VIRTUAL CHEMIST Suite 2018

FINDERS, REACT2D, CONSTRUCTS AND ACE

Tutorial

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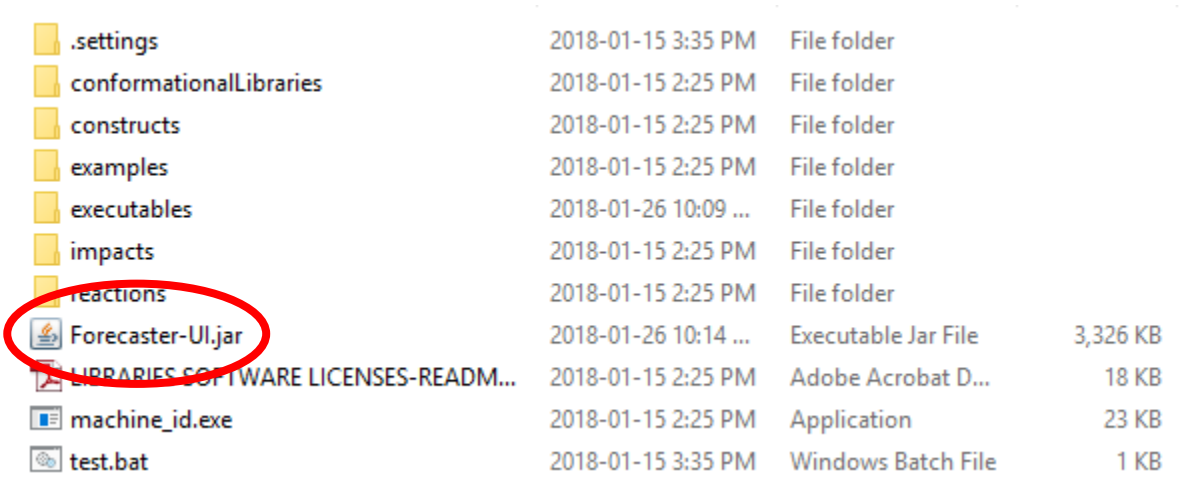
I. Running FORECASTER with the User Interface

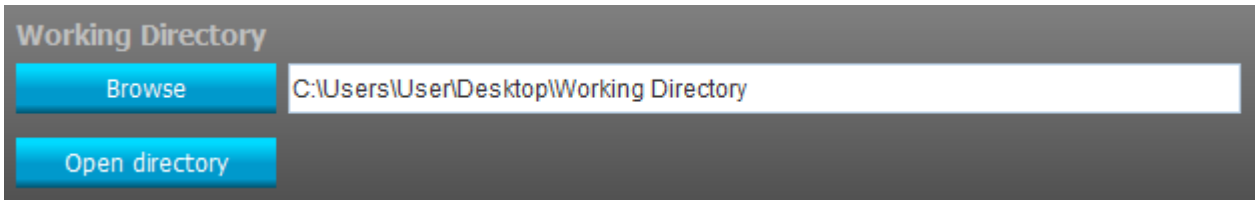
The user interface (UI) can be started by double clicking on the `Forecaster-UI.jar` file in the `Forecaster` folder. This will open the main window.

Under Linux and Mac OSX, it is recommended to launch it from a terminal window by typing the command below. Make sure that you are located in the folder where this jar file is.

Forecaster@Linux/Forecaster:~$ java -jar Forecaster-UI.jar



The first step is to set the working directory. Click **Browse**, under **Working Directory**. You will be prompted to navigate to the folder where you will save various files while working with Forecaster.



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.

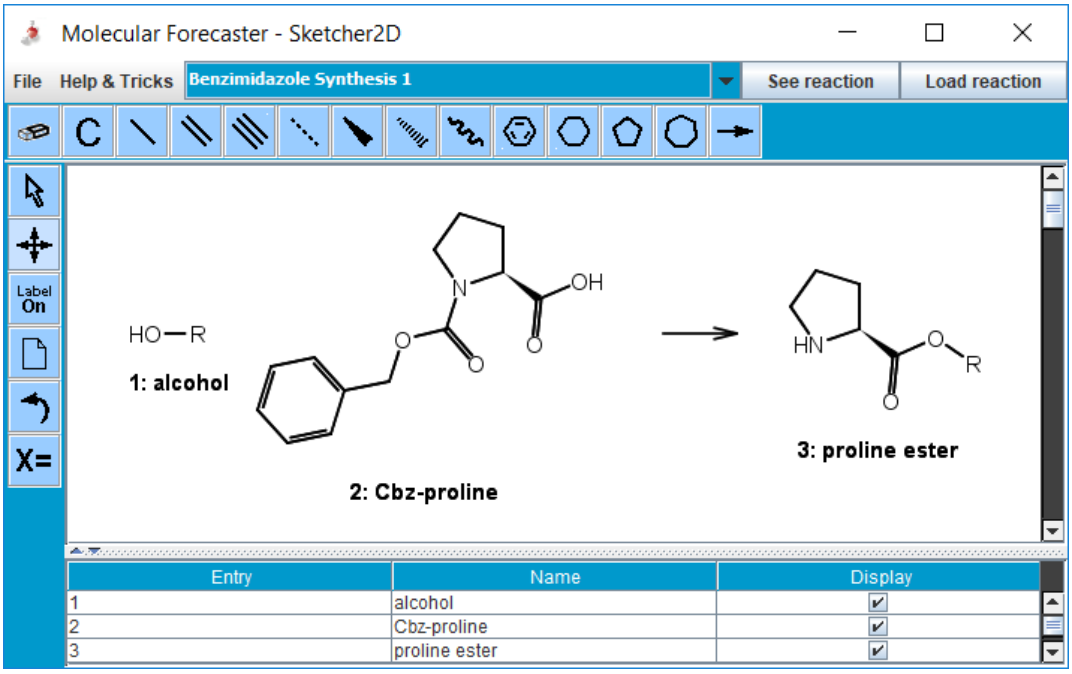
When this is done, click the **Start Forecasting** button to expand the virtual chemist workflow.

SKETCHER 2D:Drawing the chemical reaction

Using the sketcher, you will now need to define the reaction. Click on the gear icon to open sketcher2D. Dozens of predefined reactions can also be used as described throughout this tutorial.

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

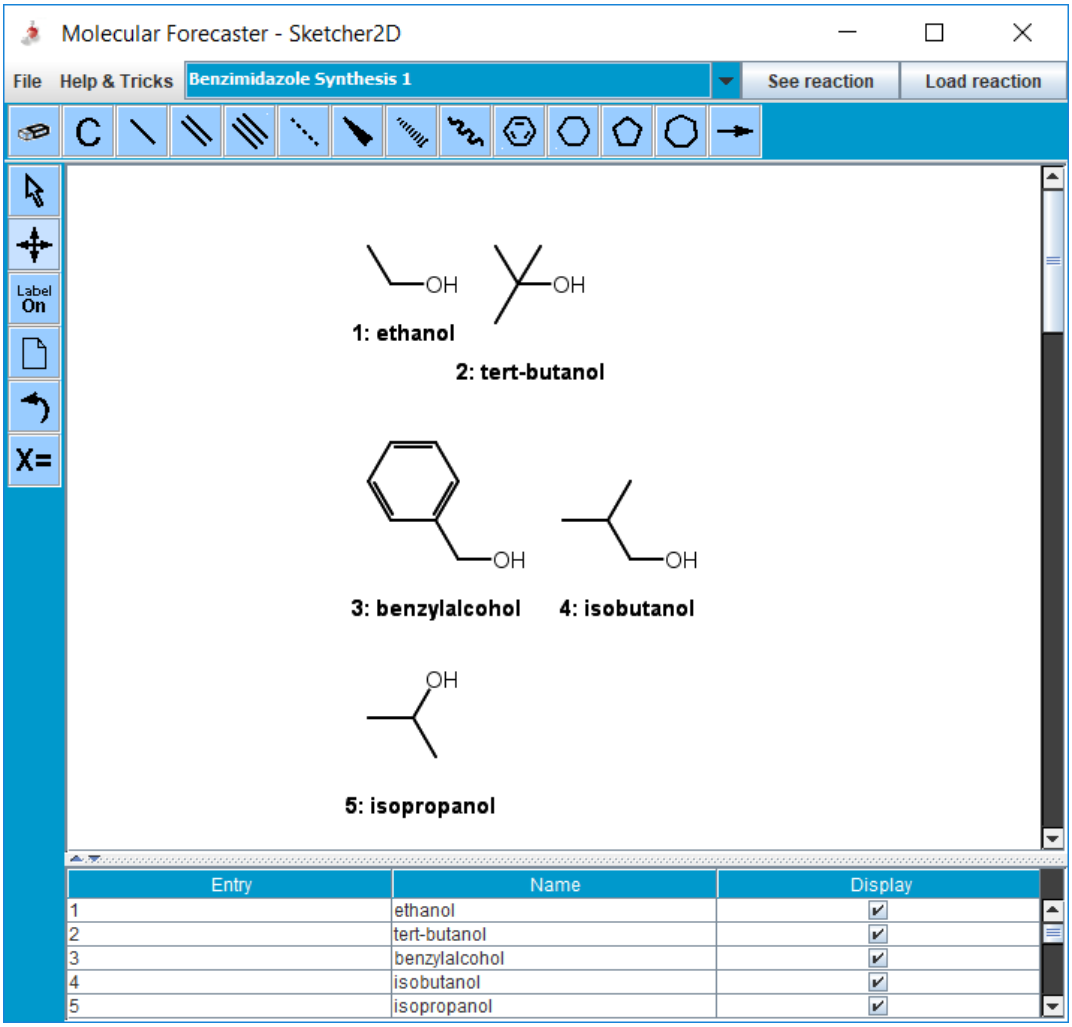
The reaction is drawn from left to right with the reactant(s) and product(s) separated by an arrow. The simplest substructure needs to be drawn and points of diversity encoded with the R, G or Ar groups (for definition click on the “Help & tricks” menu). In our example, Cbz-Proline is esterified with 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.

Alternatively, you may load one of the ca. 60 reactions already listed using the drop-down menu and **Load reaction**.

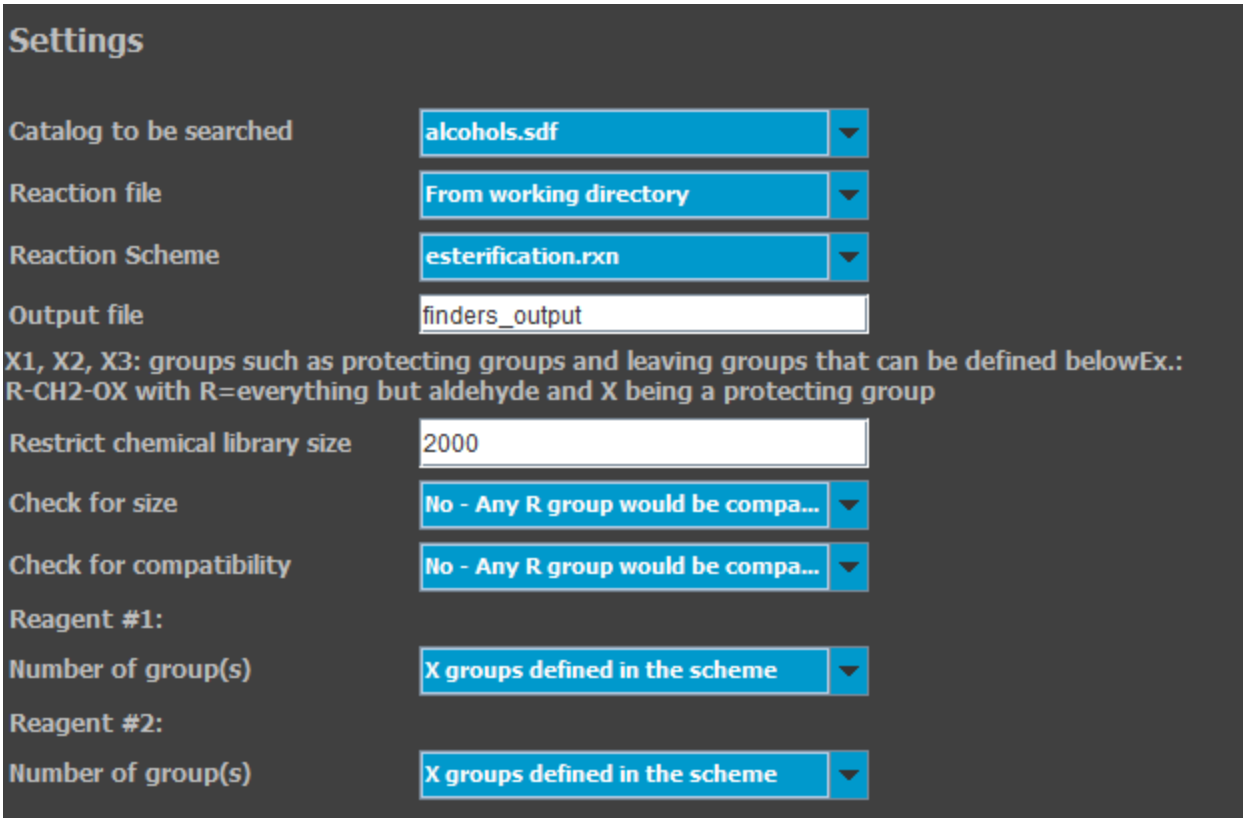
Next, using the same sketcher (page must be cleaned using the blank page icon on the left), a small library of alcohols is built and saved using the **File**, **Save structure (sdf)** option and providing alcohols.sdf as a filename. Alternatively, large libraries of chemicals may be used (sdf format).



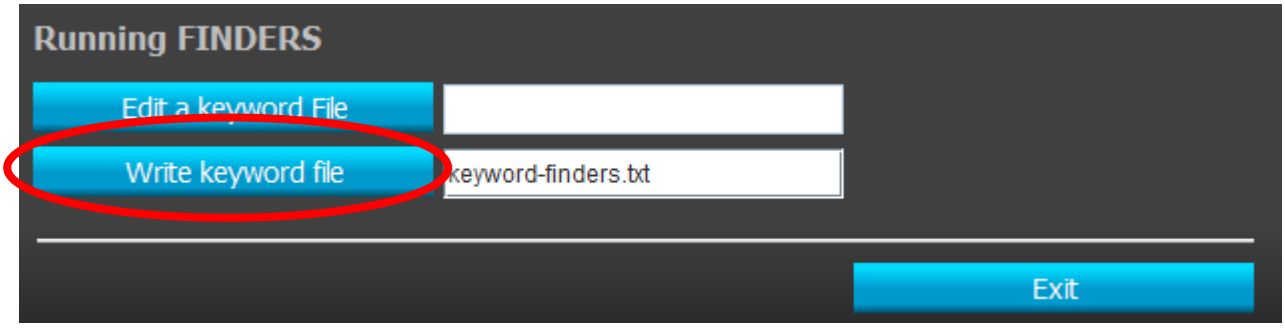
FINDERS: Searching libraries for compatible chemicals

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`" (or any library you may have downloaded), the **reaction file** "From working directory", and the **Reaction Scheme** to "`esterification.rxn`". Alternatively, you may select a reaction from the preset library rather than from the working directory.



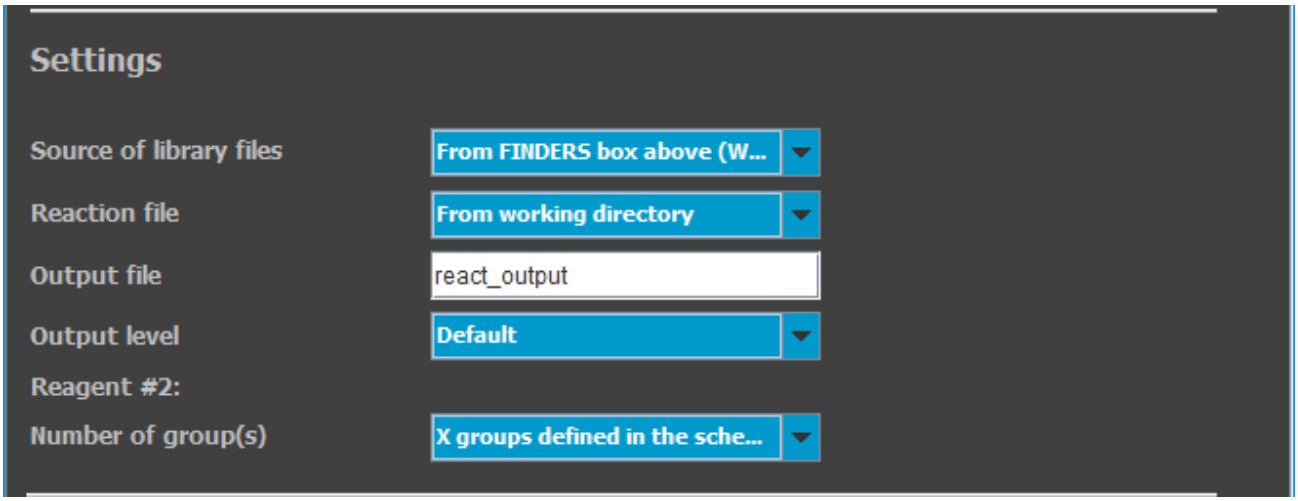
Once all the parameters are set, the keyword file needs to be written by clicking the **Write keyword file** button. Clicking the **Exit** button will close the FINDERS parameters section and return to the main workflow.



A green check should now appear in the FINDERS box.

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.

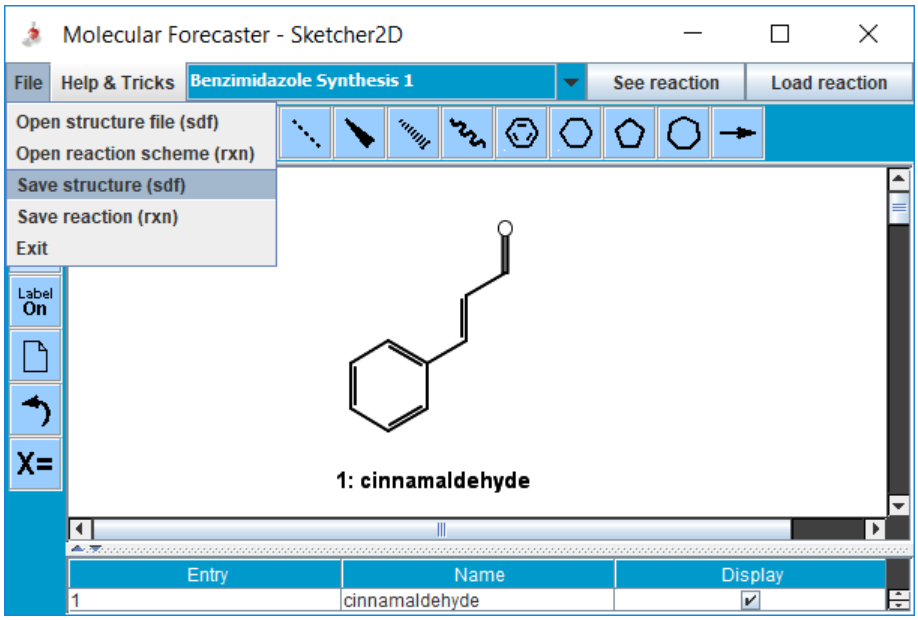
CONSTRUCTS: Building transition state structures

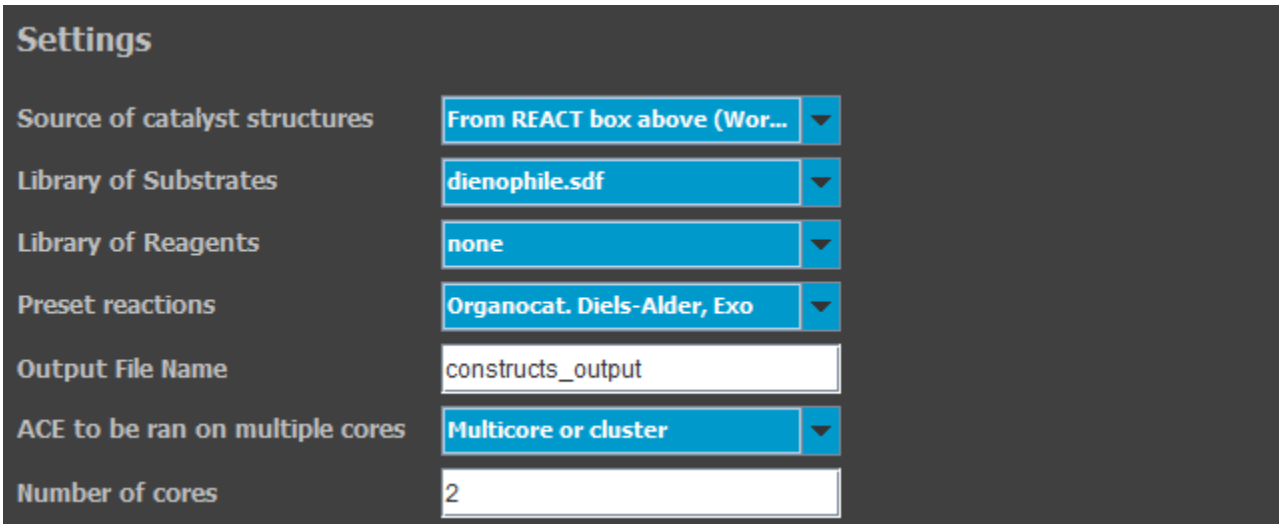
For the organocatalyzed Diels Alder reaction, we need a diene (cyclopentadiene already integrated as part of the transition state), a dienophile (which we will draw) and a catalyst (which will be built through the FINDERS/REACT2D programs as discussed above.

For this example, the dienophile will be cinnamaldehyde and can be drawn using the sketcher and saved as "dienophile.sdf".

As soon as this dienophile is ready, click on the gear icon of the CONSTRUCTS box to open the parameters section. The **Source of catalyst structures** should be "From REACT box above"; Library of substrates: "none" (the actual substrate, cyclopentadiene, is already part of the preset reaction) and Library of reagents: "dienophile.sdf". The "Organocatalyzed Diels Alder, Exo" reaction is chosen. The **output file** can be filled with anything; "constructs-output" is suggested. 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 to CONSTRUCTS. With the preset reaction used here, cyclopentadiene is used as a reagent by default and only substrates should be given.

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

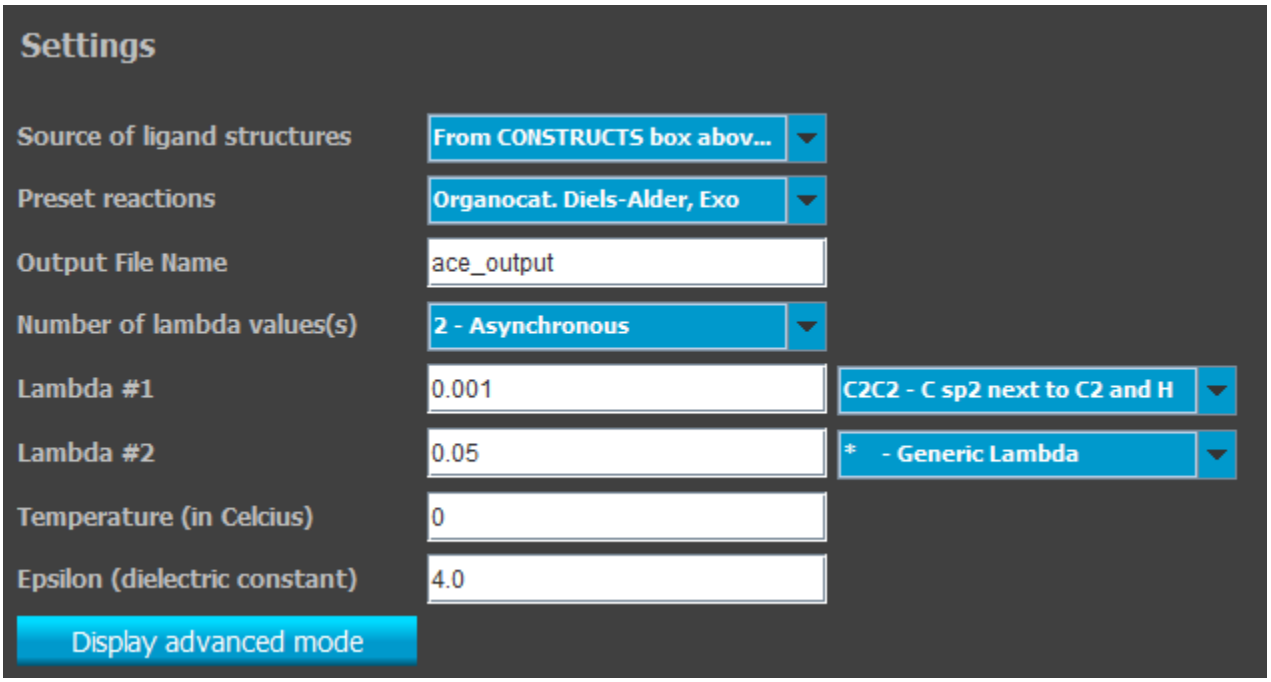




The keyword file will next be written by clicking the **Write keyword file** button. Clicking the **Exit** button will close the CONSTRUCTS parameters section and return to the main workflow. A green check should now appear in the CONSTRUCTSbox. The program will not run until the complete workflow is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

ACE: Optimizing TS structures and computing stereoselectivity

Click on the gear icon of the ACE box to 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.



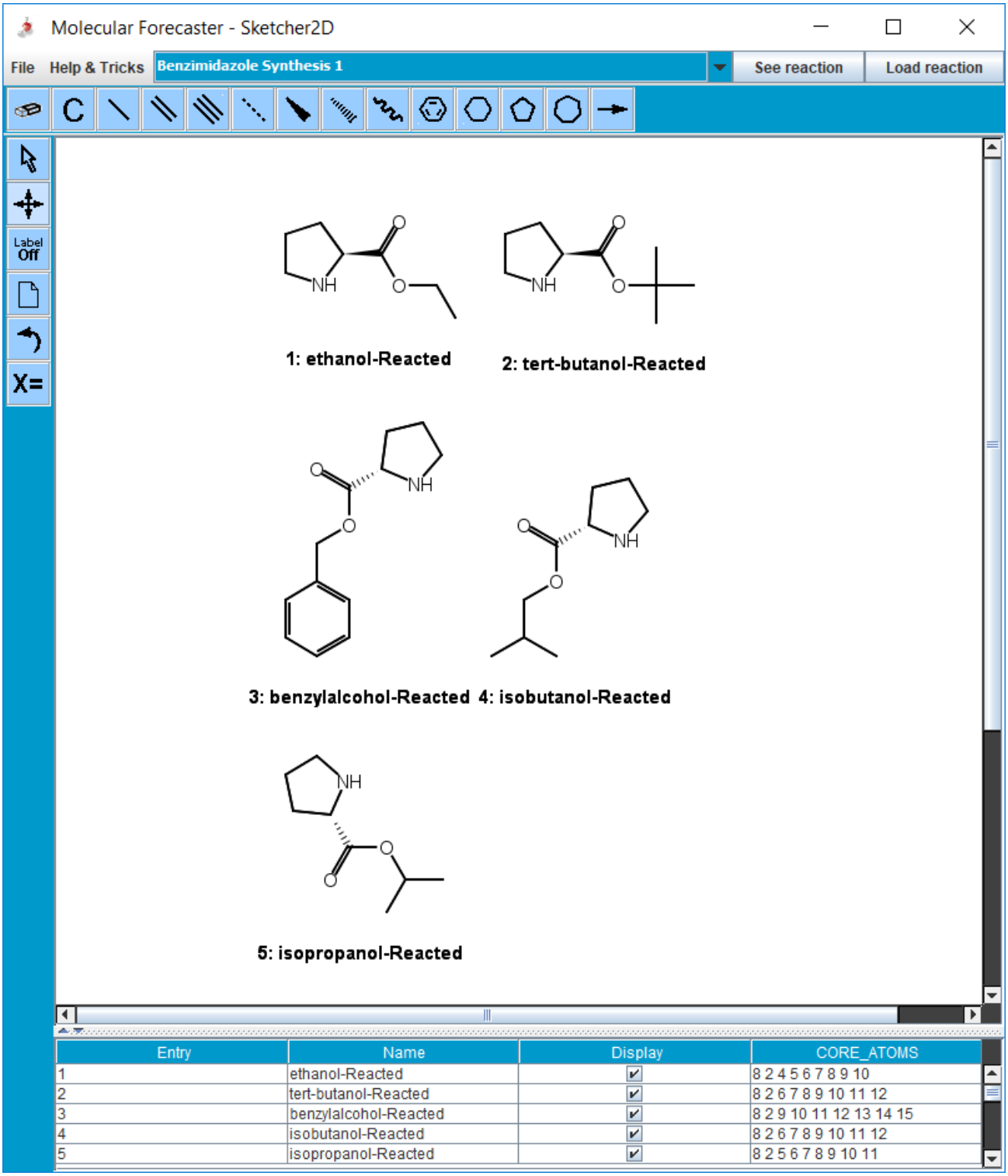
The keyword file will next be written by clicking the **Write keyword file** button. Clicking the **Exit** button will close the ACE parameters section and return to the main workflow. A green check should now appear in the CONSTRUCTS box.

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

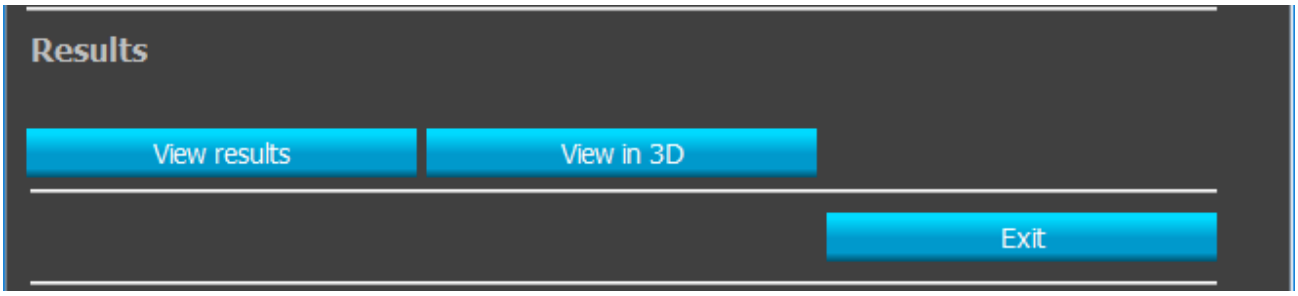
Once the workflow is complete, multiple files will be created with the names assigned in each parameter box. For instance, the files generated with REACT are `react-output.out` (output file) and `react-output.sdf` (sdf file with the new library). The `react-output.sdf` file contains the entire library 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 (see Figure below) while the **Text file** button will open the library as a text file.



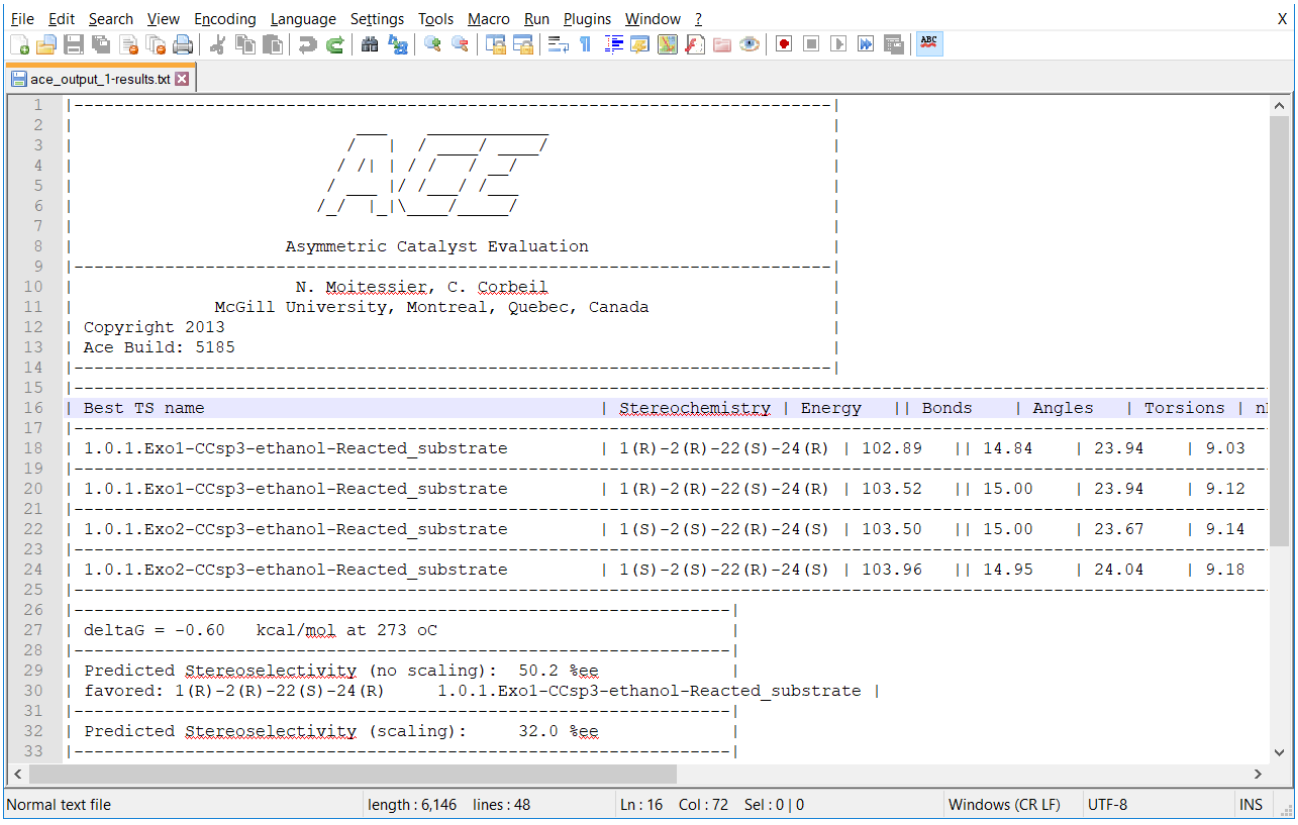
Entry	Name	Display	CORE_ATOMS
1	ethanol-Reacted	✔	8 2 4 5 6 7 8 9 10
2	tert-butanol-Reacted	✔	8 2 6 7 8 9 10 11 12
3	benzylalcohol-Reacted	✔	8 2 9 10 11 12 13 14 15
4	isobutanol-Reacted	✔	8 2 6 7 8 9 10 11 12
5	isopropanol-Reacted	✔	8 2 5 6 7 8 9 10 11

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.

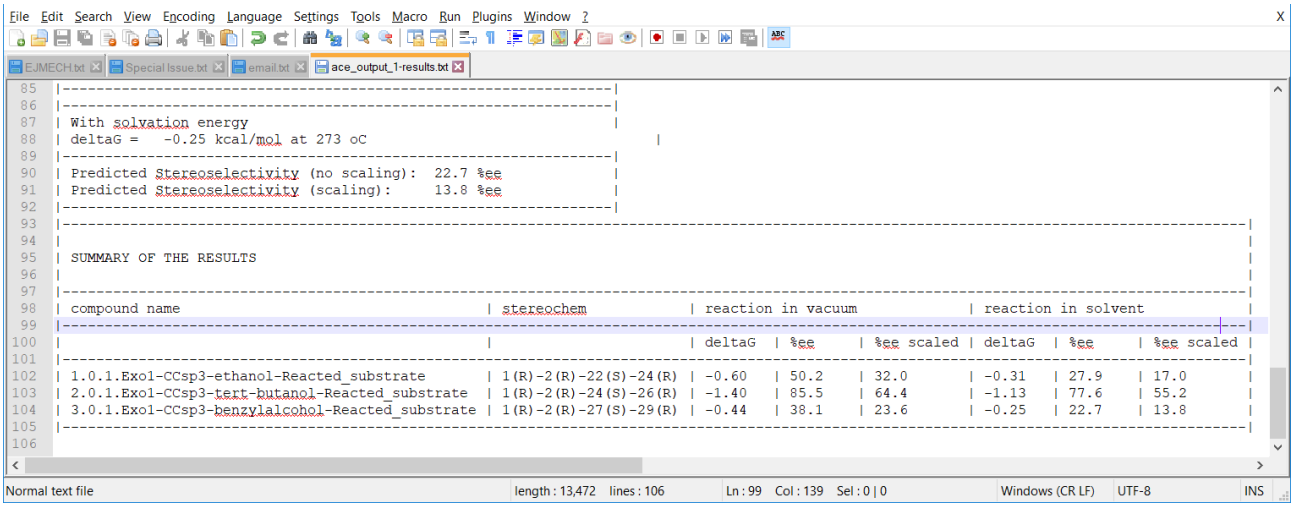
The platform can also be used. Clicking on the magnifying glass will open a new window.



By clicking on **View results**, you will open the first result file (if multiple jobs are running simultaneously, you will have to open the other result files with your favorite text editor, here Notepad++).



If you scroll down to the bottom of the file, a summary is given. The atom numbers used in the stereochemistry of each of the transitions states (e.g., 1(*R*)-2(*R*)-22(*S*)-24(*R*)) does not reflect the IUPAC nomenclature. Rather these numbers are the atom numbers in the files.



```
|-------------------------------------------------------------------|
|-------------------------------------------------------------------|
| With solvation energy                                             |
| deltaG =   -0.25 kcal/mol at 273 oC                                 |
|-------------------------------------------------------------------|
| Predicted Stereoselectivity (no scaling):  22.7 %ee               |
| Predicted Stereoselectivity (scaling):     13.8 %ee               |
|-------------------------------------------------------------------|
|-------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                               |
| SUMMARY OF THE RESULTS                                                                                                        |
|                                                                                                                               |
|-------------------------------------------------------------------------------------------------------------------------------|
| compound name                                | stereochem            | reaction in vacuum            | reaction in solvent           |
|----------------------------------------------------------------------------------------------------------------------------|
|                                              |                       | deltaG  | %ee     | %ee scaled | deltaG  | %ee     | %ee scaled |
|-------------------------------------------------------------------------------------------------------------------------------|
| 1.0.1.Exo1-CCsp3-ethanol-Reacted_substrate   | 1(R)-2(R)-22(S)-24(R) | -0.60   | 50.2    | 32.0       | -0.31   | 27.9    | 17.0       |
| 2.0.1.Exo1-CCsp3-tert-butanol-Reacted_substrate | 1(R)-2(R)-24(S)-26(R) | -1.40   | 85.5    | 64.4       | -1.13   | 77.6    | 55.2       |
| 3.0.1.Exo1-CCsp3-benzylalcohol-Reacted_substrate | 1(R)-2(R)-27(S)-29(R) | -0.44   | 38.1    | 23.6       | -0.25   | 22.7    | 13.8       |
|-------------------------------------------------------------------------------------------------------------------------------|
```

Normal text file | length : 13,472 lines : 106 | Ln : 99 Col : 139 Sel : 0 | 0 | Windows (CR LF) | UTF-8 | INS

Clicking on **View in 3D** will open the first 3D transition state structure (not necessarily the lowest in energy). In the current version, if multiple jobs of ACE are run, multiple files will be created and only the first one will be open. You may use JMol within the platform or any visualizer to display the other transition state structures.