



Asymmetric Synthesis of Critical Intermediates in ARV Drugs

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¹Amgen Summer Scholar, 2008

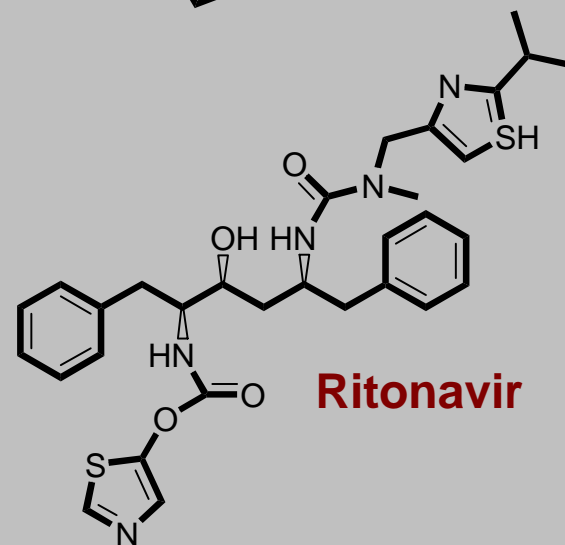
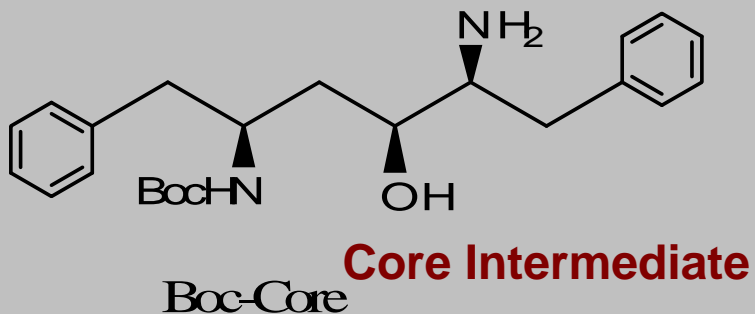
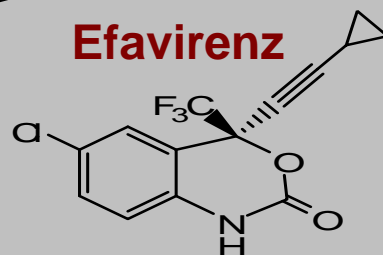
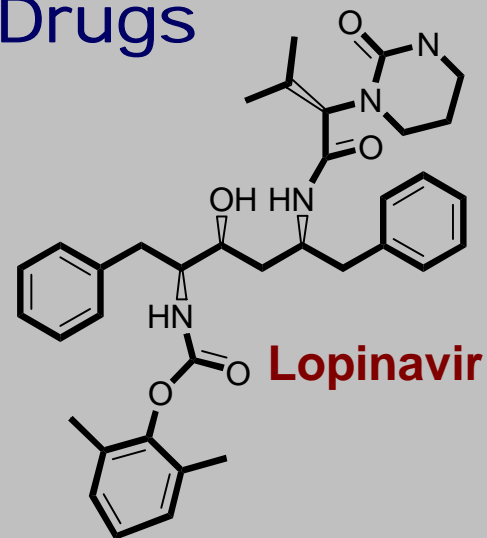
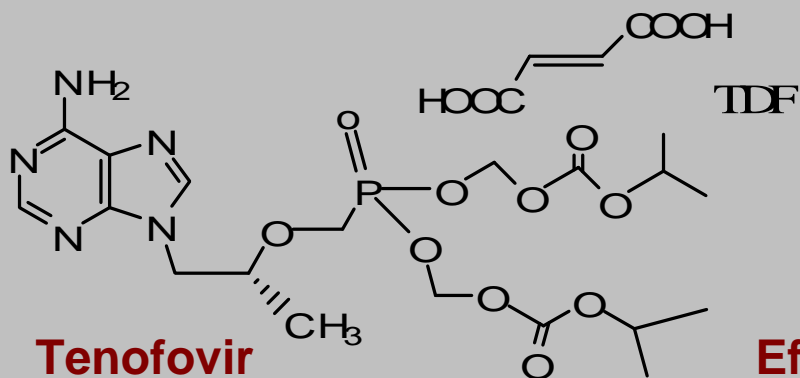
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Critical HIV/AIDS Drugs for Emerging Nations

- Efavirenz (EFV)
- Tenofovir Disoproxil Fumarate (TDF)
- Ritonavir (RTV)
- Lopinavir (LPV)
- Atazanavir (ATV)



Structures of HIV/AIDS Drugs



Background of Ritonavir (RTV) and Lopinavir (LPV)

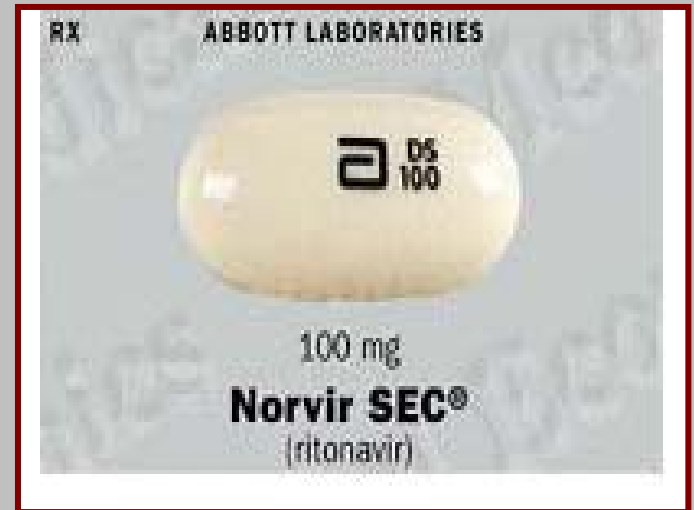
- Critical drugs for the treatment of HIV/AIDS
- 2nd – line drugs in developing world (~450,000 ppl)
- Attack viral RNA by inhibition of HIV-Protease
- \$1.5 Bn/year sales in high-income countries

Ritonavir: Is critical component for all PI regimens in emerging nations

- Inhibits CYP_{3A4} (iron bearing enzyme)
- Co-dosing with other PIs results in higher blood levels and longer $t_{1/2}$
- Co-dosing with Saquinavir, Atazanavir and Lopinavir means RTV is in ~90% of all PI use in emerging nations

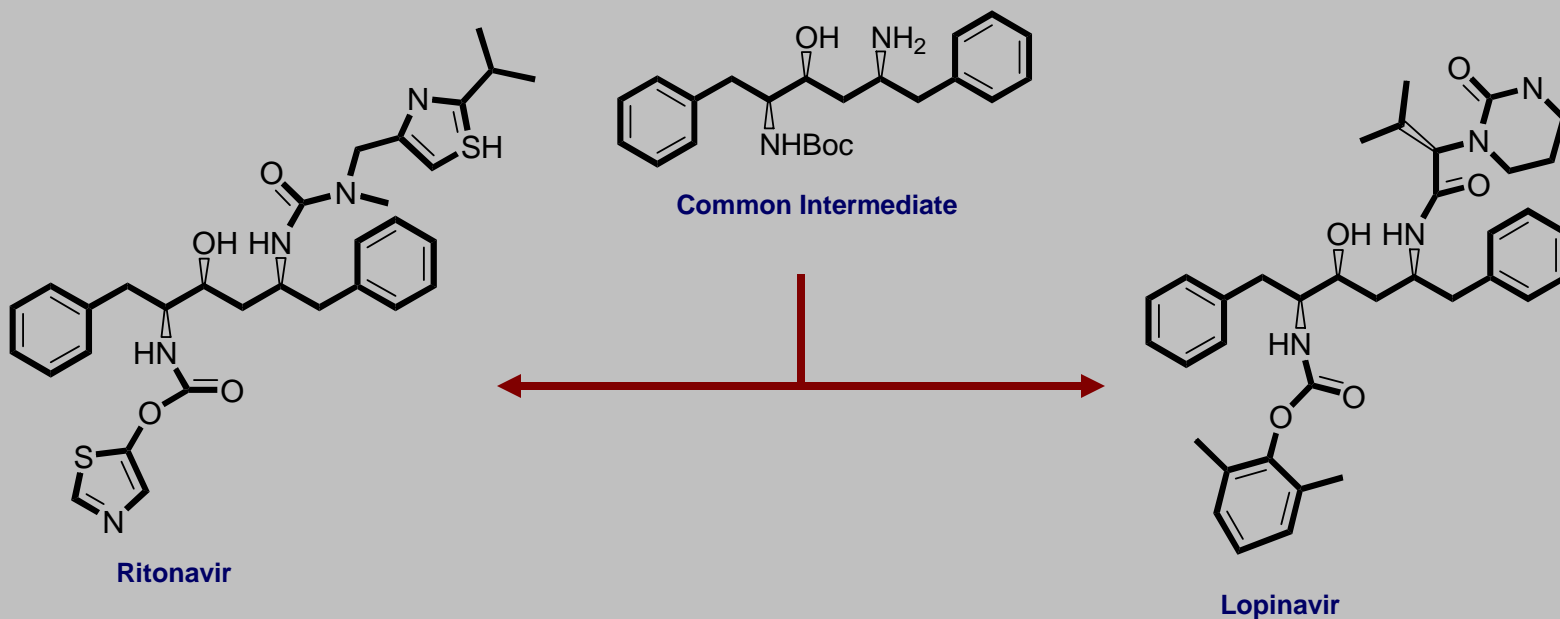
Background cont..

- RTV is sold separately and in combination with LPV in large amounts (60 MT/A each)
- Combination of RTV/LPV sold as Kaletra™ and Aluvia™ by Abbott Labs
- About \$1,000 / kg manufacturing cost of active pharmaceutical ingredient (API)
- Mandate from International Donor Agencies to lower the cost of high-quality RTV and LPV API



Objectives

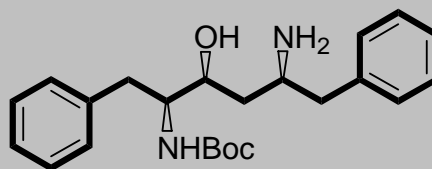
The six carbon center core, shown below, is a common structure in both RTV and LPV. This core costs around \$500/kg.



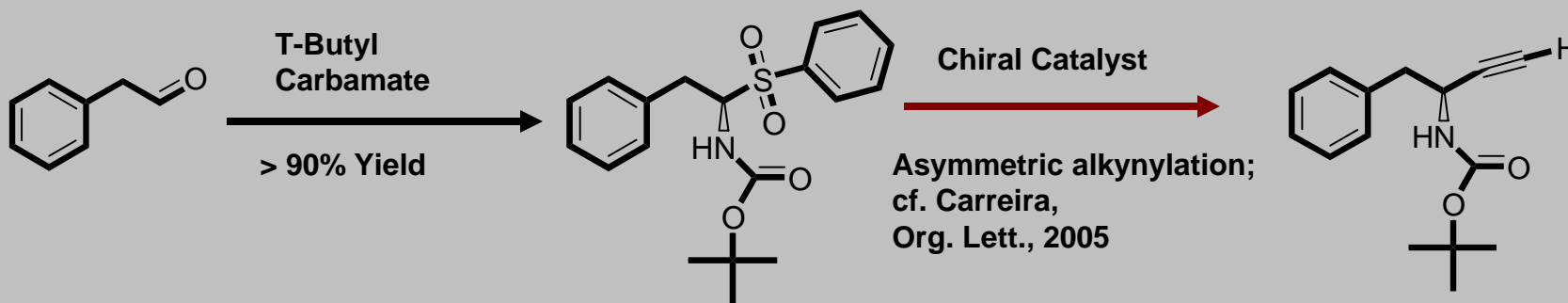
Objective: New chemistry to make the common intermediate of RTV and LPV at lower cost

Methods

Prepare the core intermediate in **three** discrete procedures with complete control of absolute asymmetry – 3 procedures

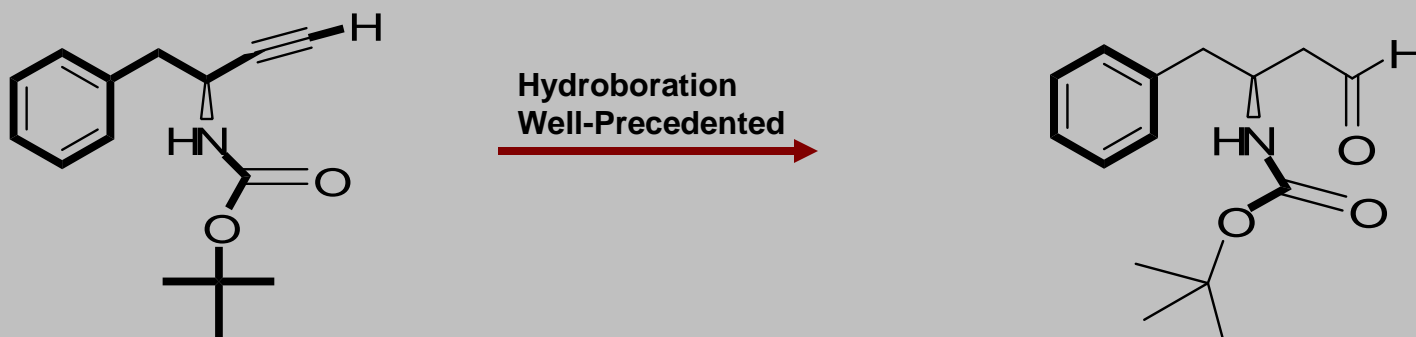


1st / 2nd Phenylacetaldehyde condensation with tert-butylcarbamate to make imine precursor



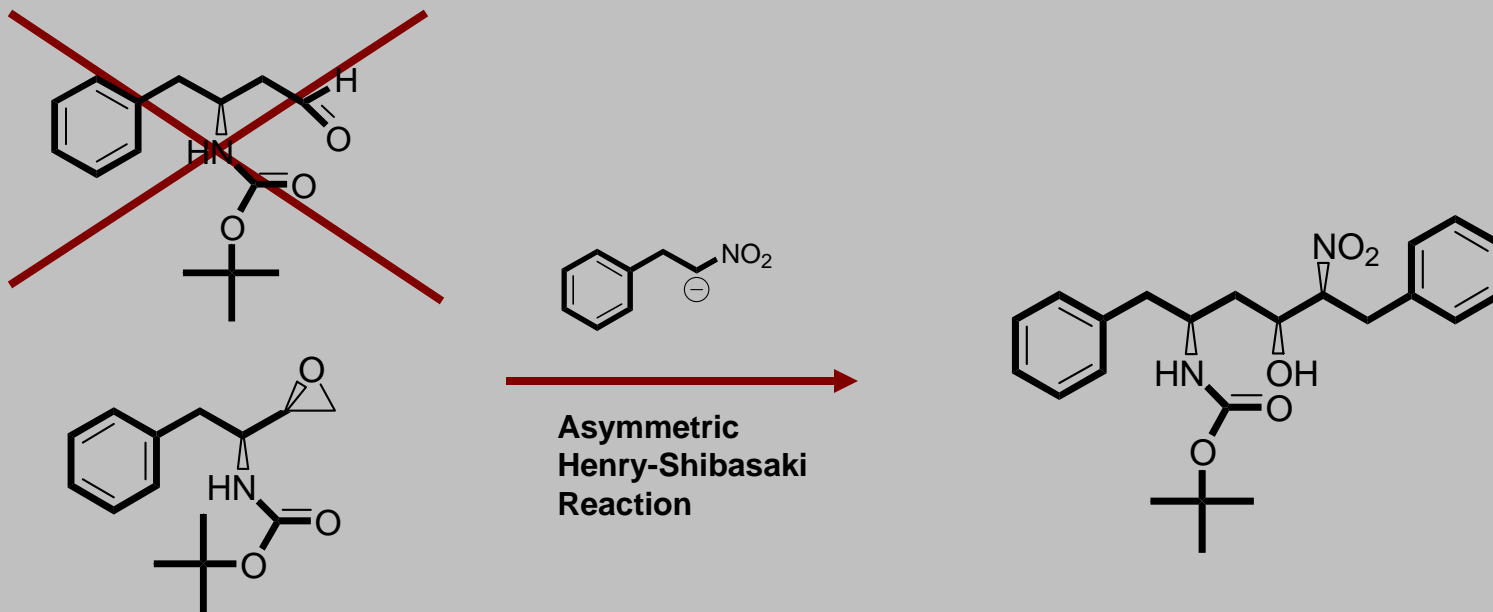
Methods Cont...

2nd cont.. *In situ* generation of N-acylimine and condensation with acetaldehyde or “masked form” = enantioselective Mannich reaction

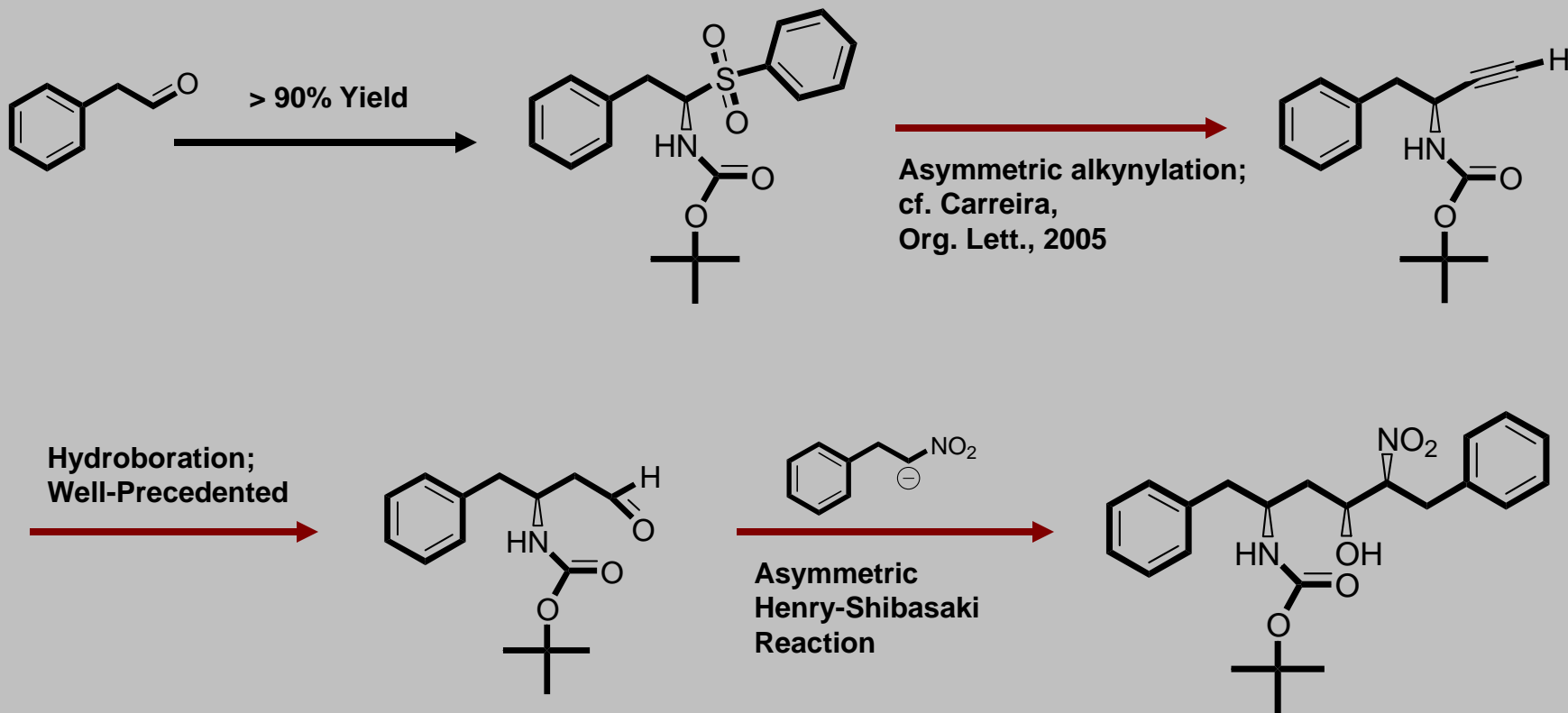


Methods Cont...

3rd Attachment of the final two carbons as 2-phenylnitroethane – asymmetric Henry-Shibasaki reaction



Synthetic Scheme



Discussions/Conclusions

Step 1: Involving the imine precursor	✓
Step 2: The synthesis of Mannich reaction	≈
Step 3: Epoxide Reaction	✓
Step 3: Henry Shibasaki Reaction	NA

➤ By acquiring the correct chemistry of the improved compound, we hope to reduce the cost of these Active Pharmaceutical Ingredients (APIs) from roughly \$1000/kg to the range of \$500/kg.

References

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