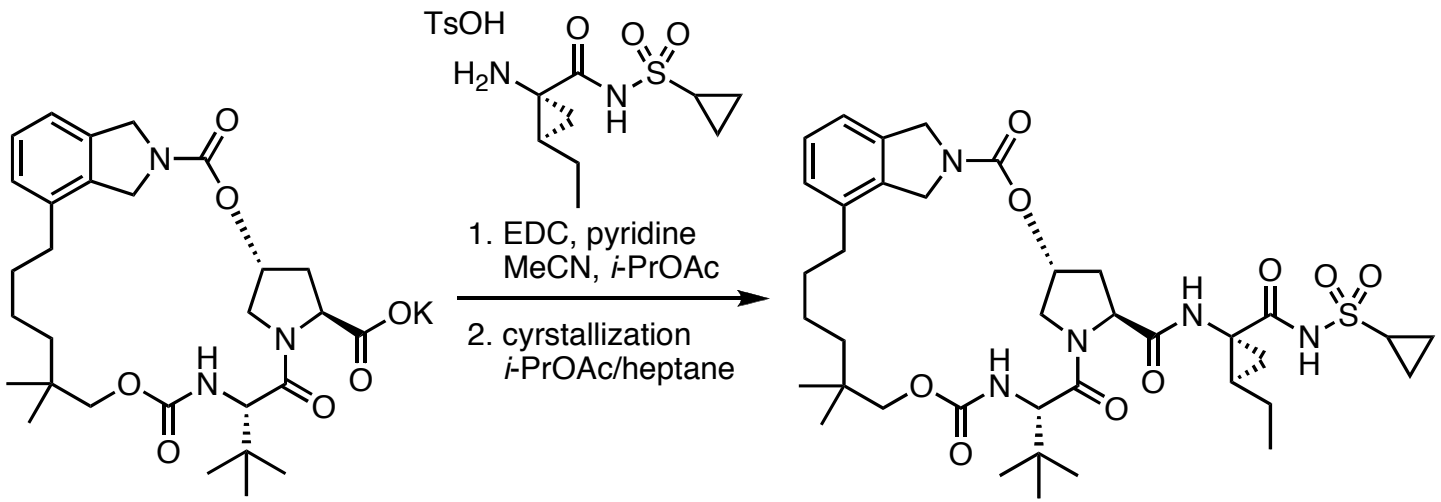
91%

82% over
two steps

Second-generation strategy provides a robust manufacturing route

J. Org. Chem. **2012**, *ASAP.* doi: 10.1021/jo3001595

Title Paper: Synthesis of Vaniprevir (MK-7009)



- Successful optimization of RCM strategy to give macrocycle in high yield and purity using low catalyst loading (0.2 mol%) and high overall concentration (0.13 M).
- Developed a robust manufacturing synthesis of Vaniprevir (MK-7009) in 55% overall yield (9 LLS)

J. Org. Chem. **2012**, *ASAP.* doi: 10.1021/jo3001595