OMICS Group International is an amalgamation of Open Access publications and worldwide international science conferences and events. Established in the year 2007 with the sole aim of making the information on Sciences and technology 'Open Access', OMICS Group publishes 400 online open access scholarly journals in all aspects of Science, Engineering, Management and Technology journals. OMICS Group has been instrumental in taking the knowledge on Science & technology to the doorsteps of ordinary men and women. Research Scholars, Students, Libraries, Educational Institutions, Research centers and the industry are main stakeholders that benefitted greatly from this knowledge dissemination. OMICS Group also organizes 300 International conferences annually across the globe, where knowledge transfer takes place through debates, round table discussions, poster presentations, workshops, symposia and exhibitions.

MERCK

About OMICS Group Conferences

OMICS Group International is a pioneer and leading science event organizer, which publishes around 400 open access journals and conducts over 300 Medical, Clinical, Engineering, Life Sciences, Phrama scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

MERCK

Green Chemistry at Merck – A Development Chemist's Perspective

Ingrid Mergelsberg

Merck Process Chemistry, Merck & Co., Inc., Whitehouse Station, NJ

International Summit on Past and Present Research Systems of Green Chemistry
August 25-27, 2014 Philadelphia, USA

MERCK

About Merck

- Named Merck in US and Canada; MSD elsewhere
- More than 120 years old
- Medicines, vaccines, animal health
  (and consumer products)
- **Our mission is to discover, develop and provide meaningful, innovative products that save and improve lives**
- Do so in a sustainable fashion so we can continue serving patients for another 120 years



MERCK

Green and Sustainable Chemistry at Merck





Presidential Green Chemistry Award Winners

2005: Merck – A Redesigned, Efficient Synthesis of Aprepitant, the Active Ingredient in Emend®

2006: Merck – Novel Green Synthesis for β-Amino Acids Produces the Active Ingredient in Januvia™

2010: Merck – Greener Manufacturing of Sitagliptin Enabled by an Evolved Transaminase

MERCK

What Do Process Chemists Do?

- Provide active pharmaceutical ingredient (API) for development
  - Preclinical: 1-10 kg
  - Ph I: 10-20 kg
  - Ph II: 50-200 kg
  - Ph III: 200-2000 kg
    - Requires a good synthetic route: safe, robust, productive, impurity control, API phase, reasonable cost, freedom to operate (intellectual property) and environmentally benign
- Identify the manufacturing route for commercial supply
  - Requires a great synthetic route to support the product for years to come. Need the lowest-cost route (consider emerging market and expanded access) and must be sustainable

MERCK

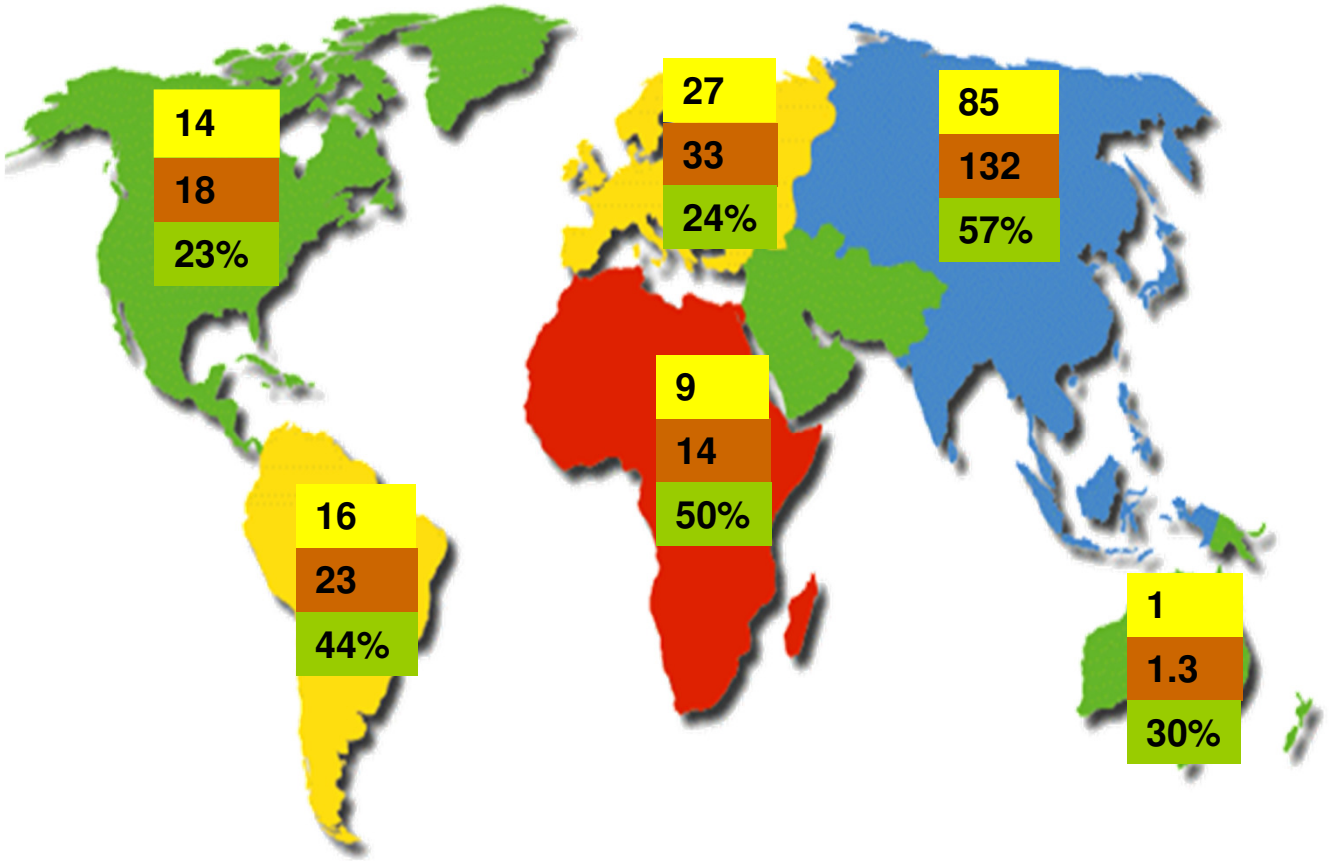
Key Message

- Good science is the key to Green Chemistry and low-cost synthesis
  - If we focus on developing the best chemistry, then, almost always, this leads to the lowest cost and greenest process
  - "Best chemistry at launch" provides environmental and economical benefit over the lifetime of the product
  - Innovation is the key for unbeatable chemistry

"In every case I know, the green option is the low-cost option" David Constable, 2008

MERCK

Diabetes: A Growing Worldwide Epidemic



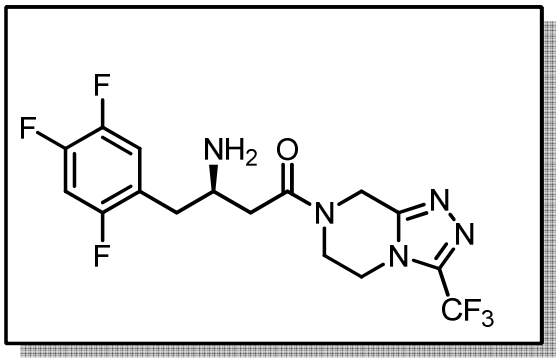
- Estimated incidence in 2000 (millions)
- Estimated incidence in 2010 (millions)
- % increase from 2000 to 2010

World
2000: 151 million
2010: 221 million (+46%)

Adapted from Amos AF et al. *Diabet Med* 1997;14:S7-S85.

MERCK

Sitagliptin: DPPIV Inhibitor for Diabetes Mellitus Type 2

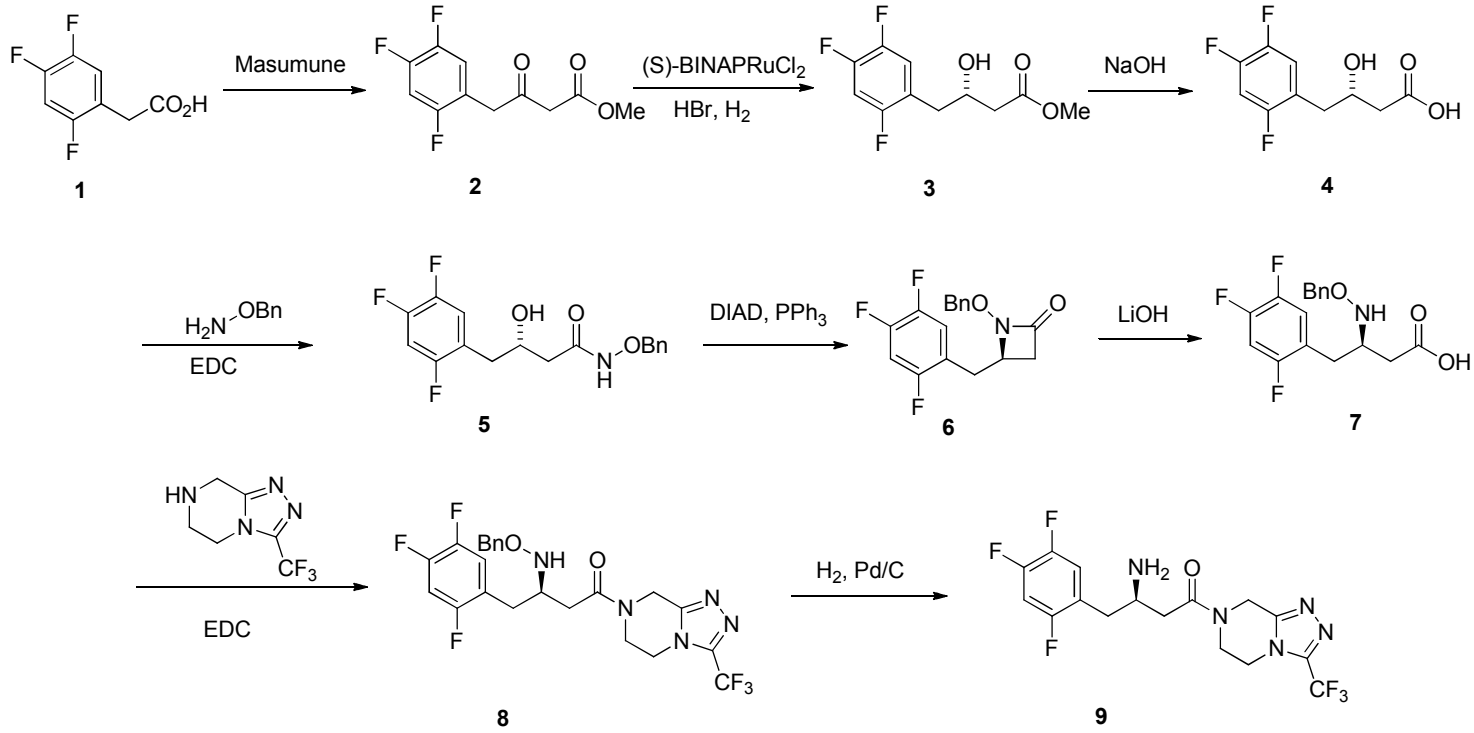


Active Ingredient in Januvia® and Janumet®

- First-in-class dipeptidyl peptidase-4 (DPPIV) inhibitor
- Once-daily oral treatment
- Approved by FDA in 2006

MERCK

Efficient Synthesis: Sitagliptin, 1st GMP Delivery

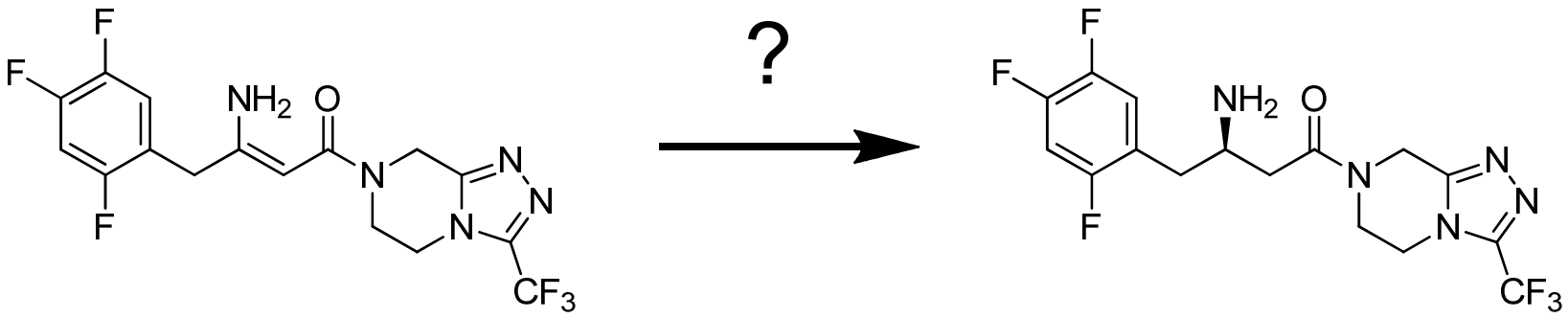


- >100 kg manufactured, 52% overall yield - 8 steps from acid 1
- 3 productive bond-forming steps **(38% desired)**
- 5 functional group manipulations **(62% undesired)**

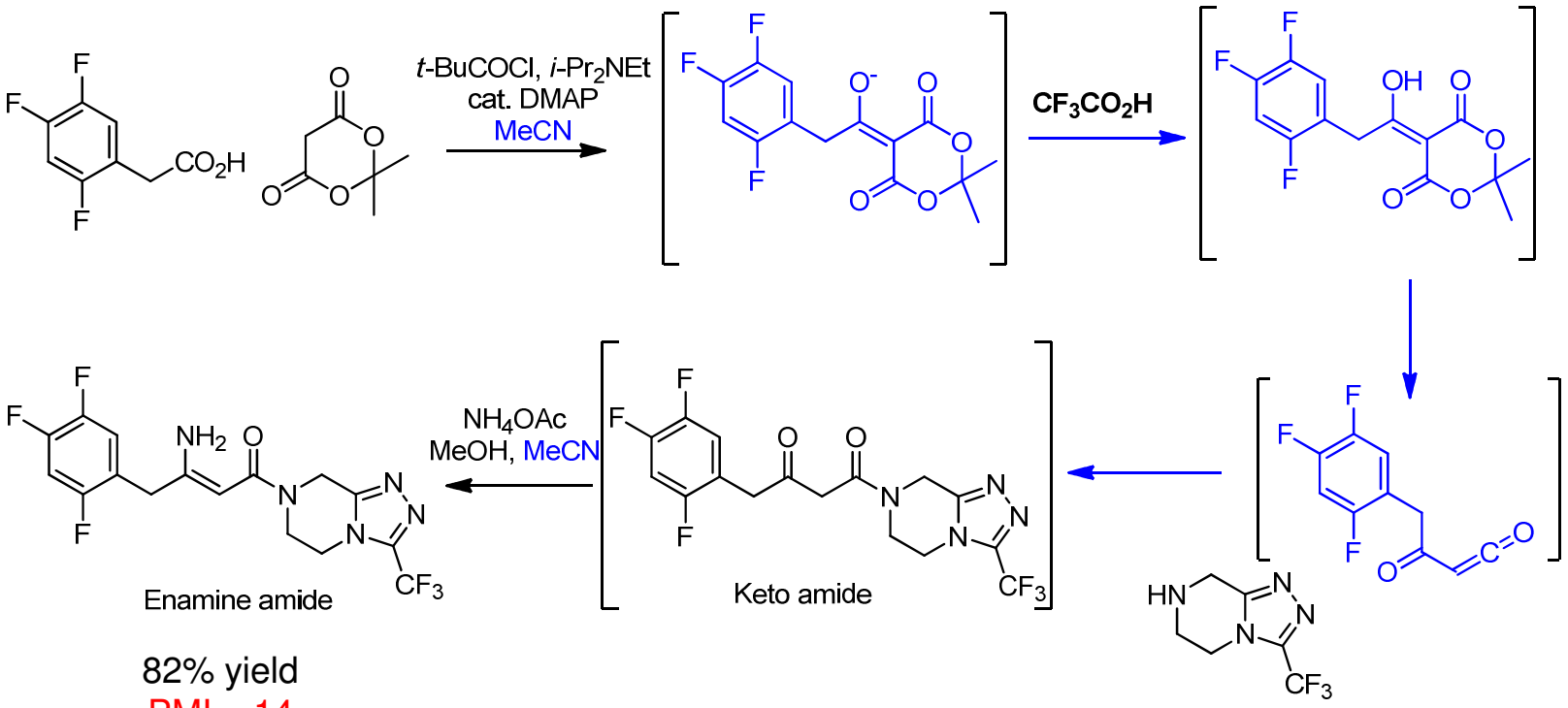
Can we do it in only 3 steps?

MERCK

Is This Reaction Possible?



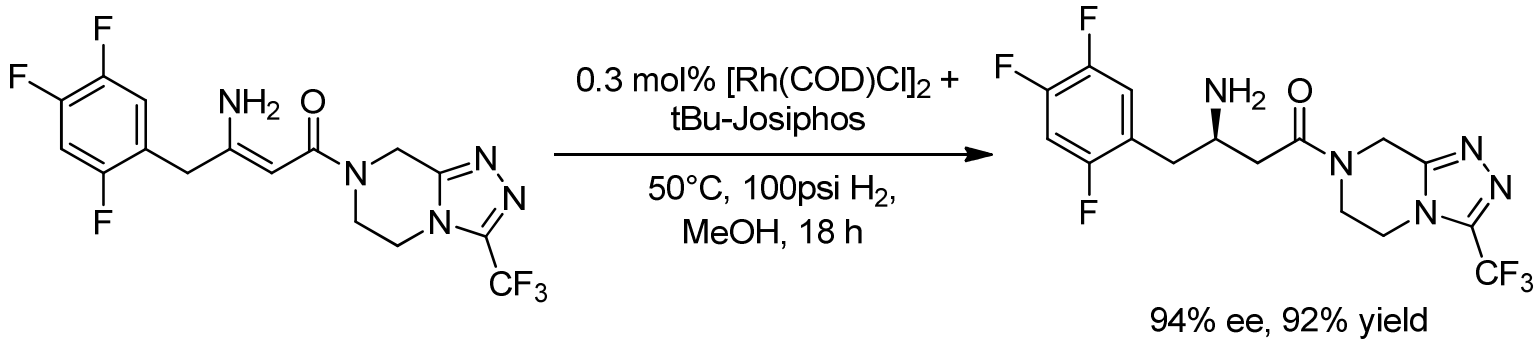
Efficient Synthesis: Sitagliptin 1st-Generation Manufacturing Route: One-Pot Reaction



- 1 step (one-pot reaction, direction isolation) to ketoamide or enamine amide!
  - Single solvent: compatible reagents to enable one-pot reaction
- Need unprecedented asymmetric hydrogenation of unprotected enamine

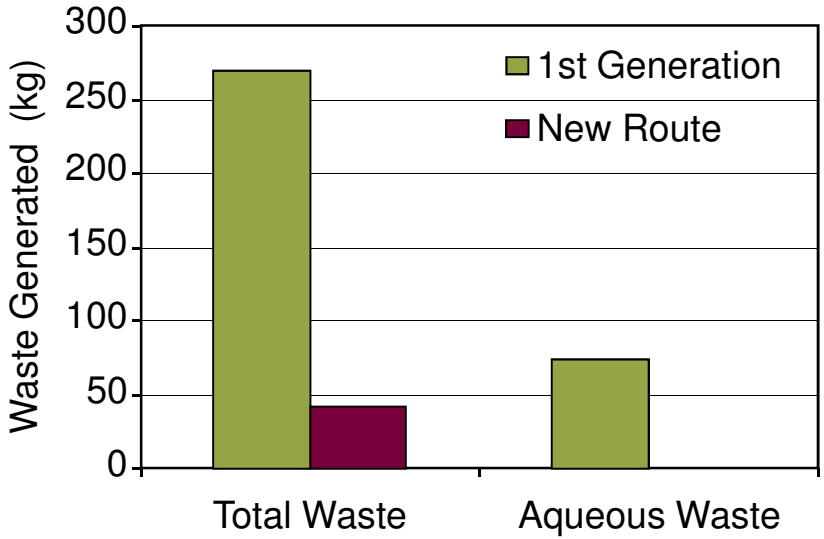
MERCK

Efficient Synthesis: Sitagliptin 2nd-Generation Manufacturing Route: Chemocatalysis



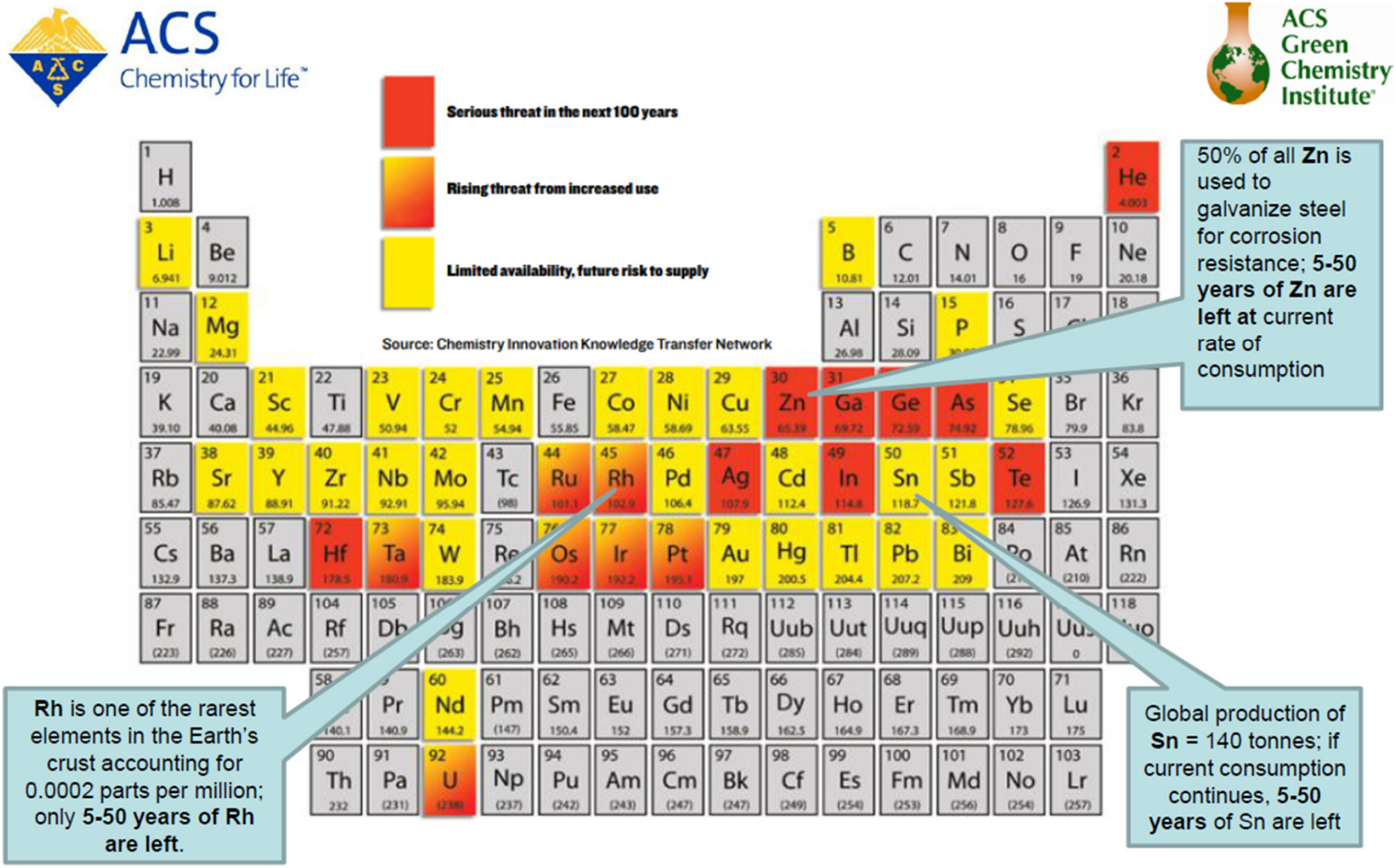
94% ee, 92% yield

- New asymmetric hydrogenation
- 2-step synthesis, 63% overall yield
- No protecting groups
- Implemented at factory scale (>100 MT produced)
- ~80% reduction in PMI, no aqueous waste



MERCK

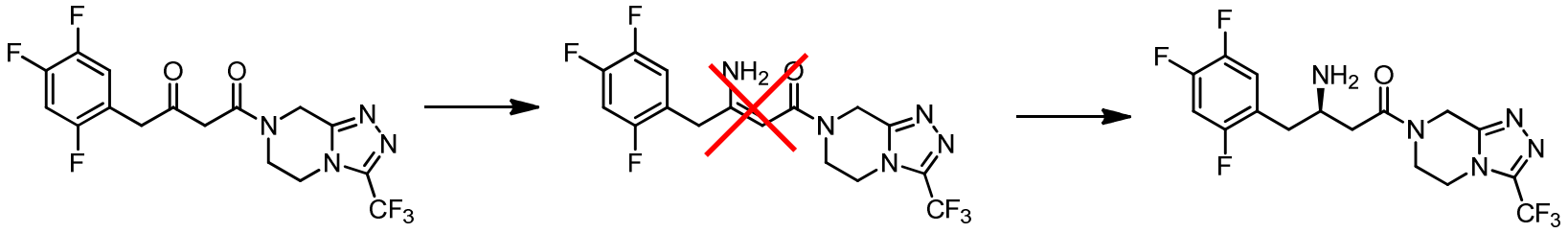
Supply of Critical Elements Is Not Sustainable



American Chemical Society
ACS Green Chemistry Institute®

MERCK

Sitagliptin 3rd-Generation Route: Ideal Process



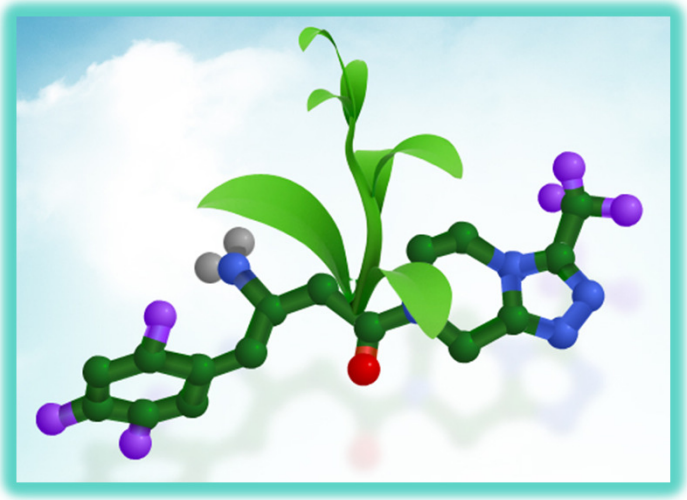
- Avoid formation of intermediate enamine?
- Improve ee and avoid isolation of crude sitagliptin for ee upgrade?
- Eliminate the high-pressure hydrogenation and specialized equipment?
- Eliminate heavy metal and carbon treatment to remove it?

  Rh: $1,000 - $10,000 per ounce
- Can we use an enzyme for the direct conversion?

MERCK

Efficient Synthesis: Biocatalysis With Enzymes

- Environmentally benign technology
  - Catalysts are grown in *E. coli*, renewable
  - Operate in aqueous systems
- Economically attractive
  - Stable manufacturing costs
- Enabling technology
  - Opens access to unique synthetic sequences

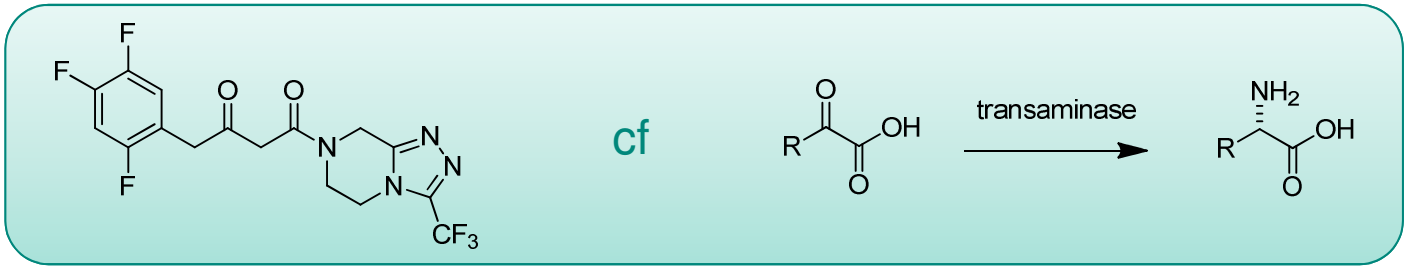


More sustainable. It's Green!

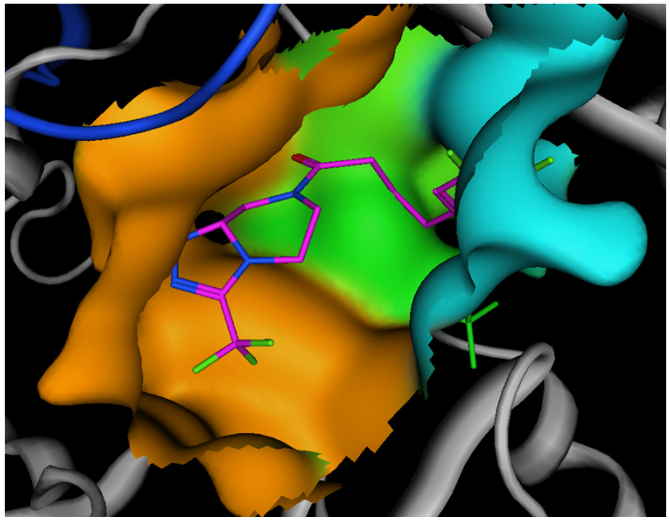
MERCK

Can We Use a Transaminase Enzyme?

Problem….Our substrate looks nothing like the natural α-ketoacid substrate



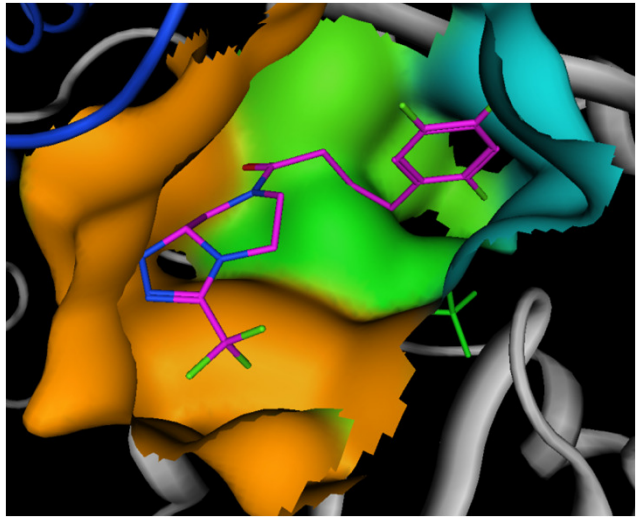
Starting protein homology model



No activity with natural enzyme

Enzyme Evolution

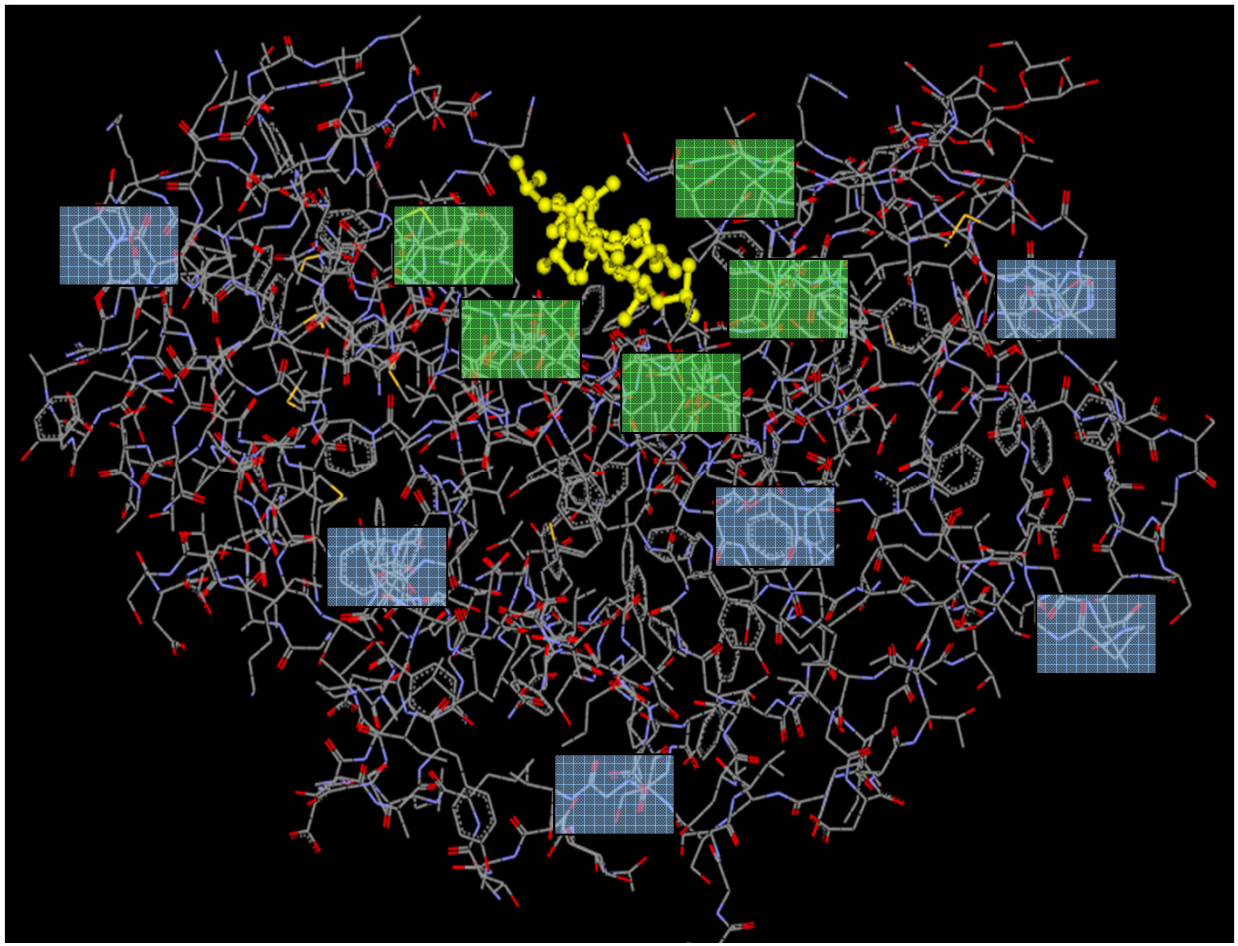
Model with accumulated pocket mutations



Activity and selectivity established

MERCK

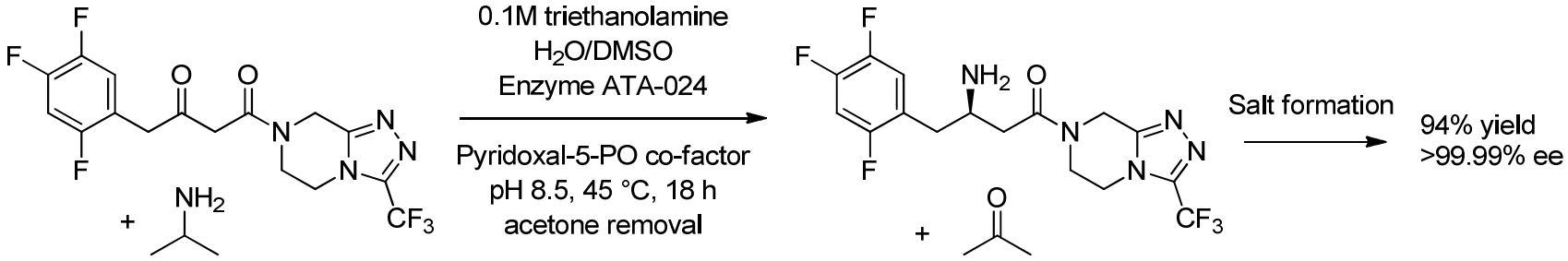
Codexis Collaboration – Enzyme Evolution



- Unique technology for making enzyme improvements through amino acid changes
- Define backbone: stable to solvents and temperature; easy to express, etc
- Develop library of specificities on this backbone

MERCK

Sitagliptin: The Ultimate Manufacturing Process?



- 7th-round enzyme evolution (collaboration with Codexis), >95% conversion, >99.9%ee
- PMI reduction from 30 to 23
- Saves multi-million $/year versus the asymmetric hydrogenation approach
- Lower costs enable the medicine to be available to emerging markets such as India
- 2010 EPA Presidential Green Chemistry award

MERCK

Conclusion

- Green Chemistry is a Merck corporate commitment
- Low costs, Green Chemistry and good science go hand-in-hand
- When it comes to developing a manufacturing route, it's easy being green





MERCK

Let Us Meet Again

We welcome you all to our future conferences of OMICS Group International

Please Visit:

www.omicsgroup.com

www.conferenceseries.com

www.pharmaceuticalconferences.com

MERCK