VIRTUAL CHEMIST Suite 2018 Tutorial

Virtual Chemist – FINDERS, REACT CONSTRUCTS and ACE

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I. Running VIRTUAL CHEMIST in Windows with the GUI

Opening the GUI

In this example, we will show how to use the in silico combinatorial chemistry programs FINDERS and REACT to build a virtual library of catalysts based a chemical reaction. This library of potential catalysts will then be used by ACE to evaluate their stereoinductive power.

Under windows, the graphical user interface (GUI) can be started by double clicking on the `Front-end.jar` file in the `fitted_exe` folder.
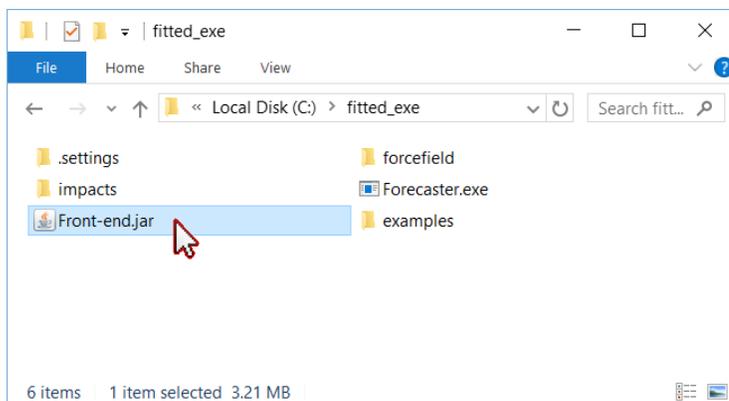
The GUI will open with Java and a list of workflows will be available.

Before starting any calcuations, the working directory must be specified. For this purpose, click on Browse to set the working directory. . You will be prompted to navigate to the desired folder. will be using `C:\Users\Nicolas Moitessier\Documents\test_Vir tualChemist\Tutorial`

All the necessary files will be written there. The molecules can be drawn using the Forecaster sketcher and the molecule/reaction files will be written there as well. If you are planning to run calculation from an external library (e.g., a catalog of chemicals, a file from the ZINC database,…), a copy should be in this directory.
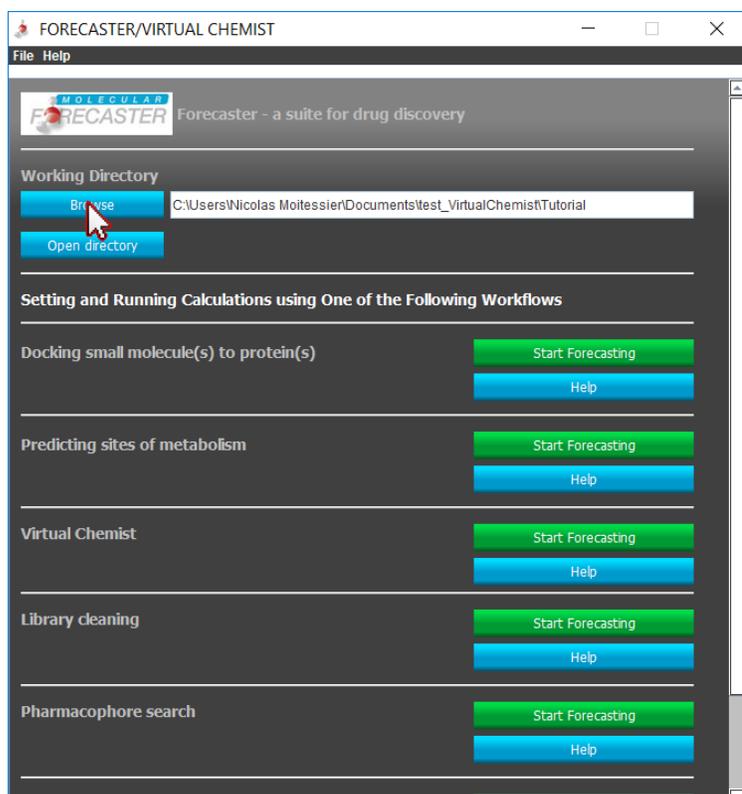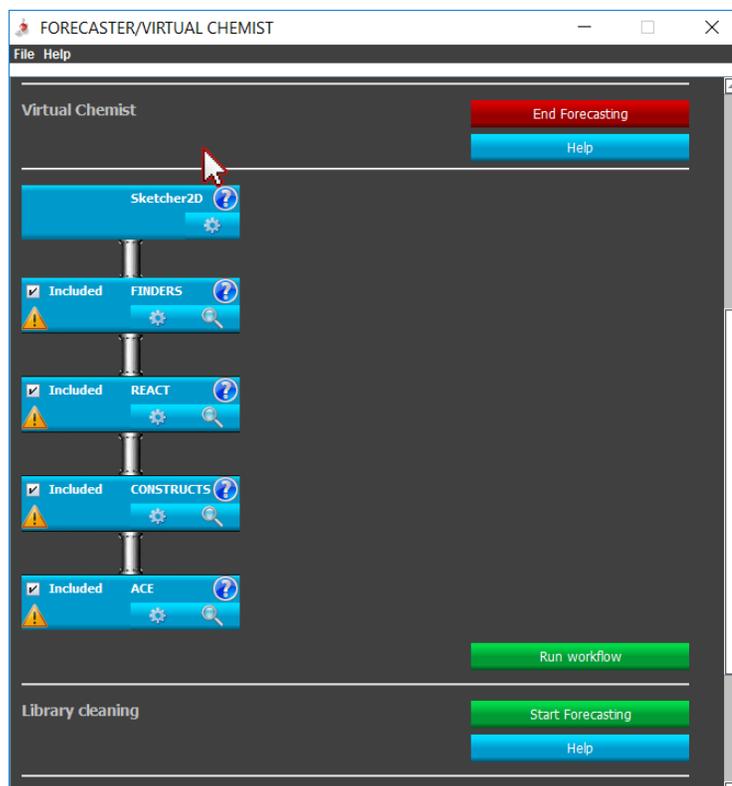
When this is done, clicking the **Start Forecasting** button will expand the virtual chemist workflow. A workflow with 5 boxes will appear.

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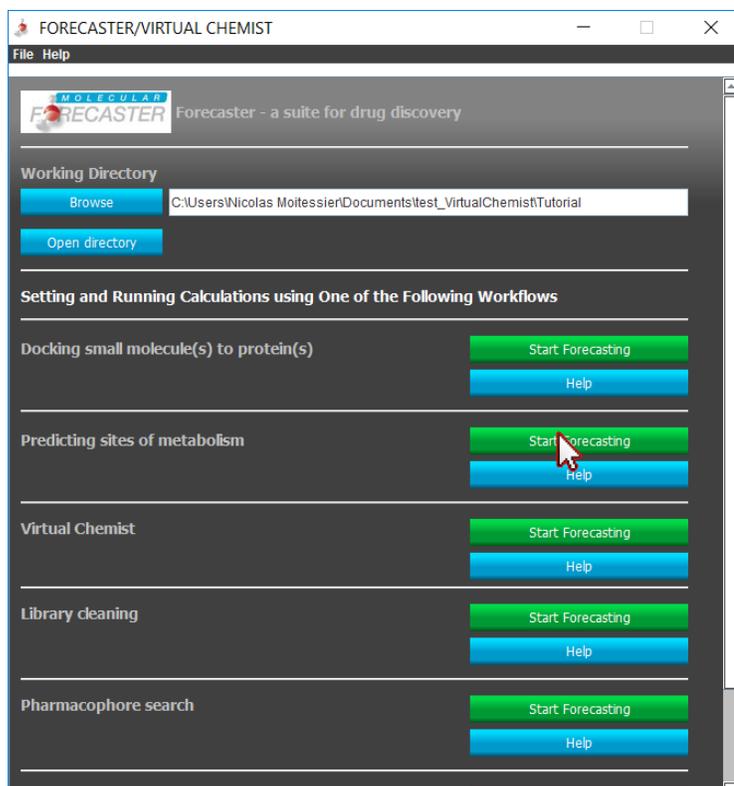
SKETCHER 2D: Drawing the chemical reaction

The first step requires to define the chemical reaction using the Sketcher2D. Clicking on the gear icon will open the sketcher2D.

The drawing the reaction should be done following some rules to ensure the programs will encode them properly.

The reaction is drawn from left to right with the reactants and the reactant(s) and product(s) separated by an arrow. The simplest substructure needs to be drawn and points of diversity encoded with the R, G or Ar groups (for definition click on the "Help & tricks" menu). In our example, Cbz-Proline is esterified with various alcohols. For more information about these features, see tutorial on FINDERS and REACT.
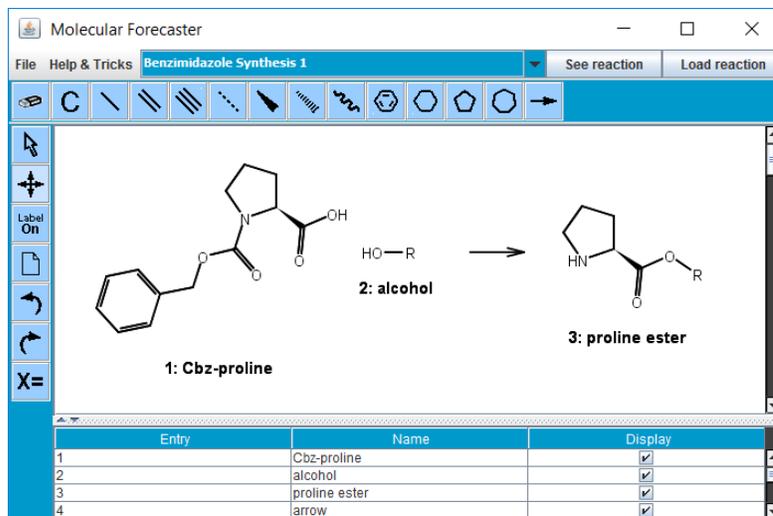
Once the reaction scheme is complete, the reaction can be saved using the **File**, **Save reaction (rxn)** option from the sketcher and providing the `esterification.rxn` filename.

Next, using the same sketcher (page must be cleaned using the blank page icon on the left), a small library of alcohols is built and saved using the **File**, **Save structure (sdf)** option and providing alcohols.sdf as a filename.

As Z-matrix cannot be built for methanol for adding hydrogens, it will be removed from the list. In this case, one can manually add an hydrogen to the scheme to keep it.
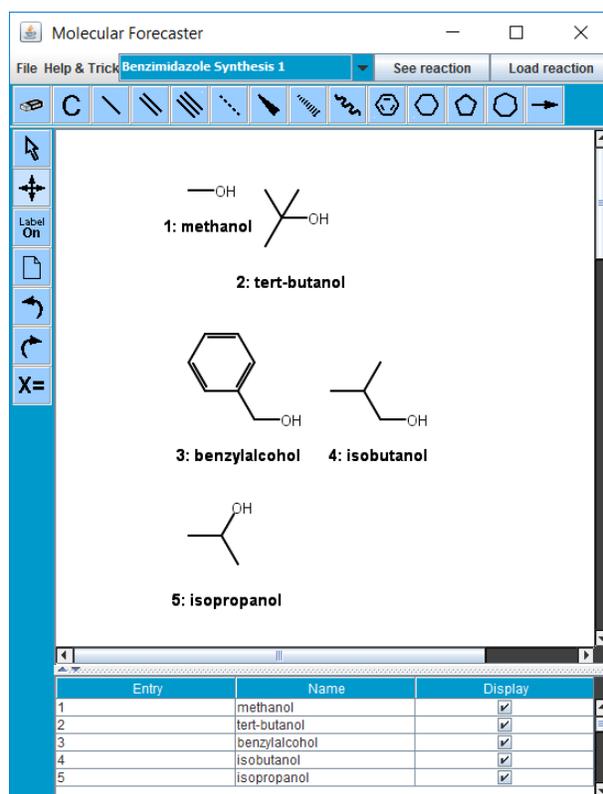
FINDERS: Searching libraries for compatible chemicals

Once the reaction scheme is defined, clicking on the gear icon of the FINDERS box will open the parameters section.

The **Catalog to be searched** should be "`alcohols.sdf`", the **reaction file** "From working directory", and the **Reaction Scheme** to point to "`esterification.rxn`". For the other boxes, see tutorial on FINDERS and REACT.

Once all the parameters are set, the keyword file needs to be written by clicking the **Write keyword file** button. Clicking the **Exit** button will close the FINDERS parameters section and return to the main workflow. A green check should now appear in the FINDERS box. The program will not run until the complete workflow is ready.
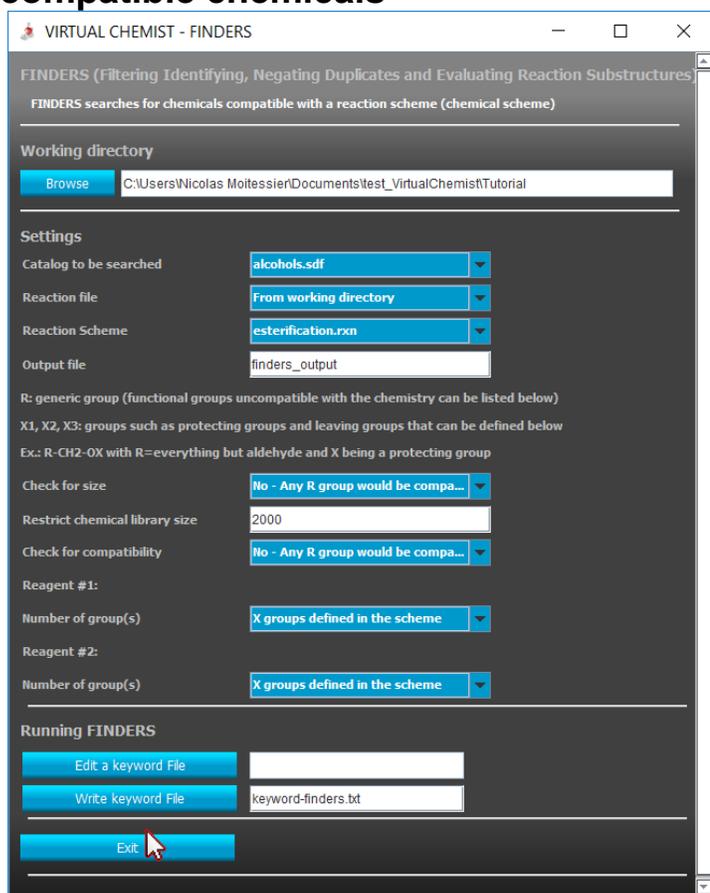
REACT: In silico combinatorial chemistry

Once the FINDERS settings are set, clicking on the gear icon of the REACT box will open the parameters section. The **Source of library files and reaction file** should be "From FINDERS box above". The **output file** can be filled with anything, "react-output" is suggested.
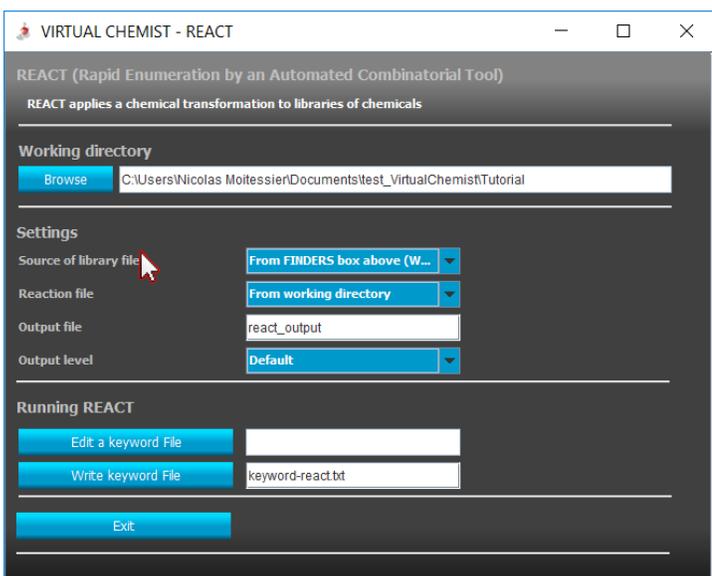
Once all the parameters are set, the keyword file needs to be written by clicking the **Write keyword file** button. Clicking the **Exit** button will close the REACT parameters section and return to the main workflow. A green check should now appear in the REACT box. The program will not run until the complete workflow is ready.

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CONSTRUCTS: **Building transition state structures**

Once the REACT settings are set, clicking on the gear icon of the CONSTRUCTS box will open the parameters section. The **Source of ligand structures** should be "From REACT box above". The **output file** can be filled with anything, "constructs-output" is suggested. The "Organocatalzed Diels Alder, Exo" reaction is chosen. A number of cores for the calculations can be changed. Here calculations are performed on a dual-core. A Library of substrates and reagents (dienes and dienophiles in a Diels Alder) can be given. With the preset reaction used here, cyclopentadiene is used and only reagents can be given.

The sketcher is used to draw cinnamaldehyde and saved as dienophile.sdf

The keyword file will next be written by clicking the **Write keyword file** button. Clicking the **Exit** button will close the CONSTRUCTS parameters section and return to the main workflow. A green check should now appear in the CONSTRUCTS box. The program will not run until the complete workflow is ready.

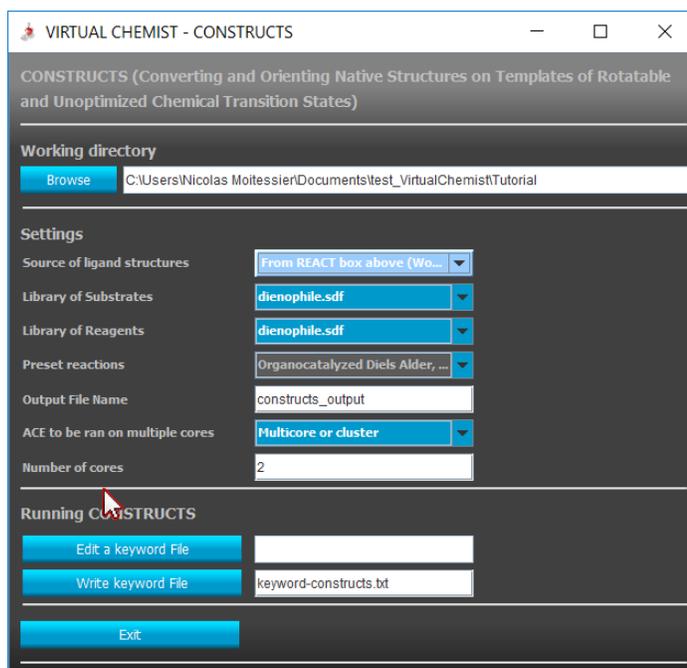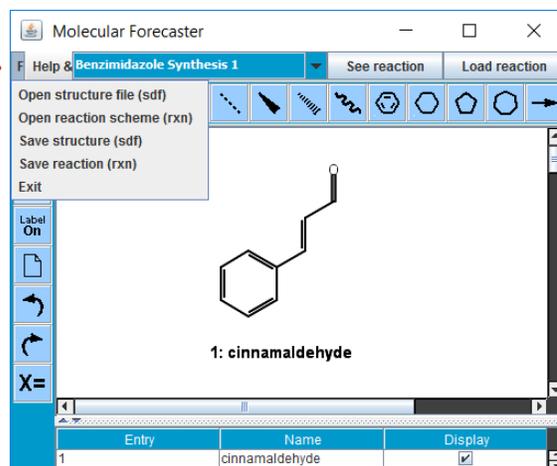## ACE: Optimizing TS structures and computing stereoselectivity

Once the CONSTRUCTS settings are set, clicking on the gear icon of the ACE box will open the parameters section. The **Source of library files and reaction file** should be "From CONSTRUCTS box above". The **output file** can be filled with anything, "ace-output" is suggested. As it is a preset reaction, the other boxes are filled. For new reaction, contact nicolas.moitessier@mcgill.ca for assistance.
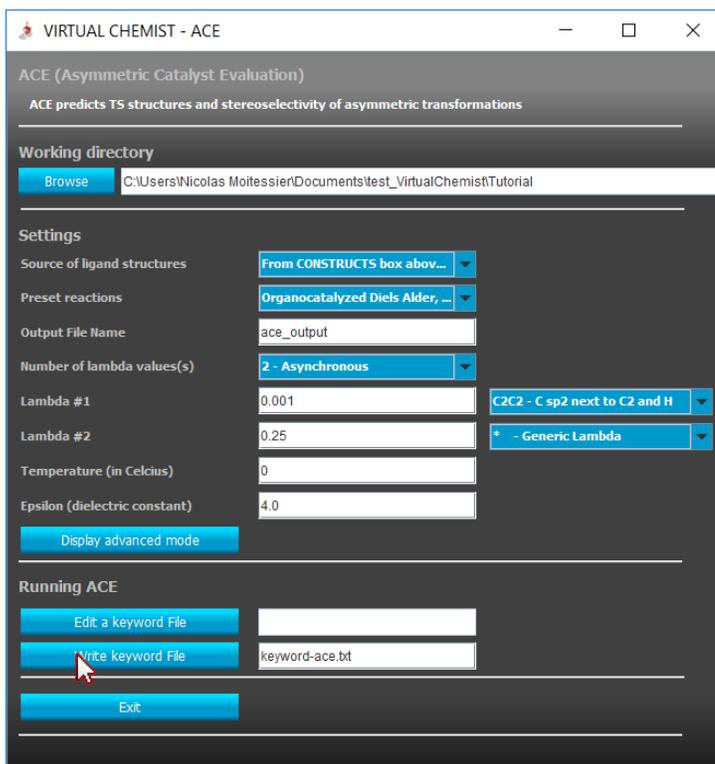
The keyword file will next be written by clicking the **Write keyword file** button. Clicking the **Exit** button will close the ACE parameters section and return to the main workflow. A green check should now appear in the CONSTRUCTS box. The program will not run until the complete workflow is ready.

Workflow: Running the virtual chemist

Once all the included steps are ready, the workflow can be executed by clicking the **Run workflow** button. The programs run in a terminal (e.g. dos) and once the complete workflow is complete, the terminal window will close.
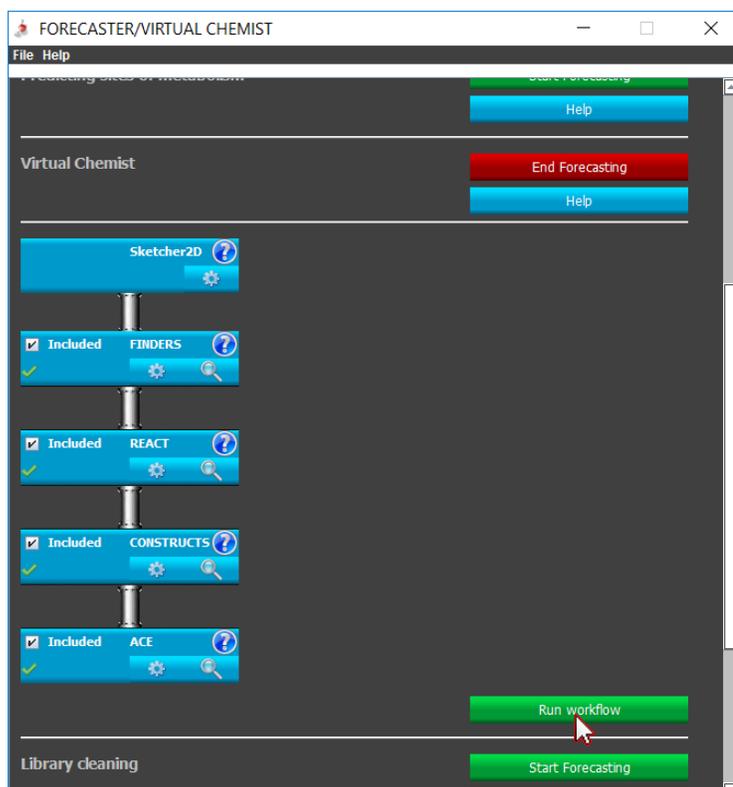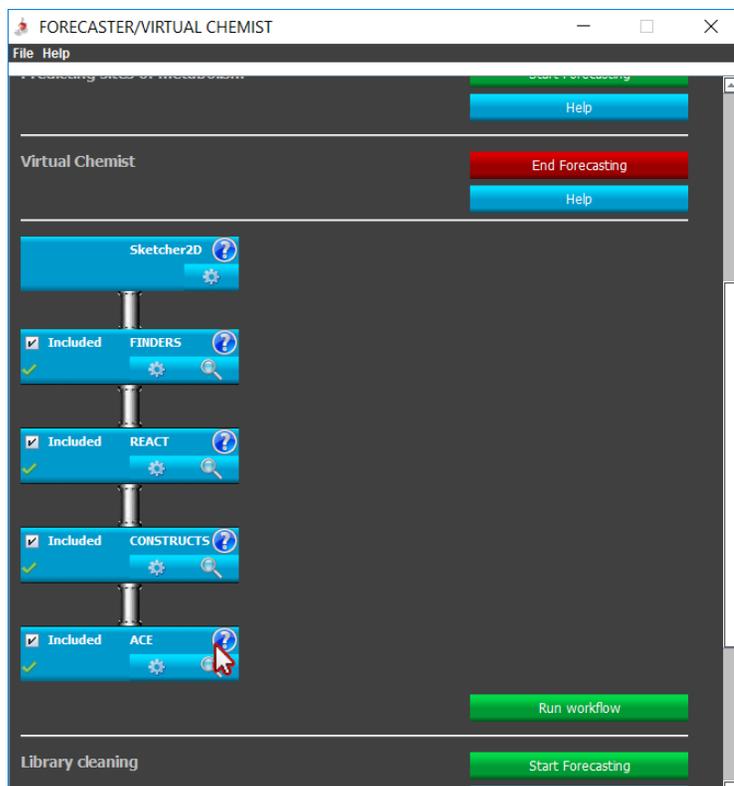
II. Analyzing the results

Once the workflow is complete, multiple files will be created with the names assigned in each parameter box. For instance, the files generated with REACT are `react-output.out` (output file) and `react-output.sdf` (sdf file with the new library). The `react-output.sdf` file contains the entire library with the 2D structure of the various catalysts. It can be visualized in your favorite graphical program. Alternatively, the output library can be visualized by clicking the magnifier icon in the REACT box. Clicking the **2D structure** button will open the library within the sketcher while the **Text file** button will open the library as a text file.

```
C:\Users\Nicolas Moitessier\workspace\CompletePackage>"C:\Users\Nicolas Moitessie
.exe keyword-finders.txt "C:\Users\Nicolas Moitessier\Documents\test_VirtualChemi
er\workspace\CompletePackage"
|-----------------------------------------------------------------|
|                 _____ _____ _   _ _____  _____ _____  _____   |
|                |  _____|_   _| \ | |  __ \|  ____|  __ \|  ___|  |
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|                |_|     |_____|_| \_|_____/|_____|_|  _____/  |
|                                                                 |
|        Filtering Identifying, Negating Duplicates and Evaluating|
|                      Reaction Substructures                     |
|-----------------------------------------------------------------|
|                  J. Pottel, N. Moitessier                       |
|            McGill University, Montreal, Quebec, Canada           |
|    Copyright 2014                                               |
|    Forecaster Build: XXXX                                        |
|-----------------------------------------------------------------|
| FINDERS prefilters the catalog with a general template          |
| CREATE generates all possible reactants from a reaction scheme then
| FINDERS searches for chemicals in a library (e.g., prefiltered catalog)
| CONVERT adds hydrogens                                          |
| SMART adds descriptors (applies to R/G groups only)             |
| REDUCE filters by descriptors                                   |
| DIVERSE removes the duplicates (e.g., Ser and Ser.HCl)          |
|-----------------------------------------------------------------|
| 1. FINDERS prefilters the library with a general template       |
|    Processing reactant(s) #1 with FINDERS...................     |
```

The ACE results can be found in ace_output_1-results.txt (calculations in the first core) and ace_output_2-results.txt (calculations in the second core) and in the mol2 files.

The platform can also be used. Clicking on the magnifying glass will open a new window.

Clicking on **View Results** or **View in 3D** will open the result file in which the predicted stereoselectivities are given or the 3D transition state structures respectively.

In the current version, if multiple jobs of ACE are run, multiple files will be created and only the first one will be open.