
Reactor

Switching on the Manual Gear

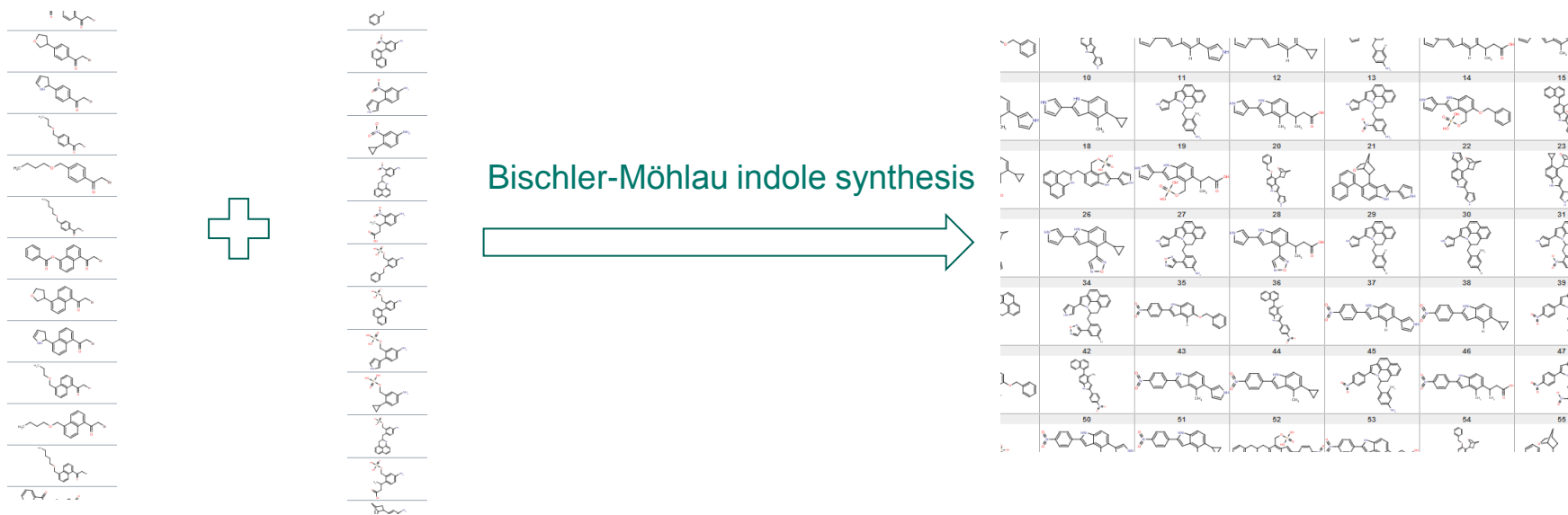
György Pirok, Zsolt Mohácsi, **Wei Deng (David)**



Reactor – Overview

ChemAxon's virtual reaction enumeration engine and application

- Generic reaction schemes to yield reaction products
- Library of organic chemical reactions
- Reaction sketching interface
- Accessibility: Standalone application, Command-line application; KNIME; JChem for Excel; Instant JChem; API

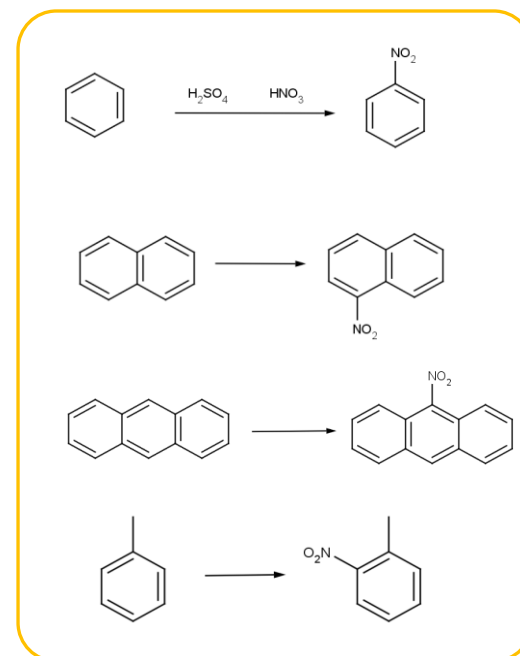
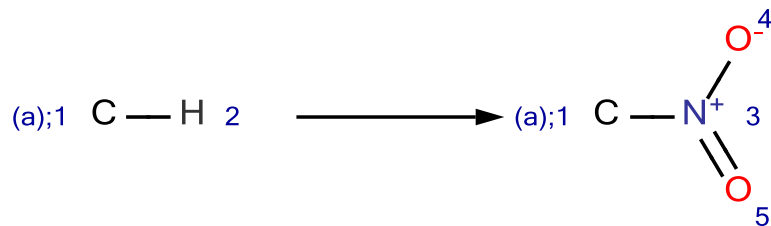


Reaction Scheme

Generic reaction equation

- Query atom specification
- Atom mapping on atoms involved in the reaction
- Orphan atoms can be present
- Implicit hydrogens not considered!

Example: nitration of aromatic hydrocarbons:

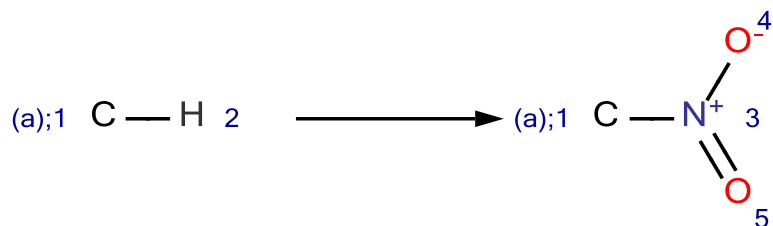


ChemAxon's Reaction Library

- Reaction Libraries (>200)
 - Commonly used organic name reactions (145)
 - New development: constantly evolving collection of reactions (114)
 - Systematic, based on different functional groups (amines, alcohols, aldehydes)
- Each reaction scheme
 - Rules (specification)
 - Description with references and preparation instructions
 - Examples (test cases)
- Extendable and customizable

Reaction Rules

- Chemical intelligence by reaction rules
- Rules evaluated by calculated chemical terms or imported properties
 - Chemical Terms is a language for adding advanced chemical intelligence to cheminformatics applications.



nitration of aromatic hydrocarbons:

Reactivity:

```
electronDensity(ratom(1))>0.75;
```

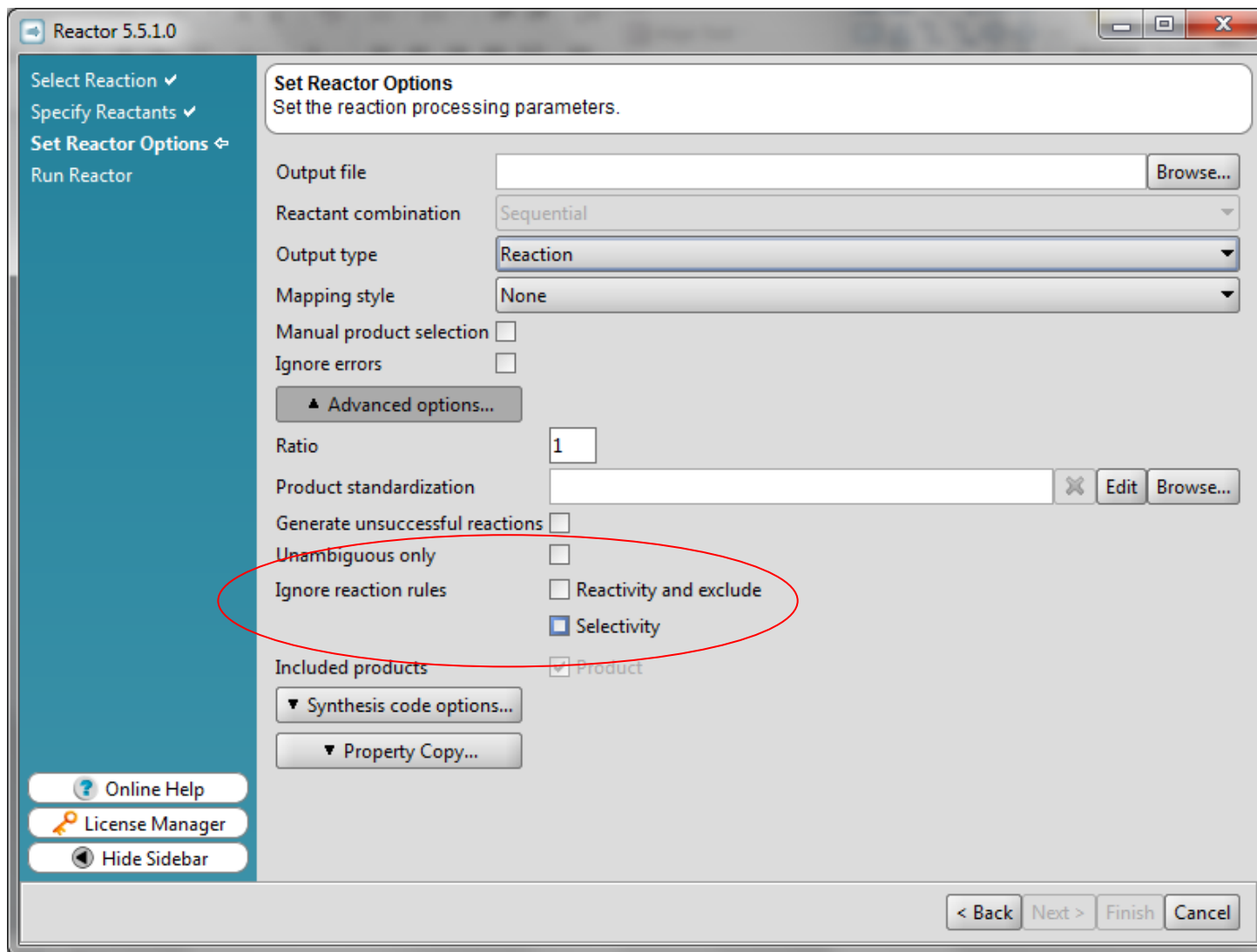
Selectivity:

```
-energyE(ratom(1));
```

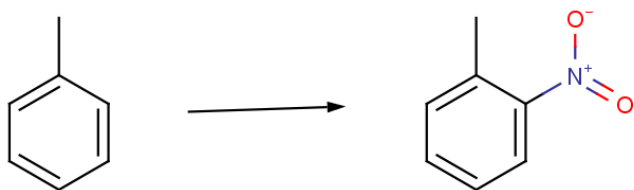
Exclude:

```
match(reactant(0), "[#6]C(=O)OC([#6])=O")  
or match(reactant(0), "[#6]-[#5,#12,#15,#16,#25,#26,#29,#33,  
#47,#50,#51,#80,#82,#83]")
```

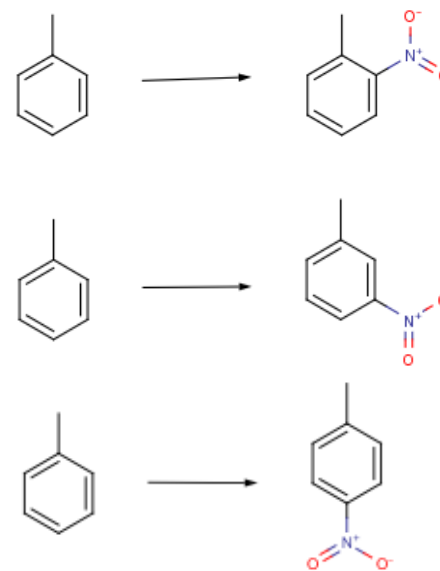

Useful Features: Ignore Rules



Useful Features: Ignore Rules

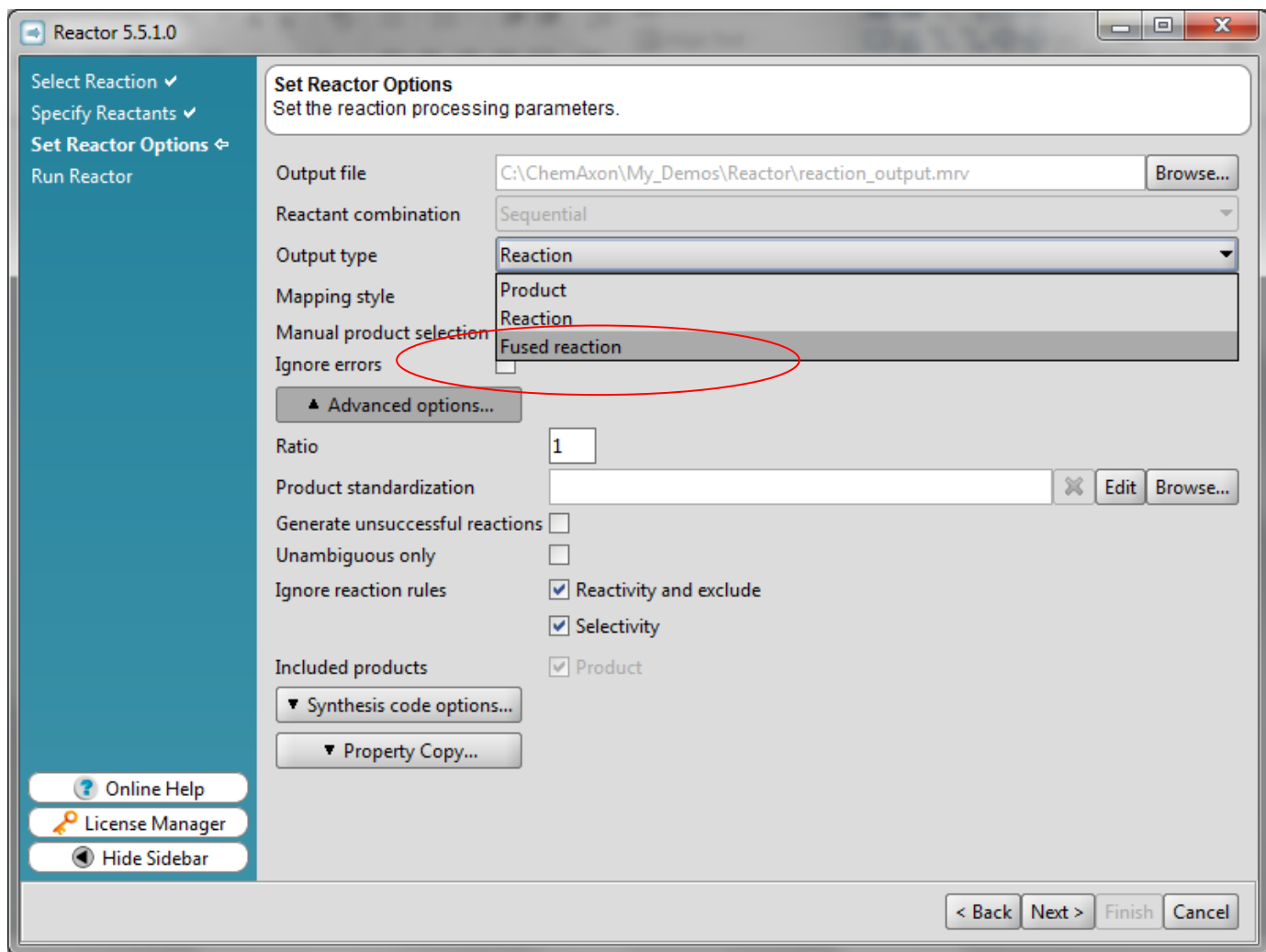


Keep selectivity rules

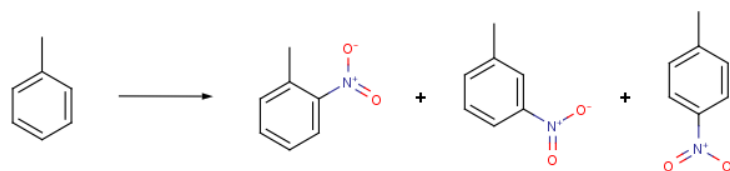
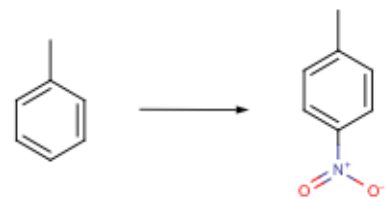
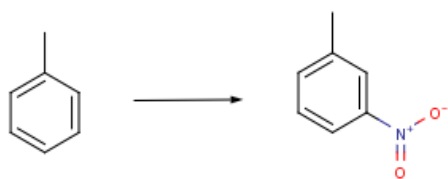


Ignore rules

Useful Features: Fused Reaction

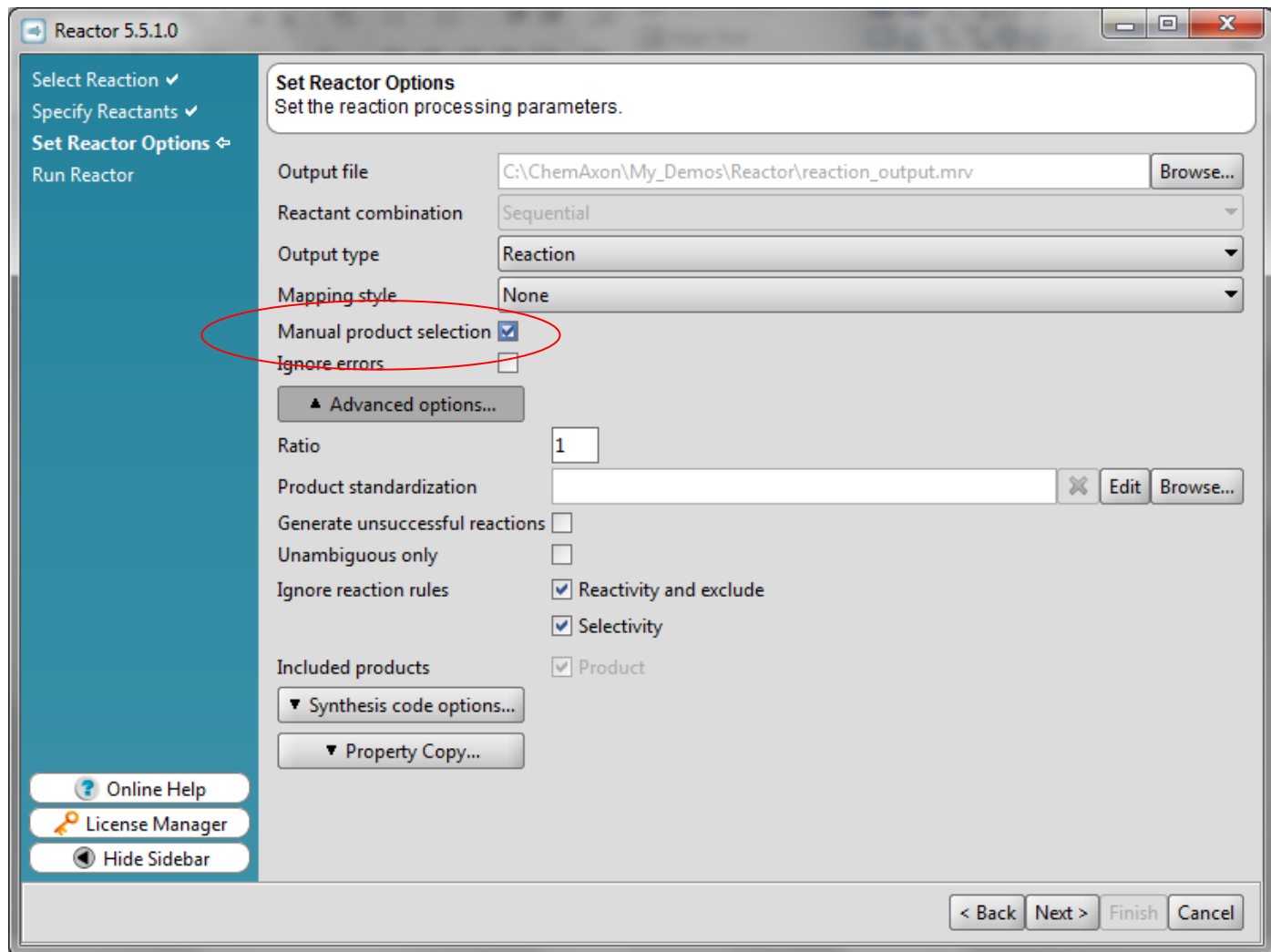


Useful Features: Fused Reaction



Fused Reaction

Useful Features: Manual Product Selection



Useful Features: Manual Product Selection

The screenshot displays the Reactor 5.5.1.0 software interface. On the left is a sidebar with menu items: "Select Reaction", "Specify Reactants", "Set Reactor Options", and "Run Reactor". At the bottom of the sidebar are buttons for "Online Help", "License Manager", and "Hide Sidebar". The main window shows a progress bar at 100% and status text: "0 reactions performed, 0 reactions exported", "elapsed time: 0h 0m 0s", and "estimated time left: 0h 0m 0s". A "Cancel" button is present. Below this is a "Toggle out unwanted results" option. The central area shows three reaction schemes, each starting with toluene (SMILES: Cc1ccccc1) and resulting in a different nitro-toluene isomer: 2-nitrotoluene (SMILES: Cc1cccc([N+](=O)[O-])c1), 3-nitrotoluene (SMILES: Cc1cccc([N+](=O)[O-])c1), and 4-nitrotoluene (SMILES: Cc1ccc([N+](=O)[O-])cc1). An "Accept" button is located at the bottom of the reaction list. At the bottom right of the window are navigation buttons: "< Back", "Next >", "Finish", and "Close".

Regioselectivity by manual product selection

Reactor in KNIME

The screenshot displays the KNIME software interface with a workflow titled "0: Multi-step synthesis". The workflow consists of the following nodes:

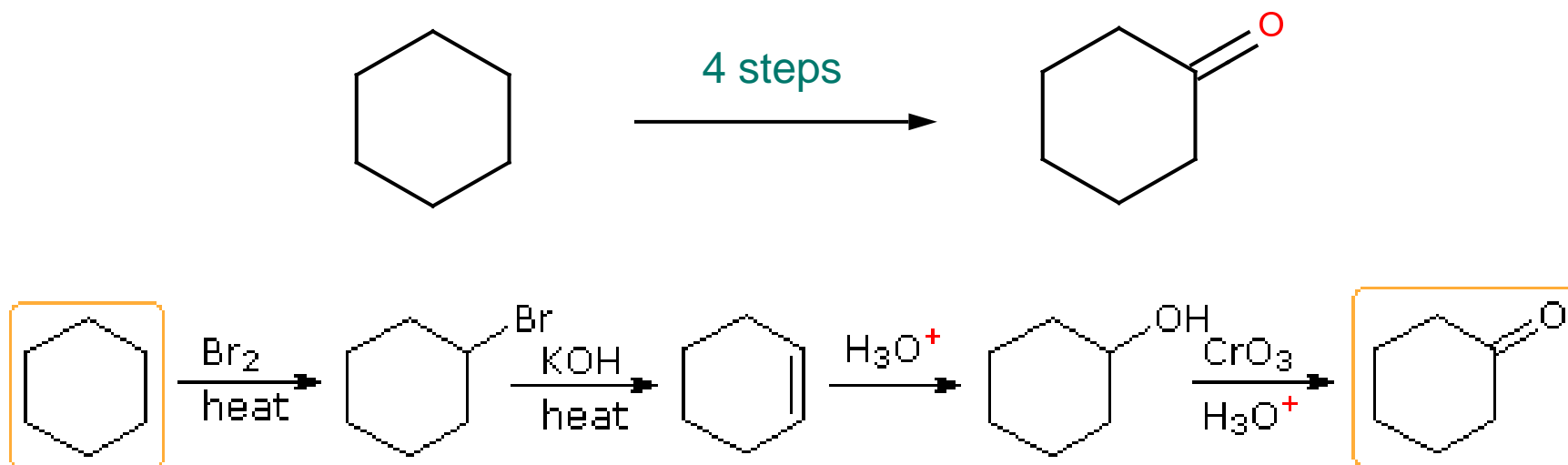
- Two **MolImporter** nodes on the left, with inputs for **Cyclohexane** and **Bromine**.
- A **Bi Reactor** node receiving input from both MolImporter nodes, with a parameter for **Halogenation**.
- A sequence of three **Reactor** nodes connected in a linear fashion:
 - The first **Reactor** node has a parameter for **Zaitsev elimination**.
 - The second **Reactor** node has a parameter for **Hydration**.
 - The third **Reactor** node has a parameter for **Oxidation of alcohol**.

The interface includes several panels:

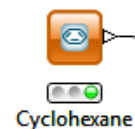
- Workflow Projects:** Shows "Multi-step synthesis" and "structure_checker".
- Favorite Nodes:** Lists "Personal favorite nodes" (Reactor, SDF Reader) and "Most frequently used nodes".
- Node Repository:** A tree view of available nodes including IO, Converter, Marvin, Calculator Plugins, JChem Base, JChem Cartridge, Standardizer, Structure Checker, Name to Structure, Screen, JKlustor, Reactor, Metabolizer, Fragmenter, Marvin, MarvinSketch, MarvinView, MarvinSpace, MolConverter, and Meta.
- Node Description:** A panel for viewing details of the selected node.
- Server Workflow Pro...:** A panel for connecting to a workflow server, showing "Workflow Server: publicserver.kn" and "Status: not con" with a "Connect" button.
- Outline:** A small thumbnail of the workflow.
- Console:** Displays the KNIME startup message:

```
*****  
*** Welcome to KNIME v2.4.1.0030379 - the Konstanz Information Miner ***  
*** Copyright, 2003 - 2011, Uni Konstanz and KNIME GmbH, Germany ***  
*****  
Log file is located at: C:\ChemAxon\knime_2.4.1\workspace\.metadata\knime\knime.log
```

Multi-step Reaction in KNIME



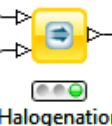
MolImporter



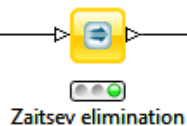
MolImporter



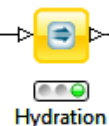
Bi Reactor



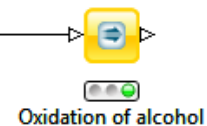
Reactor



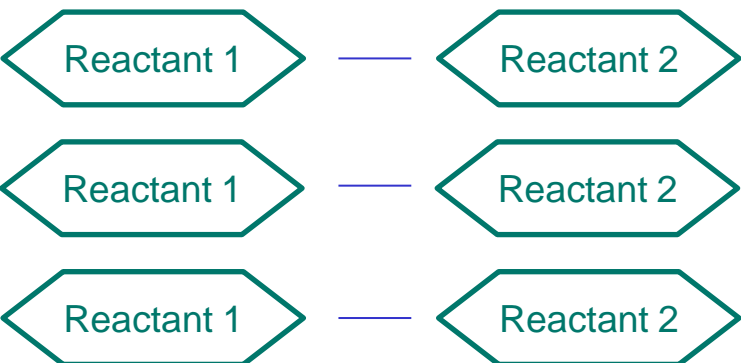
Reactor



Reactor

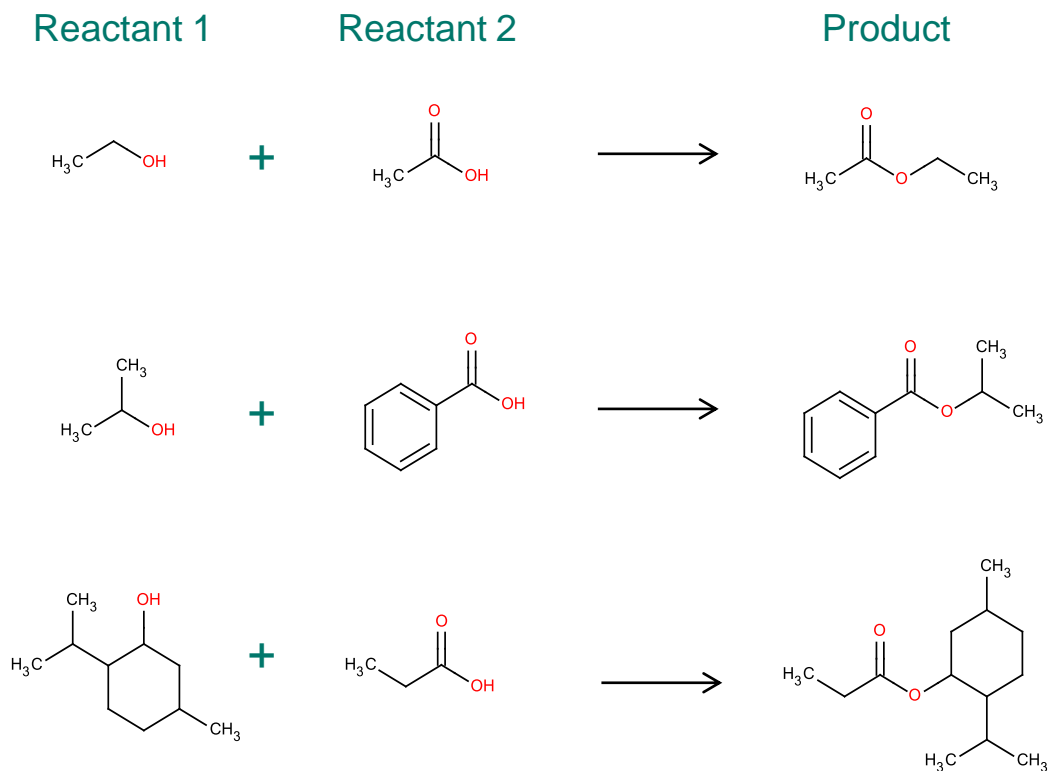


Sequential vs. Combinatorial Enumeration

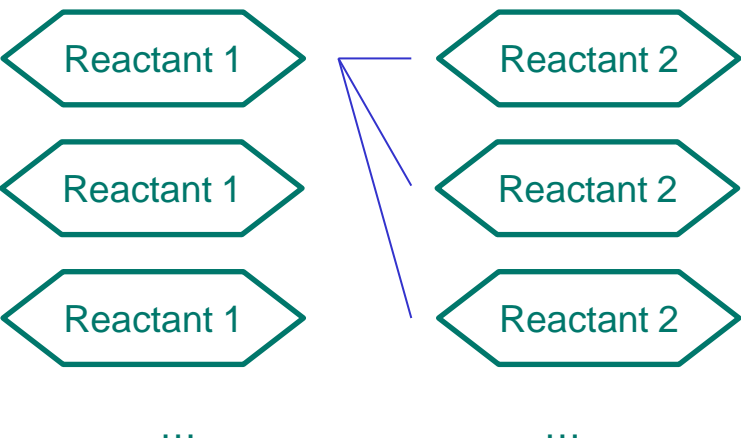


...

...



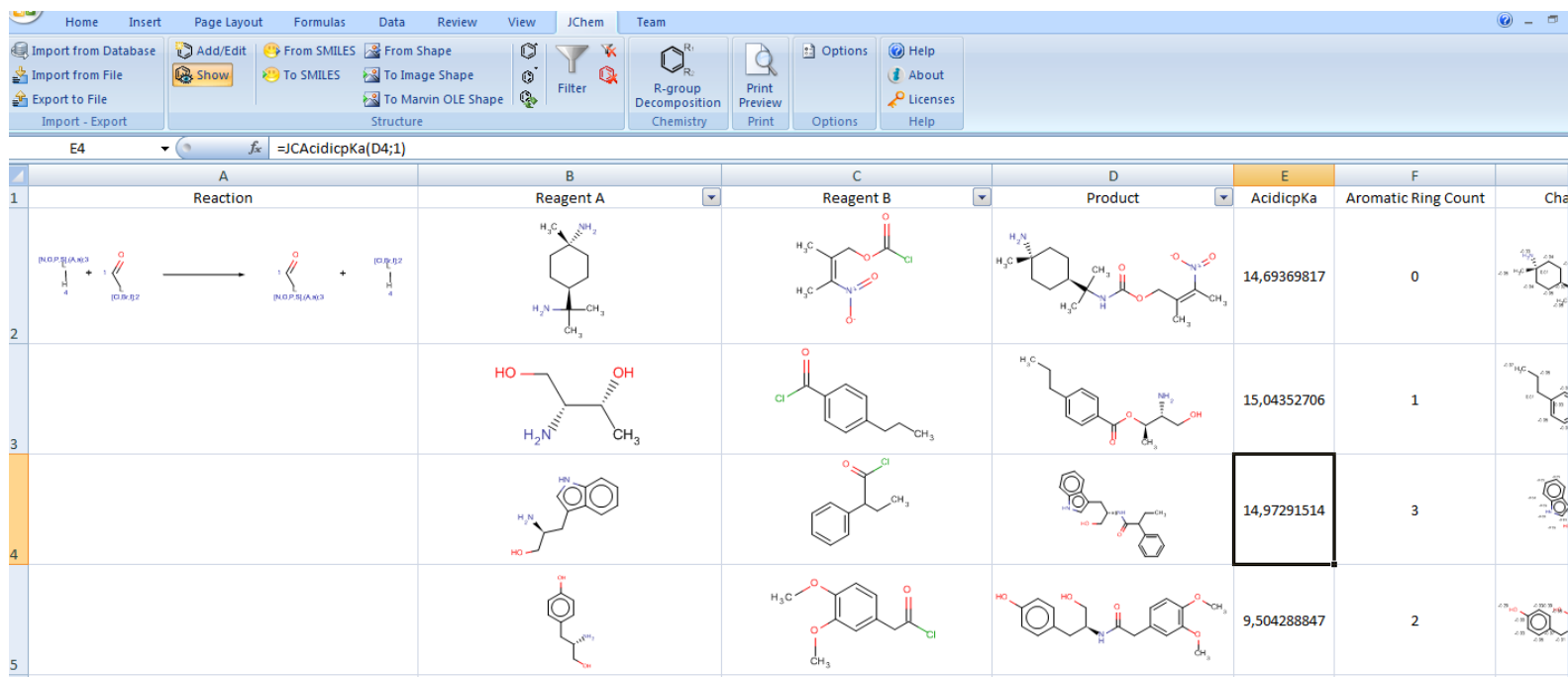
Sequential vs. Combinatorial Enumeration




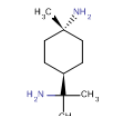
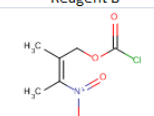
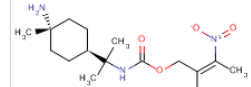

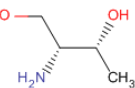
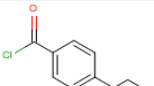
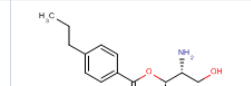

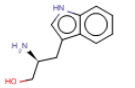
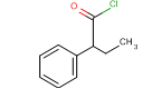
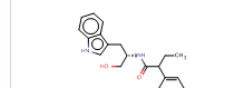

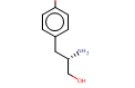
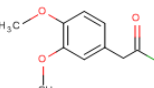
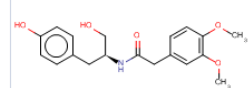

		Reactant 2		
Reactant 1				

Reactor in JChem for Excel

- Smoothly integrated into Microsoft Excel environment as functions
- Sequential and combinatorial enumeration (two reactants) available
- Direct post-processing of products



The screenshot shows the JChem for Excel interface with a table containing chemical reaction data. The table has columns for Reaction, Reagent A, Reagent B, Product, AcidicpKa, Aromatic Ring Count, and Ch. The data is as follows:

	A	B	C	D	E	F	Ch
	Reaction	Reagent A	Reagent B	Product	AcidicpKa	Aromatic Ring Count	Ch
1					14,69369817	0	
2					15,04352706	1	
3					14,97291514	3	
4					9,504288847	2	
5							

Synthesis Code

- Unique string for all enumerated products
- Synthesis definition information
 - IUPAC name
 - company registration code
 - location of reagent
 - ...
- Concatenated for multi-step reactions – synthesis path definition

▲ Synthesis code options...

Generate synthesis code

Field name in schema Name

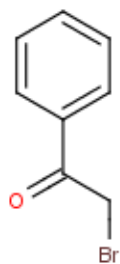
Field name in reactant 1 Compound id

Field name in reactant 2 BM-reactant1.sdf#Index
Cdid

Field name in Output Compound id

▼ Property Copy...

Formula
Location
Mol weight
New chemical terms
New chemical terms 2

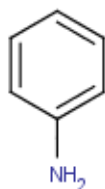


Cpd ID: CXN13367281

Location: R12/Sh10/A2

Name: 2-bromo-1-phenylethan-1-one

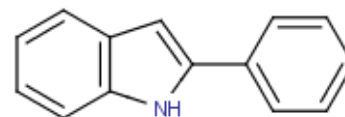
+



Cpd ID: CXN18734652

Location: R3/Sh3/A1

Name: aniline



+

HBr

→ Bischler-Mohrlau indole synthesis(CXN13367281, CXN18734652):1/1

Reactant Information

- Arbitrary fields can be copied from the input structure files to the output
 - ✓ solubility
 - ✓ toxicity
 - ✓ availability
 - ✓ price
 - ✓ microspecies information
 - ✓ ...
- Reaction databases stored with reactant information
- Reaction queries based on reactants

Manual product selection

Ignore errors

▼ Advanced options...

▼ Synthesis code options...

▲ Property Copy...

Copy from	Property name	Copy as
Reactant 1	IUPAC Name	IUPAC Name R1
Reactant 1	Major microspecies distr at pH 5.2	Major microspecies distr at pH 5.2...
Reactant 1		

Mol Weight

Formula

CdId

LogP

Chiral atoms

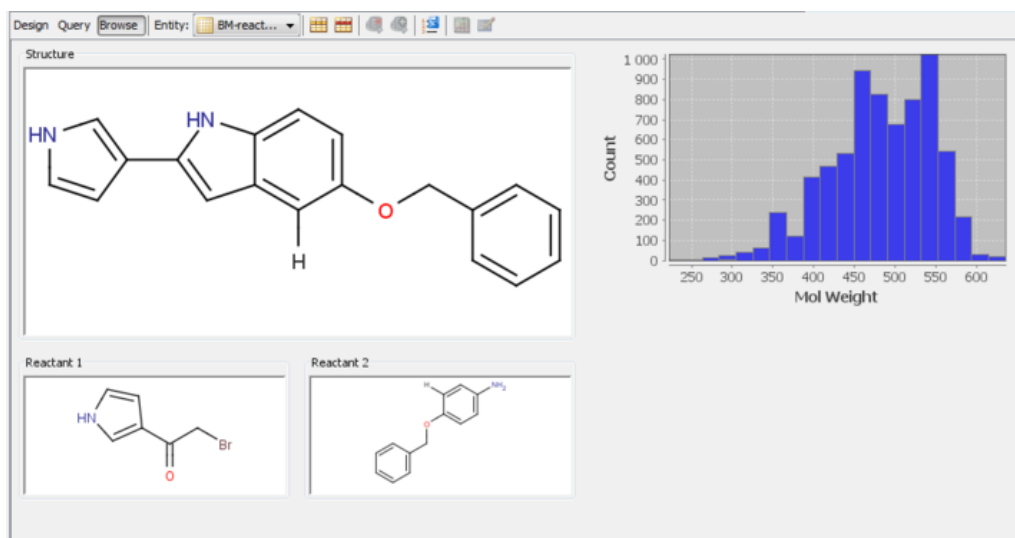
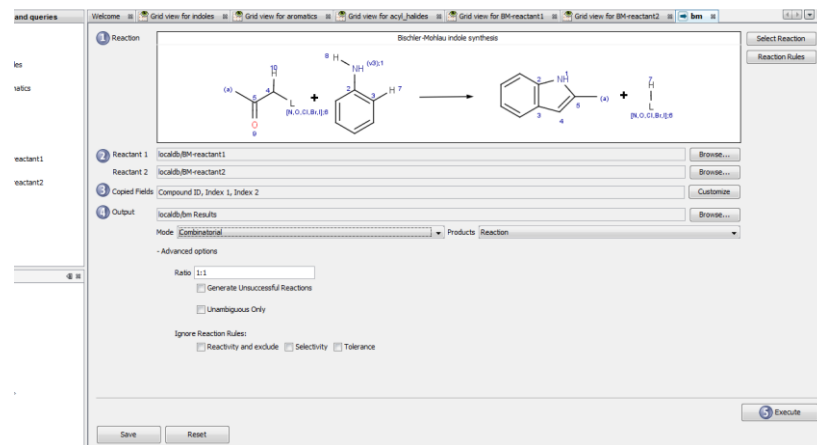
Major microspecies distr at pH 5.2

Strongest acidic pKa

Major microspecies at pH 5.2

Reactor in Instant JChem

- Instant JChem integration
- Easy direct access to chemical databases for Reactor
- Straightforward post-processing and visualization



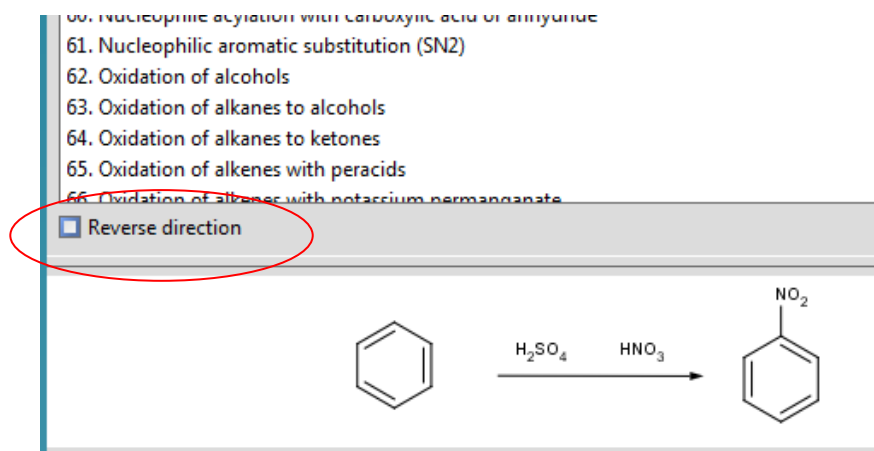
Other Useful Features

- Additional reaction information

Reference, preparation, etc.

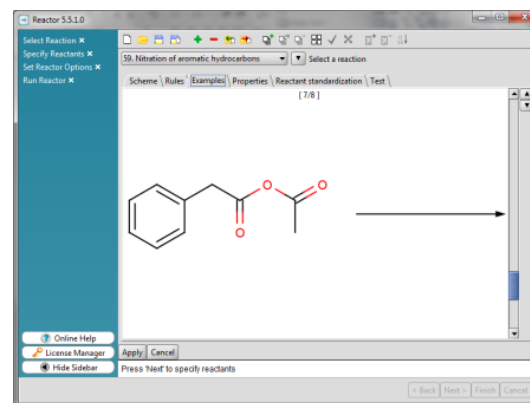
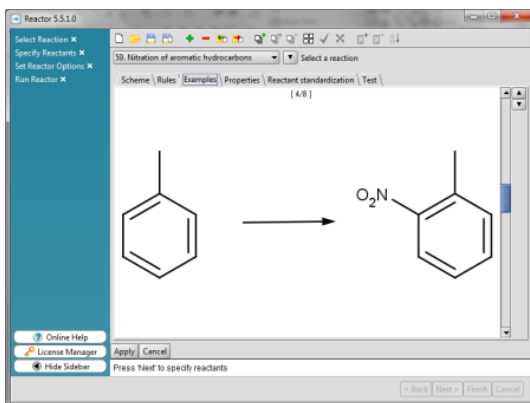
Property Name	Property Value
Reproducibility	2
Environmental Hazard	2
Safety	3
Reference	Comprehensive Practical Organic Chemistry: Preparation and Quantitative Analysis, V. K. Ahluwalia, R. Aggarwal, 2001, pg. no. 152; Organic chemistry, Marie Anne Fox, James K. Whitesell, 2004, Pg. no. 556; Advanced Organic Chemistry: Structure and mechanisms, Francis A. Carey, Richard J. Sundberg, 2007, Pg. no. 793; The nitro group in organic synthesis, Noboru Ono, 2001, Pa. no. 4.
Classification	L0
Author	A. Tomin Madhavi.Ch
Copyright	ChemAxon
Notes	Nitration of aromatic nuclei is the most basic reactions in organic synthesis and is widely used in the pharmaceutical and chemical industries. However, this reaction is notorious for several reasons, such as safety concerns, over-nitration, formation of regioisomers, and generation of impurities due to oxidation.
Preparation	Method 1: Aromatic compound was treated with a metal nitrate and p-TSA in acetone either at room temperature or at reflux to afford o-nitrophenol as the exclusive product in satisfactory to good yields. Method 2: Ortho-nitration: A solution of 5 g (25.2 mmol) of the nitric acid salt of 4-bromo-2,2-dimethylaniline in 40 mL dichloromethane was slowly added to 20 mL concentrated sulfuric acid while maintaining batch temperature at 0 ± 5 C. After
Synthesis Code	NitrAr

- Reverse reaction

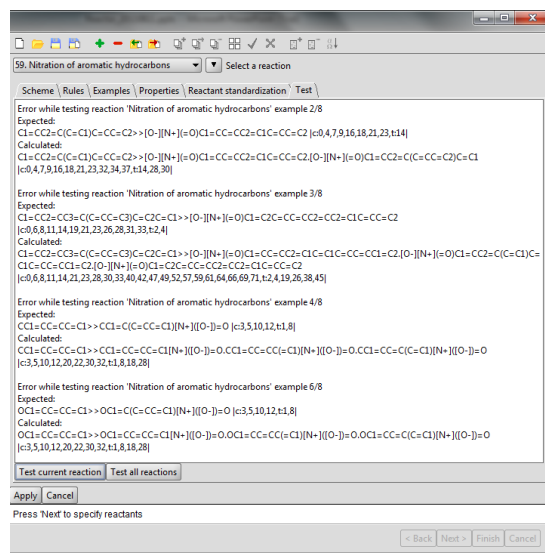


Other Useful Features

- Examples for each reaction



- Test modified reaction



```
59. Nitration of aromatic hydrocarbons
Scheme | Rules | Examples | Properties | Reactant standardization | Test
(4/8)

Error while testing reaction 'Nitration of aromatic hydrocarbons' example 2/8
Expected:
C1=CC=C(C=C1)C=C=C2>>[O-][N+](=O)C1=CC=CC=C1C=C=C2 [c:0,4,7,9,16,18,21,23,t14]
Calculated:
C1=CC=C(C=C1)C=C=C2>>[O-][N+](=O)C1=CC=CC=C1C=C=C2 [c:0,4,7,9,16,18,21,23,t14,28,30]

Error while testing reaction 'Nitration of aromatic hydrocarbons' example 3/8
Expected:
C1=CC=C(C=C1)C=C=C3[C=C=C=C1]>>[O-][N+](=O)C1=CC=CC=C1C=C=C2 [c:0,6,8,11,14,19,21,23,26,28,31,33,t2,4]
Calculated:
C1=CC=C(C=C1)C=C=C3[C=C=C=C1]>>[O-][N+](=O)C1=CC=CC=C1C=C=C2 [c:0,6,8,11,14,21,23,28,30,33,40,42,47,49,52,57,59,61,64,66,69,71,t2,4,19,26,38,45]

Error while testing reaction 'Nitration of aromatic hydrocarbons' example 4/8
Expected:
CC1=CC=C(C=C1)N>>[O-][N+](=O)C1=CC=C(C=C1)N [c:3,5,10,12,t1,8]
Calculated:
CC1=CC=C(C=C1)N>>[O-][N+](=O)C1=CC=C(C=C1)N [c:3,5,10,12,t1,8,18,28]

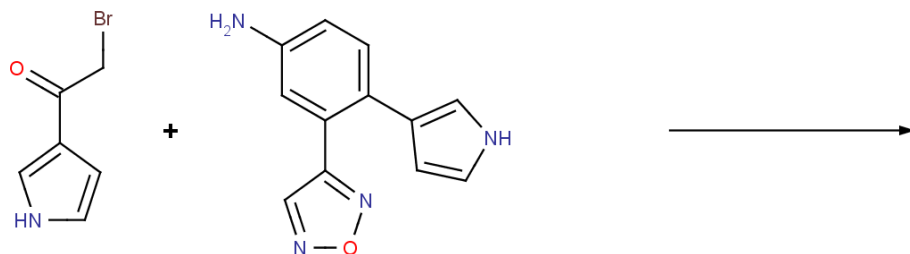
Error while testing reaction 'Nitration of aromatic hydrocarbons' example 6/8
Expected:
OC1=CC=C(C=C1)N>>[O-][N+](=O)C1=CC=C(C=C1)N [c:3,5,10,12,t1,8]
Calculated:
OC1=CC=C(C=C1)N>>[O-][N+](=O)C1=CC=C(C=C1)N [c:3,5,10,12,20,22,30,32,t1,8,18,28]

Test current reaction Test all reactions
Apply Cancel
Press Next to specify reactants
```

Other Useful Features

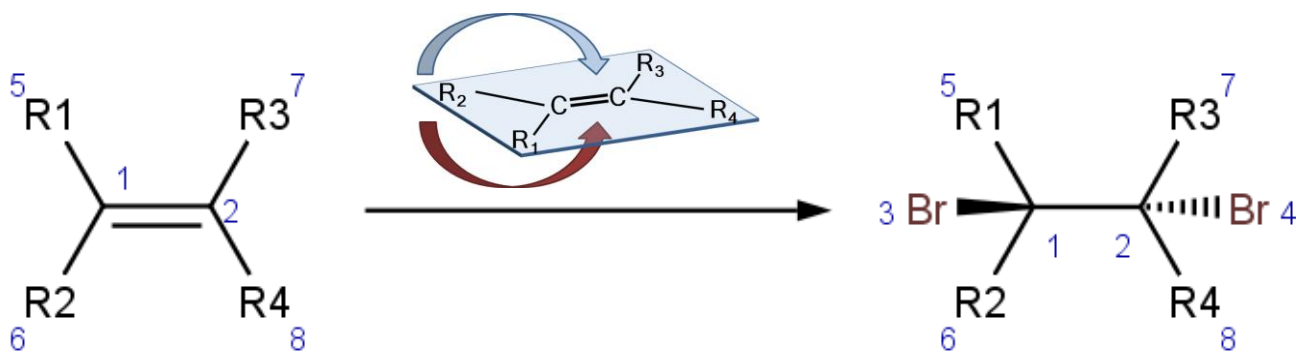
- Unsuccessful reactions

include reactions in the output that yield no products



- Prochiral reactions

syn/anti addition support on double bonds



Future plans

- Extend systematic reaction library
 - *To cover most possible reactions in organic chemistry*
- Advanced synthesis code generation
 - *Combining field copy with synthesis code to have customizable identifiers for products and synthesis paths*
- Improved prochiral reaction support
- Improved multiple product list handling in JChem for Excel

Thank you



Zsolt Mohácsi



György Pirok



Anna Tomin



Nóra Máté



Attila Szabó



Imre Barna



István Rábel