Green Chemistry Tools for Process Research

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Dr.Reddy's

Caveats

The views expressed are personal and do not necessarily reflect those of my employer or any other organisation with which I am affiliated.

Acknowledgement

Previous and Current Scientific Staff & Leadership of Dr. Reddy’s Laboratories Limited, Hyderabad, India are Acknowledged

Defining Complexity

- Number of Chiral Centers
- Type of Chemical Reactions
- Addressing Challenges Associated to API Related Substances by Using Orthogonal Analytical Tools
- State of the Material
- Operational Complexity
- Degree of Diverse Approaches in RoS
- Timeline to Target NCE-1 Date
- Process Safety

R&D Guiding Principles

- Incredibly Innovative
- Consistent Production of Highest Quality APIs
- Leading Supplier of API
- Seamless Integration of Every Component of R&D Right from Chemistry to Development, to Manufacturing, to Regulatory to Commercialization.
- Deep Science & Technology Focus to Achieve Delivery Excellence

R&D Guiding Principles

Analytical
- Faster Analytical Method Development and Validation
- Versatile Analytical Method
- Highly Sensitive Analytical Method
- Real-time Release Based on In-line Best in Class Instrumentation

Chemistry
- Cost Effective RoS Design and Implement Throughout the Value Chain
- Minimize Carbon Footprint
- Strategic Moves to Gradually Decrease the LCM and TS Project In-flow
- Faster Addressal of Deficiencies

Tools
- Innovation
- Collaboration
- Continuous improvement
- Digital intervention

Process Engineering
- Modeling and Simulation of Unit Operation
- Institutionalization of Flow Technology
- PAT at Scale
- Seamless Scale-up

Green Chemistry & Sustainability Drive

- Green chemistry & sustainability are few notable core values rooted in our purpose & strategy.
- Our core value of sustainability drives our resolve to address societal needs and guides our ambitious ESG goals for the coming decades.
- Along with deep Science & Technology we are committed for progressive people practices & good governance.
- As a part of initial start, we have evaluated the Green Metrics for all the molecules with existing process.

Green Chemistry Metrics

Green chemistry metrics describe quantifiable features of a chemical process related to the principles of green chemistry.

The metrics serve to quantify the efficiency or environmental performance of chemical processes and allow changes in performance to be measured.

Key Green chemistry common metrics:

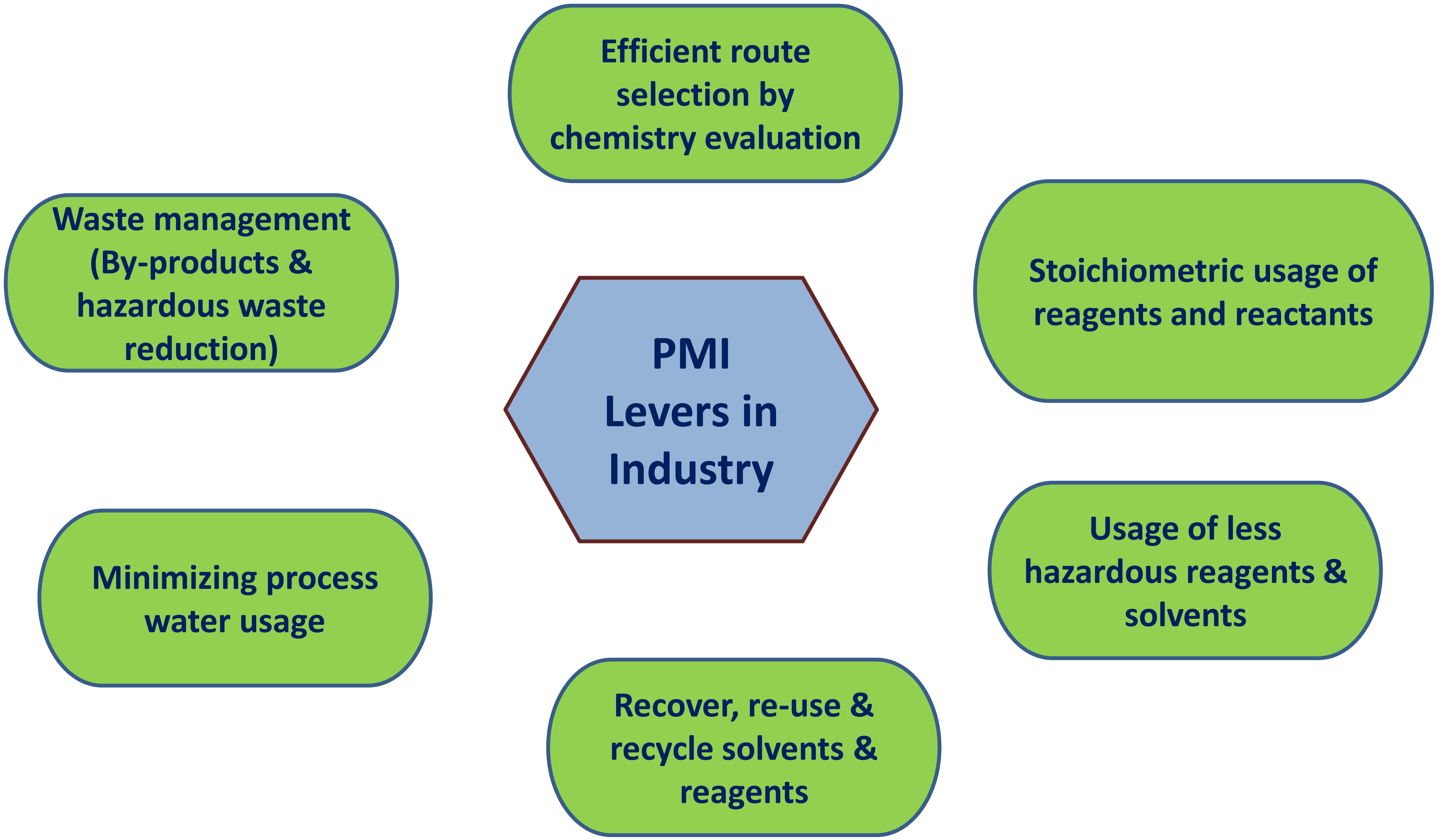
Atom Economy (AE), Environmental factor (E-factor)

Reaction Mass Efficiency (RME)

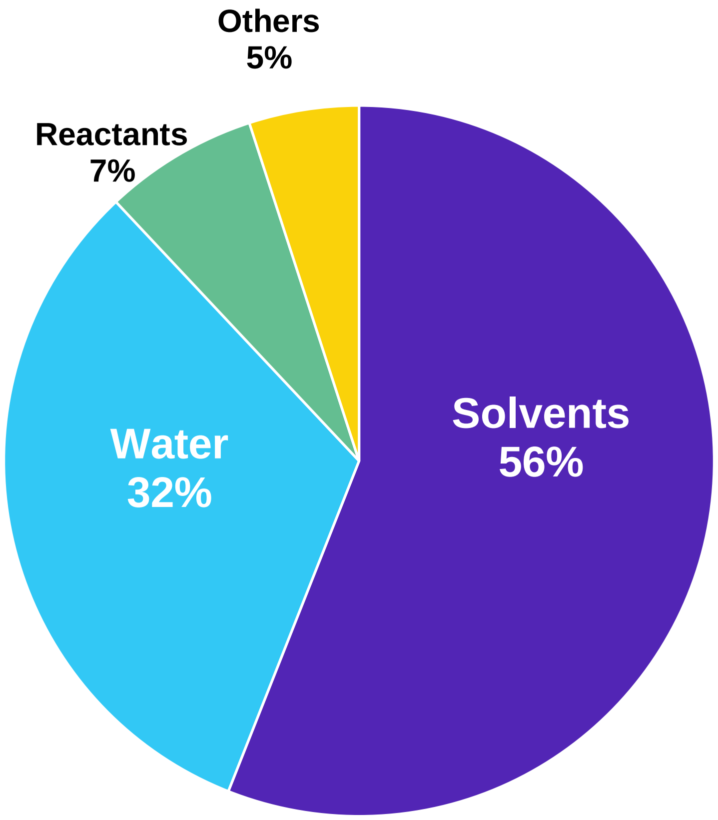
Process Mass Intensity (PMI)

Effluent Water & Hazardous Waste minimization

PMI Levers


Efficient route selection by chemistry evaluation
Waste management (By-products & hazardous waste reduction)
Stoichiometric usage of reagents and reactants
PMI Levers in Industry
Minimizing process water usage
Usage of less hazardous reagents & solvents
Recover, re-use & recycle solvents & reagents

PMI – Contributing Factors



Solvent Contribution

Solvent and water contribute ~80% of the process mass intensity.

Emphasis needs for research to reduce/replace it with Green solvents

Implementation Guideline

1
- Identification of existing products manufacturing at various CTO's

2
- Calculate PMI for all molecules

3
- Classification of molecules as per the PMI value

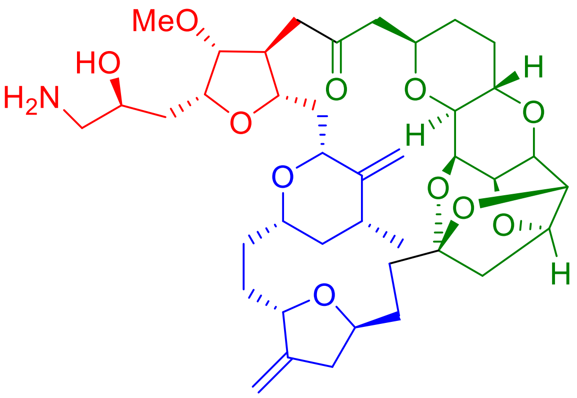
4
- Identification of products which has high volume/cost with respect to business

5
- Inclusion into development pipeline for process improvement with respect to cost & PMI advantage

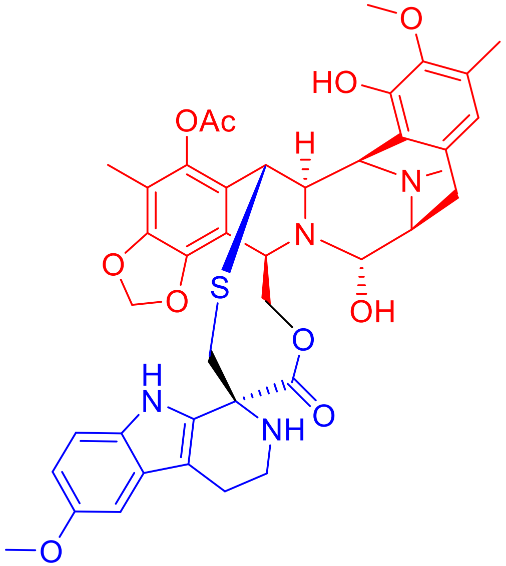
Impact & Valuation

Number of Products Evaluated for PMI	Assessment of Few High Volume Products	PMI Improvement (%) Compared to Existing Process	Revenue ($)
138	20	35 - 40	~ 2.8 Million

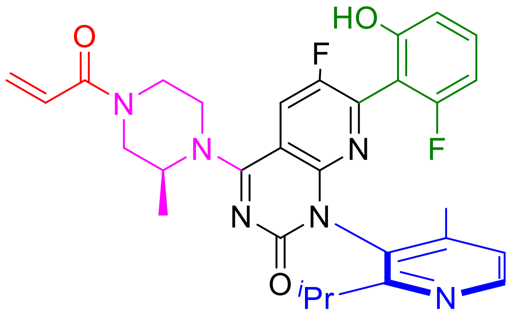
Complexity in Small Molecules



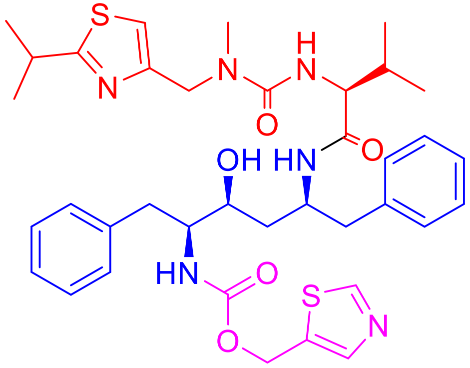
Eribulin
Anti-cancer (Breast)



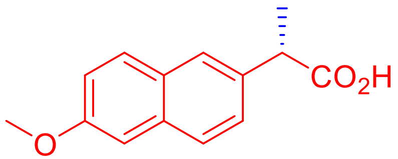
Lurbinectedin
Anti-cancer (SCLC)



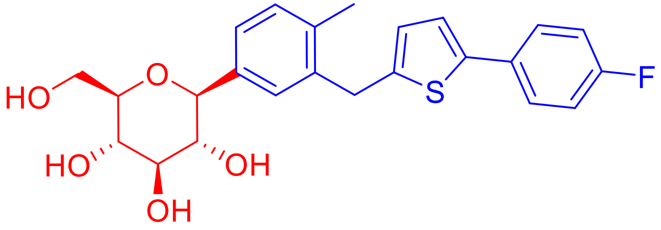
Sotorasib
Anti-cancer (NSCLC)



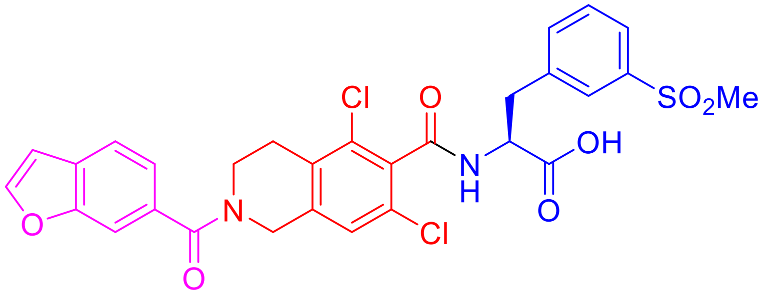
Ritonavir
(Anti-HIV)



Naproxen
(Anti-inflammatory)

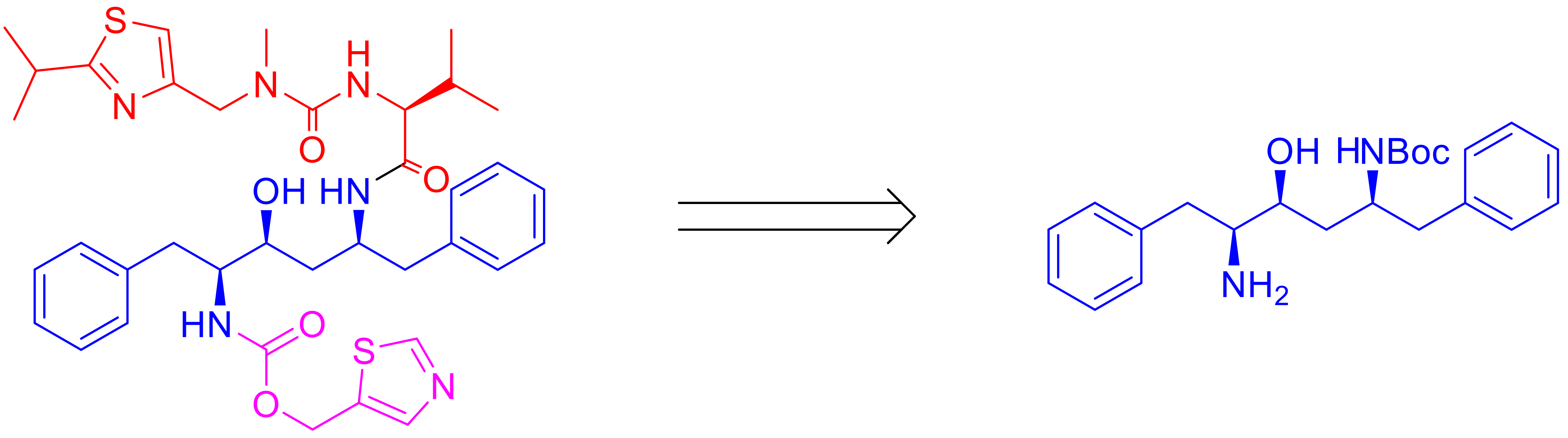


Canagliflozin
Anti-diabetic (SLG2 Inhibitor)



Lifitegrast
(For Keratoconjunctivitis Sicca)

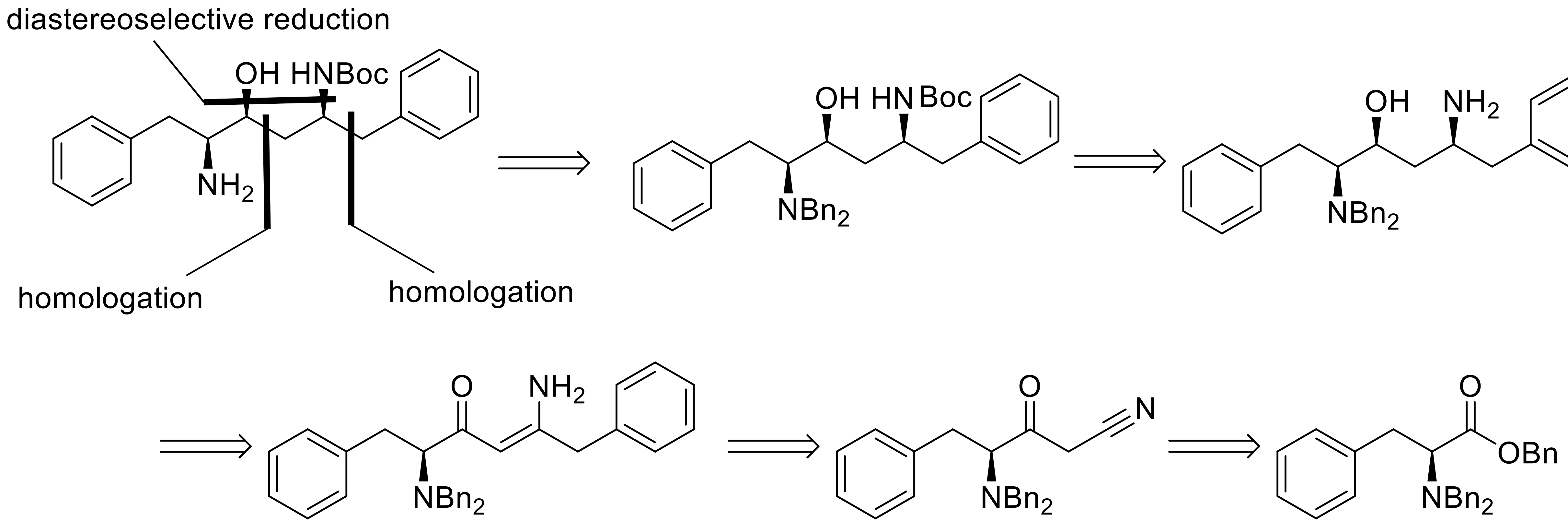
Ritonavir



Ritonavir
(Anti-HIV)

Boc-core

Precedented Route



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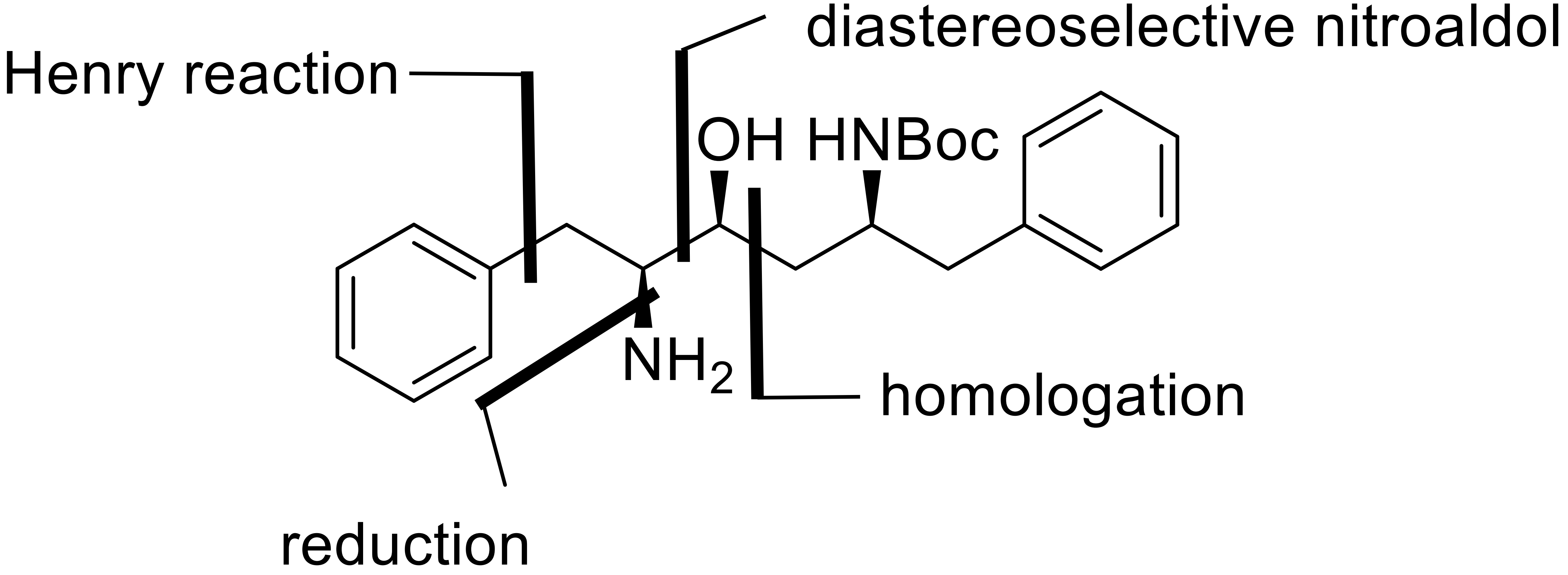
Innovative Approach Based on Henry Reaction: Part 1



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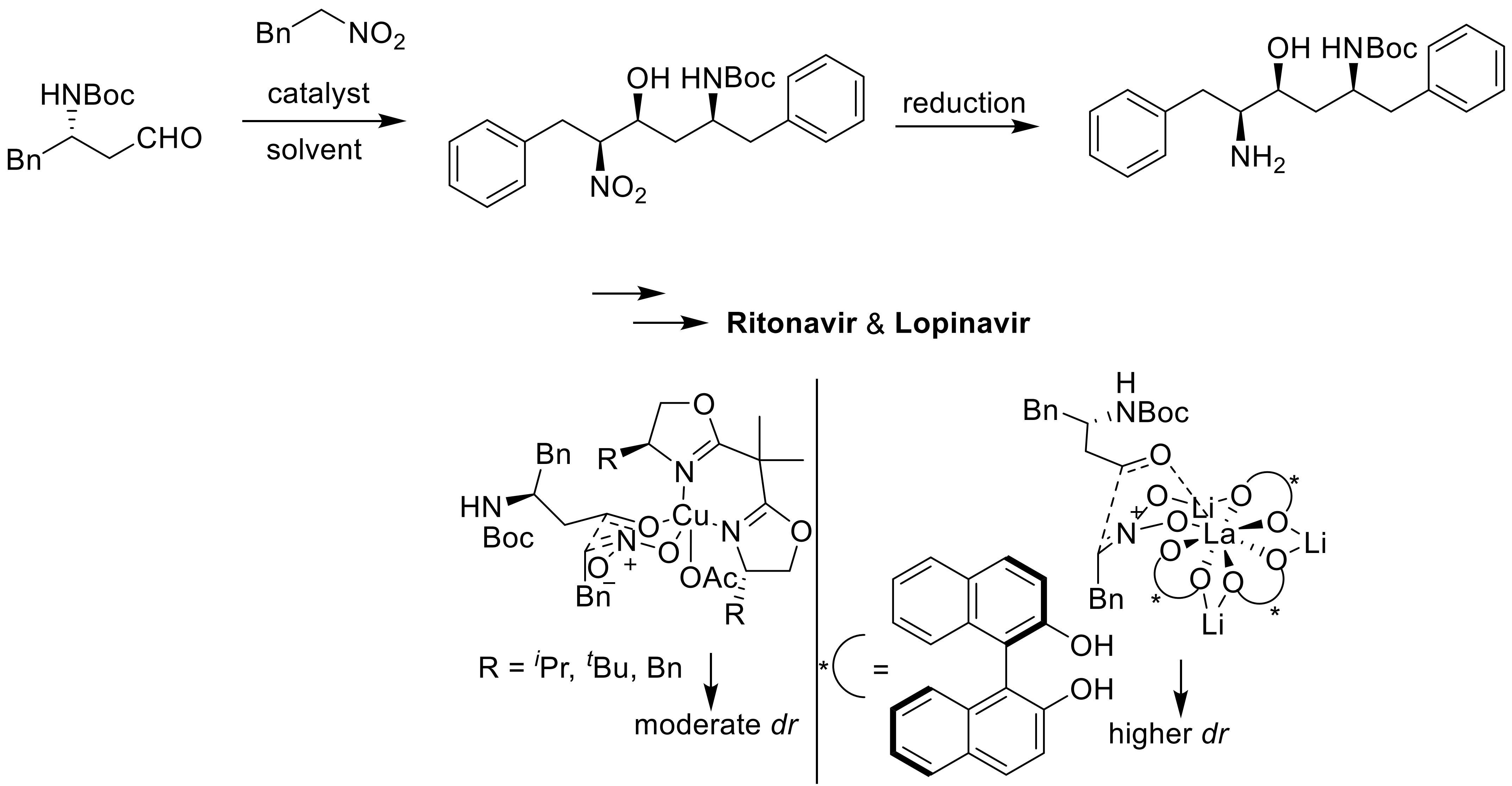
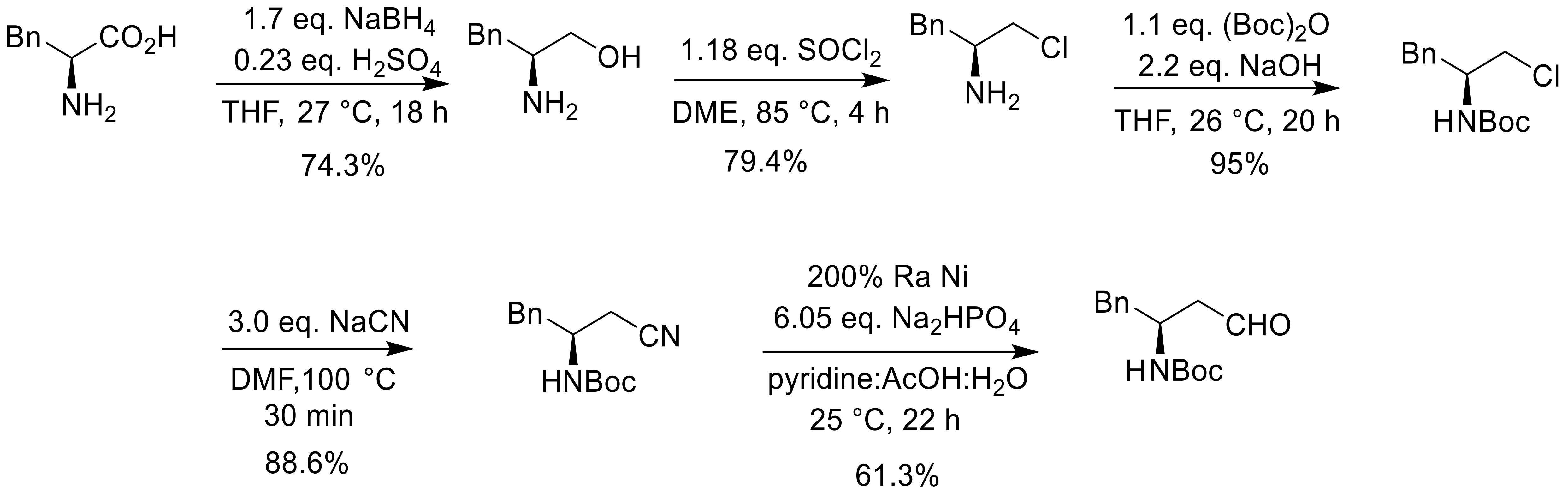


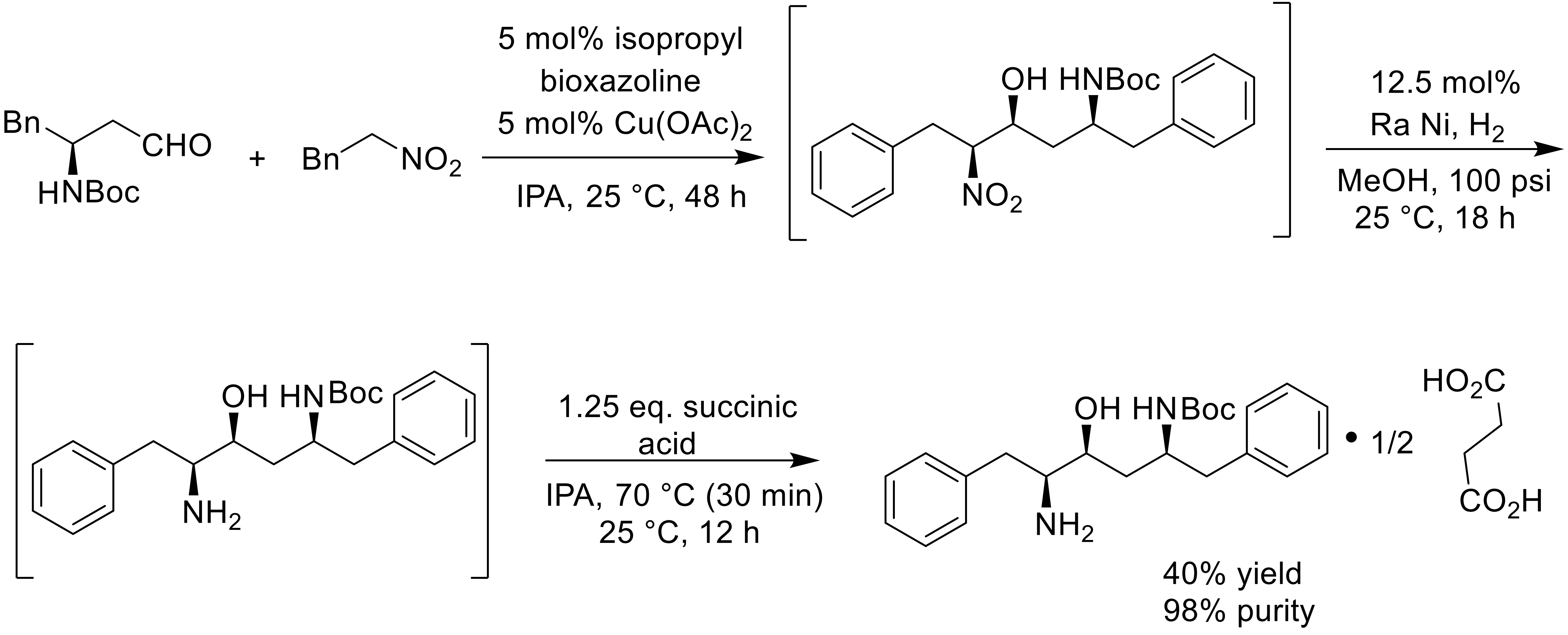
Innovative Approach Based on Henry Reaction: Part 1

S. No.	Catalyst	Sol	°C/h	*dr* (HPLC)	Yield (%) of Product
1	-	IPA	25/24	No reaction	_
2	$Cu(OAc)_2$	IPA	25/24	No reaction	_
3	^{i}PrBisoxa/$Cu(OAc)_2$	IPA	25/48	62:29:04:05	76 (47)
4	^{t}BuBisoxa/$Cu(OAc)_2$	IPA	25/48	52:38:11:09	71
5	BnBisoxa/$Cu(OAc)_2$	IPA	25/48	55:35:05:05	62
6	(*R*)-BINOL-La-Li	THF	38/24	80:09:10:01	53 (42)

Innovative Approach Based on Henry Reaction: Part 1



Innovative Approach Based on Henry Reaction: Part 1



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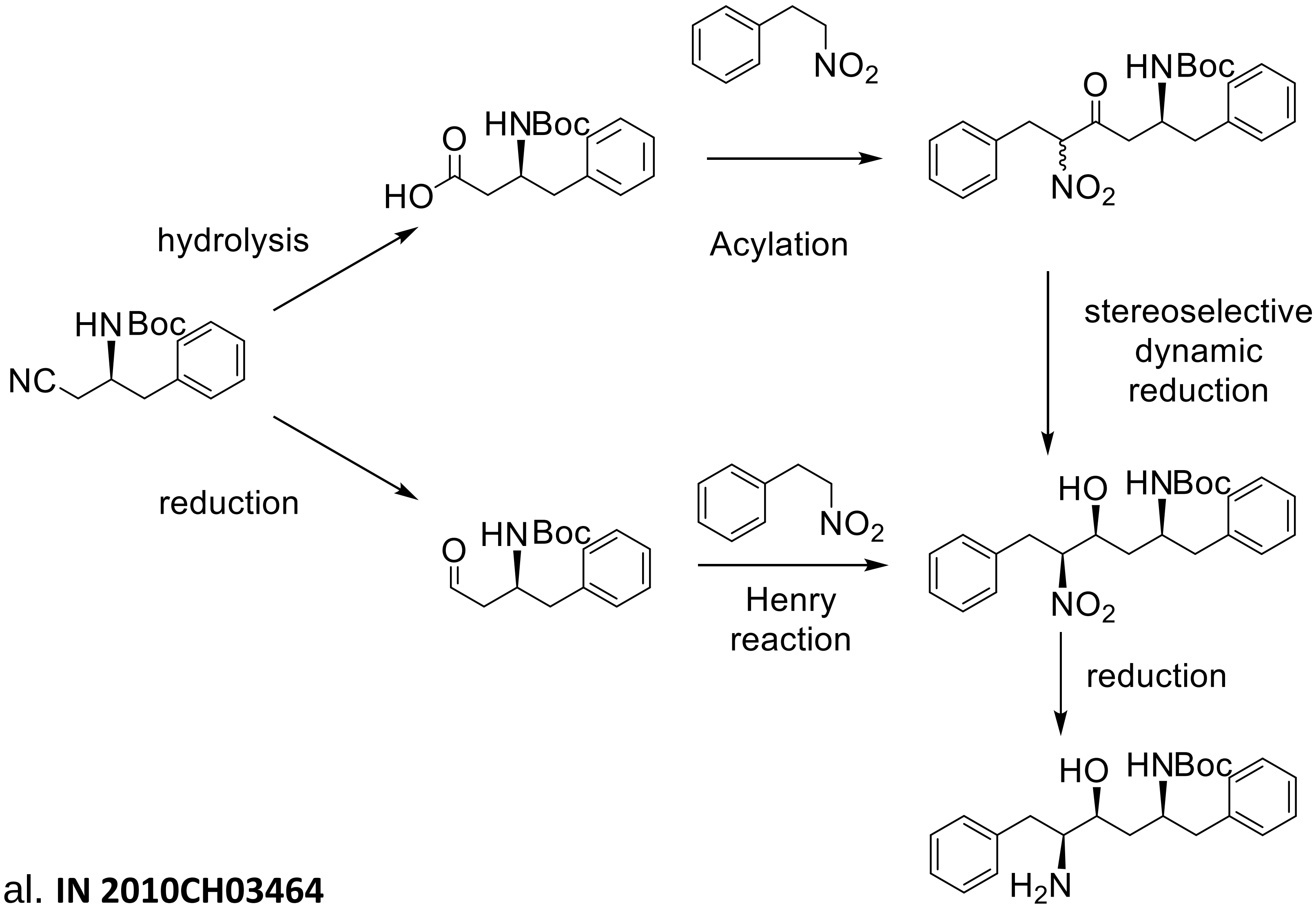
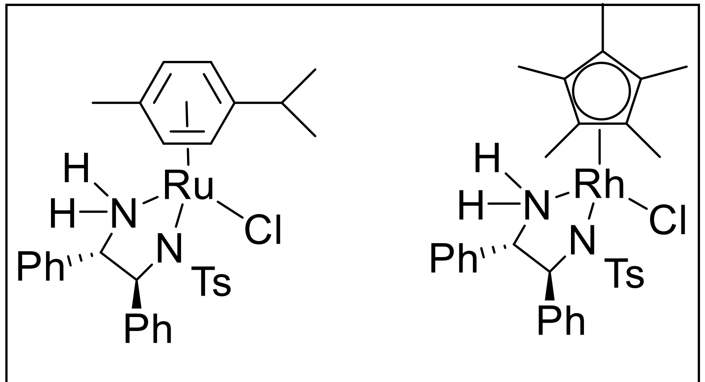
Innovative Approach Based on AH (DKR) : Part 2



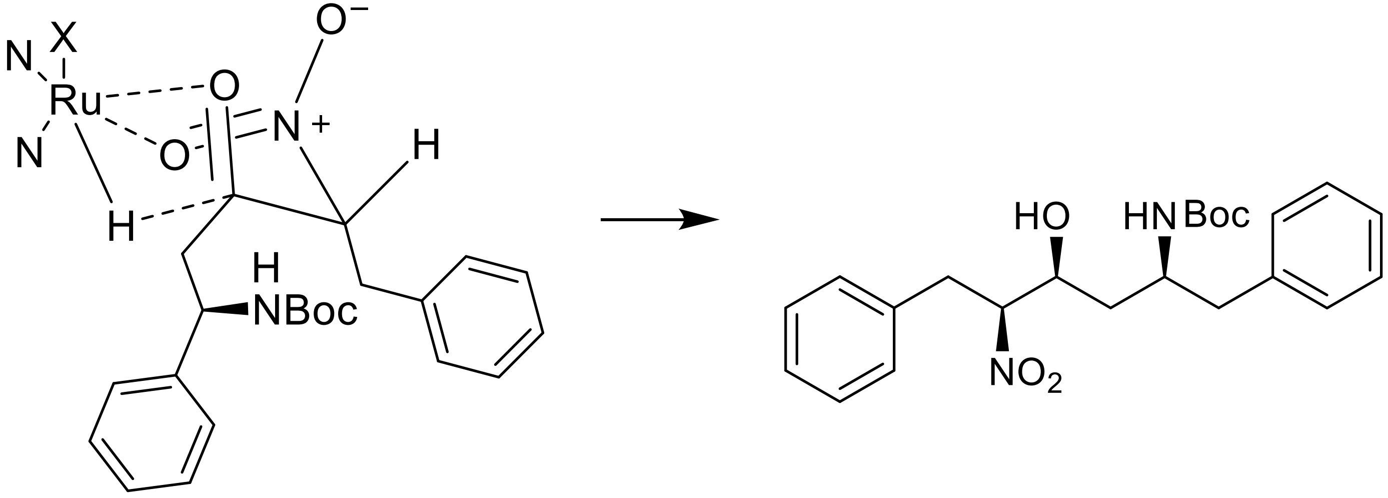
Bandichhor, R. et al. **IN 2010CH03464**

Innovative Approach Based on AH (DKR) : Part 2

Chemical DKR: Mechanistic Understanding



(*S*,*S*)-**14** (*S*,*S*)-**15**



Catalyst	*dr* (HPLC)	Conv
(*R*,*R*)-**14**	23:58:14:16	76%
(*S*,*S*)-**14**	5:3:21:72	91%
(*R*,*R*)-**15**	25:49:21:25	34%
(*S*,*S*)-**15**	4:2:30:64	51%

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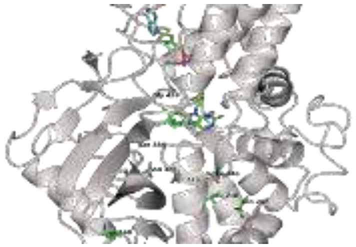
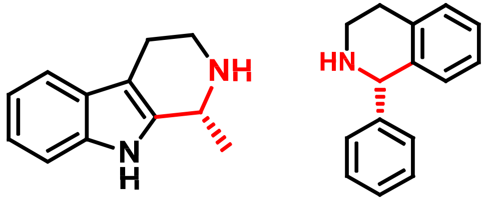
Innovative Approach Based on eDKR : Part 3

Enzymatic DKR



Directed Evolution and Rational Design

Biocatalysts for Diverse transformations



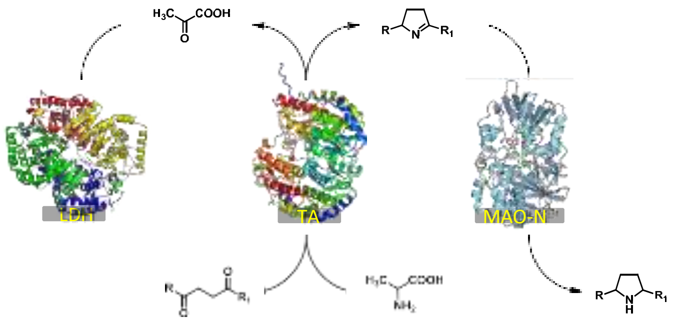
Biocatalysis on Challenging Substrates

Biocatalytic Transformations

Chemical Building Blocks
Simple, Cheap, Abundant

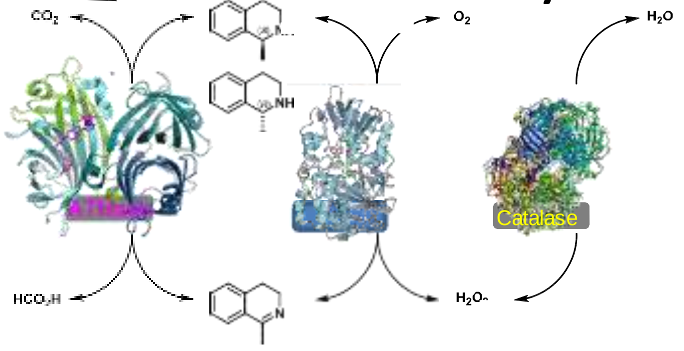
High-value Chemicals
e.g. Pharmaceuticals,
Natural Products, Biofuels

Enzymatic Cascades

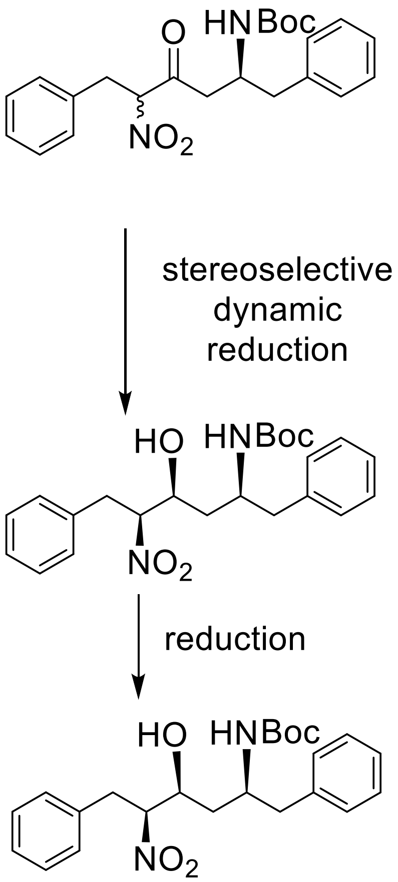


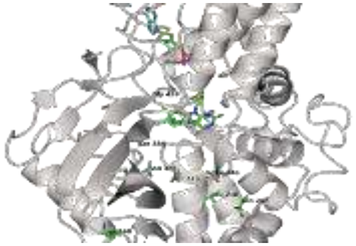
Enzyme Triggered Transformations

Biocatalysts in Combination with Chemocatalysts



Innovative Approach Based on eDKR : Part 3





Directed Evolution and Rational Design

S. No.	Enzyme	Cofactor	*dr* (HPLC)	Conv
1	KRED-101	NADP	81:18:0:0	19%
2	KRED-151	NADP	85:15:0:0	34%
3	KRED-121	NADP	46:54:0:0	39%
4	KRED-130	NADP	97:3:0:0	61%
5	KRED-114	NADP	36:64:0:0	45%
6	KRED-123	NADP	95:5:0:0	43%
7	KRED-125	NADP	93:7:0:0	73%
8	KRED-NADH-129	NADH	32:1:65:1	78%
9	KRED-NADH-109	NADH	93:7:0:0	80%
10	KRED-NADH-112	NADH	94:6:0:0	78%
11	ES-KRED-149	NADP	9:14:76:0	2%
12	ES-KRED-134	NADH	9:8:11:72	2%
13	ES-KRED-125	NADH	94:1:5:1	12%
14	CRED-A131	NADH	94:6:0:0	68%
15	CRED-A401	NADPH	95:1:3:1	11%

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Reporting Green Chemistry Comparatives

Structure of API

Name of API

Precedented Reference

Key Chemistry Gate Criteria (SELECT)	
S	Safety Hazard Usage of hazardous NaCN
E	PMI: XXX Kg (Trend: 20-125 Kg)
L	Key transformation claimed by Innovator
E	Higher RMC: XXXX USD Clean sheet XXXX USD
C	Poor control on Pd leachability when used in N-2 stage
T	Product isolated after X stages: Without process intensification

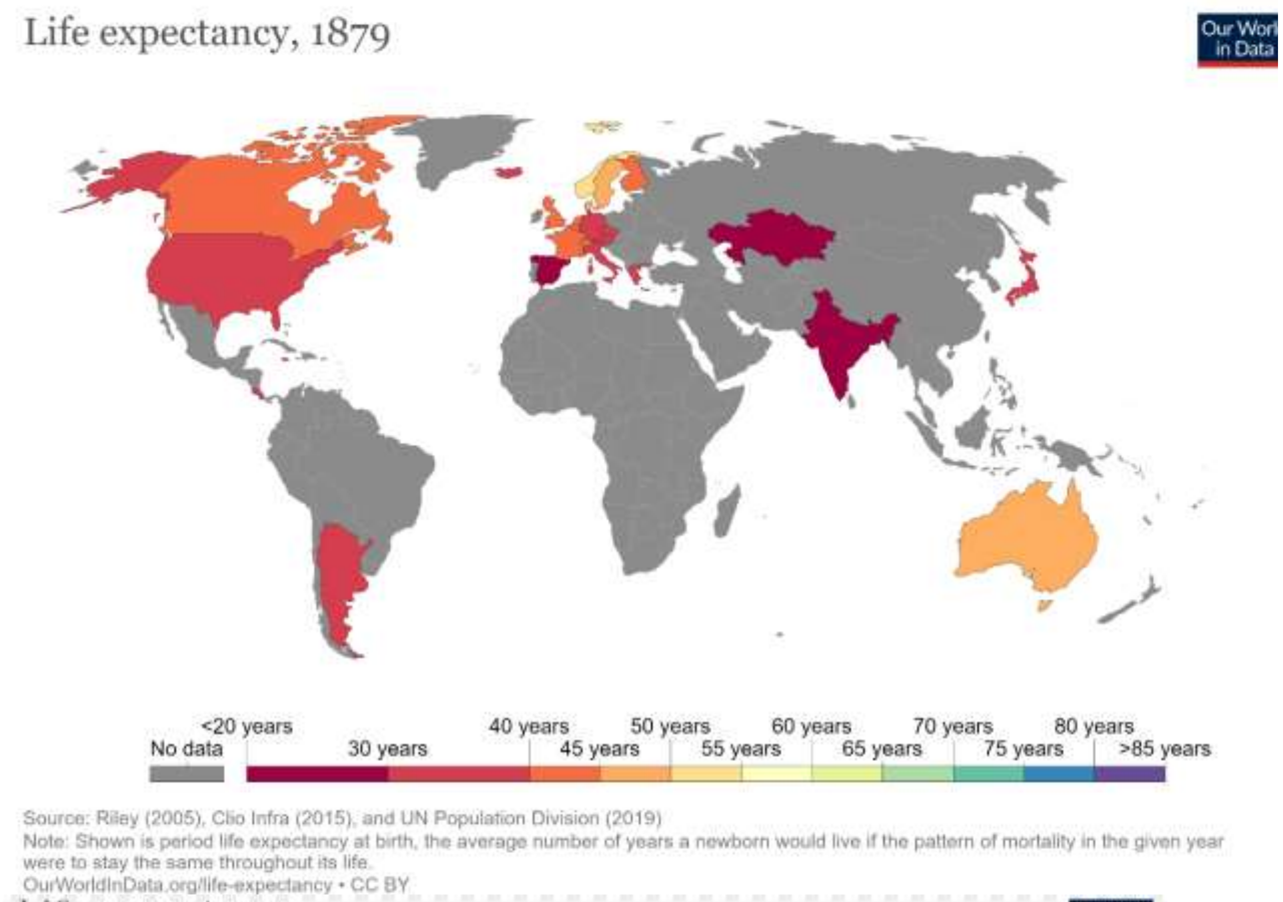
Reporting Green Chemistry Comparatives

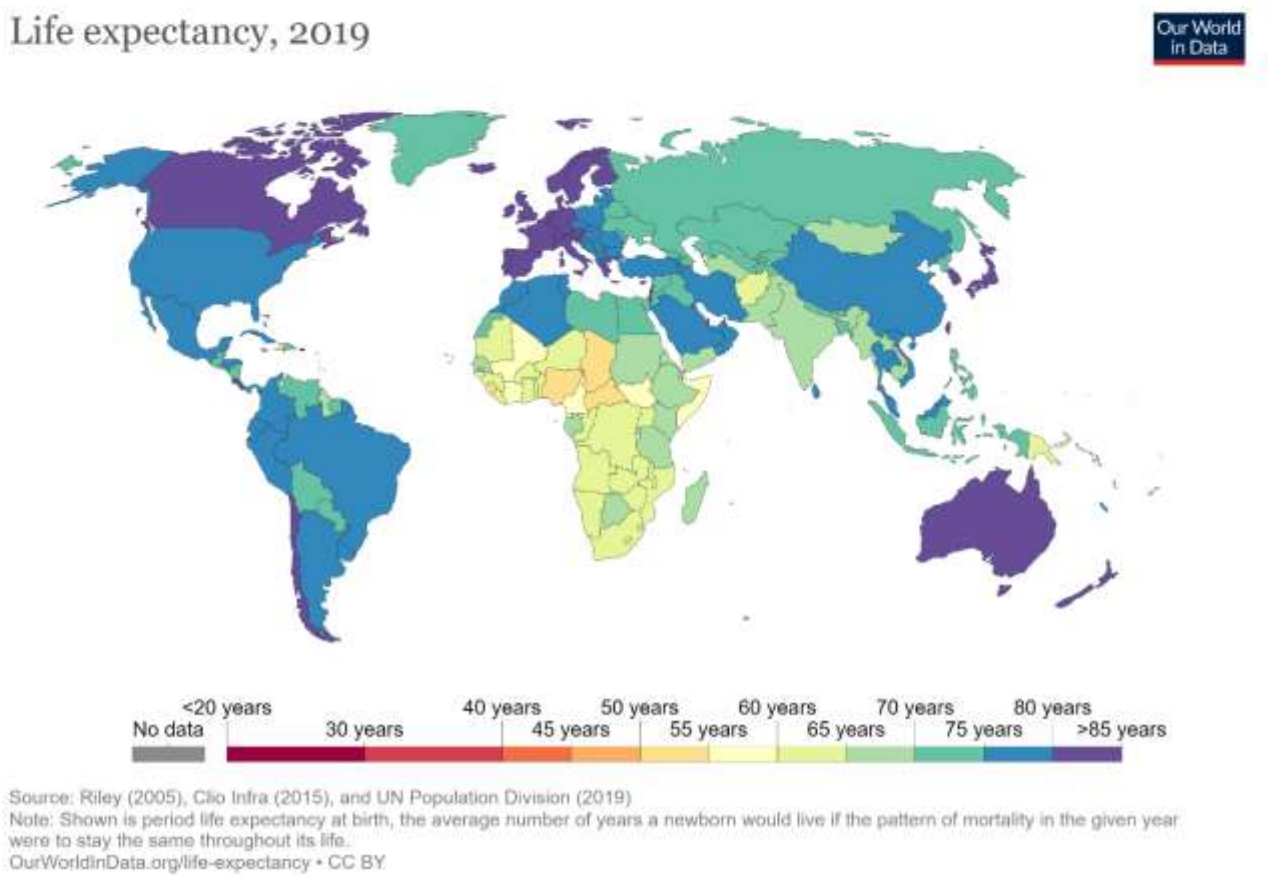
Structure of API

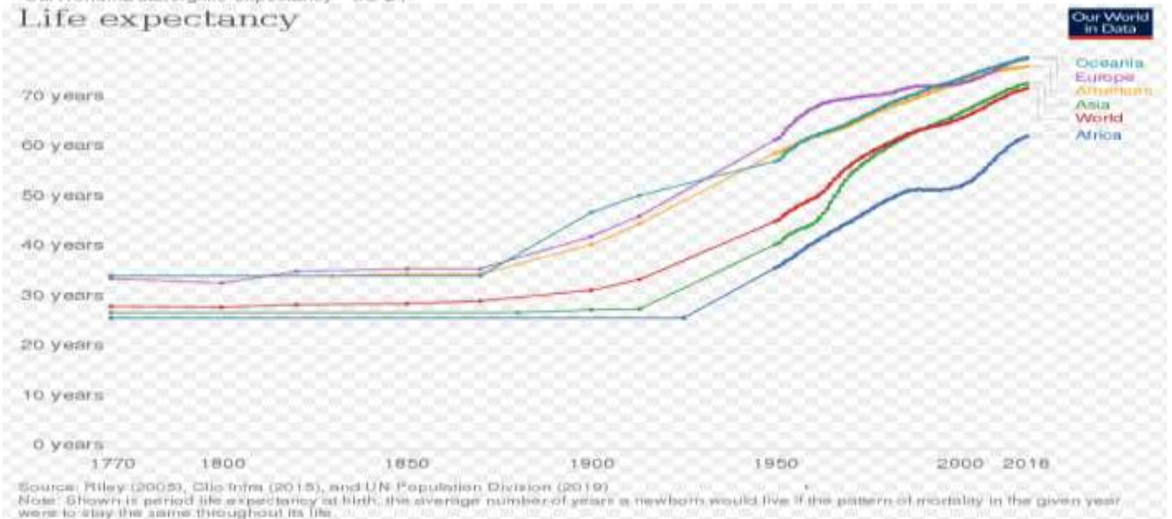
Name of the API

- There have been 10 synthetic proposals evaluated
- Synthia inspired ROS was found to have promising SELECT features
- Comparison has been made between product patent and synthia inspired ROS

Key Chemistry Gate Criteria (SELECT)	
S	Safety Hazard NaCN-free ROS
E	PMI: YYY Kg (Without recovery) YYY Kg (With recovery of solvents) (Trend: 20-125 Kg)
L	Non-infringing ROS
E	Lower RMC: YYYY USD Clean sheet YYY USD
C	Better control on Pd leachability because Pd load is reduced by 95%
T	Product isolated after Y (<X) stages: With complete backward integration of KSM







Working in the S &T Industry Allows You to Change People’s Lives for the Better Through Innovation

Opportunities

Make
the world a
healthier
place

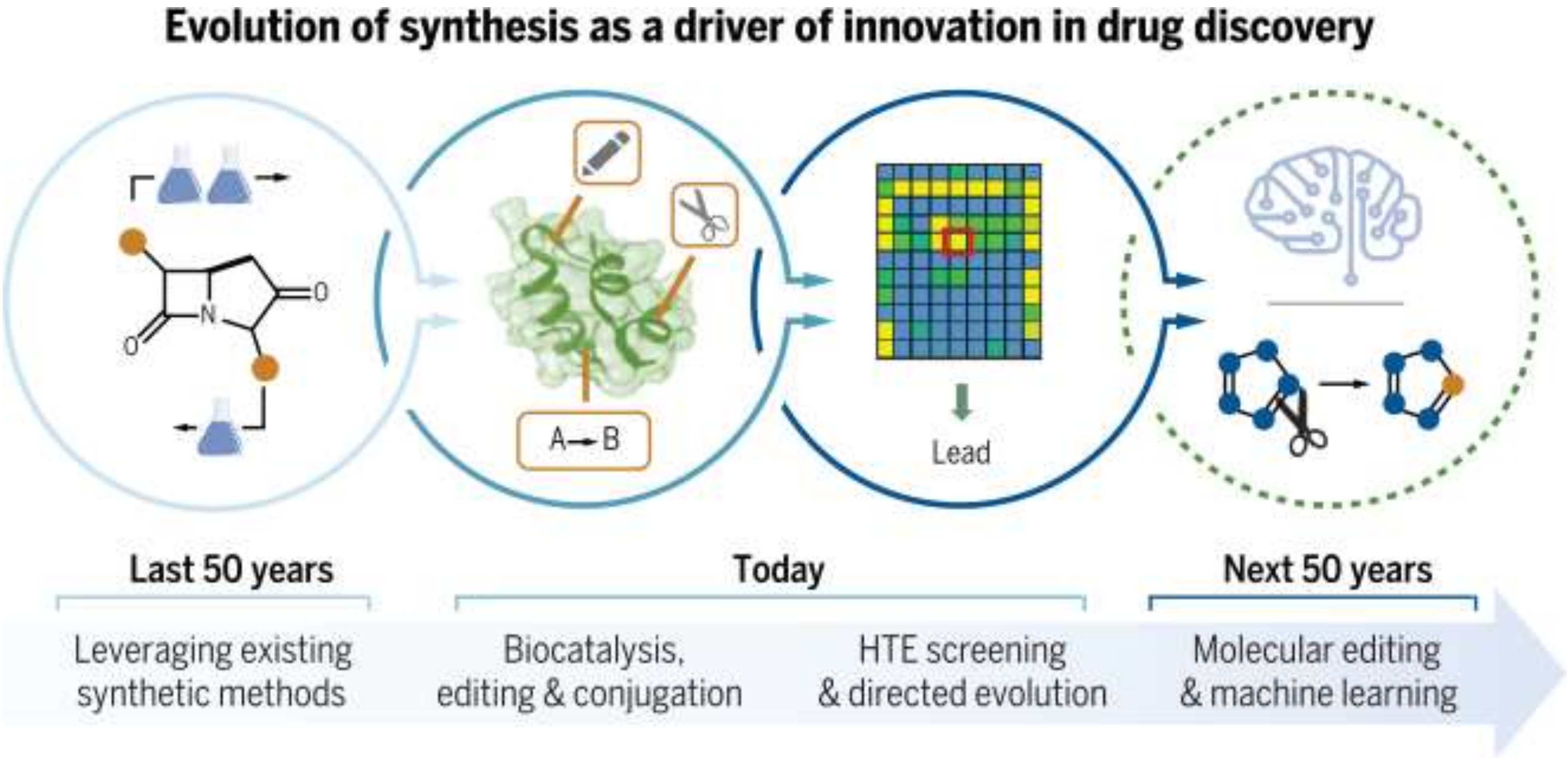
Be part
of a team that
cares

Learn continually
excel
and **grow**

Expect to
be treated with
respect

Enjoy
professional freedom
to create imapct

Future Perspective



Thank You