Working with Chemical Reaction Rules

Bernhard Thiel

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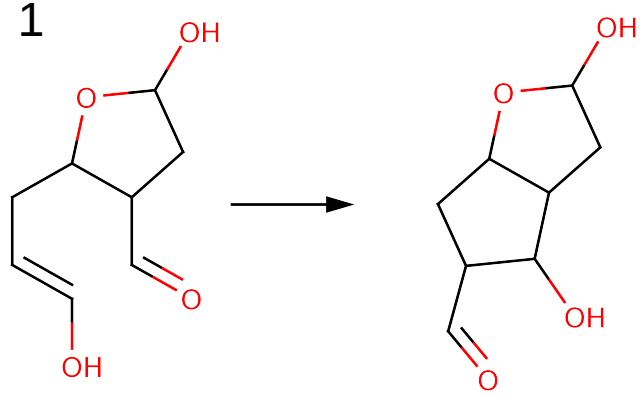
Reactions

1



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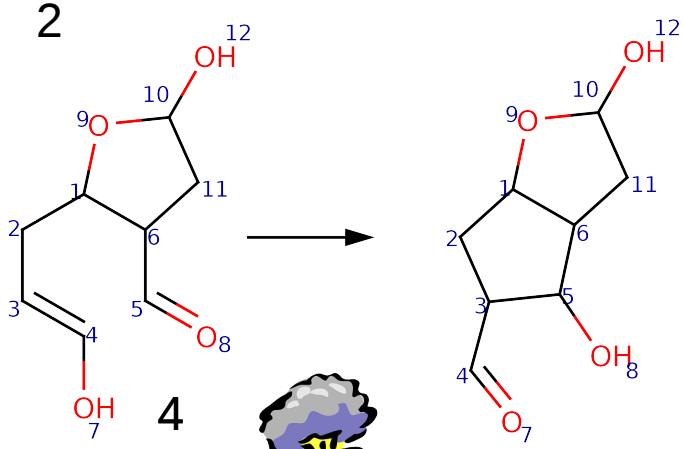

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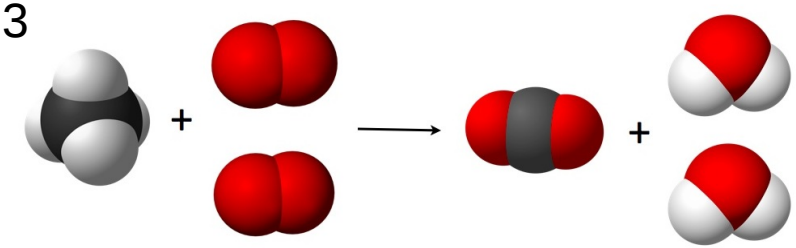

4

5

$C_6H_{12}O_6 + 6\ O_2 \rightarrow 6CO2 + 6\ H2O$

6

Glucose + Oxygen -> Water + Carbon dioxide

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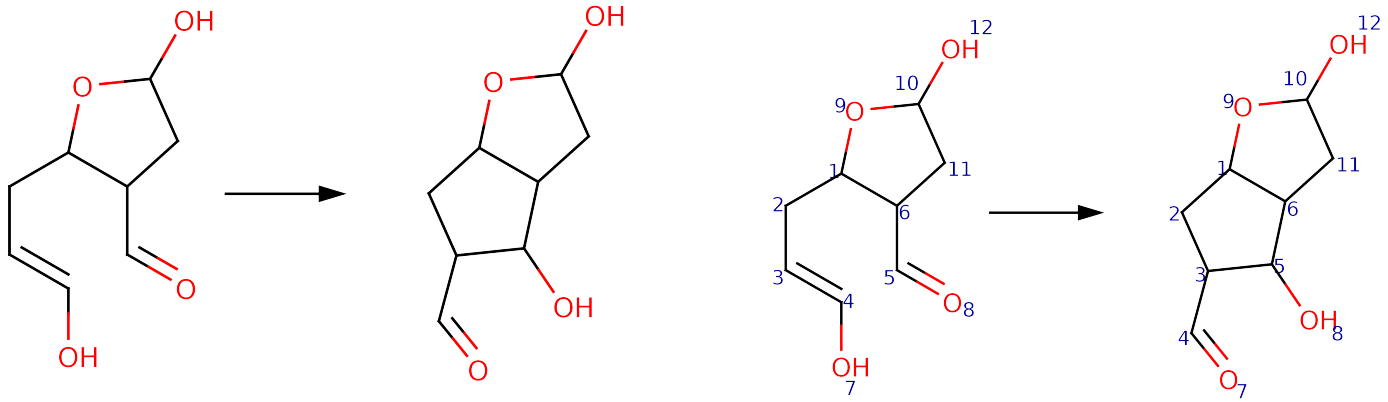
References: (1) Graeme Coulthard et al, Nature 489, 278–281 (**2012**), doi:10.1038/nature11411
(3) Picture from Jynto, Jacek FH, Robert A. Rohde via wikipedia.org

The atom mapping problem



- Minimize # of changed bonds
- Minimize weights of changed bonds
- Find cyclic imaginary transition state
- Find a reaction mechanism

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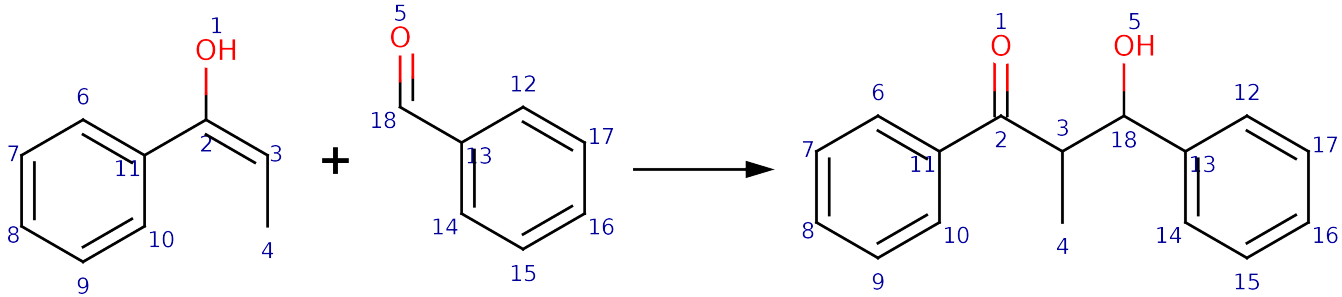
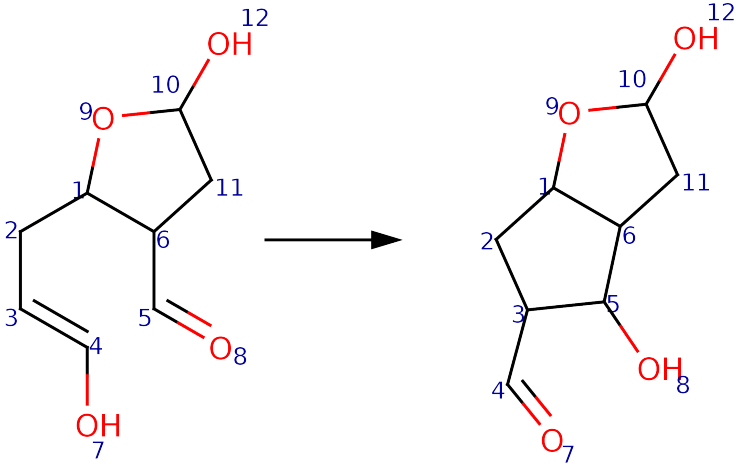
References:

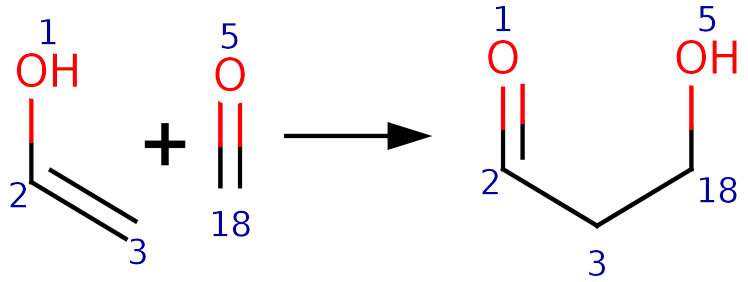
(1) Eric First et al, J.Chem.Inf.Model. 52, 84–92 (**2012**), doi:10.1021/ci200351b
(2) Mario Latendresse et al, J.Chem.Inf.Model 52, 2970–2982 (**2012**), doi:10.1021/ci3002217
(3) Mann et al. *in* Principles and Practice of Constraint Programming (**2013**), Springer, doi10.1007/978-3-642-40627-0_59:
(4) B. Thiel, Masterthesis (**2013**)

Reactions & Reaction Rules





Aldol reaction

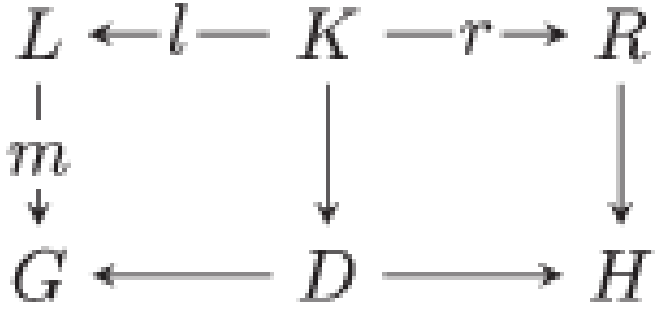


Reaction Rules

- Algorithm in imperative language (1)
  - Concept of functional groups intrinsically present

...D—C—C—W ---> D=C + C—W
...aldol
m8: ..dec 23
..alcohol; ..wgroup; ..at2 tryfgi dec 70
..bond 1 broken
..subt dec 100 if grp2; ..is primary amide
..kill if halide; ..within betato cbn2

- Double push-out formalism
  - Subgraph patterns
  - Automatic generation of rules
  - Functional group completion (2)



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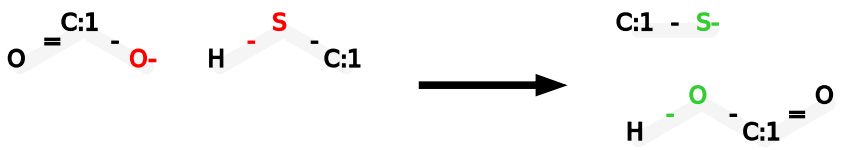
References: (1) E.J. Corey et al, J.Am.Chem.Soc. 94, 440–459 (**1972**), doi:10.1021/ja00757a022
(2) James Law et al, J.Chem.Inf.Model 49, 593–281 (**2009**), doi:10.1021/ci800228y
(3) Jakob L Andersen, J Sys Chem, 2013, 4:4 doi:10.1186/1759-2208-4-4

The GML Format

- Key-Value Pairs
- Left side graph
- Right side graph




```
rule [
  ruleID "Reaction rule 1"
  left [
    node [ id 3 label "S" ]
    node [ id 2 label "O-" ]
    edge [ source 3 target 4 label "-" ]
  ]
  context [
    node [ id 0 label "C:1" ]
    node [ id 1 label "O" ]
    node [ id 5 label "C:1" ]
    edge [ source 0 target 2 label "-" ]
    edge [ source 3 target 5 label "-" ]
    edge [ source 0 target 1 label "=" ]
    node [ id 4 label "H" ]
  ]
  right [
    node [ id 2 label "O" ]
    node [ id 3 label "S-" ]
    edge [ source 2 target 4 label "-" ]
  ]
]
```

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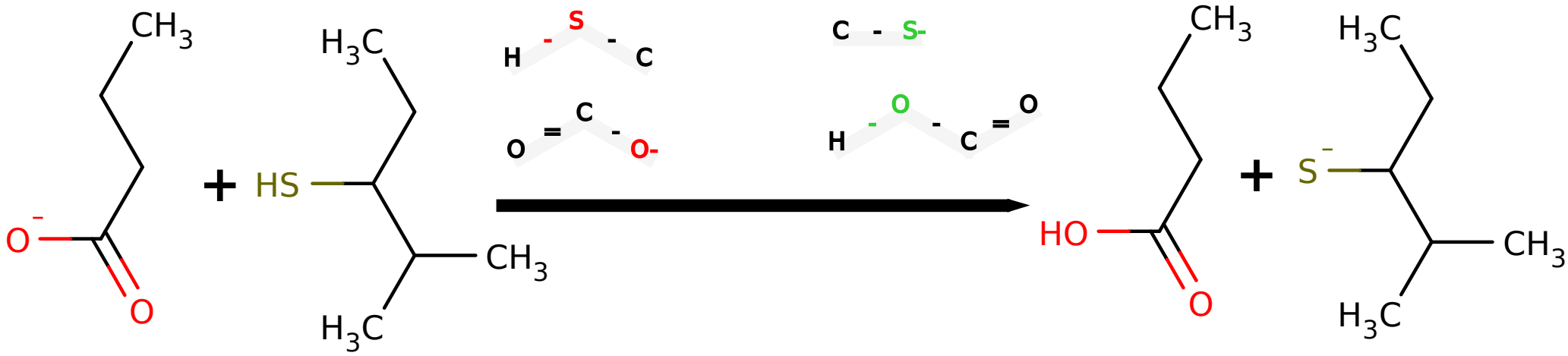
Rule application

- 1. Find all matches of the left-side pattern on the target molecules (Subgraph isomorphism)
- 2. Replace left side with right-side pattern
- Implemented in: Graph Grammar Library



References: Mann et al. *in* Theory and Practice of Model Transformations, Proc. Of ICMT 2013 (**2013**), Springer, doi 10.1007/978- 3- 642-38883-5_5

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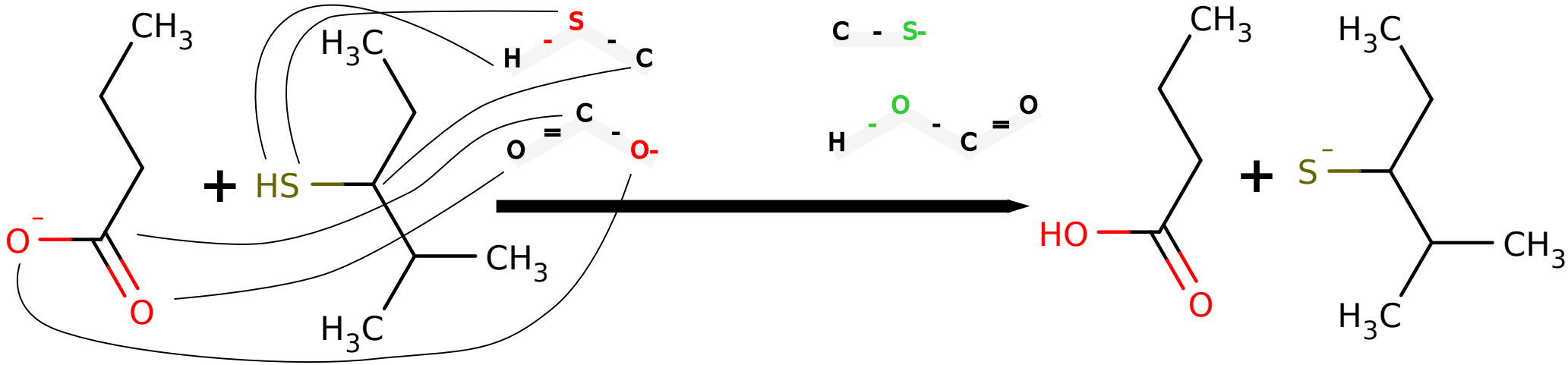

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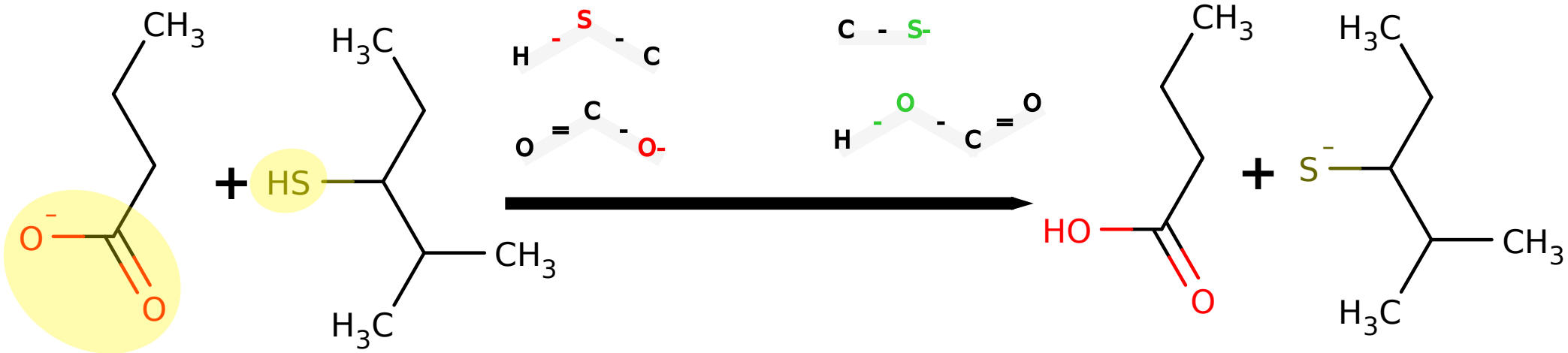

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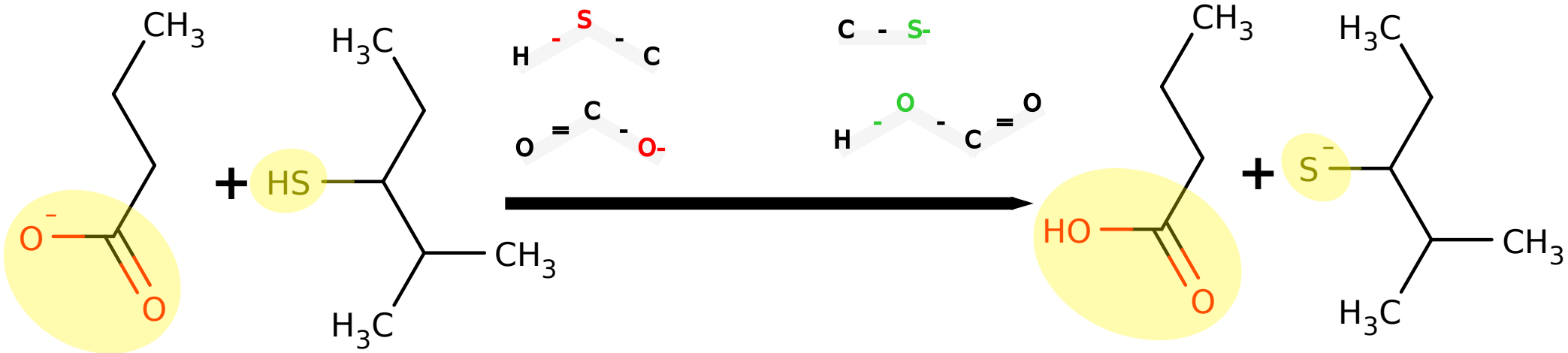

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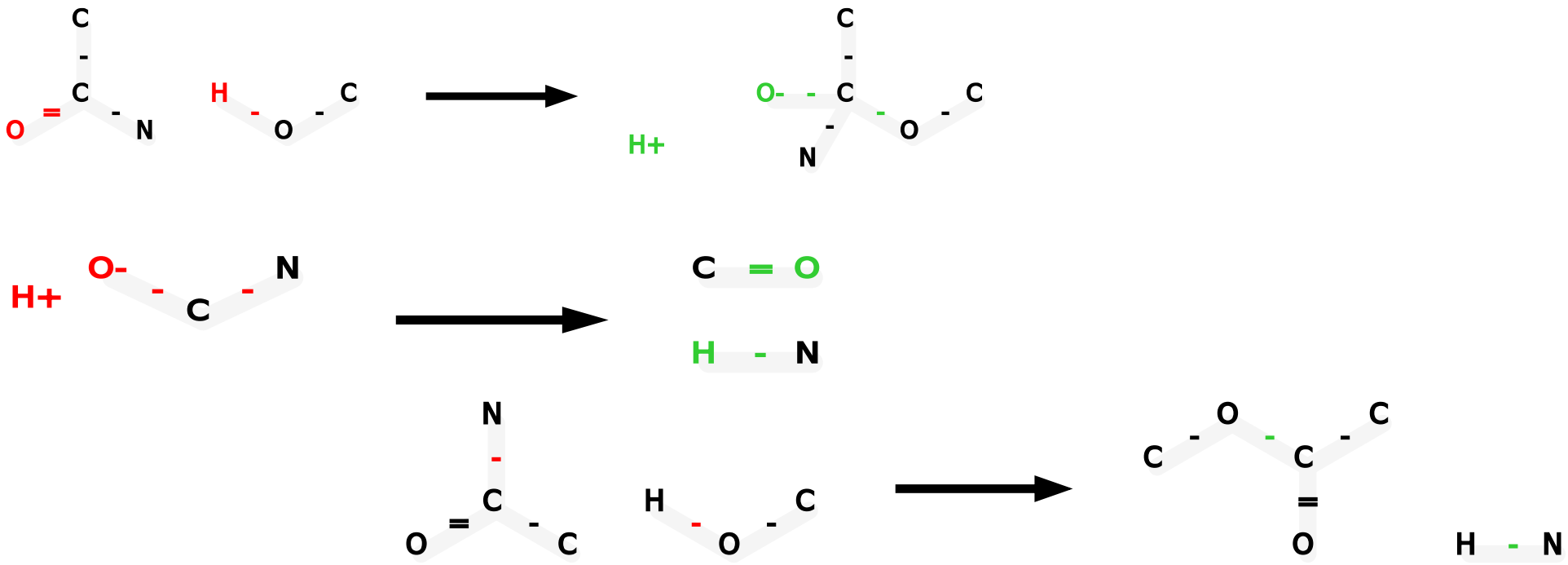
Rule combination

- Rule composition: MedØlDatschgerl
- Make 1 new rule out of two subsequent rules



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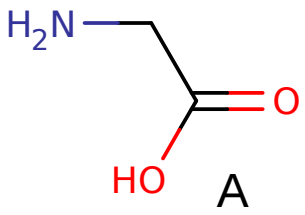
Repeated rule application

- ToyChem
- MechSearch
- MedØlDatschgerl



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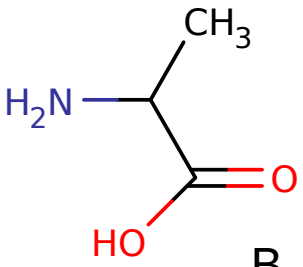

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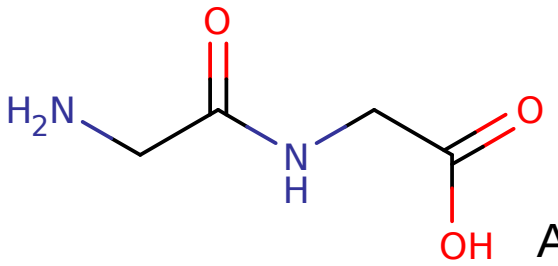

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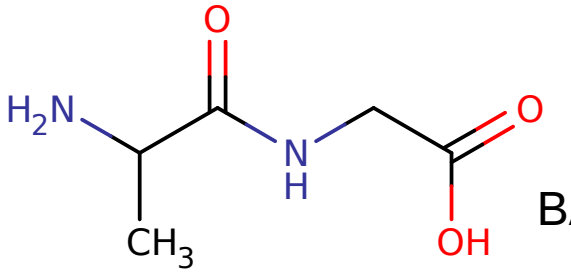

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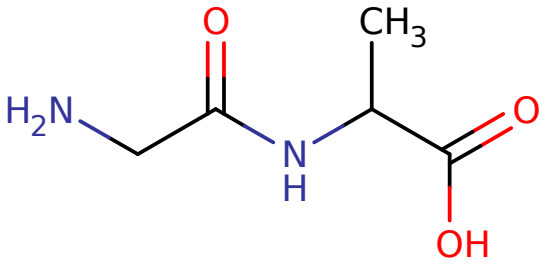

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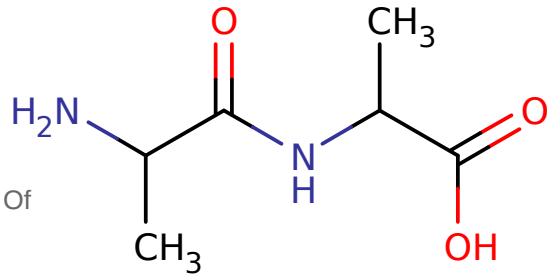

BB

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References:

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2) B. Thiel, Masterthesis 2013 University of Vienna

3) Jakob L Andersen, J Sys Chem, 2013, 4:4 doi:10.1186/1759-2208-4-4

Mini-Project: chemRULER

- Display chemical Rules
  - Uses chemrule2svg.pl by Martin Mann
- Generate chemical rules from reaction files
  - Uses known algorithms, CPLEX and openbabel
- Sanitize chemical rules
- Extract reaction core from chemical Rule
  - Uses known algorithm, Program from my Master thesis
- Compose rules
  - Uses MedØlDatschgerl

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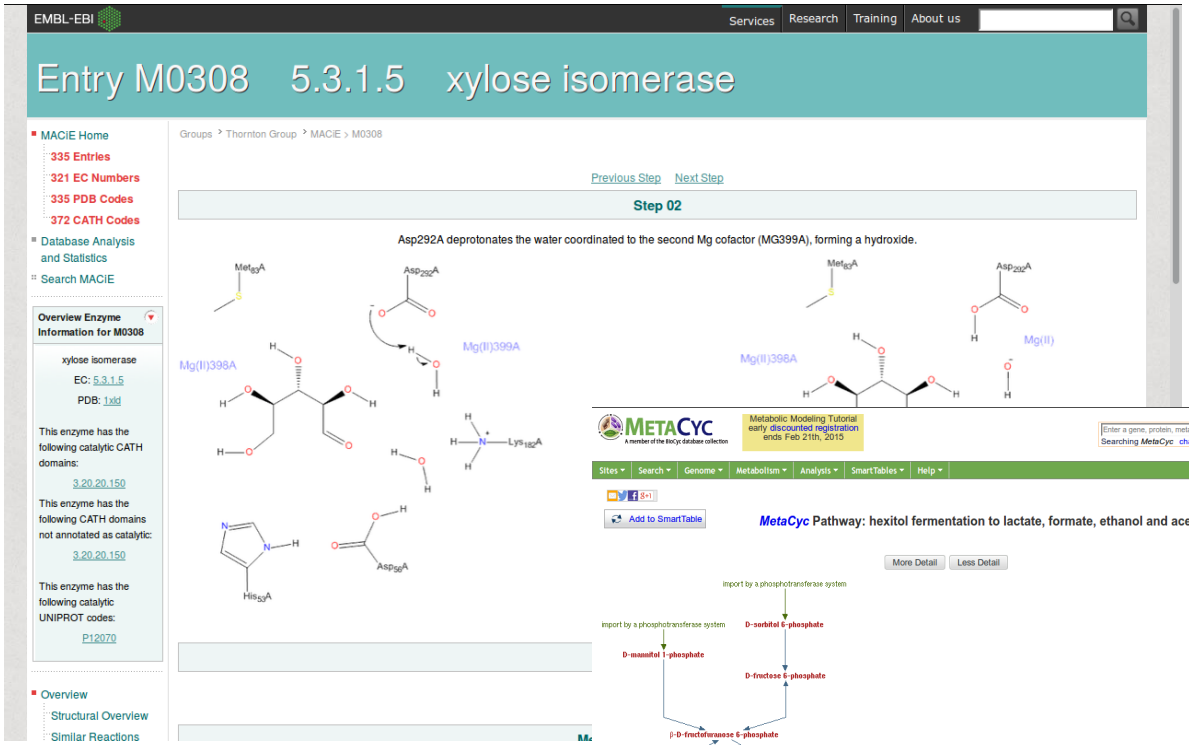
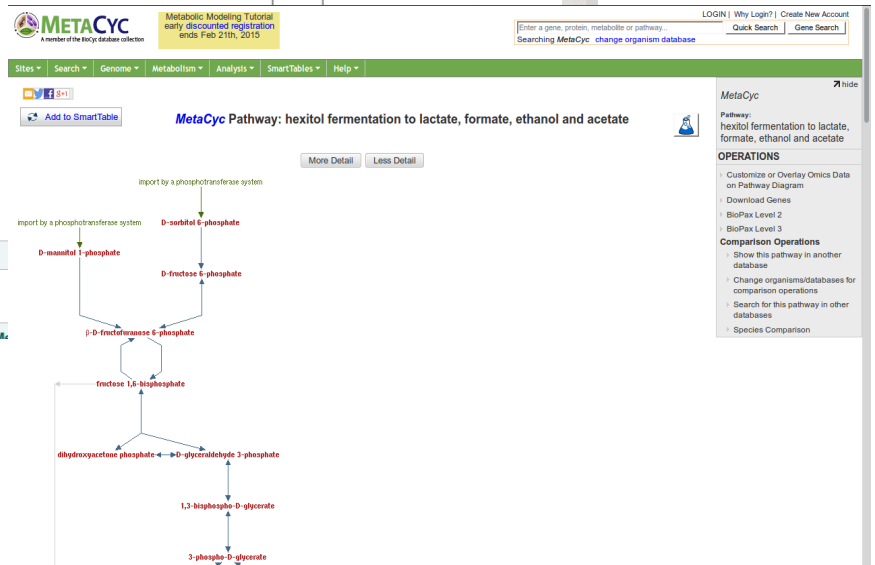
Example Application

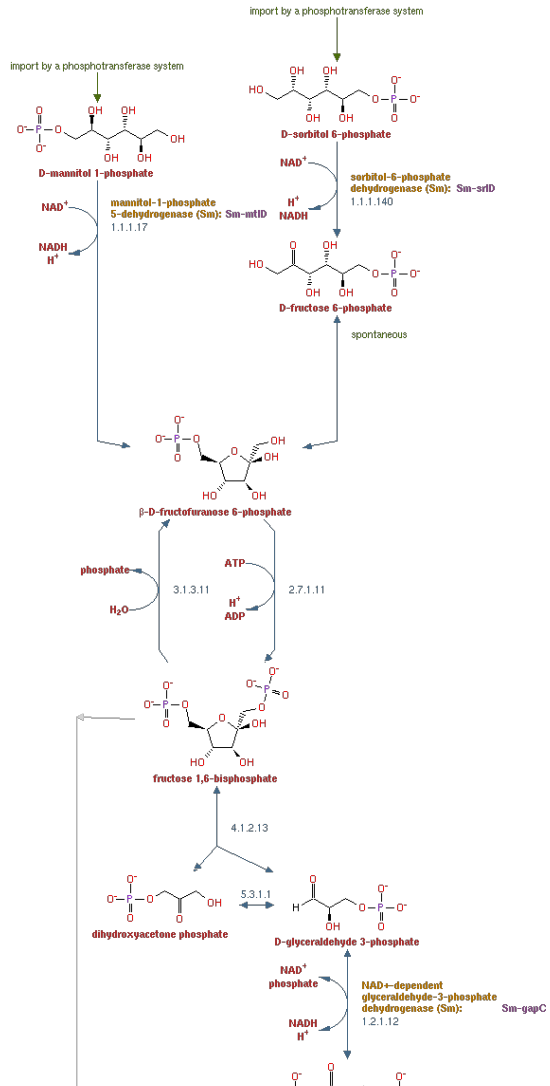
- Goal: confirm the mapping from MetaCyc database
- Extract elementary reactions from MACiE database
- Guess a mapping
- Create rules
- Perform breadth first search for mechanism
- Compose rules from resulting reaction path

Example Application

- Compare composed rule to rule from MetaCyc
  - Graph isomorphism of rules







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Homework

What does

chemRULER

stand for as an acronym?

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