Rewiring Chemistry: Algorithmic Discovery and Experimental Validation of One-Pot Reactions in the Network of Organic Chemistry

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Current Literature 12/1/12
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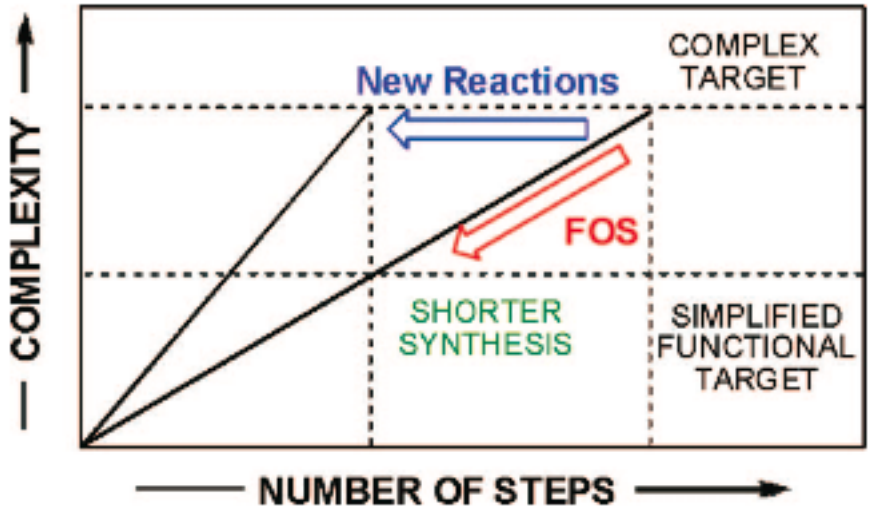
Chemistry of the future

- Atom Economy
- Step Economy
- Redox Economy
- Eintopf Reactions
  - One-pot synthesis
- Man vs. Machine



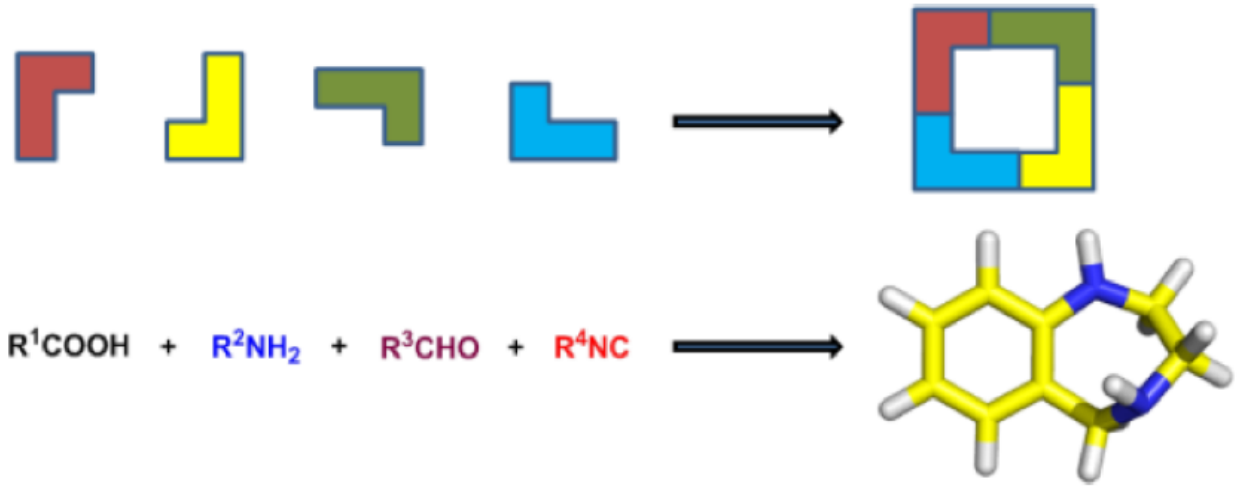
The PASE ideology

- Pot, Atom, and Step Economy
  - Reduce amount of solvents used in workup, purification, cleaning, contamination.
  - Idea to create greener chemistry to reduce environmental impact and cost.
- Annual Cost of Goods for production of pharmaceuticals $200 billion(2008)
- NIH annual budget ~31 billion

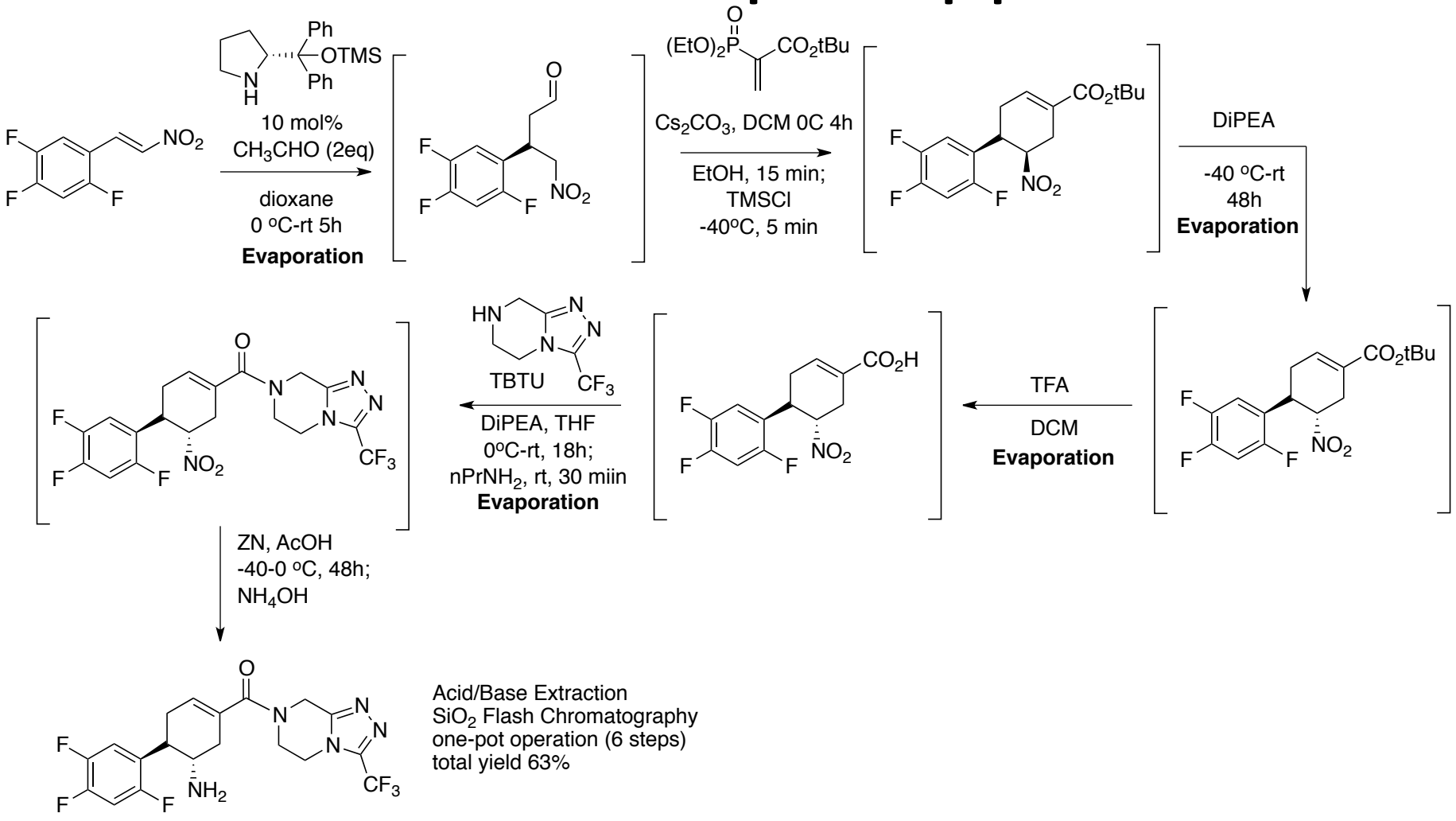
Angew. Chem. Int. Ed. 2011, 50, 3605 – 3607
Green Chem., 2007,**9**, 438-440
J Pharm Innov (2008) 3:30–40
NIH annual reports 2012

MCR as a “one-pot” synthesis

- Multi Component Reactions (MCR) have been around for over 140 years and can be used to readily access complex molecules from a series of simple precursors.
- Have been used extensively in drug discovery
- Products can also act as building blocks for further synthetic modifications.



Januvia a one pot approach



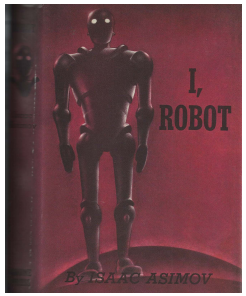
Angew. Chem. Int. Ed. 2011, 50, 2824 –2827
Hiyashi

Chematica

- Chemical Network
  - Seven million compounds linked by numerous chemical reactions
  - 86,000 chemical constraints
- Based on the Beilstein Database (BD) now known as Reaxys ca. 2009

Goals

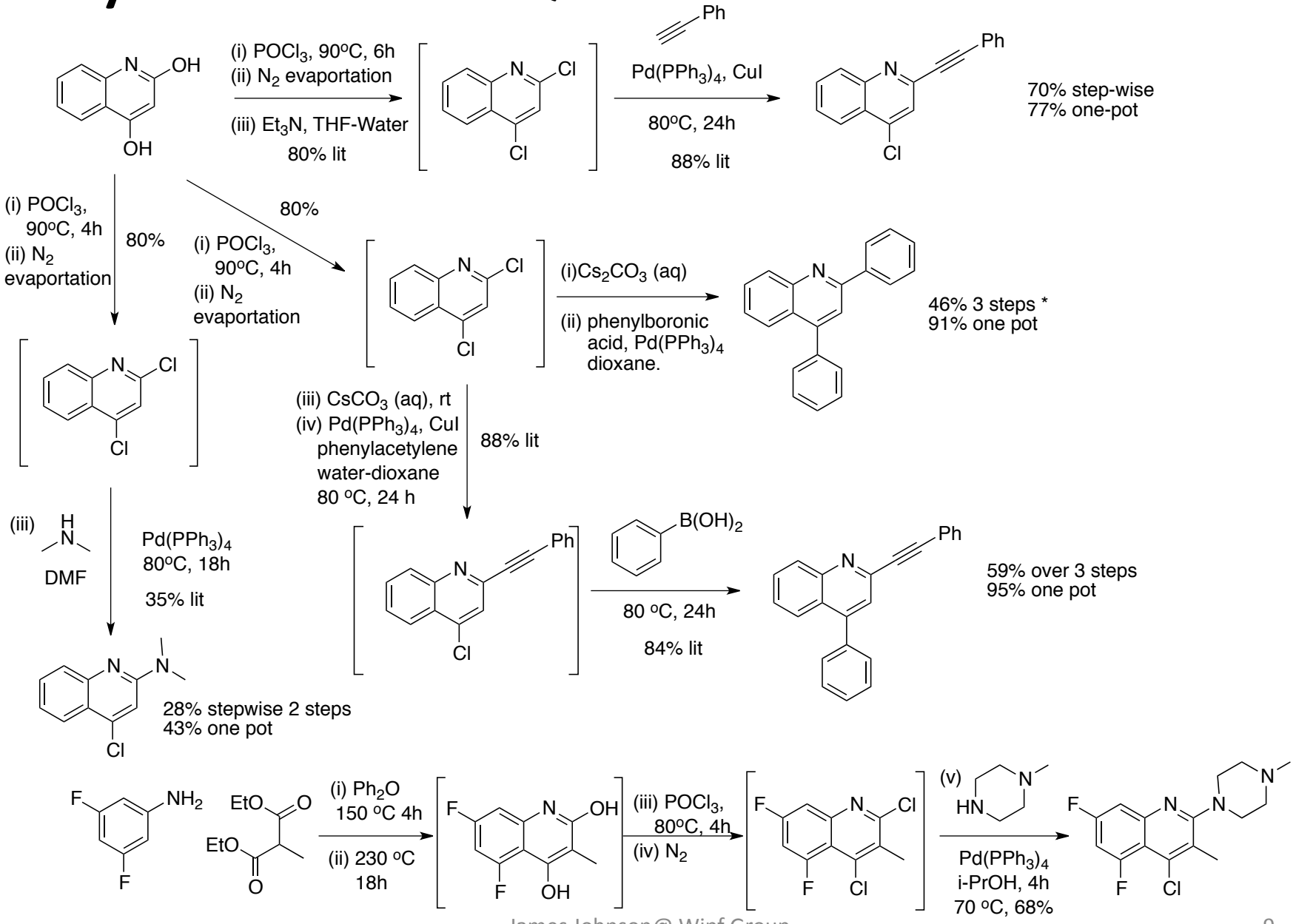
- the algorithm on a par with the detailed synthetic knowledge of experienced organic chemists (including stereoselective syntheses

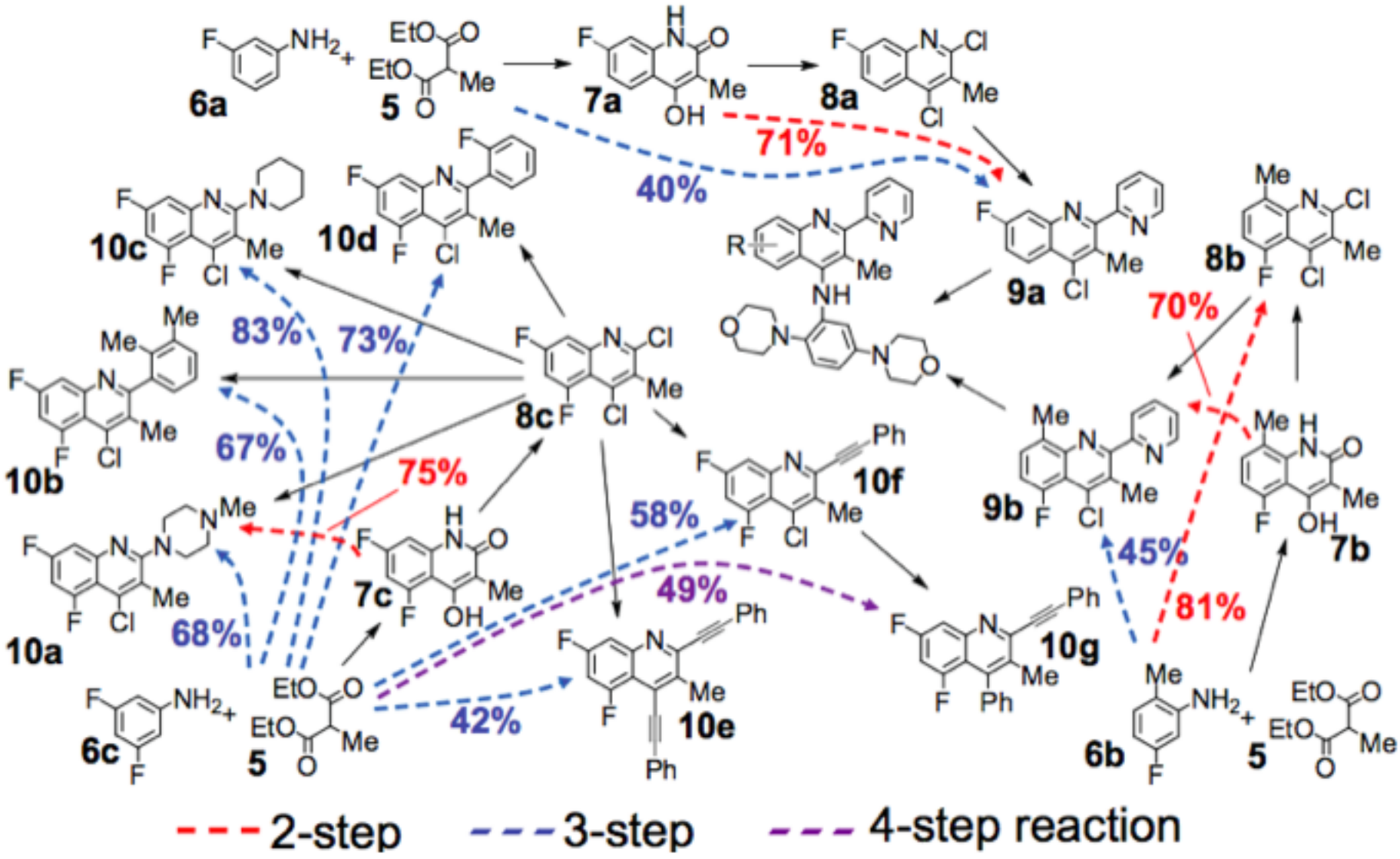


iChemist: The Five Laws

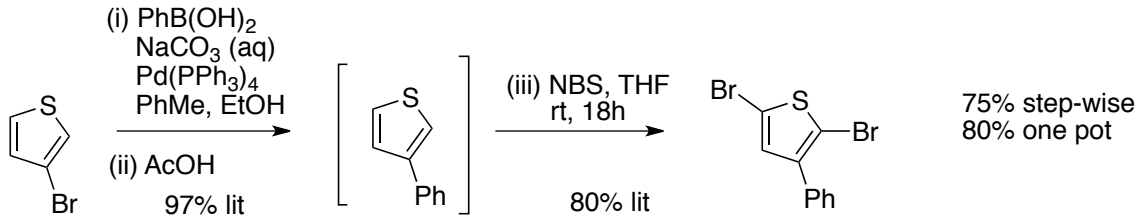
- (1) If at least one reagent used in a reaction step is water sensitive, all other reactions in the sequence have to be performed in water-free environment.
- (2) If the reagent(s) used in one reaction step is oxidizing, no reducing reagents can be used concurrently in order to avoid redox reaction between reagents.
- (3) If the reagents used in any given reaction step are acidic, basic reagents cannot be concurrently present in order to avoid acid-base reaction between them.
- (4) If the reagents used in one reaction step contains hydride source, reagents containing proton source cannot be concurrently present.
- (5) The functional groups in the reagents must be compatible between reaction steps.

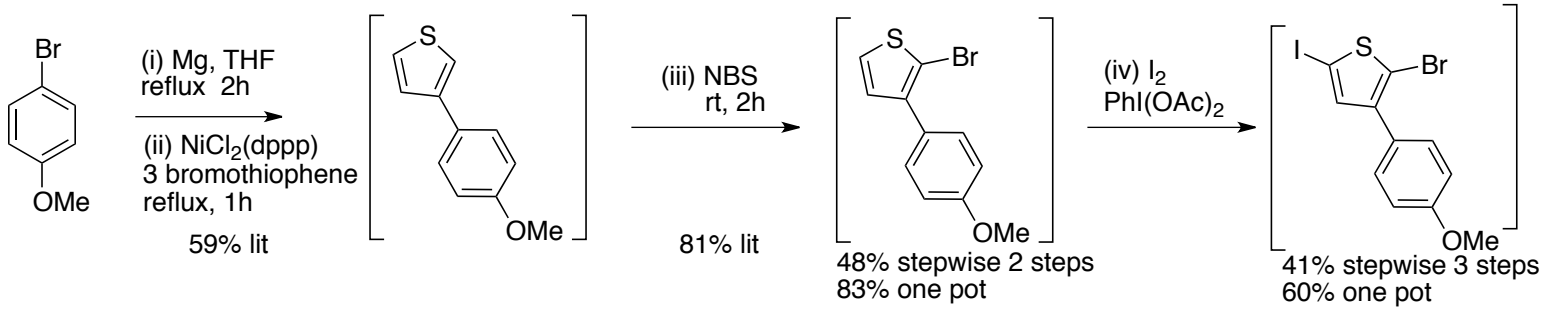
Synthesis of Quinoline derivatives

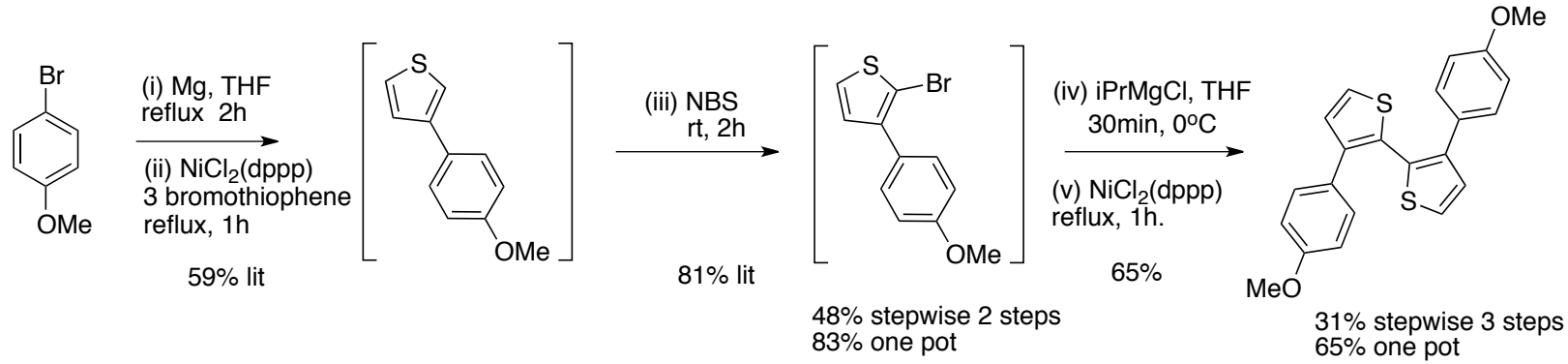



6a
5
7a
8a
71%
40%
10c
10d
9a
8b
70%
83%
73%
8c
67%
75%
10b
10f
9b
7b
58%
45%
49%
81%
10a
7c
68%
10g
42%
10e
6c
6b
2-step
3-step
4-step reaction

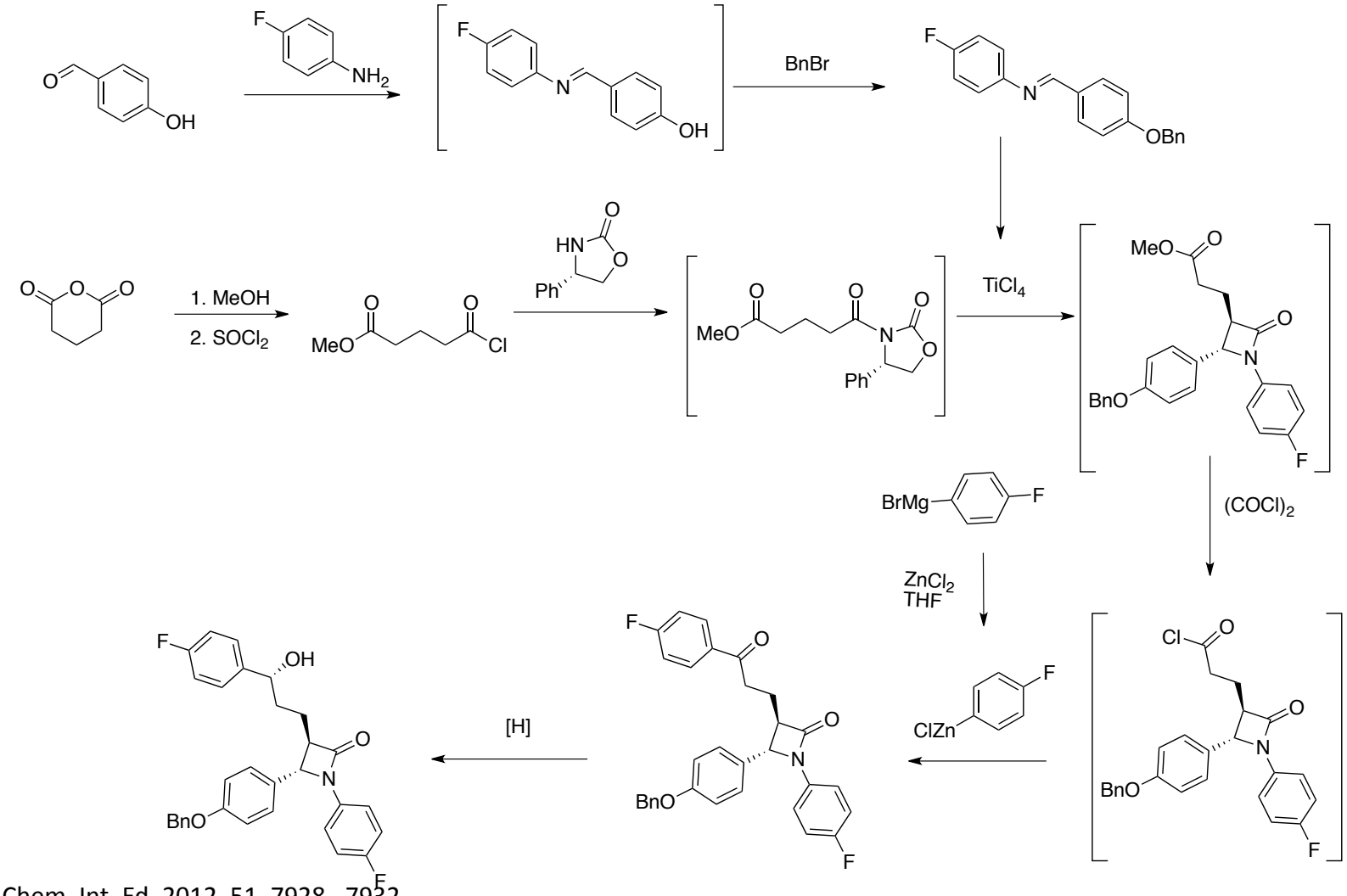
Thiophene derivatives





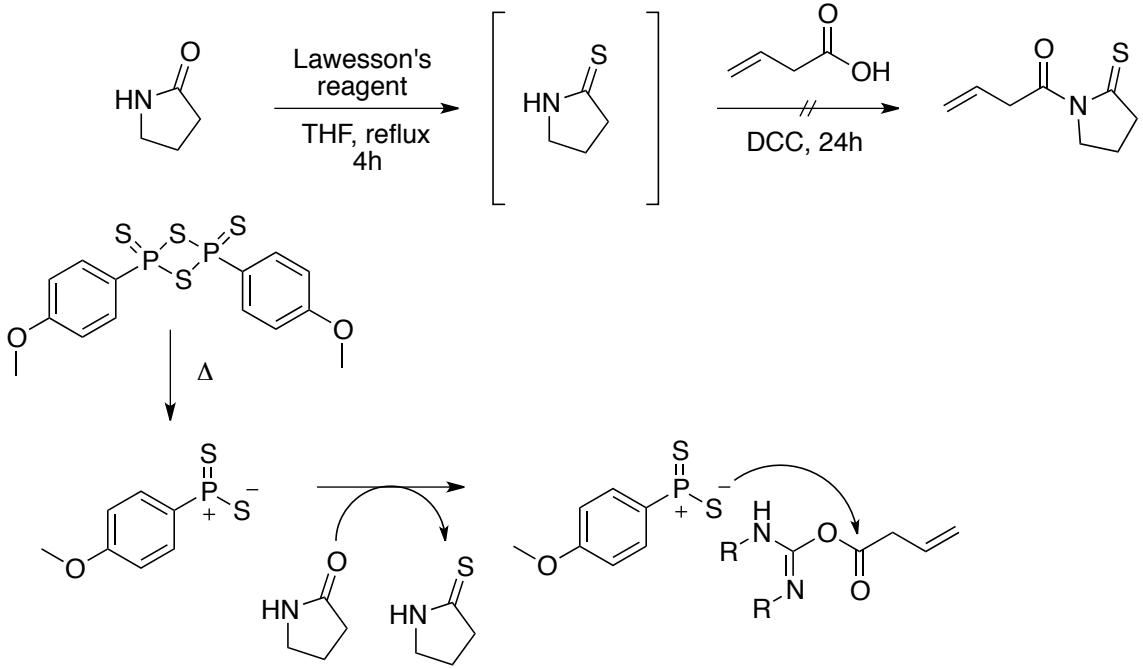


Two one-pot reactions to Ezetimibe



Angew. Chem. Int. Ed. 2012, 51, 7928 –7932
IND-SWIFT LABORATORY LIMITED. Patent WO2008/96372 A2, 2008
Veltri, Enrico P. US Patent 2006/69080 A1, 2006

Problems with the program



Parallel optimization of synthesis and cost

- Cost analysis for optimization
  - Algorithm starts with the target and works backwards to the reactants. Then in a recursive manner the algorithm returns results for each level of reactants and products.
  - This process is based on a cost benefit analysis of the reactants (commercially available vs synthetically available)
- Compounds that are chemically similar will benefit from collective optimization.

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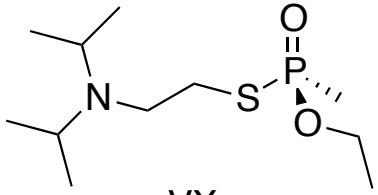
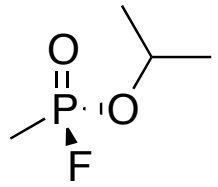
Chemical Warfare

- Large scope of reactions available to produce a large number of compounds
- Some compounds have been used in chemical warfare and through the use of this program can teach a layperson how to produce them.
- Identifying through reactants screening which precursors are the right ones to regulate.



VX

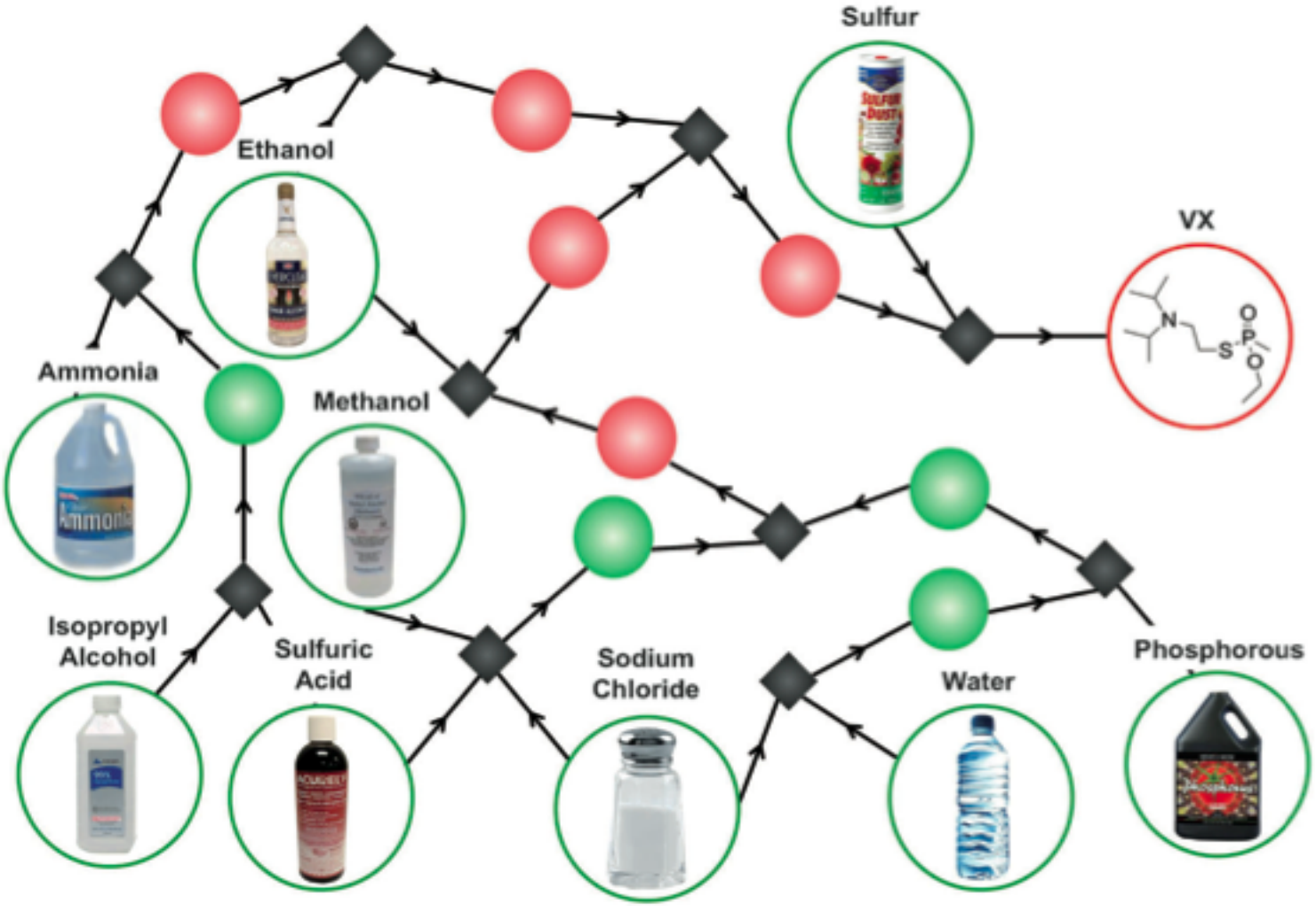
Nerve Agents



Sarin

- G series (1930s)
  - Named after the Germans who made them.
  - Inhibit acetylcholine esterase
  - Suicide binder
- V series (1960s)
  - Originally discovered in attempts to make better insecticides.
  - VX LD_{50} 10mg through skin contact
  - Cholinesterase inhibitor

Synthesis of VX



Conclusions

- Algorithm cannot recognize all possible incompatibilities of reactants
- Algorithm built off existing chemistry and is not discovering new chemistry
- By making this chemistry available to everyone are we threatened by what they can and will make.