Symyx®

Reaction Searching using DiscoveryGate

DiscoveryGate®
Exercise Guide

Reaction Searching using DiscoveryGate

DiscoveryGate® Exercise Guide

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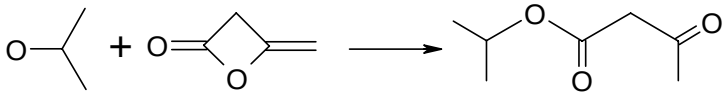
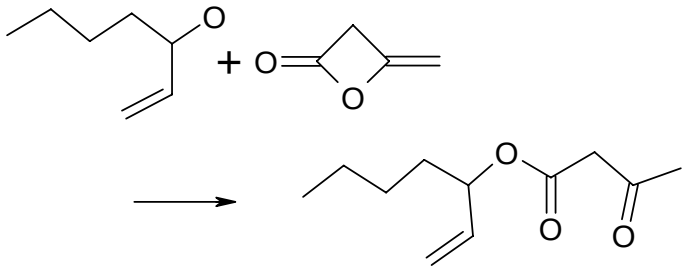
Exercise descriptions

The following descriptions explain the goal of each exercise. If you like to figure things out on your own, use the descriptions to conduct the exercises. If you prefer step-by-step instructions, go to the page listed below the description.

Exercise 1

- Conduct a reaction substructure search for synthesis of keto esters. Examples of the desired transformations are shown below. Do not draw each of the reactions shown. Draw a single reaction that is representative of the desired transformation.



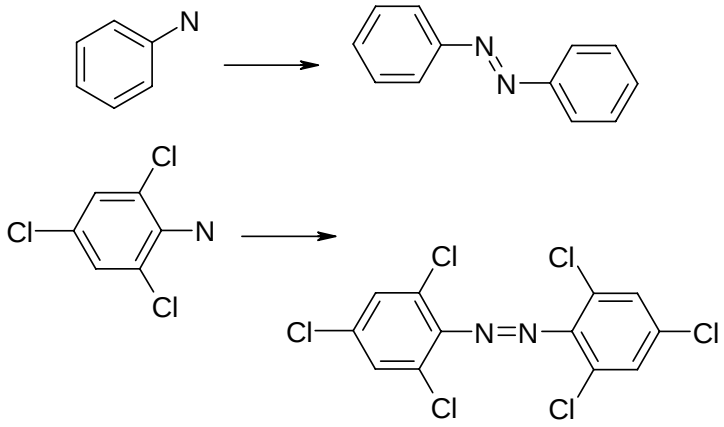


- View the details for one of the reactions retrieved.

For a step-by-step solution, see page 1-4.

Exercise 2

- Conduct a search to retrieve methods for preparing azo compounds from aniline. Examples of the desired transformations are shown below. Do not draw each of the reactions shown. Draw a single reaction that is representative of the desired transformation. Use substitution count to specify the unsubstituted nitrogen on the reactant and prevent amine oxides in the product.

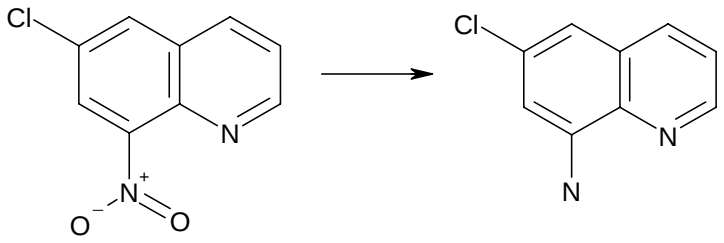


- Use one of the reactions retrieved to find similar reactions in IMRW.

  For a step-by-step solution, see page 1-7.

Exercise 3

- Search for the reduction of a halogenated aromatic nitro group to a primary amine. An example of this type of reaction is shown below.

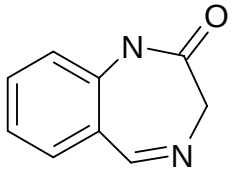


- Use one of the reactions retrieved to find similar reactions in MDL Patent Chemistry.

  For a step-by-step solution, see page 1-11.

Exercise 4

- Retrieve synthetic methods for 1,4 benzodiazepine that use THF or ethanol as a solvent. Conduct a substructure search with benzodiazepine as product not reactant. Conduct a formula search for the solvent.



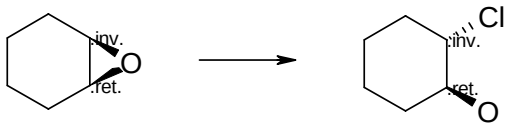
THF	Ethanol
C_4H_8O	C_2H_6O

- Use one of the reactions retrieved to find similar reactions in CrossFire Beilstein.

  For a step-by-step solution, see page 1-17.

Exercise 5

- Retrieve reactions that open epoxide rings with stereo inversion and halogenation. Allow five- and six-membered rings.

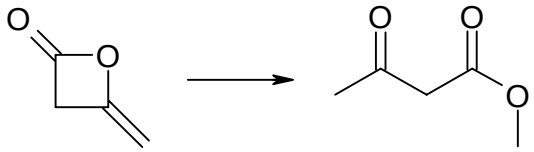


For a step-by-step solution, see page 1-24.

Synthesis of esters

Exercise 1

Conduct a reaction substructure search to retrieve methods for the synthesis of keto esters.



Launch the MDL Database Browser

1. From the DiscoveryGate home page, click **Search Databases**.

Choose the Synthetic Methodology Information database

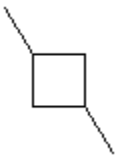
2. Choose **Synthetic Methodology Information** from the Database list.

3. Double-click the **Reaction** box to launch MDL Draw.

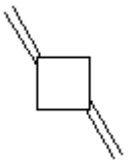
Draw the reactant

4. Click the **cyclobutane** template. Click the drawing area.

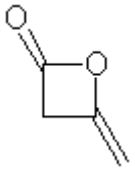
5. Click the **All-Purpose Drawing** tool. Drag the mouse to draw the two single bonds.



6. Click the single bonds to change them to double.

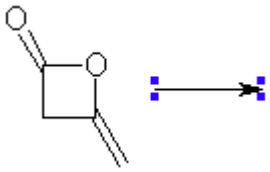


7. Shift-click to select the atoms that you want to change to oxygen. Type **o**.



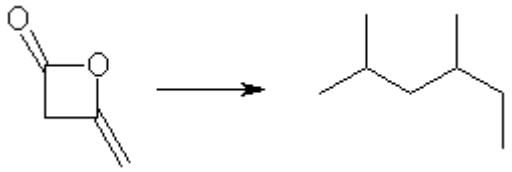
Draw the reaction arrow

8. Click the **Arrow** tool. Then click the drawing area to the right of the reactant structure.

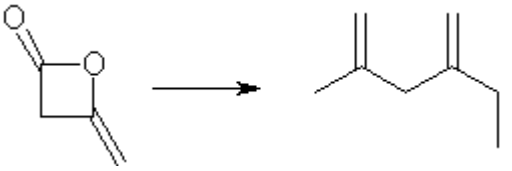


Draw the product

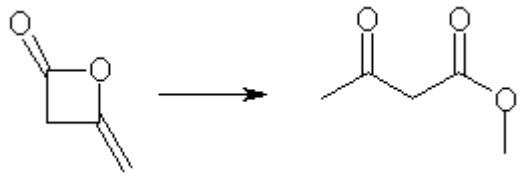
9. Click the **All-Purpose Drawing** tool. Drag to draw the carbon framework.



10. Click the bonds to change them to double.



11. Shift-click to select the atoms that you want to change to oxygen. Type **o**.

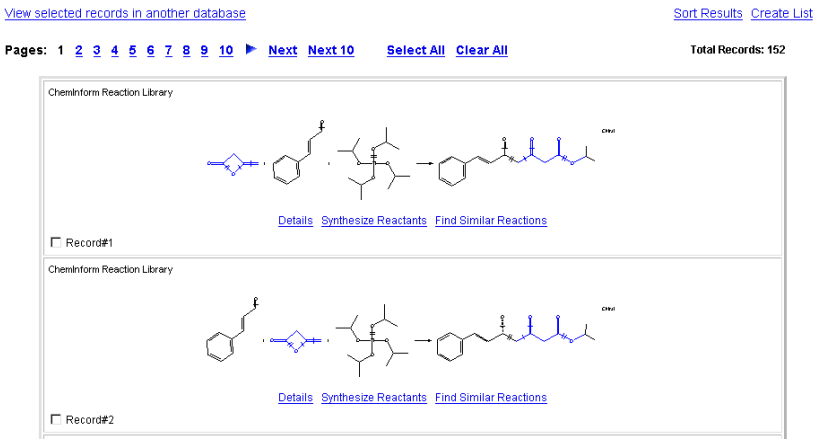


Conduct the search

12. Click **Done**.

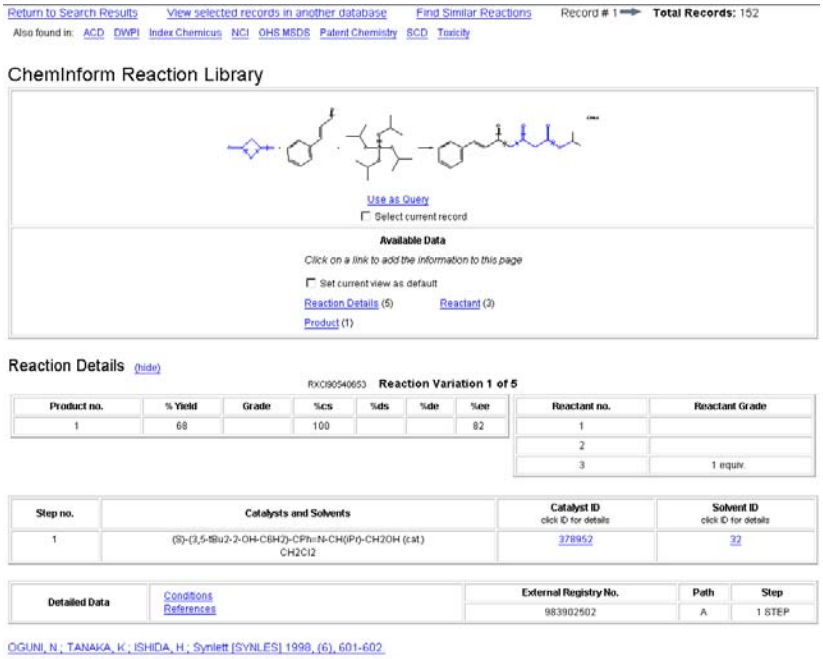
13. Choose **Reaction Substructure** as the search type.

14. Click **start search**. The results are displayed.



View the search results

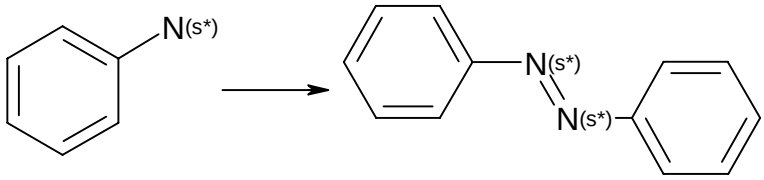
15. Click **Details** for one of the reactions. Scroll to view the data.



Preparation of azo compounds from aniline

Exercise 2

Conduct a reaction substructure search using the following query:



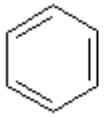
1. Click the **queries** tab.

2. Click the **Reset** link located to the right of the reaction box.

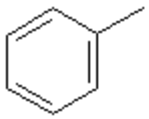
Draw the query

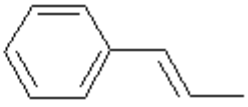
3. Double-click the **Reaction** box.

4. Click the **benzene** template. Click the drawing area to draw two separate rings.

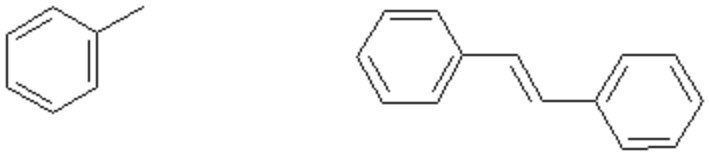


5. Click the **All-Purpose Drawing** tool. Drag the mouse to draw the bonds shown. Click the single bond to change it to double.

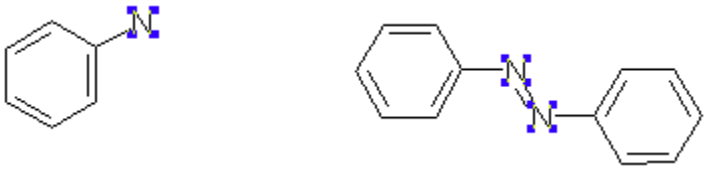




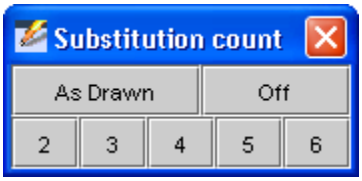
6. Click the **benzene** template, and then click the end of the single bond to attach the ring.



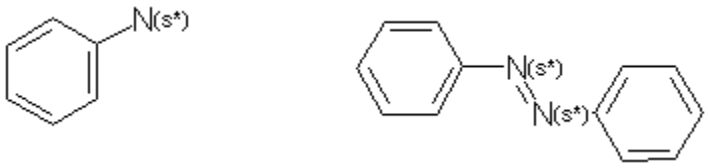
7. Click the **Lasso Select** tool. Shift-click to select the atoms that you want to change to nitrogen. Type **n**.



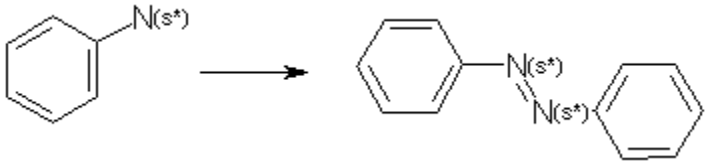
8. Right-click one of the selected nitrogen atoms, and choose **Number of nonhydrogen substituents**.



9. Click **As Drawn**.



10. Click the **Arrow** tool. Click the drawing area between the two structures.



11. Click **Done**.

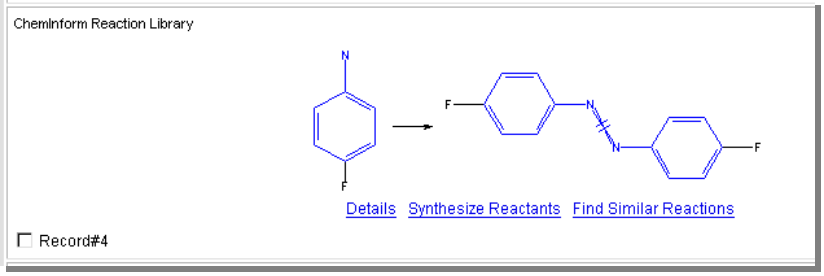
Conduct the search

12. Choose **Reaction Substructure** as the search type.

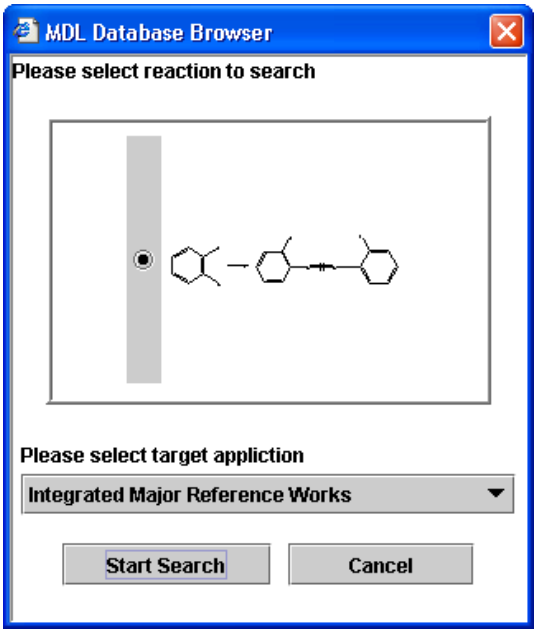
13. Click **start search**.

From the results, find similar reactions in the Integrated Major Reference Works

14. For one of the reactions retrieved, click **Find Similar Reactions**. For example:



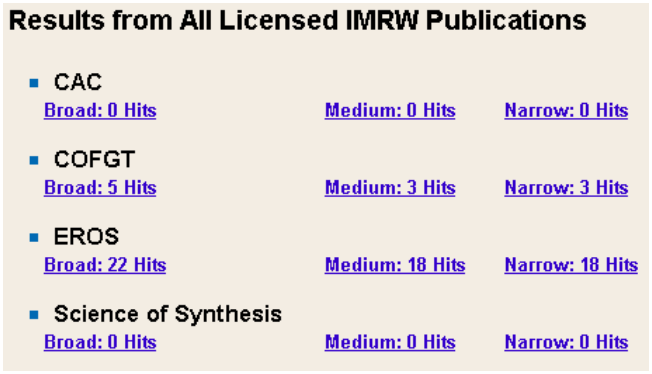
15. Choose **Integrated Major Reference Works** as the target application. Click **Start Search**.

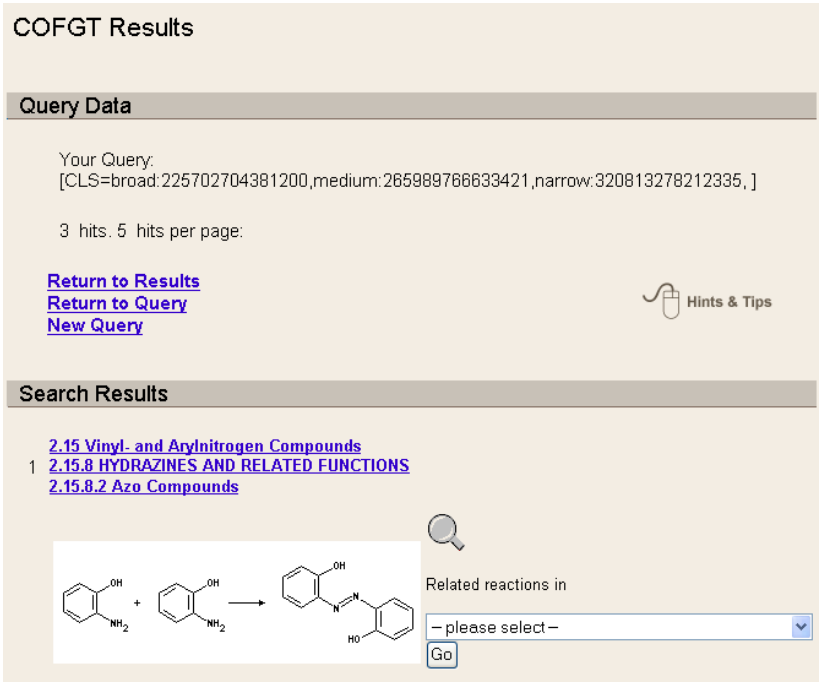


16. If necessary, enter your Username and Password to login to the IMRW database.

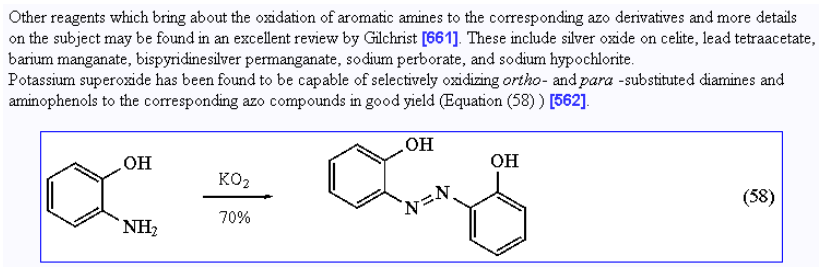
17. Click a link for Broad, Medium, or Narrow search results from one of the licensed IMRW publications. In this

example, you would click the **Narrow: 3Hits** link for COFGT.





18. Click the reference link to view the article text. For example:

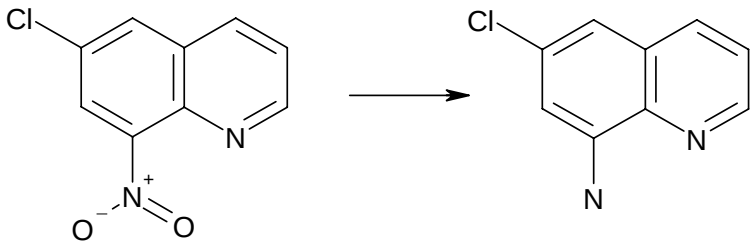


19. Close the IMRW publication windows.

Reduce halogenated aromatic nitro to an amine

Exercise 3

Conduct a reaction substructure search to retrieve reactions of the following type:



Return to the Query page

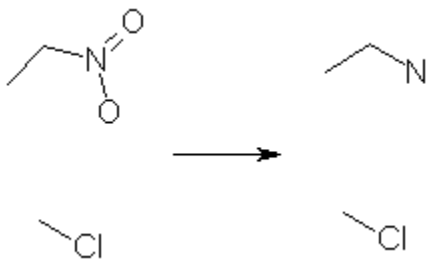
1. Click the **queries** tab.

2. Click the **Reset** link located to the right of the reaction box.

Draw the query

3. Double-click the **Reaction** box.

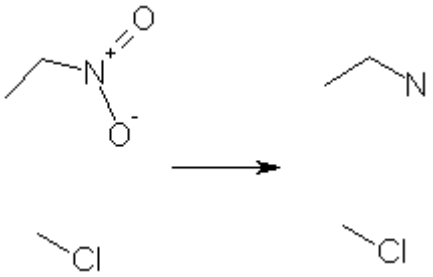
4. Click the **All-Purpose Drawing** tool. Draw the fragments shown below. Use the **Arrow** tool to draw the arrow.



Apply charges

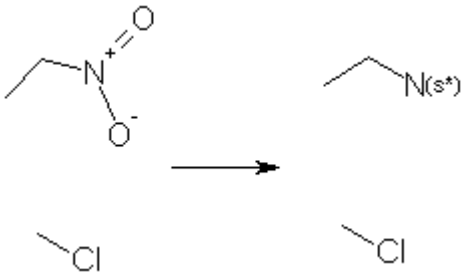
5. To apply the charges, right-click the nitrogen atom in the nitro group. Choose **Charge**, and then click **+1**.

6. Use the same technique to add the **-1** charge to the oxygen.



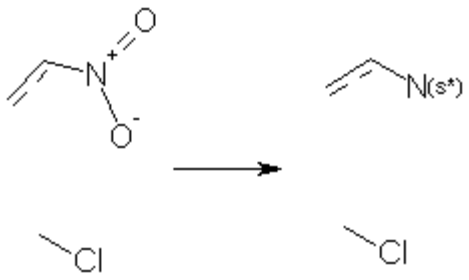
Specify substitution count

7. Right-click the uncharged nitrogen and choose **Number of nonhydrogen substituents**. Click **As Drawn**.



Apply Aromatic query bond

8. Shift-click to select the carbon-carbon bonds in the reactant and product fragments. Right-click one of the selected bonds, and choose **Query bond type** > **Aromatic**.



9. Click **Done**.

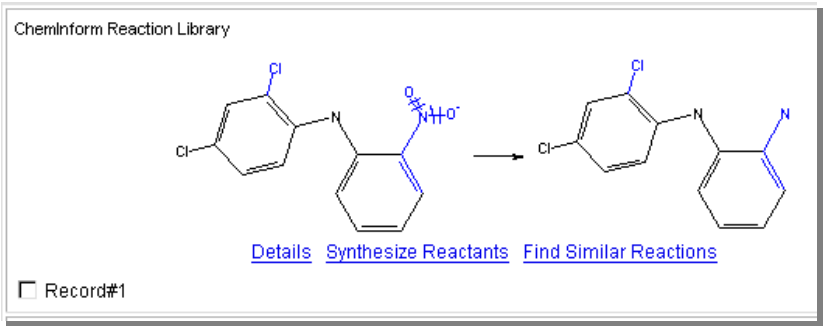
Conduct the search

10. Choose **Reaction Substructure** as the search type.

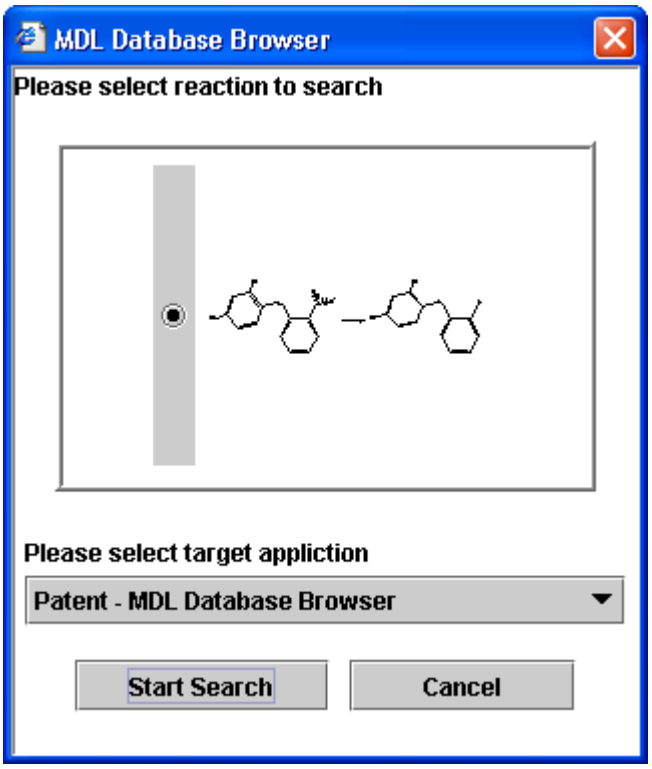
11. Click **start search**.

Find similar reactions in CrossFire Beilstein

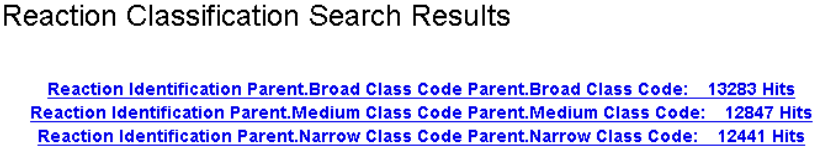
12. For one of the reactions retrieved, click **Find Similar Reactions**. For example:



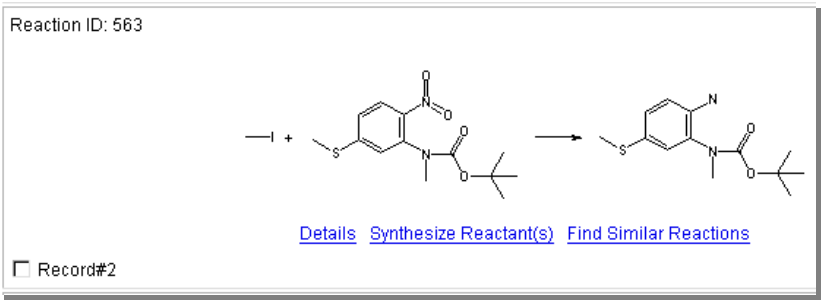
13. Choose **Patent – MDL Database Browser** as the target application. Click **Start Search**.



14. Click the link for the **Narrow Class Code** search results.

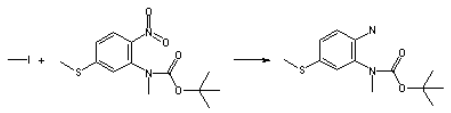


15. For one of the similar reactions, click **Details**. For example:



The reaction details are displayed.

Patent Chemistry Reaction 563



Use as Query Synthesize Reactant(s)

☐ Select current record

Reaction Identification

Reaction Identification record 1 of 1	
Reaction ID	563
Reactant	**Reactant PRN**: 122294 **Reactant**: iodo-methane **Reactant PRN**: 134307 **Reactant**: N-(2-nitro-5-methylthiophenyl)-N-methylcarbamic acid t-butyl ester
Product	**Product PRN**: 134306 **Product**: 2-(N-t-butoxycarbonyl-N-methylamino)-4-methylthioaniline
Reaction Specification	full reaction
Reaction Entry Date	2003/12/24
Reaction Update Date	2003/12/24

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Reaction Details

Reaction Details record 1 of 1	
Citation	1073
Topic of Interest	Preparation
Example Name	Example 41
Location in Patent	Page 126
Product	**Product PRN**: 134306 **Product**: 2-(N-t-butoxycarbonyl-N-methylamino)-4-methylthioaniline
Stage Number	1
Reactant	**Reactant PRN**: 122294 **Reactant**: iodo-methane **Reactant PRN**: 134307 **Reactant**: N-(2-nitro-5-methylthiophenyl)-N-methylcarbamic acid t-butyl ester
Reagent	**Reagent PRN**: 240067 **Reagent**: 10 percent palladium on carbon
Solvent	**Solvent PRN**: 7574 **Solvent**: methanol **Quantity in Solvent Mixture**: 300 ml **Solvent PRN**: 126957 **Solvent**: dioxane **Quantity in Solvent Mixture**: 300 ml
Reaction Details Citations	• Patent; Sankyo Company, Limited; Publ.: EP1167357 A1 (2002/01/02), Appl.: EP2000-915361 (2000/04/06)

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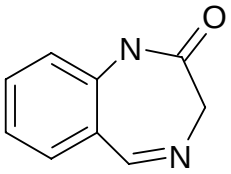
Show Substances for this Reaction Show Citations for this Reaction

Synthesis of benzodiazepine

Exercise 4

Conduct a substructure search to retrieve synthetic methods for 1,4 benzodiazepines that use THF or ethanol as a solvent.



THF C_4H_8O

Ethanol C_2H_6O

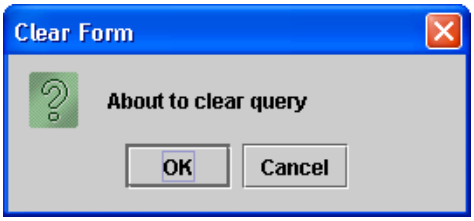
Construct the query

1. Click **queries**.

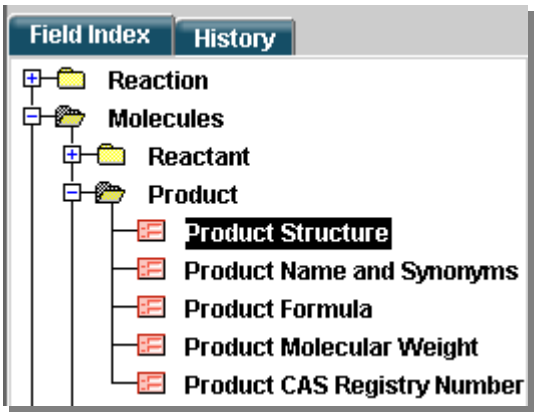
2. Choose **Synthetic Methodology Information** from the Database list.

Build a custom form

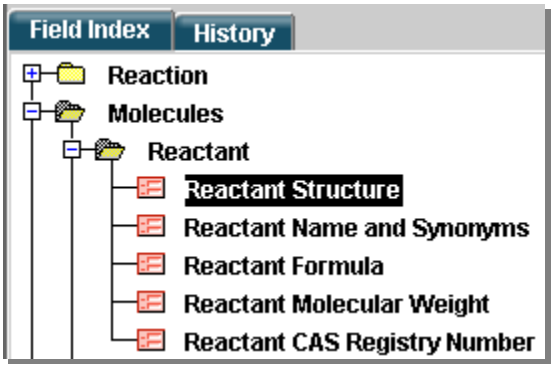
3. Click **clear form** on the top menu bar. Click **OK** at the confirmation prompt.



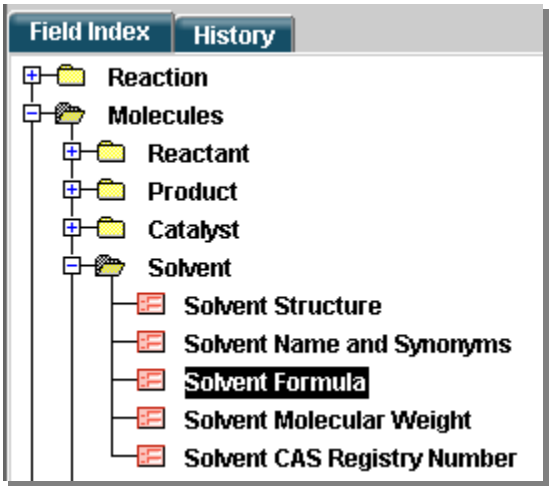
4. In the Field Index, open the **Molecules** > **Product** folder. Double-click **Product Structure**.



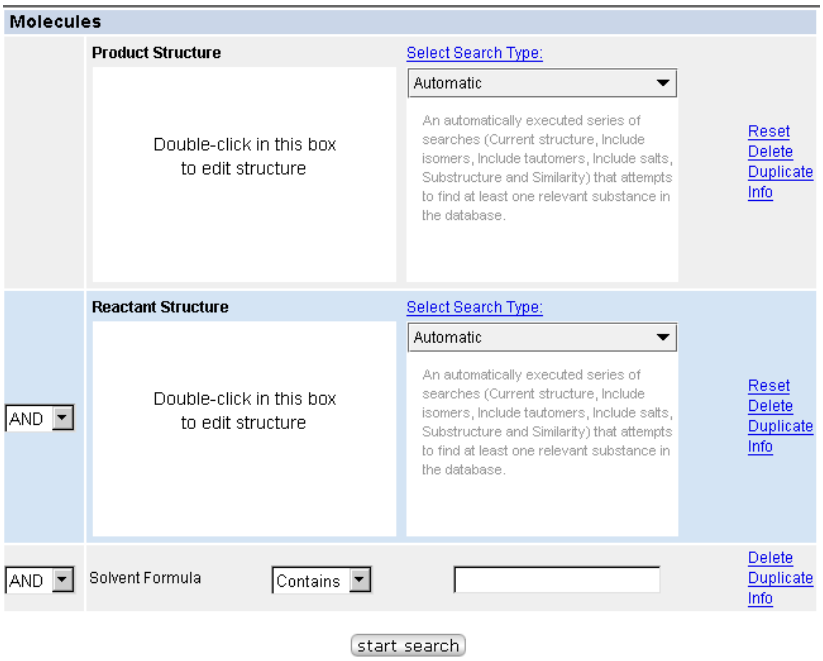
5. In the Field Index, open the **Molecules > Reactant** folder. Double-click **Reactant Structure**.



6. In the Field Index, open the **Molecules > Solvent** folder. Double-click **Solvent Formula**.

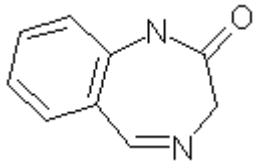


The query form looks like this:



Draw the product structure

7. Double-click the **Product Structure** box. Draw the structure for 1,4 benzodiazepine.



8. Click **Done**.

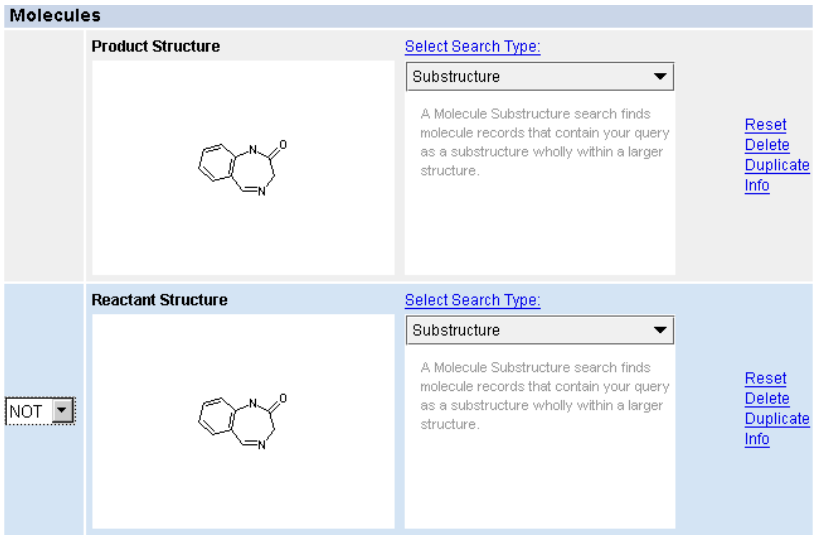
Copy and paste the product structure

9. Right-click the structure in the Product Structure box. Choose **Copy**.

10. Right-click the **Reactant Structure** box. Choose **Paste**.

Set the search type and logic

11. Choose **Substructure** as the search type for both the Product and Reactant. Then change the logical operator for the Reactant Structure to **NOT**.

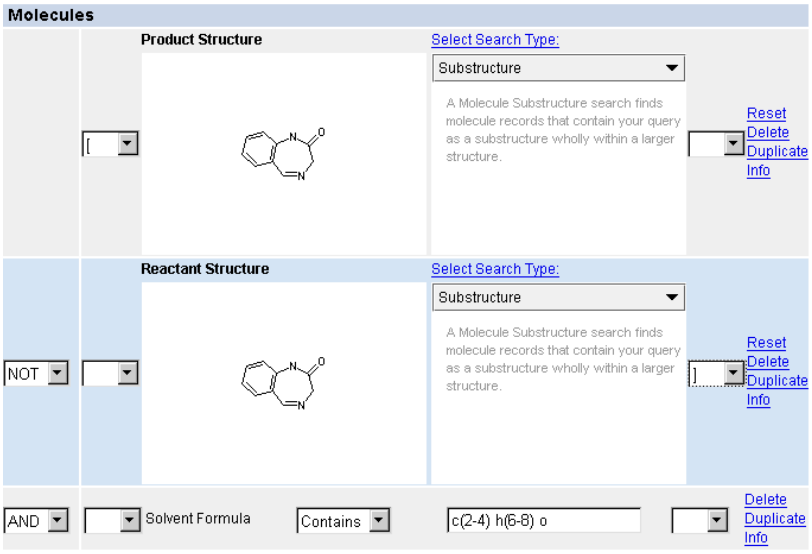


Enter the Solvent query

12. For the Solvent field, enter the formula query that will retrieve both THF (C4H8O) and Ethanol (C2H6O).

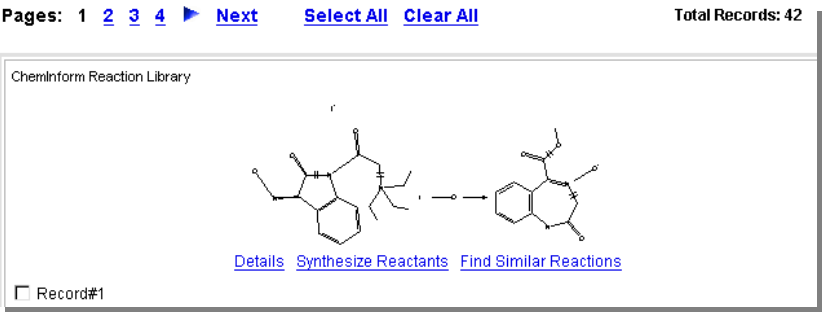
Use parentheses to clarify search logic

13. Click **show brackets**. Then apply parentheses around the two structure queries.



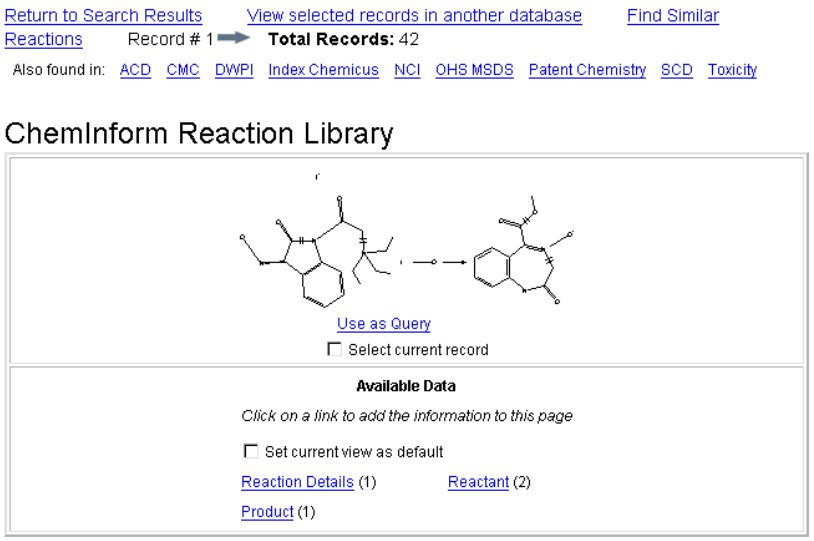
Execute the search

14. Click **start search**.



View details for a reaction

15. For one of the reactions retrieved, click **Details**. For example:



Reaction Details (hide)

RXCI05004297 **Reaction Variation 1 of 1**

Product no.	% Yield	Grade	%cs	%ds	%de	%ee	Reactant no.	Reactant Grade
1	50		100					

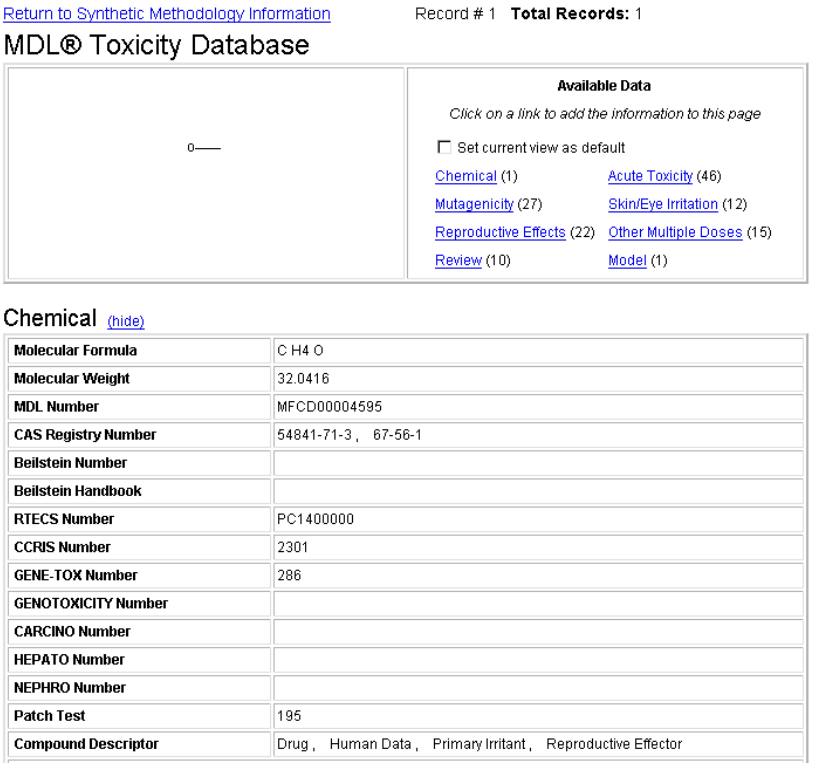
Step no.	Catalysts and Solvents	Catalyst ID click ID for details	Solvent ID click ID for details
1	DMF		38

Detailed Data	Conditions References	External Registry No.	Path	Step
		1050316101	A	4 OF 5
		1050316101	B	4 OF 5

SIROHI, R.; SINGH, A.; SHASTRI, S.; KISHORE, D.; J Indian Chem Soc [JICSAH] 2004, 81 (3), 254-257.

View Toxicity data for a reaction

16. Click the **Toxicity** link for "Also found in." In this example, toxicity data for one of the reactants is retrieved.


Return to Synthetic Methodology Information Record # 1 **Total Records:** 1

MDL® Toxicity Database

Available Data

Click on a link to add the information to this page

☐ Set current view as default

Chemical (1) Acute Toxicity (46)
Mutagenicity (27) Skin/Eye Irritation (12)
Reproductive Effects (22) Other Multiple Doses (15)
Review (10) Model (1)

Chemical (hide)

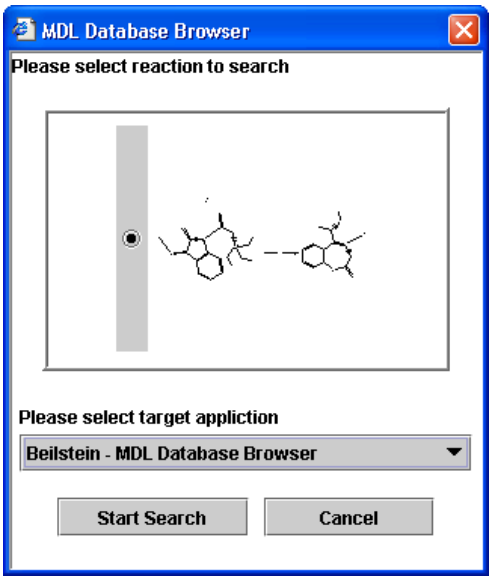
Molecular Formula	C H4 O
Molecular Weight	32.0416
MDL Number	MFCD00004595
CAS Registry Number	54841-71-3 , 67-56-1
Beilstein Number	
Beilstein Handbook	
RTECS Number	PC1400000
CCRIS Number	2301
GENE-TOX Number	286
GENOTOXICITY Number	
CARCINO Number	
HEPATO Number	
NEPHRO Number	
Patch Test	195
Compound Descriptor	Drug , Human Data , Primary Irritant , Reproductive Effector

17. Click **Return to Synthetic Methodology Information**.

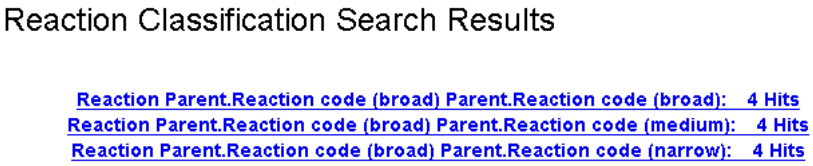
18. Click **Return to Search Results**.

Find similar reactions in CrossFire Beilstein

19. For one of the reactions, click **Find Similar Reactions**. Enter **Beilstein – MDL Browser** as the target application. Click **Start Search**.



20. Click the **narrow** results link.

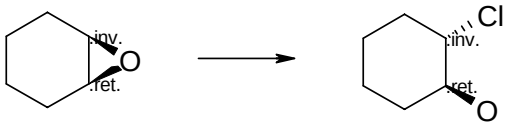


21. View the similar reactions retrieved.

Open epoxides with stereo inversion

Exercise 5

Conduct a reaction substructure search to retrieve reactions of the following type:



Return to Synthetic Methodology Information

1. Click **queries**.

2. Choose **Synthetic Methodology Information** from the Database list.

Draw the query

3. Double-click the **Reaction** box.

4. Click the **cyclopentane** template. Click the drawing area twice to draw two separate rings.

Draw stereo bonds

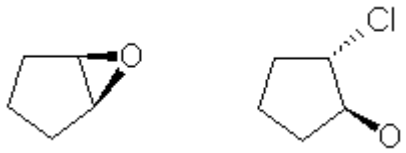
5. Click the **Up Wedge** tool. Drag the mouse to draw the wedged bond. For the reactant, join the ends of the two wedge bonds.

6. Click the **Down Wedge** tool. Drag the mouse to draw the bond on the product.

Add atom symbols

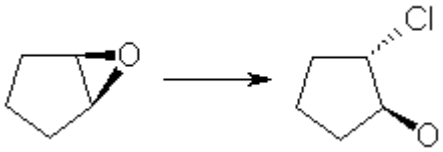
7. Click the **Lasso Select** tool. Shift-click to select the two atoms that you want to change to oxygen. Type **o**.

8. Select the atom that you want to change to chlorine. Type **cl**.



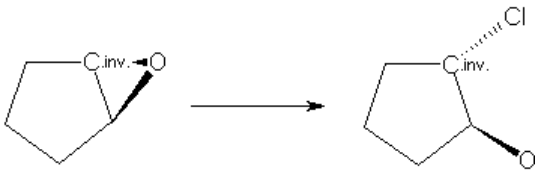
Draw the reaction arrow

9. Click the **Arrow** tool. Click the drawing area between the two structures.

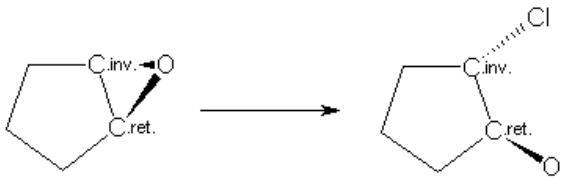


Add stereoconfiguration labels

10. Click the **Lasso Select** tool. Shift-click to select the stereocenters that will invert during the reaction. Right-click one of the selected atoms and choose **Stereoconfiguration at atom > Inverted in reaction**.

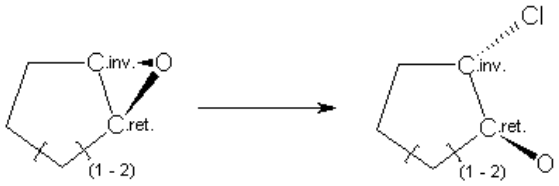


11. Shift-click to select the stereocenters that will be retained during the reaction. Right-click one of the selected atoms and choose **Stereoconfiguration at atom > Retained in reaction**.



Add repeat atoms to allow ring expansion

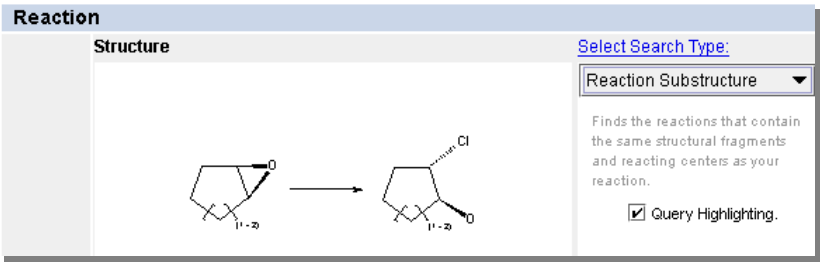
12. Shift-click to select the two atoms that can repeat to expand the rings from five-membered to six-membered rings. Right-click one of the selected atoms and choose **Repeat atom 1 to N**. Click **2**.



13. Click **Done**.

Conduct the search

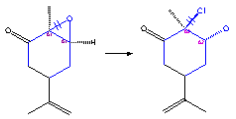
14. Choose **Reaction Substructure** as the search type.



15. Click **start search**.

16. View the details for some of the reactions retrieved. Scroll to view the data. For example:

ChemInform Reaction Library



Use as Query

Select current record

Available Data

Click on a link to add the information to this page

Set current view as default

Reaction Details (1) Reactant (1)

Product (1)

Reaction Details (hide)

RXCI05069381 **Reaction Variation 1 of 1**

Product no.	% Yield	Grade	%cs	%ds	%de	%ee	Reactant no.	Reactant Grade
1	90		100					

Step no.	Catalysts and Solvents	Catalyst ID click ID for details	Solvent ID click ID for details
1	1.5 equiv. 1-(carboxymethyl)-3-methylimidazolium chloride neat	1053340	372397

Detailed Data	Conditions References	External Registry No.	Path	Step
		1054406011	A	1 STEP

RANU, B. C.; BANERJEE, S.; J Org Chem [JOCEAH] 2005, 70 (11), 4517-4519.