Science of Synthesis

Houben–Weyl Methods of Molecular Transformations

Getting Started Manual

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Preface

Facing dramatic developments in chemistry during the last few decades, which have provided chemists with a wealth of new reagents and reactions, the need for a new, comprehensive, and critical treatment of synthetic chemistry has become apparent. To meet this challenge an entirely new edition of the esteemed reference work Houben–Weyl Methods of Organic Chemistry was launched in the year 2000.

This new edition is entitled **Science of Synthesis, Houben–Weyl Methods of Molecular Transformations** and is edited by D. Bellus (Basel, Switzerland), E. N. Jacobsen (Cambridge, USA), S. V. Ley (Cambridge, UK), R. Noyori (Nagoya, Japan), M. Regitz (Kaiserslautern, Germany), P. J. Reider (New Jersey, USA), E. Schaumann (Clausthal-Zellerfeld, Germany), I. Shinkai (Tokyo, Japan), E. J. Thomas (Manchester, UK), and B. M. Trost (Stanford, USA).

Science of Synthesis is a balanced and critical reference work, produced by the collaborative efforts of chemists, from both industry and academia, selected by the editorial board. All published results from journals, books, and patent literature from the early 1800's until the year of publication are considered by the authors, who are among the leading experts in their field, to provide chemists with the most reliable methods to solve their synthesis problems. Science of Synthesis will be updated periodically and will become a prime source of information for chemists in the 21st century.

Science of Synthesis is organized in a logical, hierarchical manner based on the target molecule to be synthesized. The critical coverage of methods is supported by information intended to help the user choose the most suitable method for their application, thus providing a strong foundation from which to develop a successful synthetic route. Within each category of product, illuminating background information such as history, nomenclature, structure, stability, reactivity, properties, safety, and environmental aspects are discussed along with a detailed selection of reliable methods. Each method and variation is accompanied by reaction schemes, tables of examples, experimental procedures, and a background discussion of the mechanistic rationale, stereochemistry, and scope of the reaction, as well as its limitations and functional group compatibility. In a format consisting of 48 volumes, Science of Synthesis is a unique reference work, selecting and evaluating all synthetic methodology and thus providing more than just a compound database or an indiscriminate review of the literature.

To best meet the needs of the scientific community, Science of Synthesis is being published as an electronic version and also in print. The electronic version has been developed under the guidance of an advisory board comprising A. Barth (Fachinformationszentrum Karlsruhe, Germany), G. Baysinger (Stanford University, USA), A. Mullen (Bayer AG, Germany), H. Rzepa (Imperial College, UK), and E. Zass (ETH Zurich, Switzerland). It is equipped with a powerful and user-friendly information retrieval system to allow for keyword, text, substructure, structure, and reaction searches. Science of Synthesis provides a hypertext navigation system and thesaurus support. Crossovers to other databases and electronic journals are fully supported. Science of Synthesis is at the heart of the fully integrated laboratory of the future.

The Publisher

Technical Support

Please e-mail your queries to the Science of Synthesis Helpdesk at:

soshelpdesk@thieme-chemistry.com

or fax us at:

+49 (711) 8931-777

We will endeavor to answer your query as soon as possible.

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D-70469 Stuttgart
Germany

New Features: Release Version 3.7

This new release includes:

New Content

- One new content volume has been added in Category 4 (Compounds with Two Carbon—Heteroatom bonds), as follows:
    - Volume 32 [X—Ene—X (X = F, Cl, Br, I, O, S, Se, Te, N, P), Ene—Hal, and Ene—O Compounds]; Mulzer/Schaumann, 914 pages in total.

      Category 4 is now available online in its entirety.

- One new content volume has been added in Category 6 (Compounds with All-Carbon Functions), as follows:
    - Volume 43 (Polyynes, Arynes, Enynes, and Alkynes); Hopf/Thomas, 744 pages in total.

This brings the number of volumes online to 40.

Software Upgrade

- The ICEdit drawing tool ("Java Applet") has been upgraded: Version: 1.7.5.9 (20.10.2008), JVM Version: 1.6.0_01, (c) Copyright InfoChem GmbH 2008. All rights reserved.

IMPORTANT NOTE: A NEW INFOCHEM PLUGIN BECAME AVAILABLE IN LATE JULY 2006. IT IS STRONGLY RECOMMENDED THAT ALL SCIENCE OF SYNTHESIS USERS DOWNLOAD AND USE THE NEW PLUGIN "ICCLIENT-SETUP.ZIP". PLEASE VISIT WWW.INFOCHEM.DE FOR FURTHER DETAILS.

Table of Contents

1 System Requirements and Login

1.1 System Requirements

Science of Synthesis is an entirely web-based product, which does not require the installation of specialized software on your computer. However, **popup blockers must be deactivated to use Science of Synthesis**. **Please contact your IT support if you require assistance with deactivating this function.** Structure searching within **Science of Synthesis** is possible using various software packages.

The following procedure will determine if your system meets **Science of Synthesis** requirements.

STEP 1: Confirm that your system meets the following system requirements:

- PC with compatible operating system (Windows NT 4.0/95/98/2000/XP or higher) or a Macintosh computer (OS-X or higher) and an Internet connection
- Microsoft Internet Explorer 5.5 and above, Mozilla Firefox, or Safari for Macintosh computers (Netscape is not supported)
- Popup blocker must be deactivated
- Adobe Acrobat Reader 4.0 or higher required (for the electronic backfile). Which may be downloaded free of charge from the Adobe Web site (www.adobe.com).

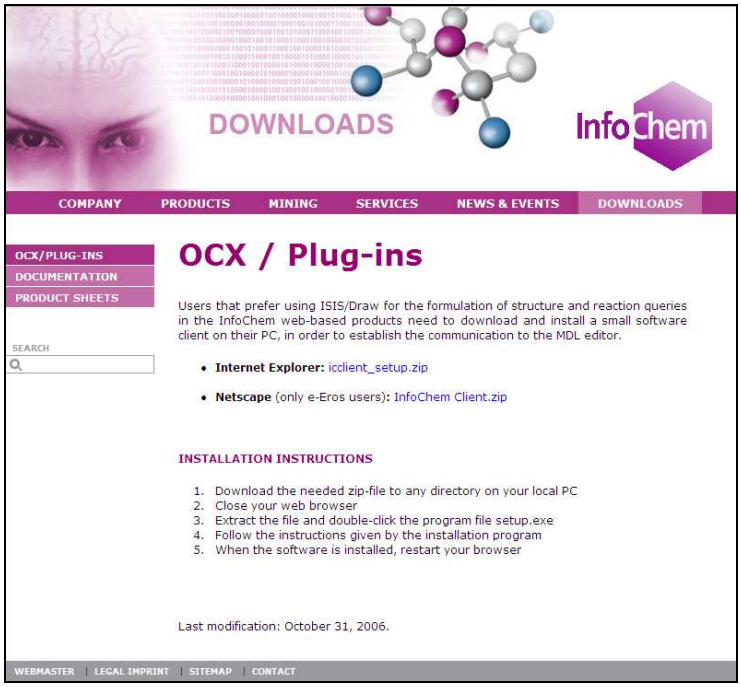
STEP 2: Confirm that you have one of the following chemical drawing packages installed on your computer:

ICedit Java Drawing Tool:
The most basic of the three drawing packages; may be used to quickly submit simple structures. Provided your system allows java to operate you can use the built-in ICedit Java Drawing Tool to carry out structure searching. To enable java the full java runtime environment (JRE) is required, which may be downloaded from the Sun Microsystems website (www.sun.com).

ISIS/Draw:
ISIS/Draw 2.5 is available free of charge (for academic and personal use only) following registration with the Symyx Technologies website (www.mdli.com). Commercial and corporate users should purchase an appropriate license for ISIS/Draw 2.5. After installation restart your computer.

To use ISIS/Draw you must download and install our client plugin *icclient_setup.zip*.
ISIS/Draw must be installed before the plugin, as the plugin must be saved in the ISIS/Draw folder.

A newer version (July 2006) of the plugin is available from the Infochem Web site (www.infochem.de/). However, both versions will continue to be usable with Science of Synthesis.



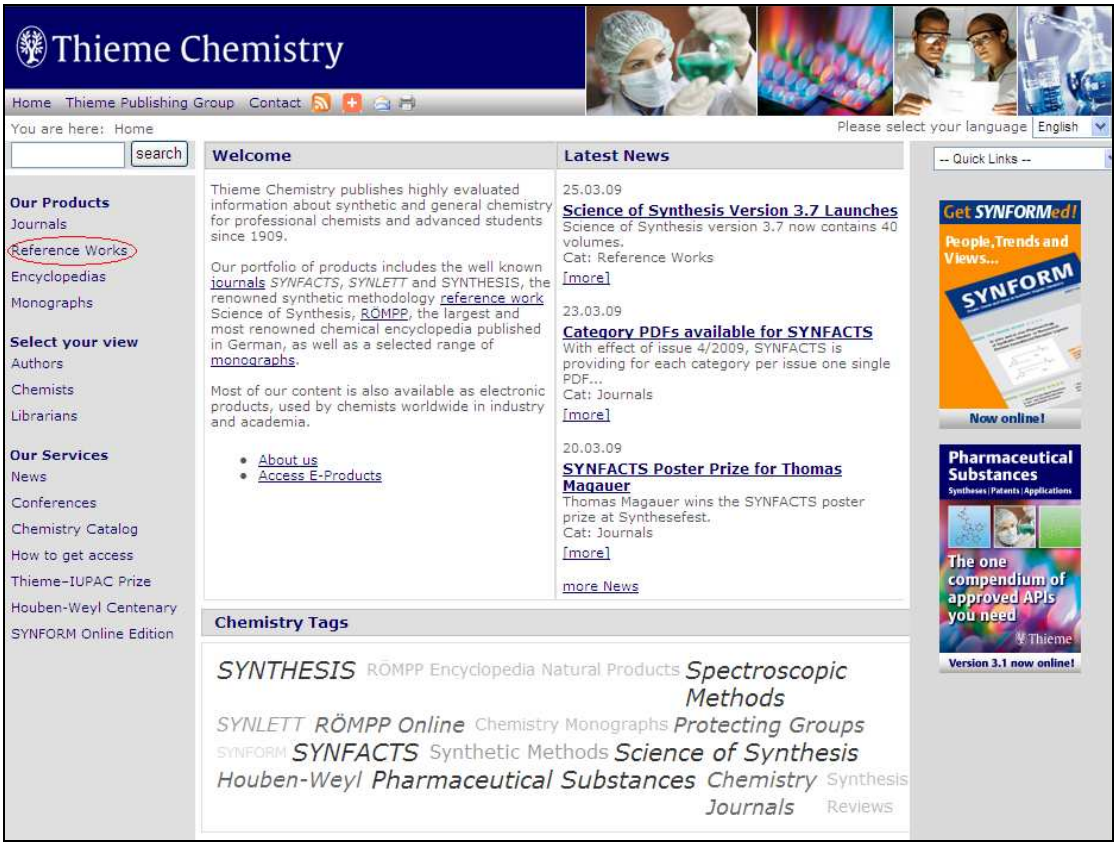
ChemDraw:
Science of Synthesis supports ChemDraw 7.0, 9.0, and 10.0 available from the CambridgeSoft Web site (www.cambridgesoft.com). No additional software is required. However, it is recommended that all users carefully review the ChemDraw system requirements to ensure that you are using a version of ChemDraw 7.0, 9.0, or 10.0 that is compatible with your system.

Please note that a fully licensed version of ChemDraw 7.0, 9.0 or 10.0 is required.

1.2 Accessing Science of Synthesis on the Web

Science of Synthesis may be accessed via the Thieme Chemistry Web site: www.thieme-chemistry.com

Click on the blue "Reference Works" link contained under "Our Products" in the grey sidebar on the left hand side of the screen.

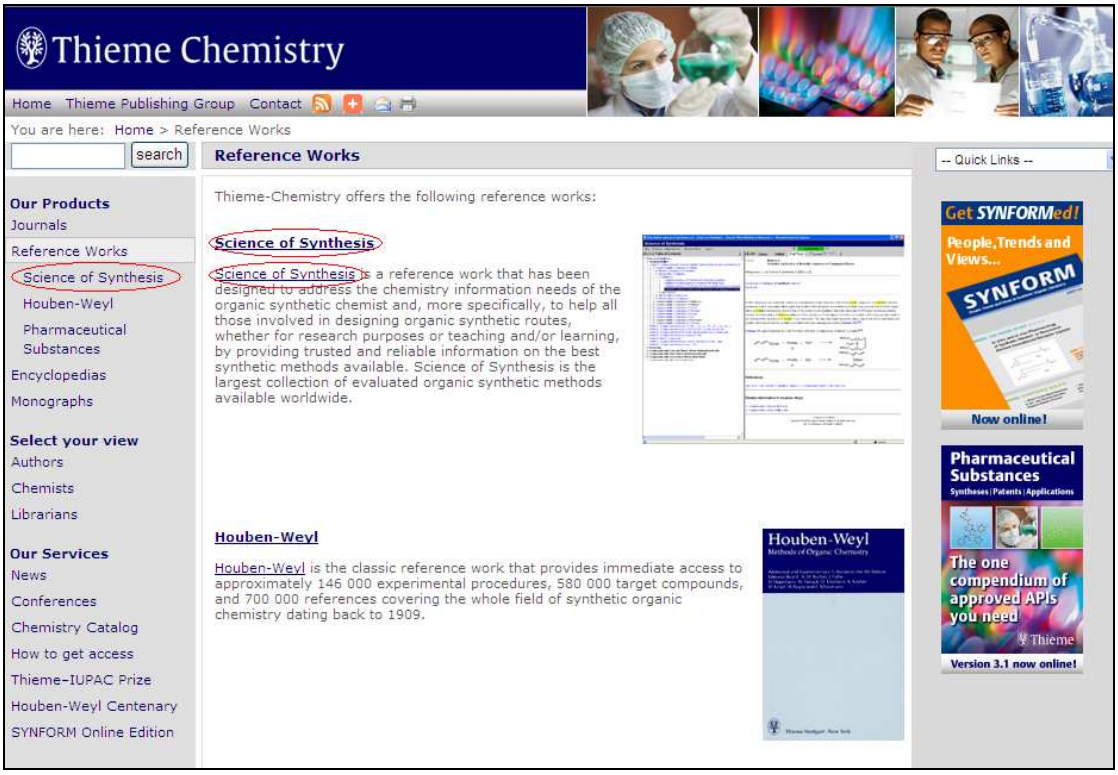


From the "Reference Works" Page (see below), information specific to Science of Synthesis may be accessed by clicking on one of three links, either:

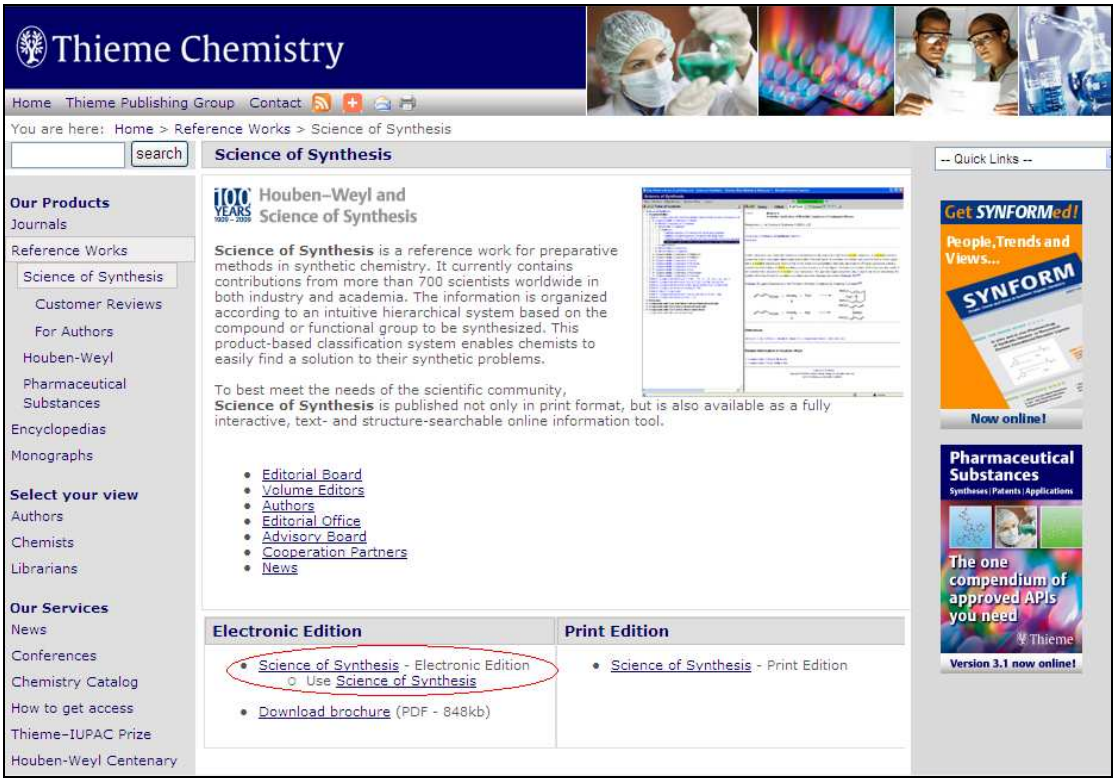
- "Science of Synthesis" under "Reference Works" in the grey sidebar on the left hand side of the screen

Or:

- Either of the "Science of Synthesis" links next to the thumbnail screenshot in the centre of the page.



This will take you to the page shown below, where the electronic version of Science of Synthesis may be accessed by clicking on the "Use Science of Synthesis link" under the "Electronic Edition" heading.

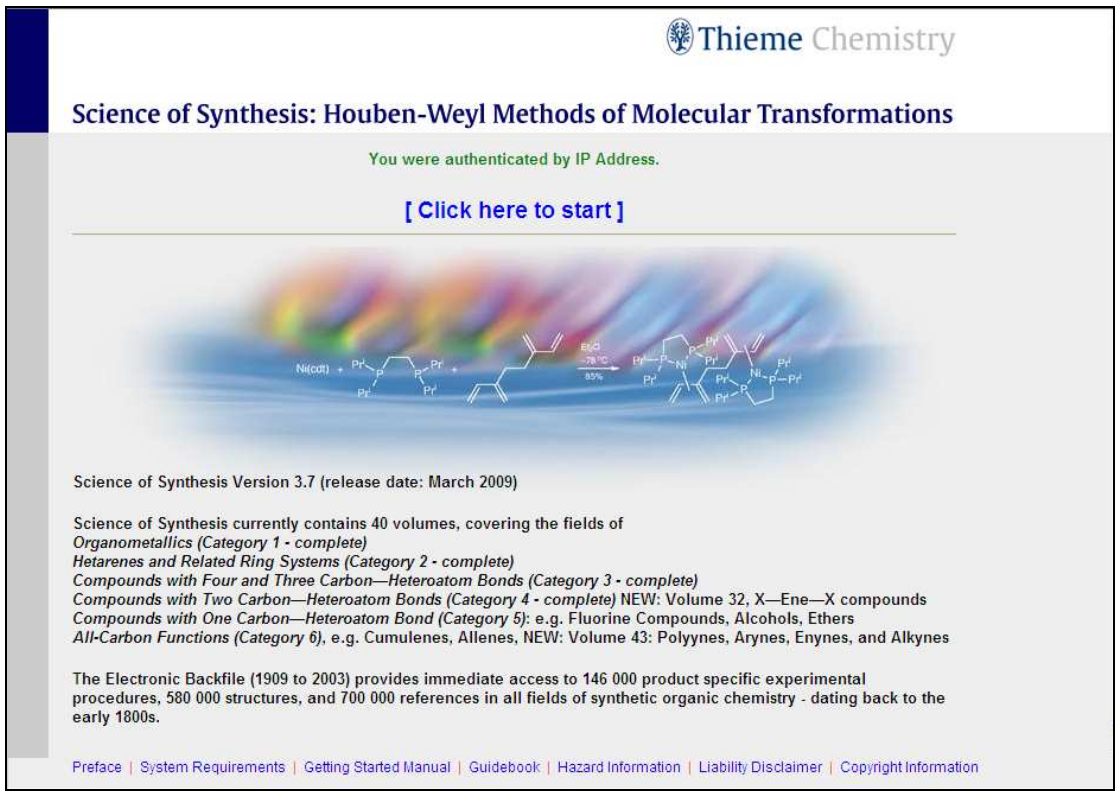


Remember to download and install the plugin icclient_setup.zip if you intend to use ISIS/Draw for the structure search functionality of **Science of Synthesis**!

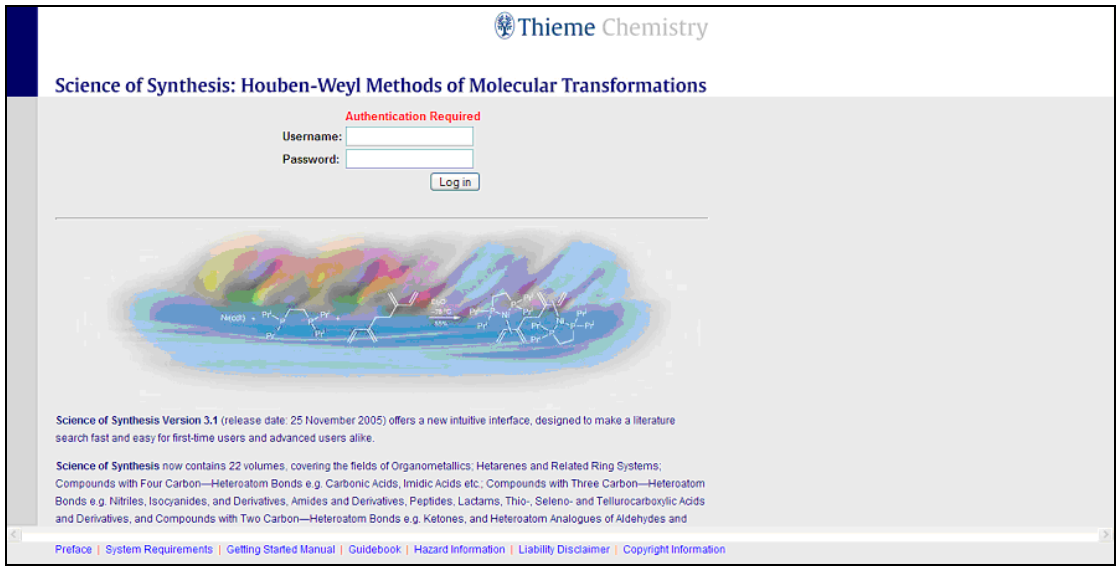
1.3 Login Page

Having arrived at the **Science of Synthesis** Login Page (see Section 1.2) there are two possible ways to proceed:

If your IP address is authenticated automatically, click on the blue [Click here to start] button to access the **Science of Synthesis** start page.



- If your IP address is not automatically recognized you will need to obtain a username and password to log onto **Science of Synthesis**. In this case, or if login problems persist please e-mail our help desk (e-mail: soshelpdesk@thieme-chemistry.com).



- If you wish to register a new account with **Science of Synthesis** please contact our marketing team (e-mail: marketing@thieme-chemistry.com). Institutional users should contact their representative in the appropriate territory.

The Americas
Thieme Institutional Sales
Tel: +1-212-584-4695
Fax: +1-212-947-1112
esales@thieme.com

Outside The Americas
Thieme Institutional Sales
Tel: +49-711-8931-407
Fax: +49-711-8931-797
eproducts@thieme.de

At the bottom of the login page several links provide more information on various aspects of **Science of Synthesis** including:

1) The series preface

2) A page detailing the system requirements (make sure to read this carefully before you use Science of Synthesis)

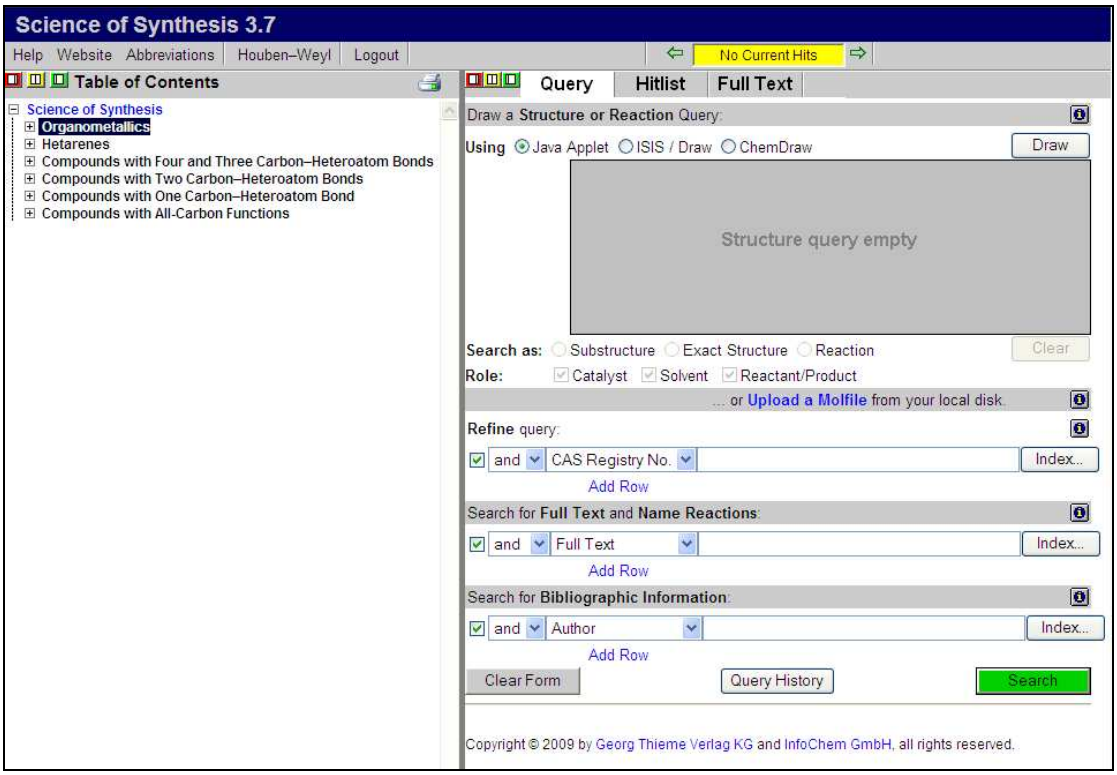
3) The Getting Started Manual

4) The Science of Synthesis Guidebook

5) Hazard, liability and copyright information (make sure to read these documents carefully before you use Science of Synthesis!)

The popup blocker must be deactivated to use **Science of Synthesis**. Please contact your IT support if you require assistance.

1.4 Start Page



The principle features of the start page include:

Table of Contents: Access to the individual documents of **Science of Synthesis** can be achieved via the interactive Table of Contents, which is always displayed on the left-hand side of the screen. Here, the user is able to constantly view their current location within **Science of Synthesis** in accordance with the **Science of Synthesis** classification system, and use the links to move systematically around the product.

Query Page: Displays the current search criteria.

Hitlist Display: Displays the hitlist generated by the current search.

Full Text Display: Displays the full text of a selected hit.

Displays the number of Hits produced by a search. Hits may be navigated using the green arrows, with the right arrow showing the next hit, and left arrow returning to the previous hit.

The radio buttons allow the user to toggle between different display formats. Both screens may be shown (yellow) or only the Table of Contents (red) or search page (green) as required.

Displays a history of previously used search terms.

Help: Provides a link to the Getting Started Manual.

Website: Provides a link to the Thieme Chemistry web page for information about **Science of Synthesis**.

Abbreviations: Provides a downloadable list of all the abbreviations used in Science of Synthesis in pdf format.

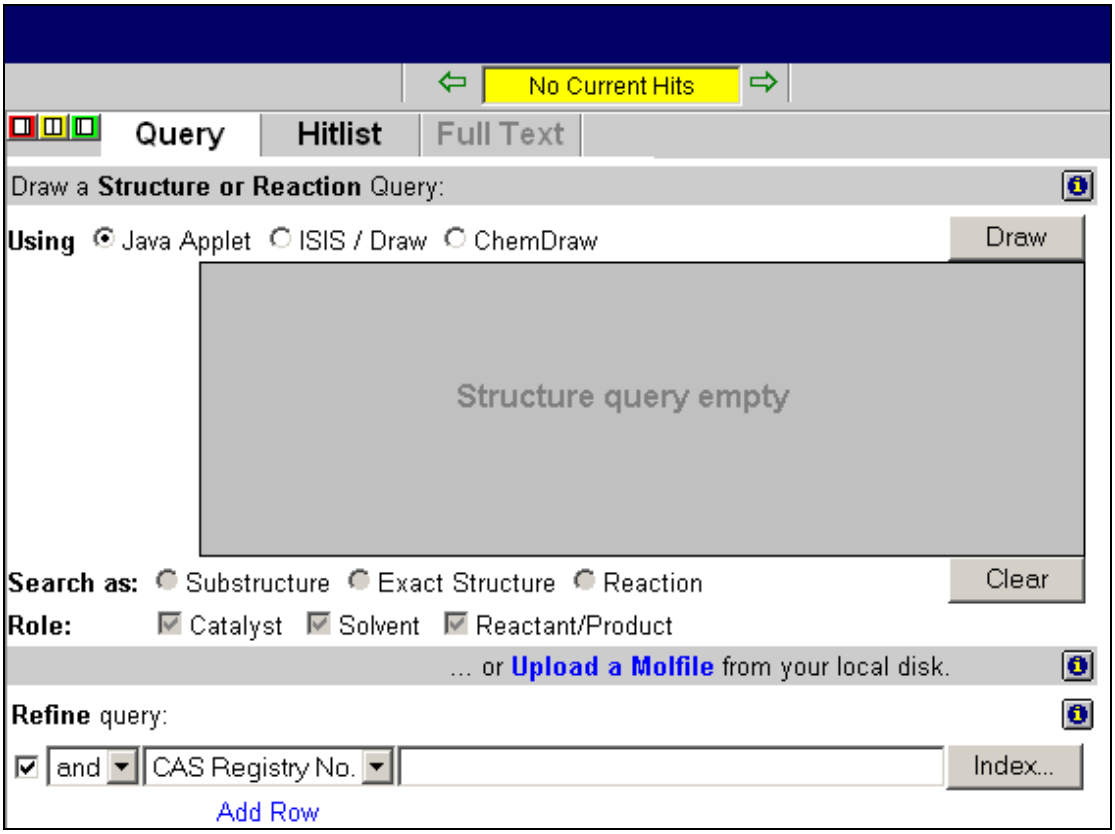
Houben–Weyl: Provides access to the electronic backfile (1907–2004).

Logout: Allows the user to disconnect from the **Science of Synthesis** Web site at the end of a session. Alternatively, the connection will be automatically terminated after a 20-minute period of inactivity.

2 Structure Searching

2.1 Structure Search Fields

The structure query section of the start page is laid out as shown below. Further information on each section may be found by clicking on the information button .



2.1.1 *Drawing Package Options*

The user may choose from three drawing packages to input a structure. These may be selected by clicking on the relevant button. They are:

- ICedit Java Drawing Tool or "Java Applet" (built-in)
- ISIS/Draw 2.5 (commercial, requires plugin)
- ChemDraw 7.0, 9.0, and later (commercial)

In all cases it is recommended that users consult the system requirements for **Science of Synthesis** (Section 1.1) to check that their drawing packages meet the necessary requirements.

2.1.2 *Structure Search Options*

Three options are available for searching structures within the **Science of Synthesis** electronic product: You may search by Substructure, Exact Structure, or Reaction.

Substructure: Locates all molecules containing the substructure drawn. Variable substitution is allowed at on non-specified atoms within the structure.

Exact Structure: Finds only those molecules with the exact structure drawn.

Reaction: Allows the specification of reactants and/or products within a reaction scheme, and finds all molecules with the substructure drawn.

The default setting for any search is Substructure.

In order to carry out a reaction search an arrow must be drawn using a drawing package.

It is not possible to specify intermediate products within a multi-step reaction i.e. a reaction scheme A→B→C is not searchable. However, it is, of course, possible to search for the reactions A→B, A→C, or B→C.

2.1.3 Structure Role Options

It is possible to specify the role of a given structure. There are currently three options:

Catalyst: The given structure acts as a catalyst.

Solvent: The given structure acts as a solvent.

Reactant/Product: The structure is a reactant or product.

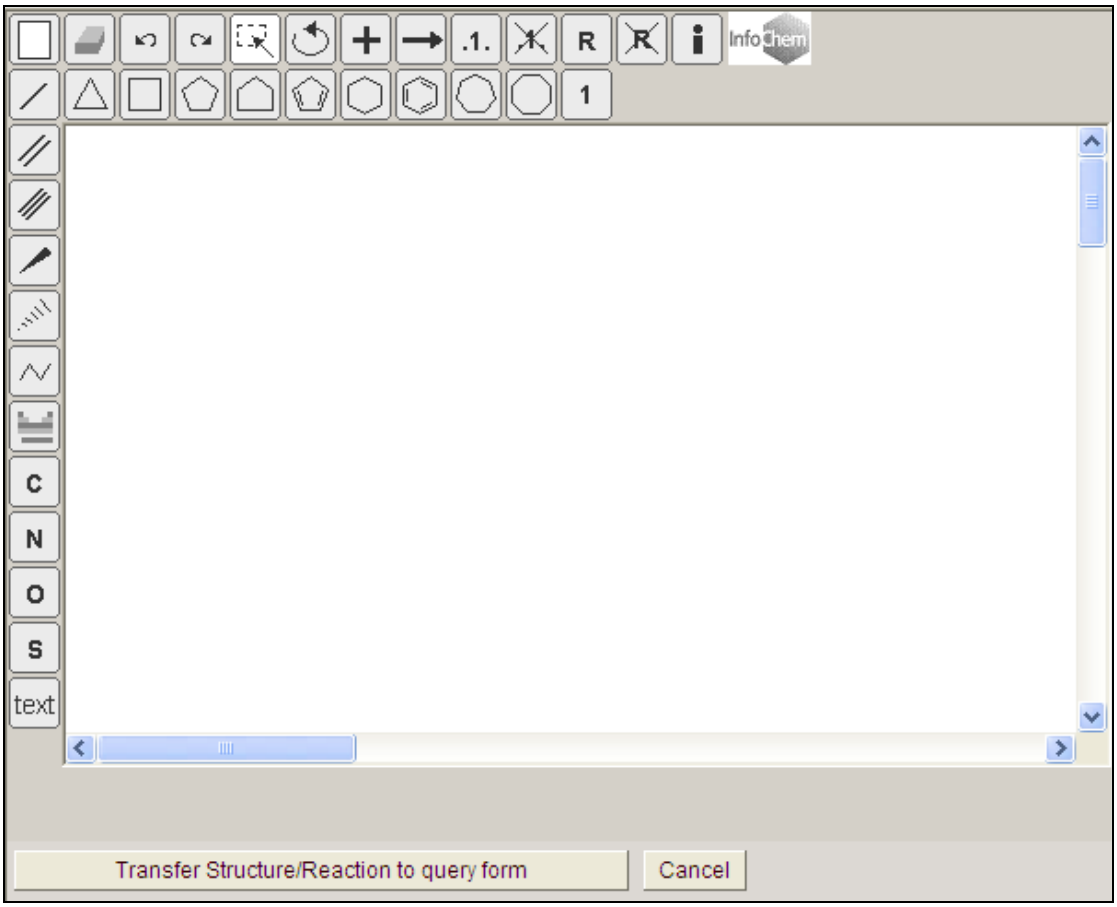
The default search setting is for all options to be active.

2.2 Drawing a Structure or Reaction Query

2.2.1 Drawing with the ICedit Java Drawing Tool

2.2.1.1 Starting ICedit

Select the ICedit (Java Applet) drawing package. Then click Draw, or click on the structure window. The drawing software will start automatically, and the drawing window will be displayed.



The following buttons are available in the drawing window

Button	Title	Usage
	single bond	draws a single bond or changes an existing bond
	double bond	draws a double bond or changes an existing bond
	triple bond	draws a triple bond or changes an existing bond
	wedged bond	draws a wedged bond or changes an existing bond
	hatched bond	draws a hatched bond or changes an existing bond
	draw chain	draws a chain of varying length

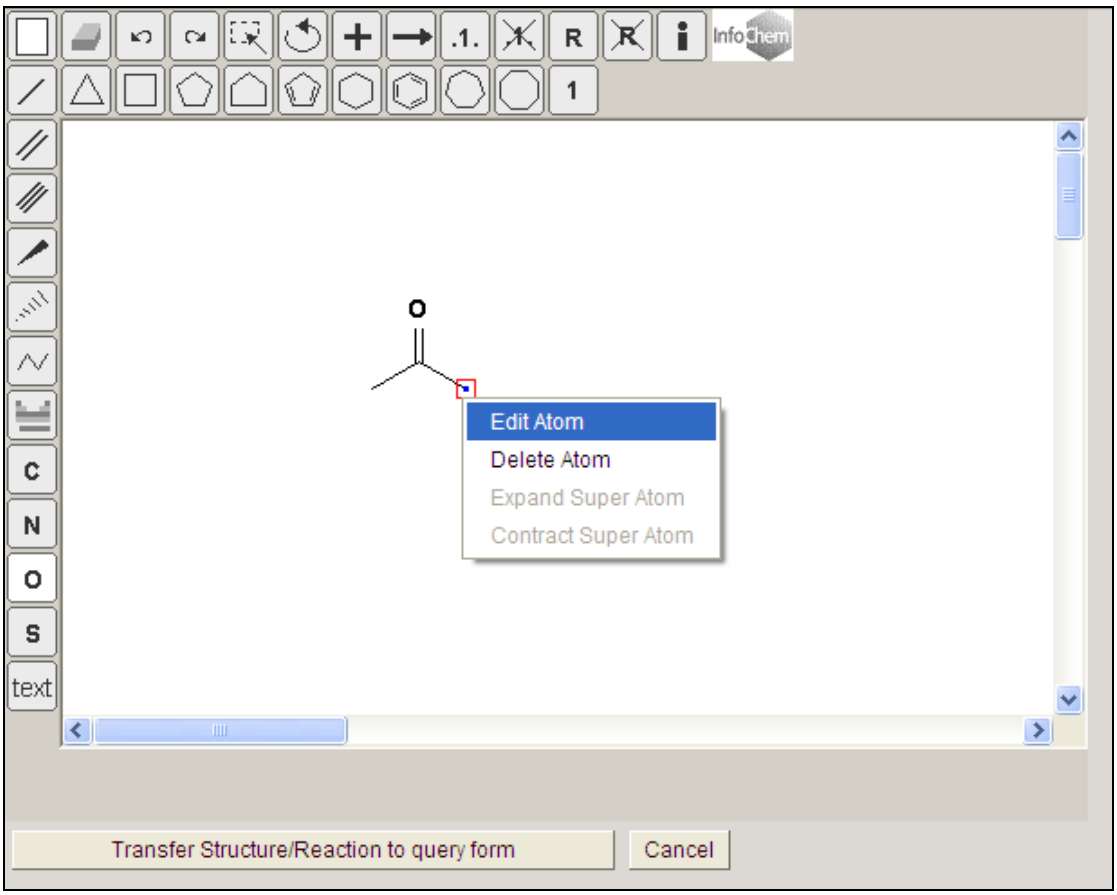
	open periodic table	opens a periodic table to select any atom and specify its charge, valence, isotope etc
	draw C atom	draws a C atom or converts an existing atom
	draw N atom	draws a N atom or converts an existing atom
	draw O atom	draws a O atom or converts an existing atom
	draw S atom	draws a S atom or converts an existing atom
	text tool	add text to the drawing window-no current application
	cyclopropane	draws a cyclopropane ring
	cyclobutane	draws a cyclobutane ring
	cyclopentane	draws a cyclopentane ring
	cyclopentane	draws a “flat” cyclopentane ring
	cyclopentadiene	draws a cyclopentadiene ring
	cyclohexane	draws a cyclohexane ring
	benzene	draws a benzene ring
	cycloheptane	draws a cycloheptane ring
	cyclooctane	draws a cyclooctane ring
	atom numbering	shows atom numbering in the drawing window
	clear screen	opens a new drawing window
	delete object	deletes selected object
	undo	undoes the last action
	redo	repeats last action
	select object	selects a single object or an entire structure
	rotate	rotates a selected object
	reaction plus	adds a reaction plus when drawing components for a reaction query
	reaction arrow	adds a reaction arrow when drawing reactants and products for a reaction query
	atom mapping	adds atom mapping to selected atoms
	atom mapping	removes atom mapping from selected atoms
	R-group	adds a user defined R-group to a search query
	R-group	removes a user defined R-group from a search query
	dialogue box	shows information on this version of ICedit

2.2.1.2 Drawing Features in ICedit

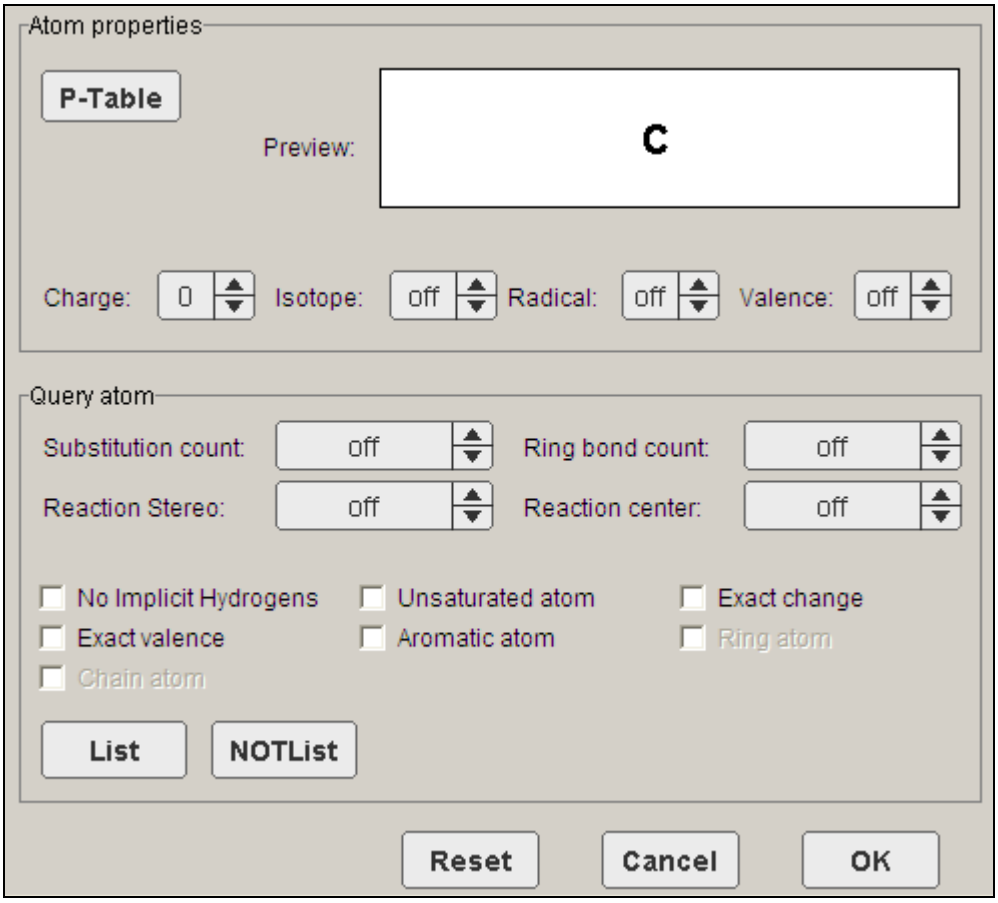
The button panels within the ICedit drawing window may be used to draw simple structures. However, the ICedit drawing tool contains several functions by which additional information may be added to a structure. This is especially useful in that it allows detailed searches without the need to explicitly draw out the entirety of a structure.

2.2.1.2.1 Using the Edit Atom Function

It is possible to define the properties of an atom in a structure by using the atom query feature. To access this function move the cursor over any atom in a structure, such that it is highlighted by a red box. Click on the atom using the right mouse button and select "Edit Atom" from the available list.



This gives access to the "Draw an atom" window where most of the search options are located.



Substitution Count: Allows the user to specify the number of non-hydrogen substituents on an atom.

Ring Bond Count: Allows the user to specify the number of bonds to the atom that are part of rings.

Reaction Stereo: Allows the user to indicate whether the stereochemistry at a center is retained or inverted.

Reaction center: Allows the user to indicate whether the atom is a reacting center.

No implicit Hydrogens: The atom has zero hydrogen atoms attached.

Unsaturated atom: The atom is unsaturated (but not aromatic).

Exact valence: The exact valence on an atom is shown.

Aromatic atom: The atom is part of an aromatic system.

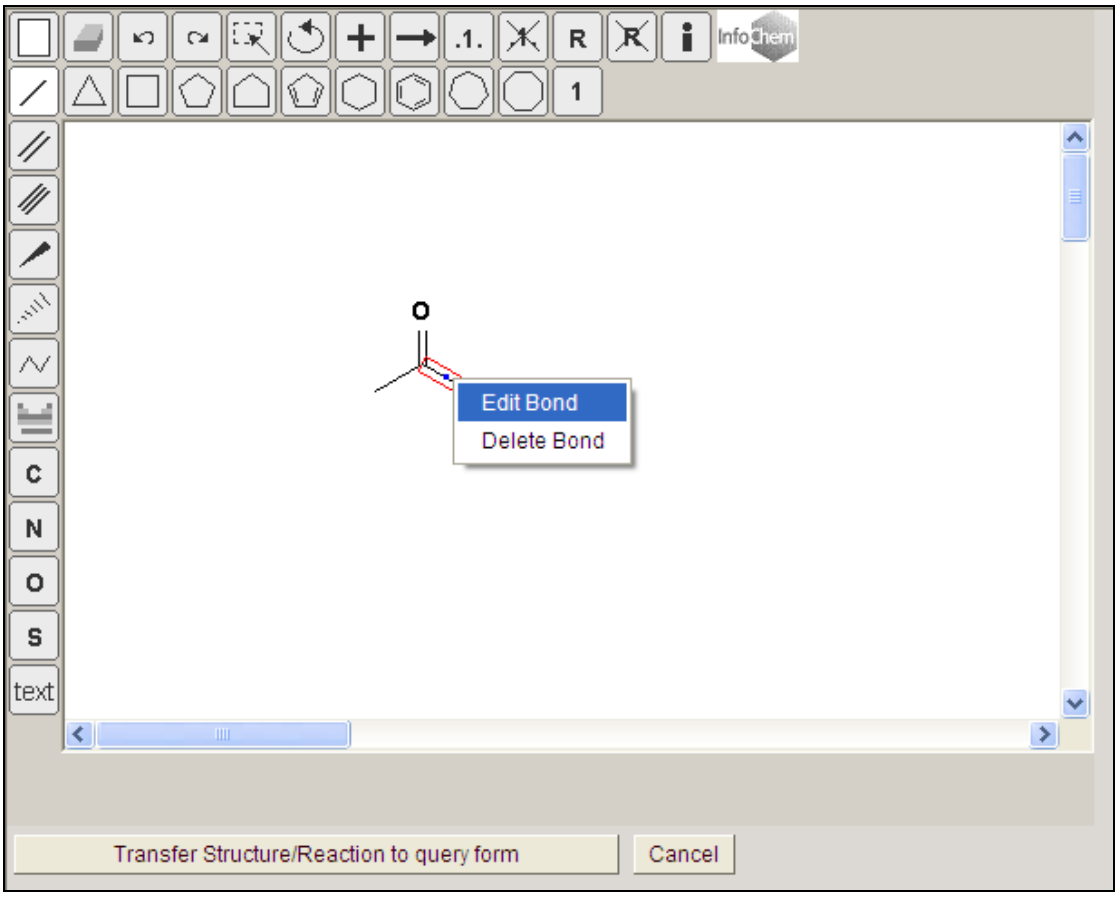
Ring atom: The atom is part of a ring.

Chain atom: The atom is part of a chain.

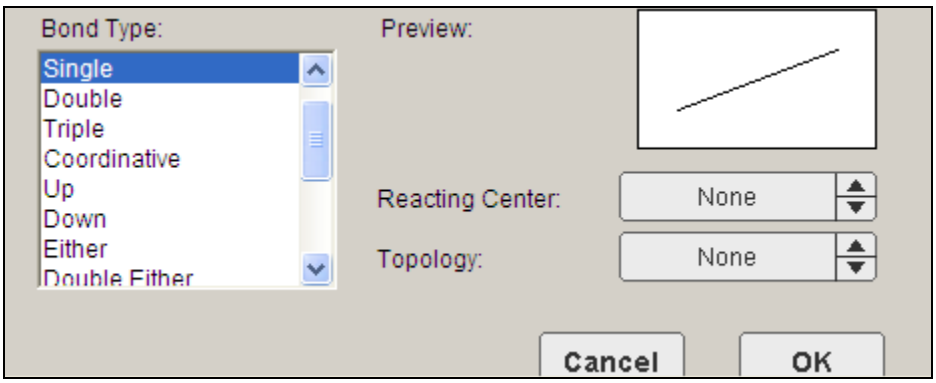
Once the required settings have been chosen, clicking on "OK" returns the settings to the drawing window. "Cancel" closes the query window without making any changes, and "Reset" returns all checked boxes to the default settings.

2.2.1.2.2 Using the Edit Bond Function

In a manner analogous to that for atom queries, it is possible to add further information to chemical bonds within a structure. To access this function, hold the mouse over the bond in question, click on it using the right mouse button and select "Edit Bond" from the menu.



This opens the Edit Bond window, in which are contained the various available options.



Bond Type: Allow the user to specify the type of bond.

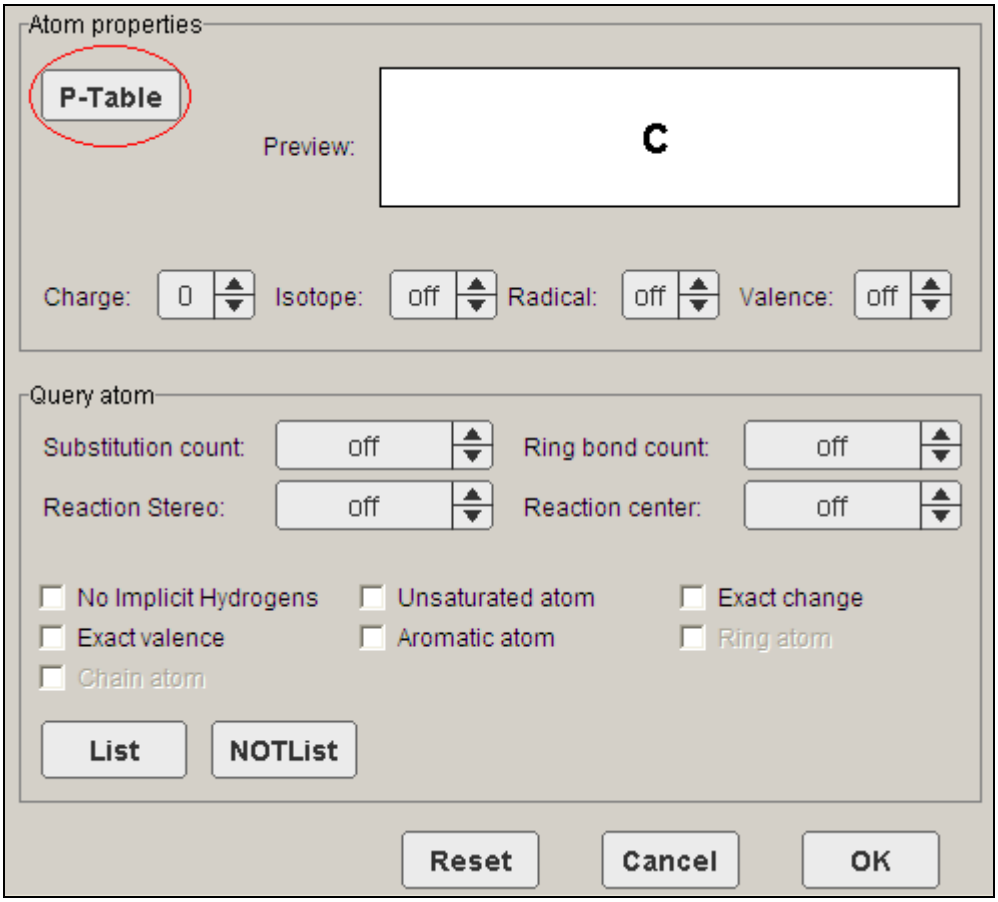
Preview: A graphical display of the type of bond currently selected.

Reacting Center: Allows the user to assign a bond as being unchanged, made, broken, or otherwise altered.

Topology: Allows the user to specify whether a bond is in a ring or a chain.

2.2.1.2.3 Using Generic Groups (A, Q, X, R)

Clicking on the "P-Table" link in the "Draw an atom" window, or on the button in the main drawing pane (see Section 2.2.1.1) loads a periodic table:



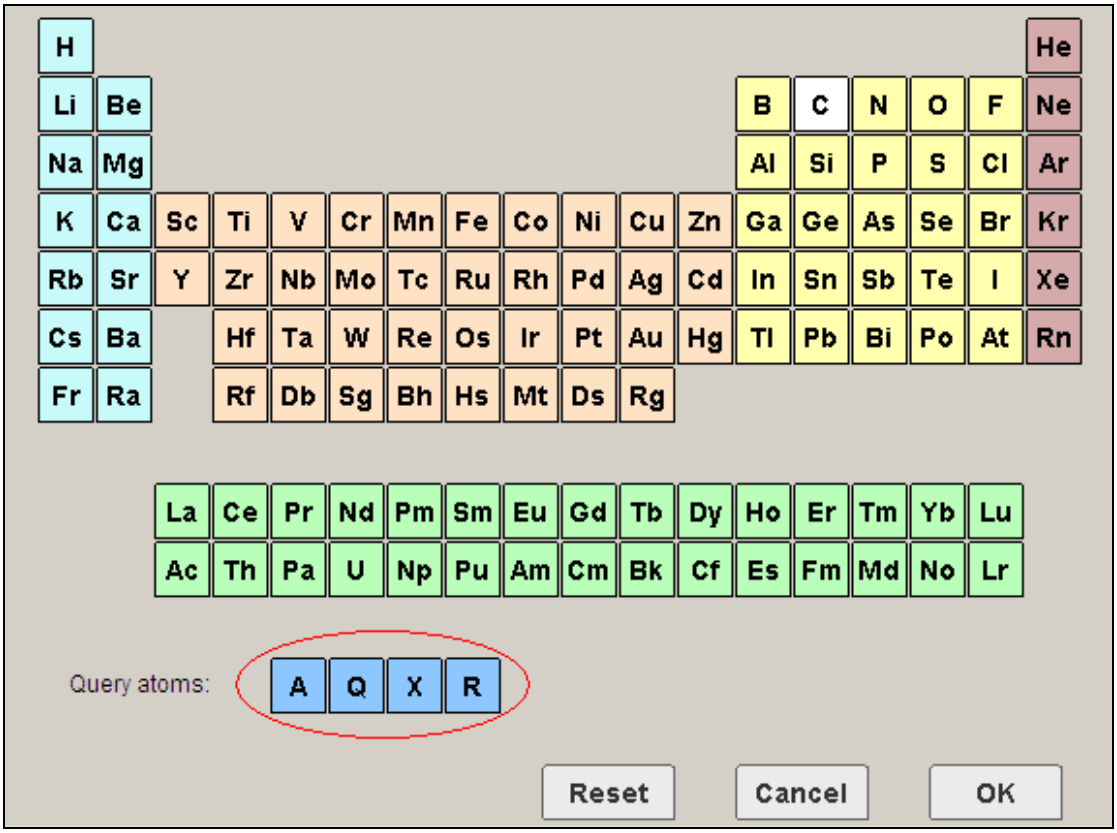
This periodic table features a series of blue buttons (A, Q, X, R) that may be used to search for generalized structures, where:

A: Any atom except hydrogen

Q: Any atom except hydrogen and carbon

X: Any halogen atom (not currently available)

R: Any R-group (defined by molecular weight)

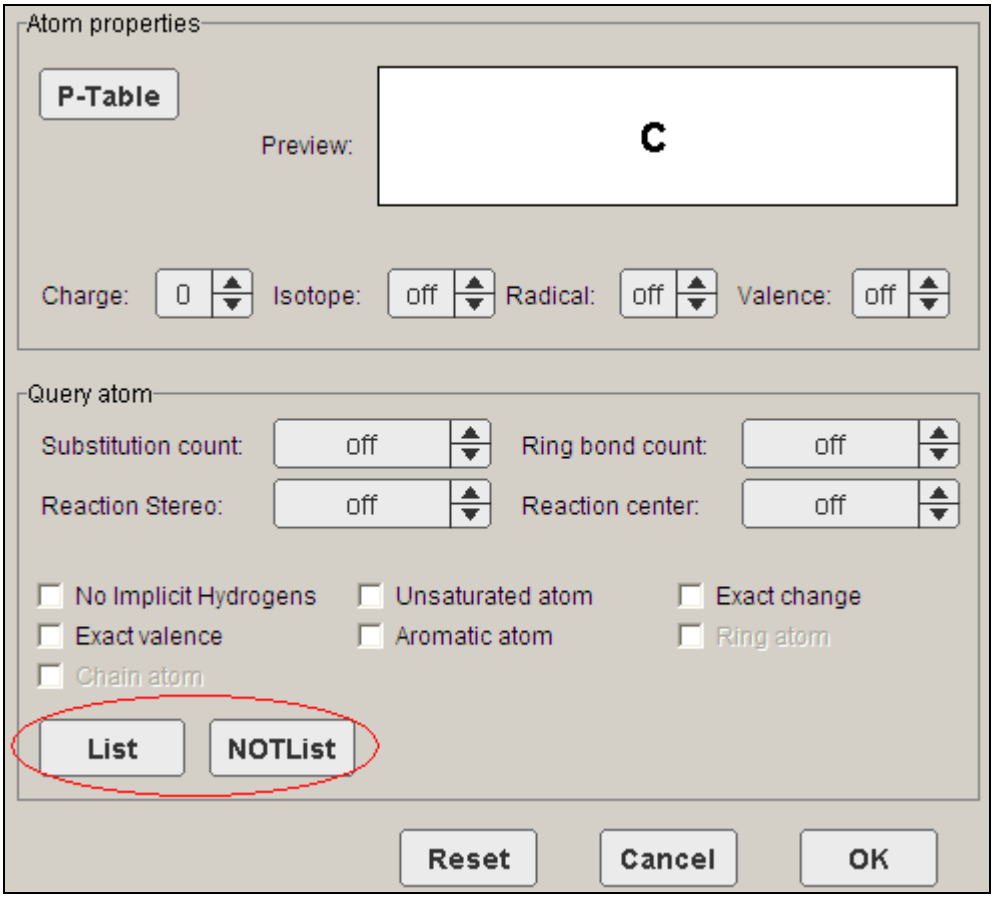


The following procedure is thus required to introduce a general group:

- Select a highlighted atom with the right mouse button.
- Select the Edit Atom option.
- Click on P-Table.
- Select a query atom as required.
- Click OK

2.2.1.2.4 Using Lists and NotLists

As well as specifying the single element that comprises each centre in a structure, it is also possible to group elements together at a single position, and run a search where only those elements are considered (List) or only those elements are excluded (NOTList).

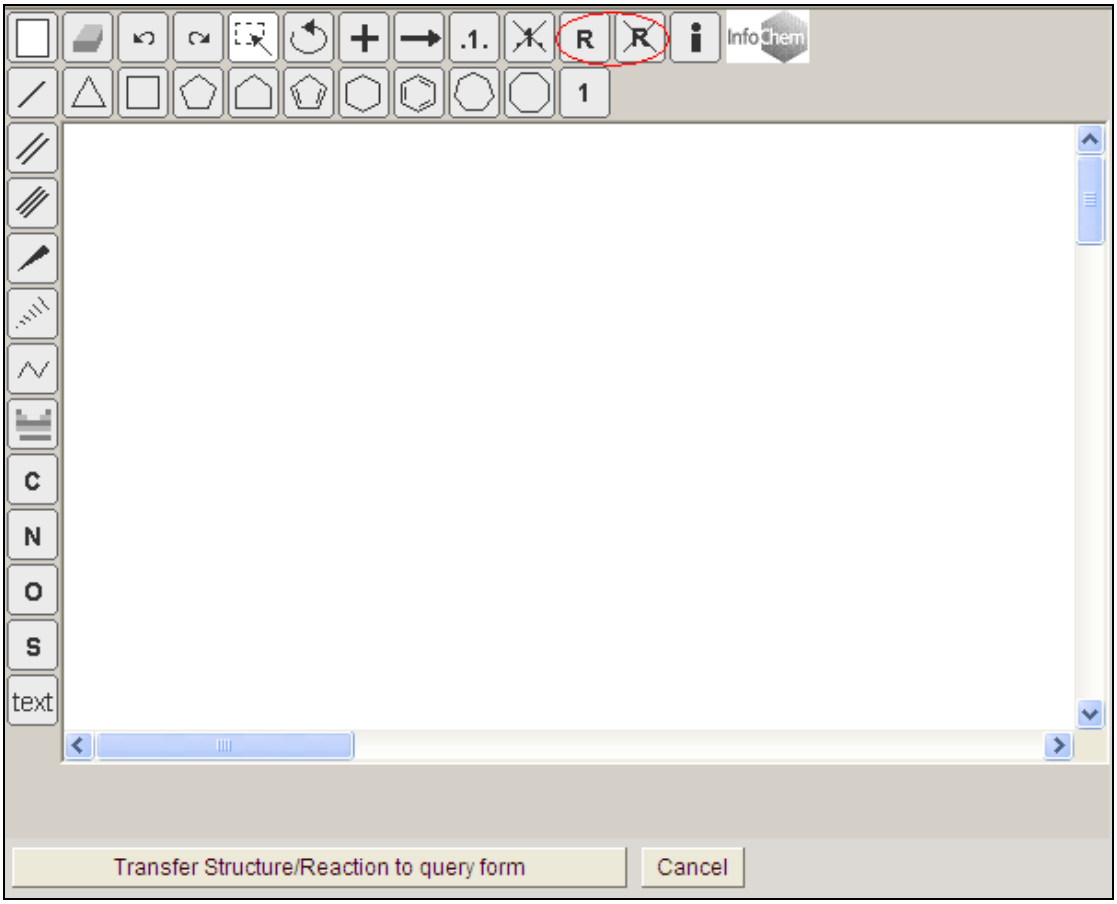


The following procedure is thus required to introduce a list:

- Select a highlighted atom with the right mouse button.
- Select the Edit Atom option.
- Click on LIST or NOTList as required.
- Select from the resulting periodic table those elements that are to be added to the group.
- Click OK

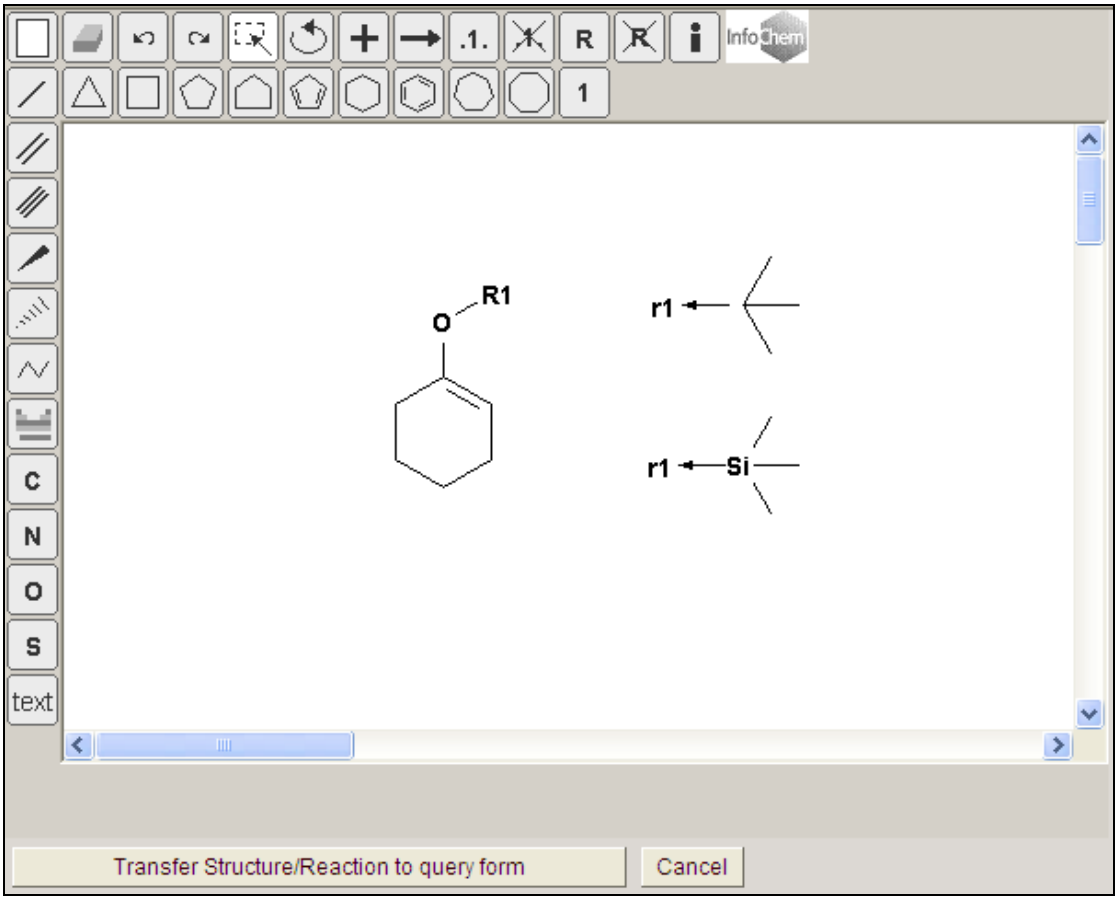
2.2.1.2.5 User Specified R-groups

It is possible for the user to define variable substituents. This is accomplished using the R-group buttons in the main drawing panel.



The procedure is as follows:

- Draw the structure to be used as a search query.
- Click on the R-Button, and click on the point of attachment of the R-group.
- Adjacent to this structure draw the various R-groups to be considered.
- In each case click on the R-button and then on the point of attachment.



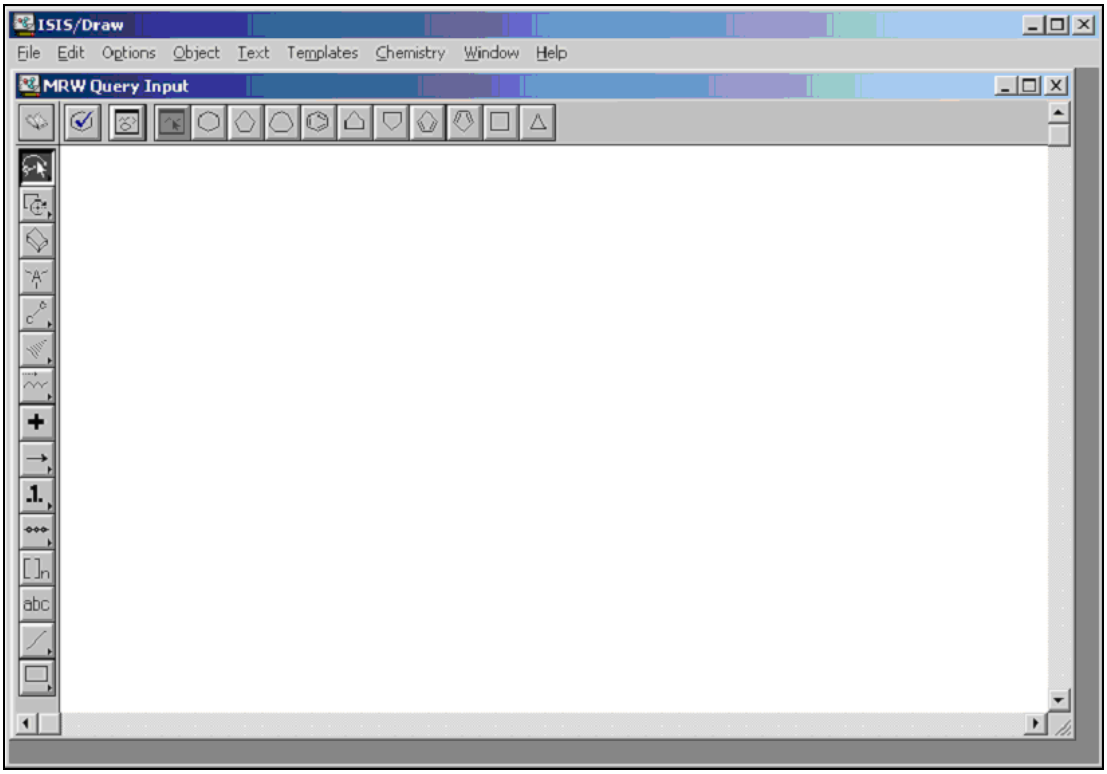
2.2.1.3 Transferring a Structure to the Search Window

Once drawing is complete the 

button on the bottom left hand corner of the window may be used to transfer the structure to the search window.

2.2.2 Drawing with ISIS/Draw

Select the ISIS/Draw drawing package. Then click Draw, or click on the structure window. The drawing software will start automatically, and the drawing window will be displayed.

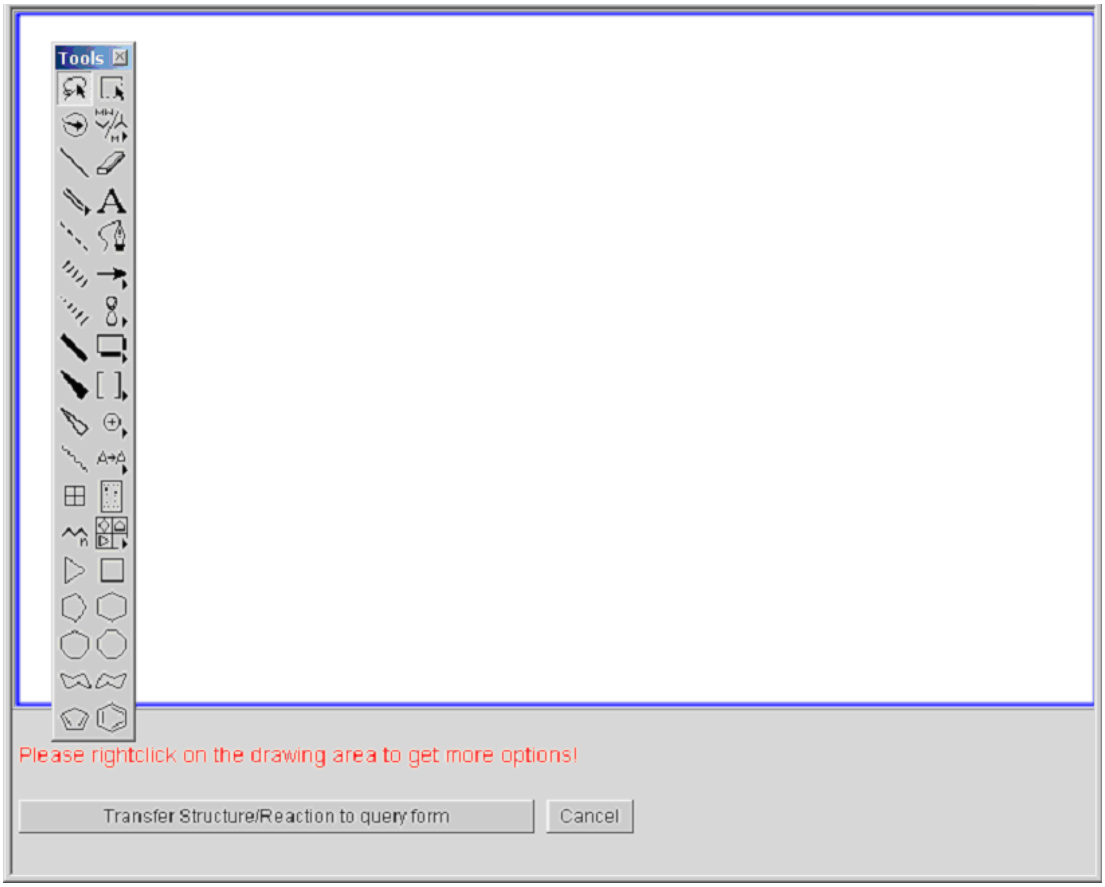


The open book icon found in the top left hand corner of the screen is used to transfer the structure to the search screen once drawing is complete.

2.2.3 Drawing with ChemDraw

Select the ChemDraw drawing package. Then click 

, or click on the structure window. The drawing software will start automatically, and the drawing window will be displayed.



The initial window is featureless. The main tool bar used in ChemDraw can be activated by the following procedure:

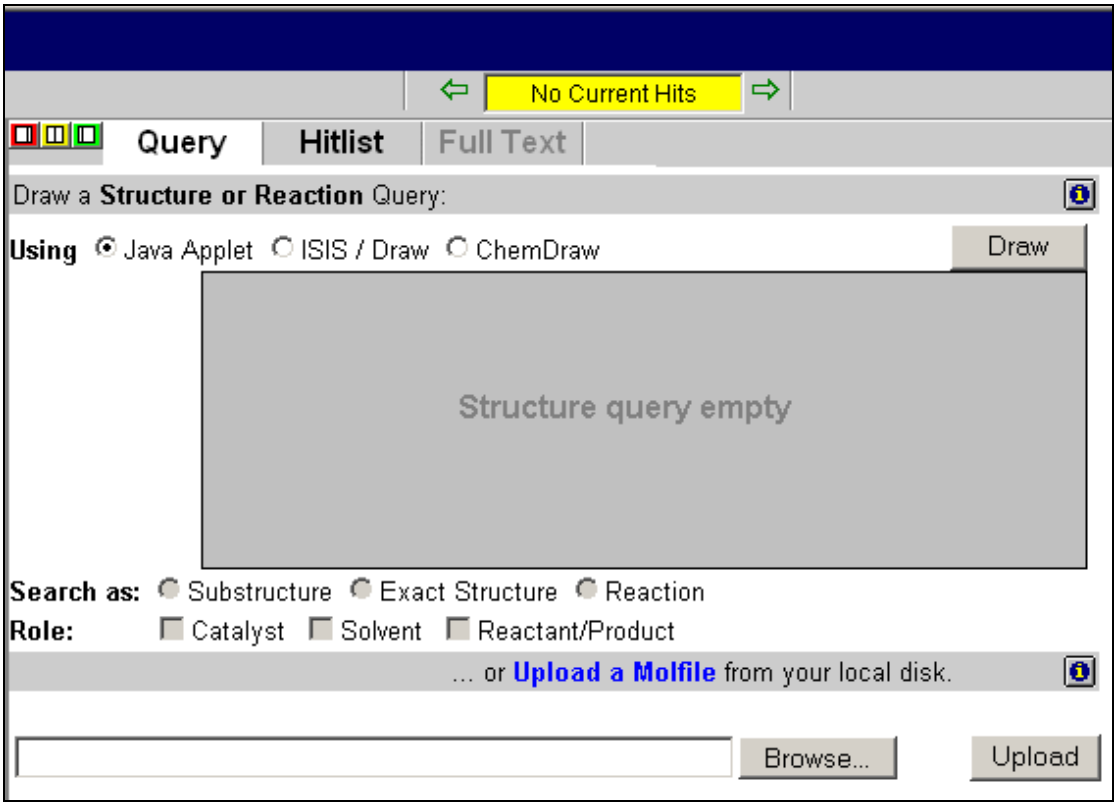
- Right click on the drawing area to activate the menu system.
- Selecting View.
- Select Show Main Tools.

Once drawing is complete the 

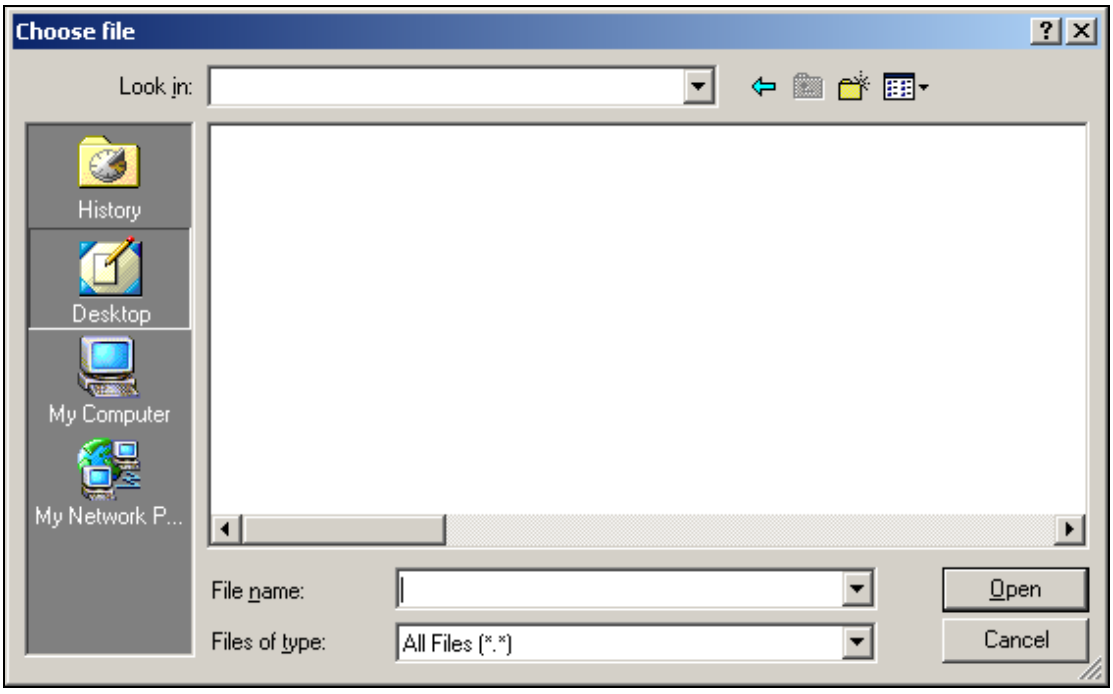
button on the bottom left hand corner of the window may be used to transfer the structure to the search window.

2.2.4 Uploading a Molfile

It is possible to load a previously saved structure in Molfile format from your local disk into the search window instead of drawing a structure. To do this click on **Upload a Molfile**. A Browse field will be opened:



Click on Browse... to find the directory where your Molfiles are saved.

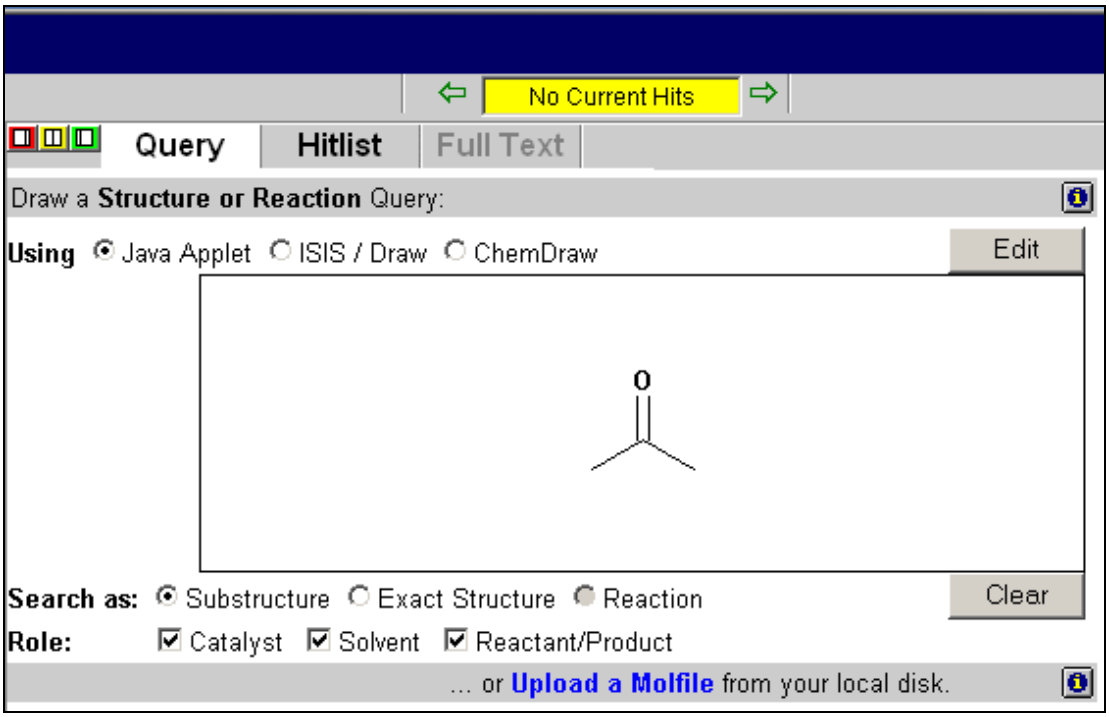


Select the Molfile you want (name.mol), click on Open, and then on Upload on the start page, and the structure will appear in the search window.

To remove the Browse window from the start page, click on **Upload a Molfile** a second time.

2.3 Running a Structure Search

To run a structure search transfer the structure to be searched to the search window of the start page.



- Select whether the structure is a substructure or an exact structure.

  NOTE: The default setting is substructure. Reaction will be chosen automatically if the structure imported contains a reaction arrow.

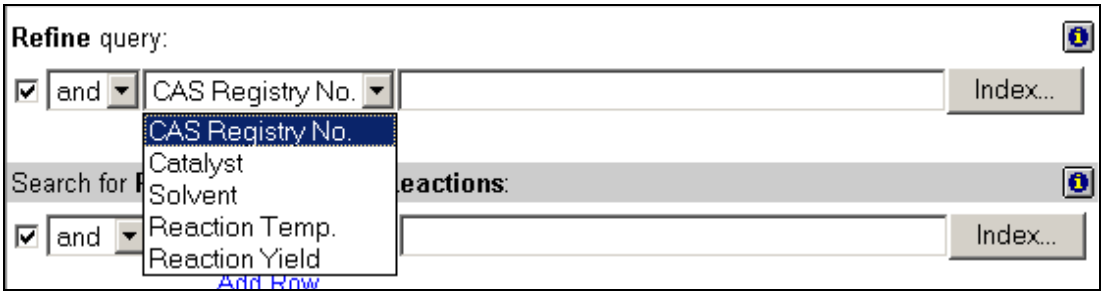
- Chose the role of the structure in a reaction (i.e., catalyst, solvent, reactant/product).

  NOTE: The default setting is for all three options to be selected

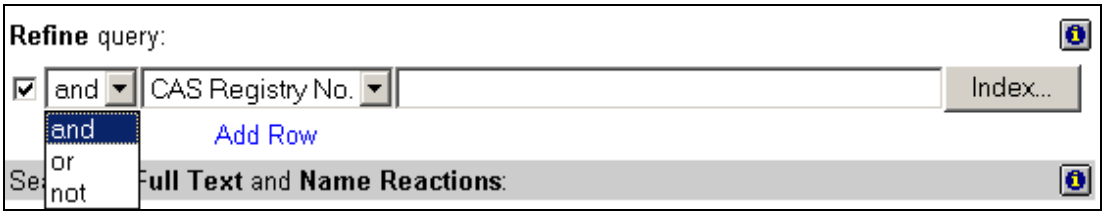
- To start the search within **Science of Synthesis**, simply click on Search. If you wish to edit the structure, you can return to the drawing window by clicking on Edit.

2.4 Refining a Structure Search

It is possible to refine a structure search by including further information that must be contained in a scheme with the structure. This includes the ability to search by CAS registry number, and also to include catalysts, solvents, and reaction temperatures as well as yields.

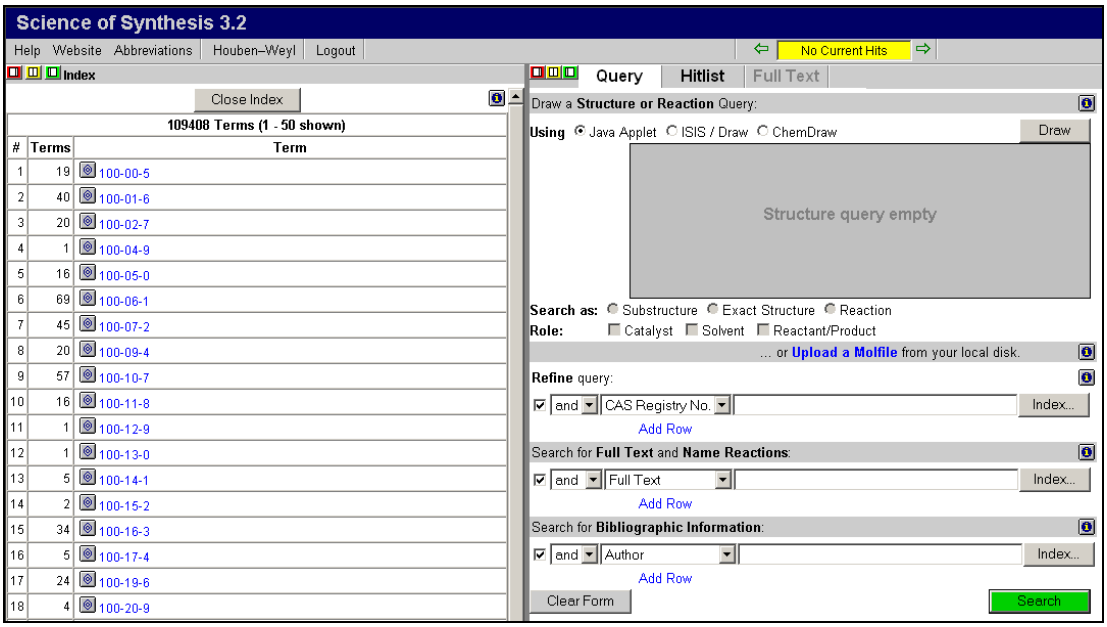


To search for more than one variable, click on Add Row. These variables may be searched in a variety of combinations through the use of logical instructions (AND, OR, NOT) that are available from the drop down box shown below.

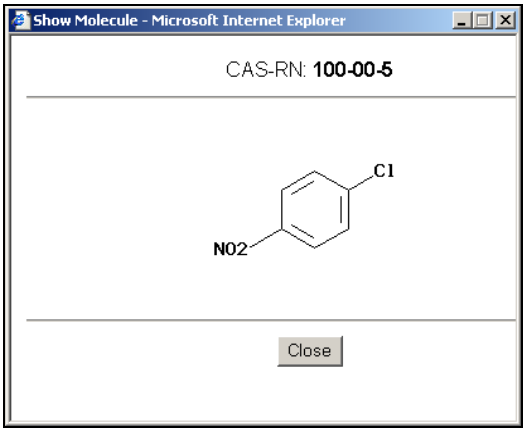


2.4.1 CAS Registry Number

The CAS registry number search field enables you to search exact structures without using the Structure or Reaction query. Clicking on Index... will give all available registry numbers. Alternatively a partial CAS number may be entered, and those entries from the index containing the relevant fragment will be shown.



Clicking on displays the chemical structure together with the CAS registry number. For example:



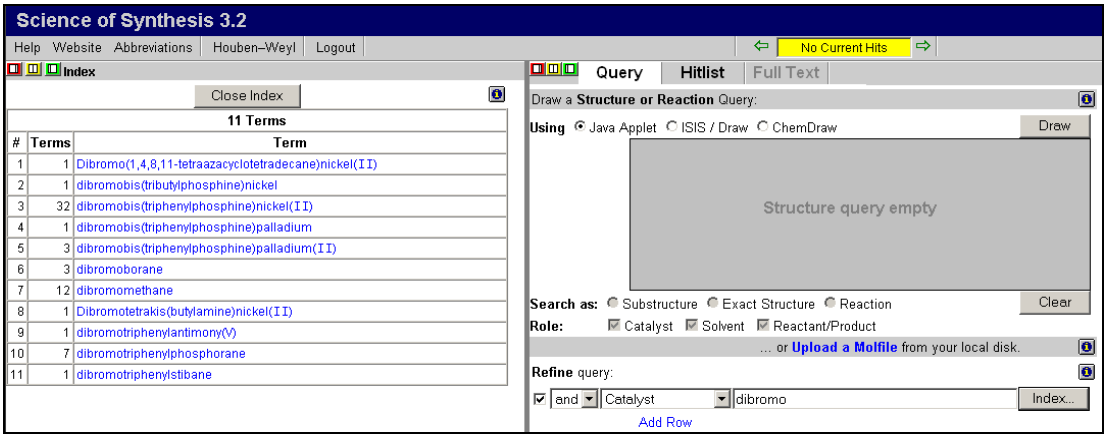
If you click on the blue Registry number, e.g. 100-00-5 the number will be transferred into the search field.

The index may be closed by clicking on the Close Index button that is found at the top of the left hand screen.

2.4.2 Catalyst

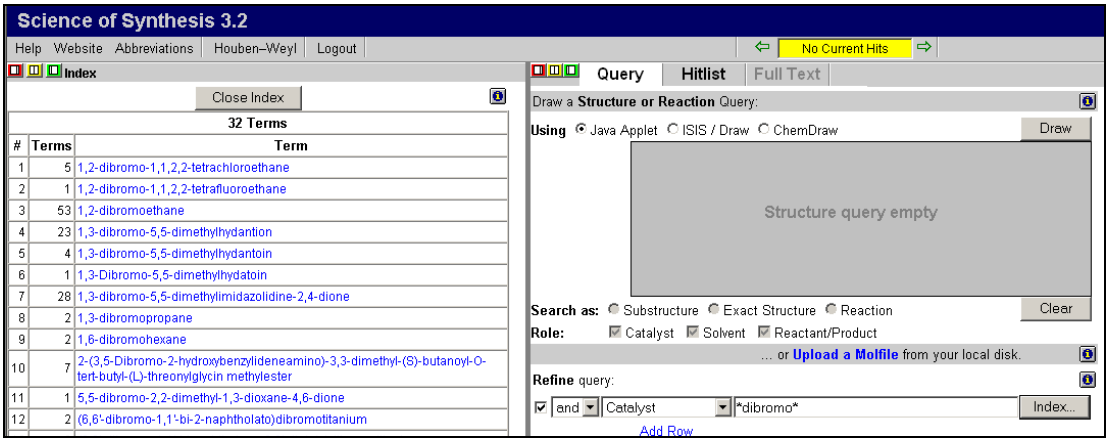
The catalyst index contains the complete or abbreviated names of all the catalytic species that feature in Science of Synthesis.

To refine a structure search using the catalyst option enter the name of the catalyst in its entirety, or enter a fragment of the name and click on Index... to find the correct name



The index will be searched alphabetically for the fragment entered in the catalyst field. To search for an internal fragment (i.e. once which is part of a name but does not start it) then wildcards must be used.

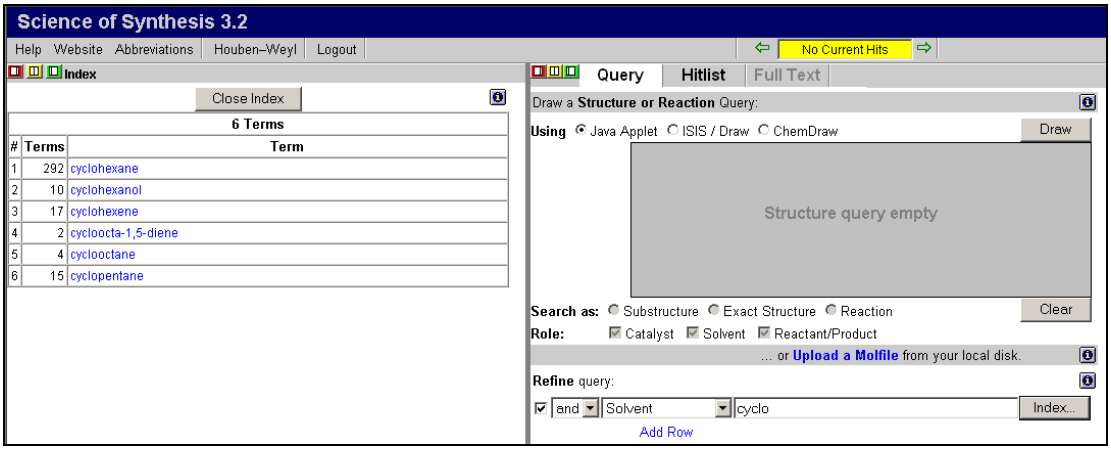
For example, to find "1,6-dibromohexane" you have to enclose dibromo with asterisks as *dibromo* before you click on Index....



To find out more about the use of wildcards in the Index, please see Section 3.1.1.

2.4.3 Solvent

The solvent index contains all the names and abbreviations of solvents used in Science of Synthesis. To refine a structure search by the solvent used simply enter the name of the solvent, or its abbreviation, in the solvent field. Alternatively a fragment of the name may be entered, and the solvent index searched for a match. For example, to find a cycloalkane-based solvent, enter "cyclo" in the solvent field and click Index....



2.4.4 Reaction Temperature

The reaction temperature search field enables refinement of a structure search based on experimental conditions. Temperature ranges may be specified using the numeric operators:

- Closed Range

< Less than

> Greater than

<= Less than equal

>= Greater than equal

The temperature index also lists all reaction temperatures that feature in Science of Synthesis and is useful if searching for unusual reaction conditions.

2.4.5 Reaction Yield

The reaction yield search field enables refinement of a structure search based on experimental yield. Yield ranges may be specified using the numeric operators:

- Closed Range

< Less than

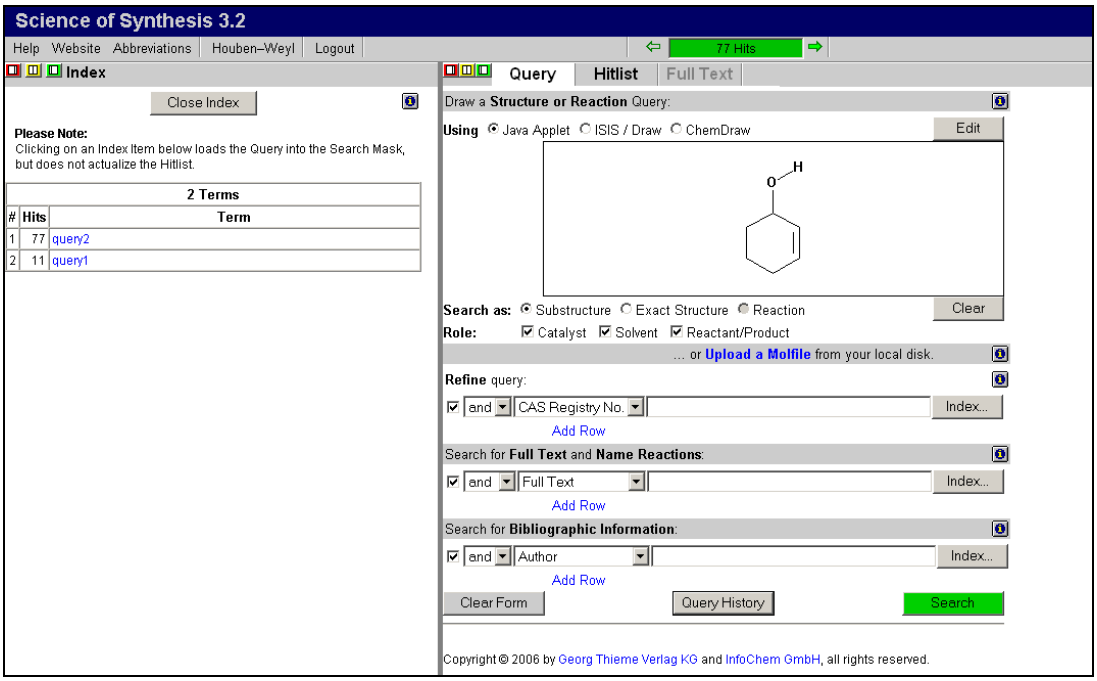
> Greater than

<= Less than equal

>= Greater than equal

2.5 Returning to a Previous Structure Search

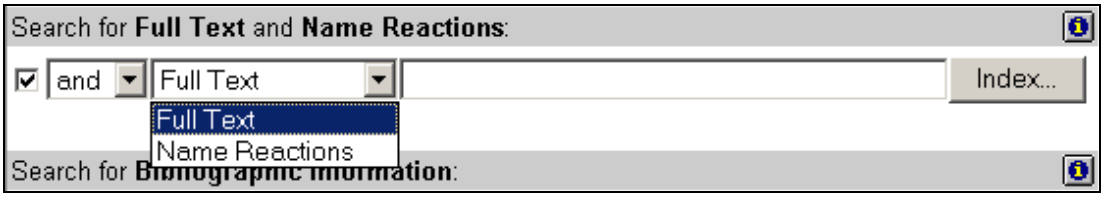
The Query History button may be used to access all the searches that have been run in a particular session. Clicking on the history button opens a sequential index in the left hand screen. This index lists all searches in the order they were performed, and the number of hits for each search.



To access a particular search, click on the blue text shown in the index (e.g., query2), and the details of the search will be automatically loaded into the search page.

3 Full Text and Name Reaction Searching

Full text and name reaction searching is available under the "Search for **Full Text** and **Name Reactions**" drop down menu.



3.1 Full Text Searching

The full text search field allows the user to search for keywords contained within the written text and titles of Science of Synthesis. However, it will not search text contained within schemes or tables.

To perform a full text search, the following procedure should be used:

- Select the desired field from the drop-down menu.
- Enter the keyword(s) required and click on  .

Any number of keywords may be entered, and hits will be generated that contain all of those keywords. Keywords may be grouped together as a single item in two ways:

- Using double quotation marks (e.g., "magnesium chloride").
- Using a hyphen (e.g., magnesium-chloride).

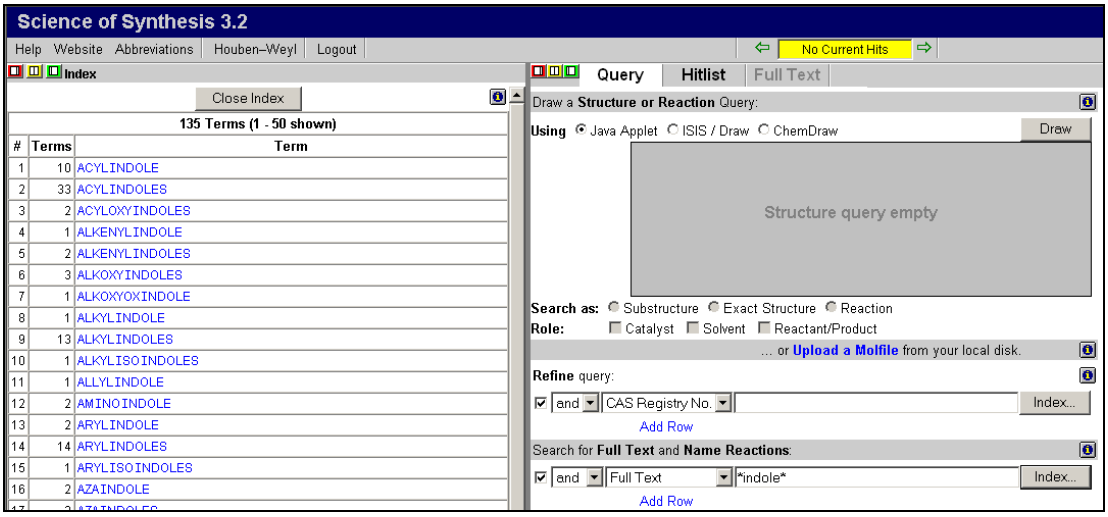
Any hits generated by a full text search formatted in this style should now contain the keywords closely associated in the text. Other points of note include:

- Search terms are non-case sensitive.
- Greek letters (α, β etc) must be written out (alpha, beta etc).

3.1.1 Using the Index and Wildcards

The Index may be used to find variations on a keyword that occur in Science of Synthesis.

To check the index for variations, the following procedure should be used:



- Type the keyword/keyword fragment into the full text field.
- Click on the index button Index....
- Select the desired keyword in blue text.
- Click on Search.

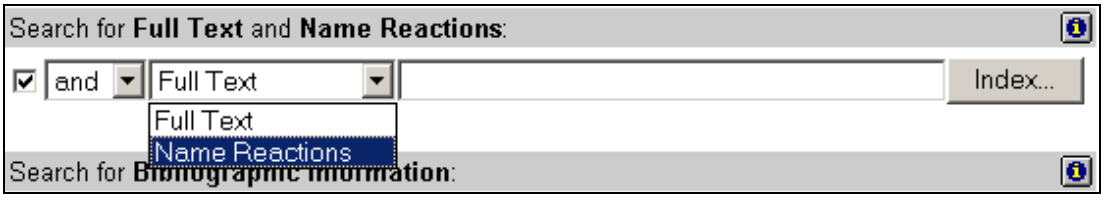
Note: While the full text field can handle multiple keywords, the index function can deal with only one keyword at a time. If multiple keywords are submitted to the index, then only the first in the sequence will be processed.

Wildcards (*, ?) may be used within a keyword search term as substitute for a character, or at the beginning or end of a keyword to truncate the term (see Section 2.4.2). A number of options are possible:

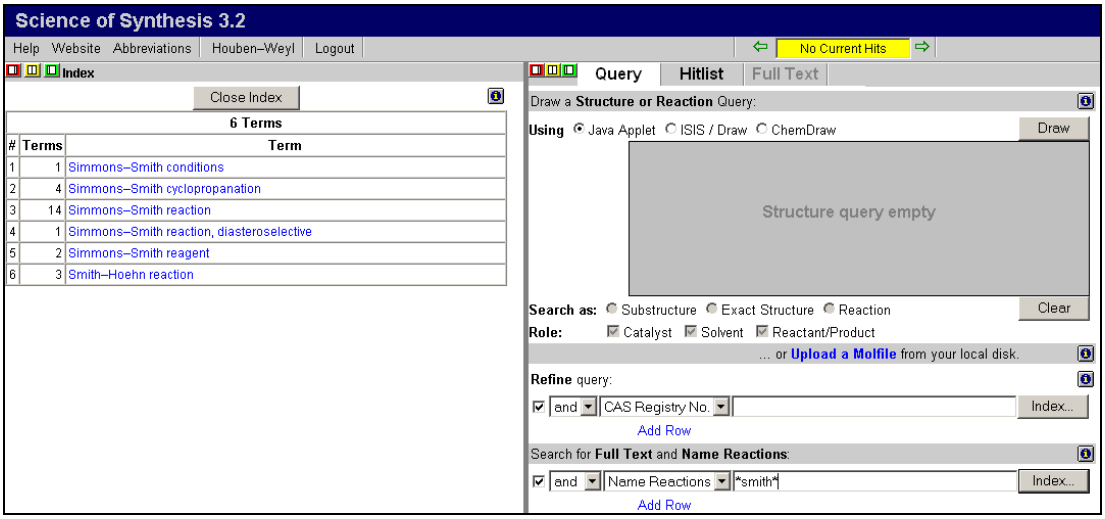
- Asterisks (*) may be used to represent any number of additional characters, including none.
- Question marks (?) may be used to represent either one or no additional characters.

3.2 Name Reaction Searching

The Name Reactions field allows the user to search for a reaction commonly named after a person or persons, and may be accessed by selecting the Name Reactions option in the drop down menu, as shown below.



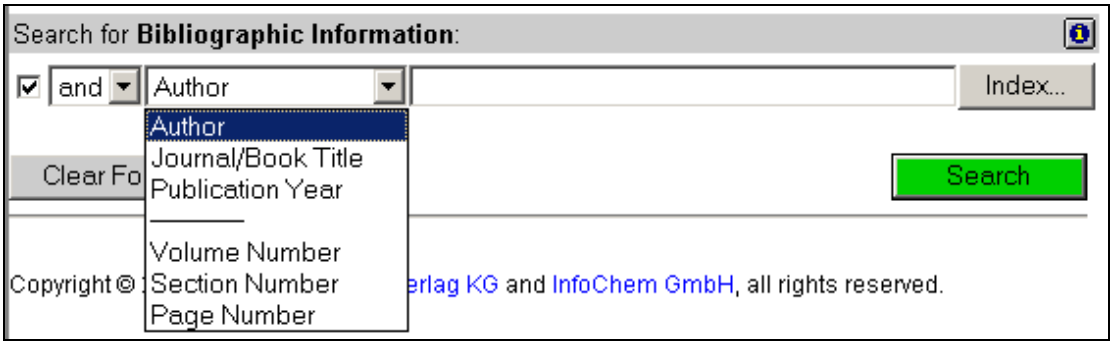
The Name Reaction field may be searched directly, by inputting the full name of the reaction into the text box and pressing Search. Alternatively a fragment of the name may be entered, and all variations contained in Science of Synthesis may be searched using the Index....



NOTE: The name reactions contained in Science of Synthesis have been manually selected. Therefore, a search of this sort will also include any hits where the name of the reaction is not explicitly mentioned but the reaction is of the correct type.

4 Bibliographic Information Searching

The Bibliographic Information field allows the user to search for information regarding reference citations in Science of Synthesis.



Several settings are available from the drop down menu, and these may be combined using logical instructions (AND, NOT, OR). The search terms are split into two groups, those that are used to search primary literature references, and those that are used to search within Science of Synthesis.

Author: Finds any incidence of an author's name in the references (includes Science of Synthesis sections). The author's name must be entered before the initials. Initials and spellings may be checked using Index....

Journal/Book Title: Finds any incidence of a journal or book title. Journal abbreviations may be checked using Index....

Publication Year: Finds any incidence of a reference (including Science of Synthesis sections) published in a given year.

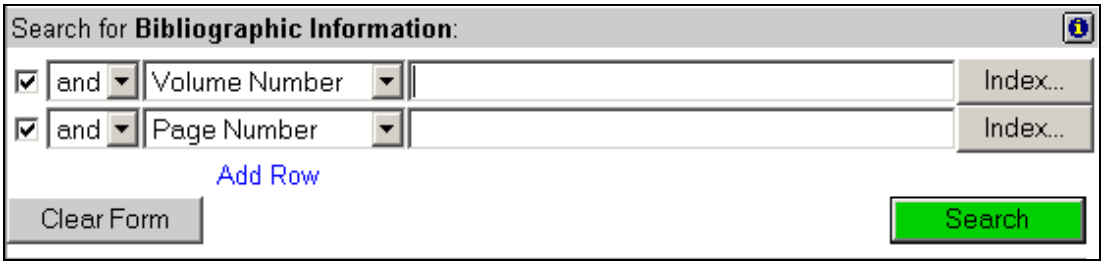
Volume Number: Finds all sections of a Science of Synthesis volume.

Section Number: Finds a section within a Science of Synthesis volume. **NOTE:** The section number search will only find sections that contain text before the next section heading.

Page Number: Finds a particular page within a Science of Synthesis volume. **NOTE:** If the page required contains no titles, the page number search will generate a hit for the title page of the relevant section.

4.1 Searching a Reference to Science of Synthesis

To locate a reference in Science of Synthesis of the format "Author, A. B., *Science of Synthesis,* (Year) **Volume**, Page." the following procedure should be used:

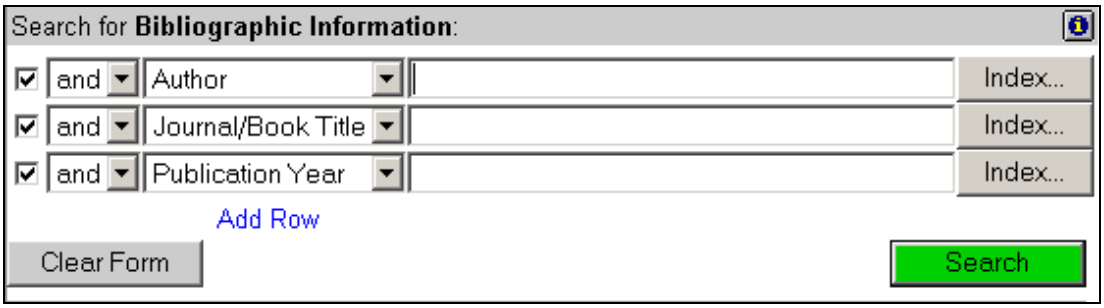


- Select "Volume Number" and enter Science of Synthesis volume information.
- Click on "Add Row".
- Select "Page Number" and enter *Science of Synthesis* page information.
- Select Search.

NOTE: If the page required contains no titles, the search will generate a hit for the title page of the relevant section. The user must then scroll to the relevant part of the document.

4.2 Searching a Primary Reference in Science of Synthesis

To locate any incidence of a primary reference in Science of Synthesis, the following procedure should be used:



- Select "Author" from the drop down menu and enter the author's name. The Index... may be used to check initials.
- Click on "Add Row".
- Select "Journal/Book Title" from the drop down menu and enter the publication title. The Index... may be used to check journal abbreviations.
- Click on "Add Row".
- Select "Publication Year" and enter the date of publication.
- Click on Search.

5 Display of Results

Once a search of Science of Synthesis has been completed, the results are displayed in two ways, as a numerical hitlist (see Section 5.1), and as a full text display (see Section 5.2) that has the same format as the printed version of Science of Synthesis.

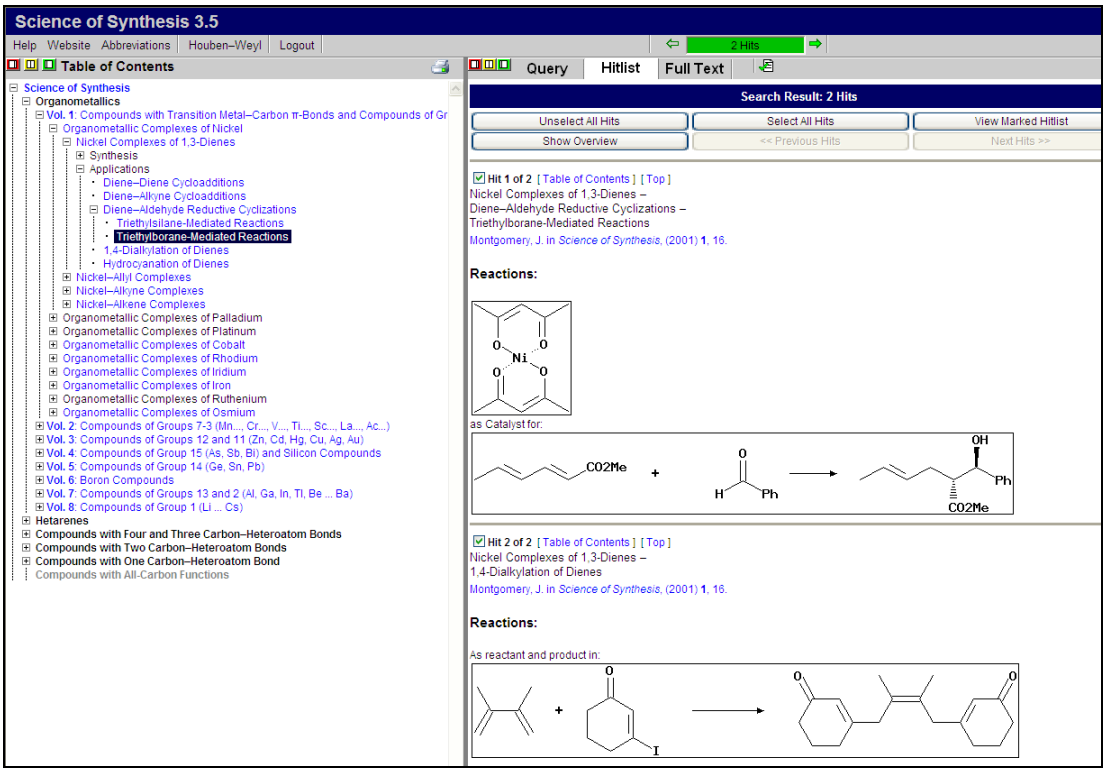
5.1 Hit List Screen

All search results are displayed as a numbered hitlist. The layout of this list varies depending on whether the hits are the result of a structure search (see Section 5.1.1) or a text search (see Section 5.1.2).

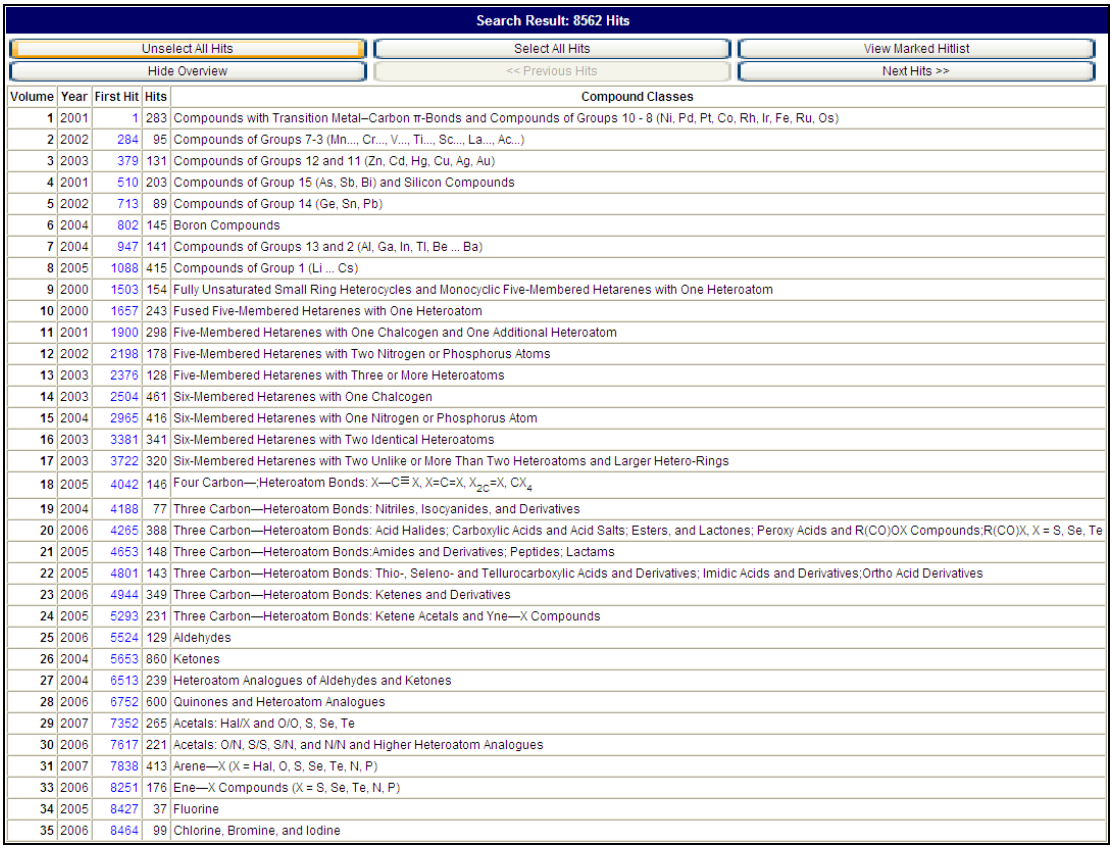
5.1.1 Structure Search Hitlist

5.1.1.1 Navigating the Hitlist

A structure search will produce a results page with the following format:



All hits are listed sequentially, according to the volume in which they appear. To see an overview of all hits, ordered by volume, click on Show Overview. To close this overview, click on Hide Overview.



Search Result: 8562 Hits

Unselect All Hits | Select All Hits | View Marked Hitlist

Hide Overview | << Previous Hits | Next Hits >>

Volume	Year	First Hit	Hits	Compound Classes
1	2001	1	283	Compounds with Transition Metal–Carbon π-Bonds and Compounds of Groups 10 - 8 (Ni, Pd, Pt, Co, Rh, Ir, Fe, Ru, Os)
2	2002	284	95	Compounds of Groups 7-3 (Mn..., Cr..., V..., Ti..., Sc..., La..., Ac...)
3	2003	379	131	Compounds of Groups 12 and 11 (Zn, Cd, Hg, Cu, Ag, Au)
4	2001	510	203	Compounds of Group 15 (As, Sb, Bi) and Silicon Compounds
5	2002	713	89	Compounds of Group 14 (Ge, Sn, Pb)
6	2004	802	145	Boron Compounds
7	2004	947	141	Compounds of Groups 13 and 2 (Al, Ga, In, Tl, Be ... Ba)
8	2005	1088	415	Compounds of Group 1 (Li ... Cs)
9	2000	1503	154	Fully Unsaturated Small Ring Heterocycles and Monocyclic Five-Membered Hetarenes with One Heteroatom
10	2000	1657	243	Fused Five-Membered Hetarenes with One Heteroatom
11	2001	1900	298	Five-Membered Hetarenes with One Chalcogen and One Additional Heteroatom
12	2002	2198	178	Five-Membered Hetarenes with Two Nitrogen or Phosphorus Atoms
13	2003	2376	128	Five-Membered Hetarenes with Three or More Heteroatoms
14	2003	2504	461	Six-Membered Hetarenes with One Chalcogen
15	2004	2965	416	Six-Membered Hetarenes with One Nitrogen or Phosphorus Atom
16	2003	3381	341	Six-Membered Hetarenes with Two Identical Heteroatoms
17	2003	3722	320	Six-Membered Hetarenes with Two Unlike or More Than Two Heteroatoms and Larger Hetero-Rings
18	2005	4042	146	Four Carbon—;Heteroatom Bonds: X—C≡X, X=C=X, X_{2C}=X, CX_4
19	2004	4188	77	Three Carbon—Heteroatom Bonds: Nitriles, Isocyanides, and Derivatives
20	2006	4265	388	Three Carbon—Heteroatom Bonds: Acid Halides; Carboxylic Acids and Acid Salts; Esters, and Lactones; Peroxy Acids and R(CO)OX Compounds;R(CO)X, X = S, Se, Te
21	2005	4653	148	Three Carbon—Heteroatom Bonds:Amides and Derivatives; Peptides; Lactams
22	2005	4801	143	Three Carbon—Heteroatom Bonds: Thio-, Seleno- and Tellurocarboxylic Acids and Derivatives; Imidic Acids and Derivatives;Ortho Acid Derivatives
23	2006	4944	349	Three Carbon—Heteroatom Bonds: Ketenes and Derivatives
24	2005	5293	231	Three Carbon—Heteroatom Bonds: Ketene Acetals and Yne—X Compounds
25	2006	5524	129	Aldehydes
26	2004	5653	860	Ketones
27	2004	6513	239	Heteroatom Analogues of Aldehydes and Ketones
28	2006	6752	600	Quinones and Heteroatom Analogues
29	2007	7352	265	Acetals: Hal/X and O/O, S, Se, Te
30	2006	7617	221	Acetals: O/N, S/S, S/N, and N/N and Higher Heteroatom Analogues
31	2007	7838	413	Arene—X (X = Hal, O, S, Se, Te, N, P)
33	2006	8251	176	Ene—X Compounds (X = S, Se, Te, N, P)
34	2005	8427	37	Fluorine
35	2006	8464	99	Chlorine, Bromine, and Iodine

Each hit shows a single step reaction that meets the search criteria. Up to 50 hits are displayed at any one time. If a search produces more than 50 hits, clicking on Next Hits >> will load the next 50 entries of the hit list. To view a hit on a previous page, click on << Previous Hits to move backwards.

By default, all hits in the hitlist are selected, as indicated by the tick boxes located next to the hit number (e.g., ☑ **Hit 1 of 100**).

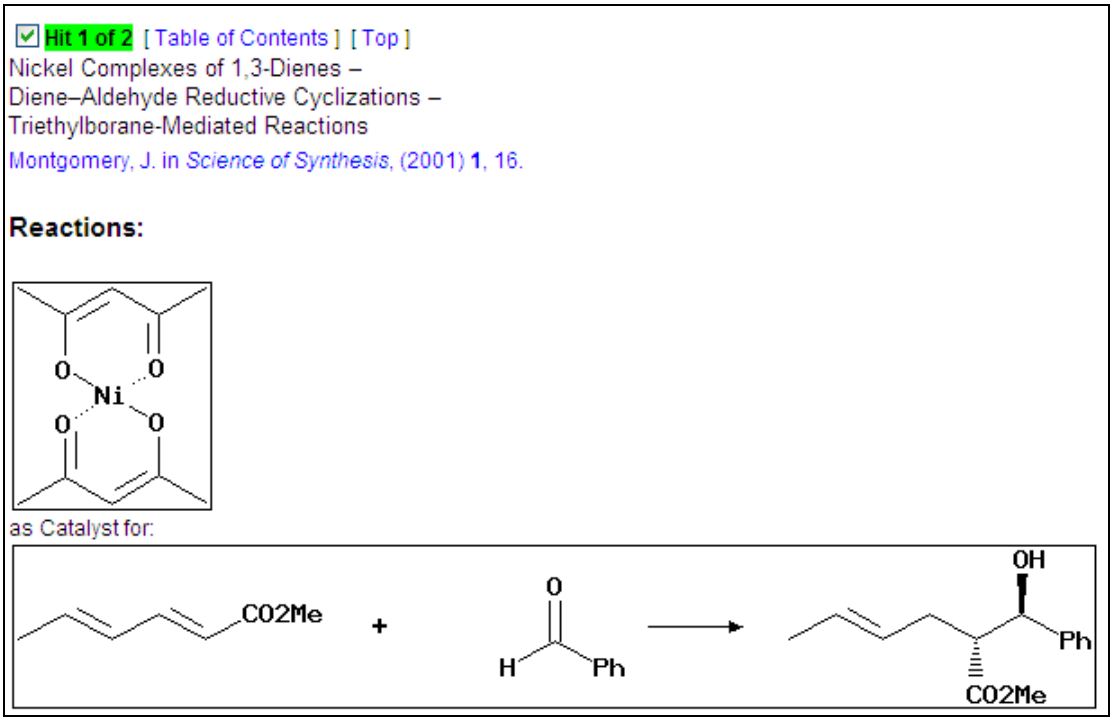
The user may refine the hitlist by deselecting specific documents. Alternatively, it is possible to deselect all hits using Unselect All Hits. The user may then select only those hits that are of interest. The Unselect All command, or any manual refining of the hitlist may be undone using the Select All Hits button. Once the list has been refined to the users satisfaction the altered hitlist may be viewed using the View Marked Hitlist button or alternatively the button.

5.1.1.2 Hit details

Each hit in the hitlist is numbered. The hit currently selected for display in the full text screen is highlighted in green (e.g., **Hit 1 of 100**). The following functionality is also available:

[Table of Contents]: Shows the position of the hit in the table of contents.

[Top]: Moves to the top of the hitlist.



Each hit also contains the title of the section where the hit is located, and a reference citation (e.g., Montgomery, J. in *Science of Synthesis*, (2001) **1**, 16). Clicking on the reference citation or the picture will immediately open the hit in full text view.

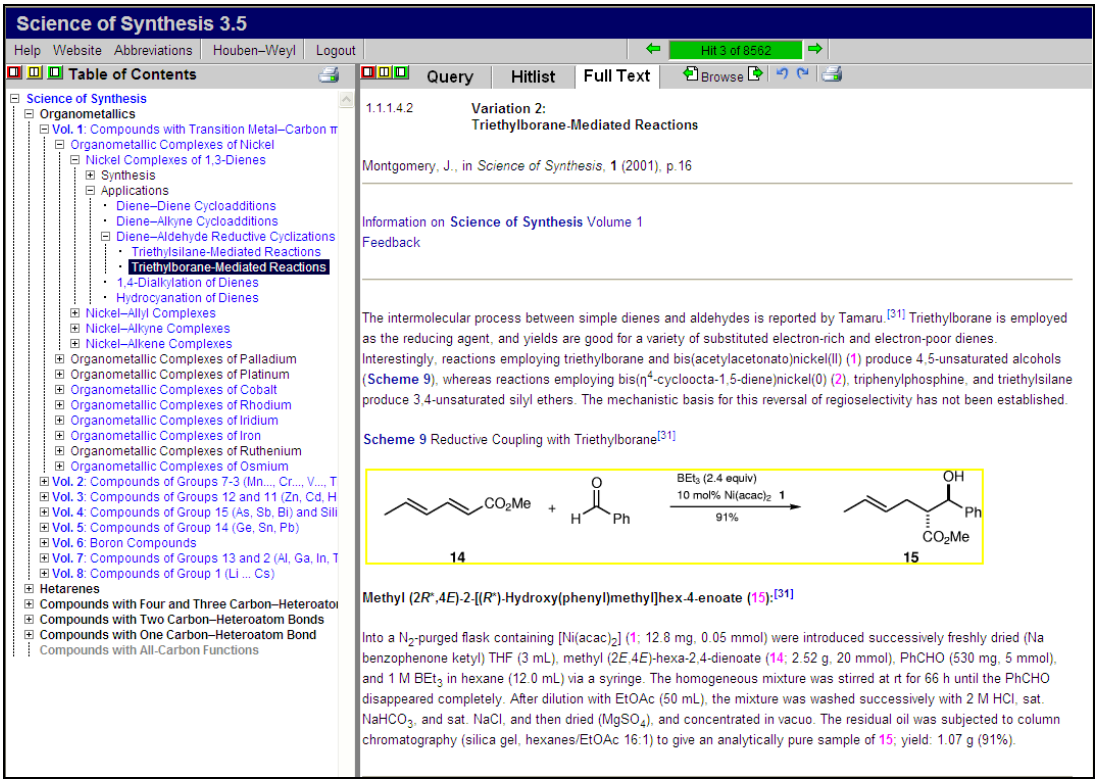
All hits are shown in pictorial form, as single step processes. In each case it is indicated whether the hit structure is a reactant, product, solvent or catalyst. If the hit is for a solvent or catalyst, the associated process is also shown.

5.1.2 Full Text Search Hitlist

The results from a text search are presented in the same format as the results from a structure search (see Section 5.1.1.2), except that there is no pictorial representation of the material discussed in the text.

5.2 Full Text Screen

Clicking on the reference citation or graphic contained in a hit transfers the user directly to the full text screen.



Hits that feature in schemes are shown in yellow boxes, while hits contained in the text are highlighted in yellow. The interactive Table of Contents will also show the position of the hit in the Science of Synthesis hierarchy.

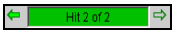
All sections of Science of Synthesis loaded in full text view show the section title and the volume reference. Two links are provided at the start of the document:

Information on **Science of Synthesis** Volume: Provides a link to volume information on the Thieme Chemistry website.

Feedback: Allows the user to report errors or send queries related to the document to the Science of Synthesis helpdesk.

5.2.1 Navigating the Full Text Screen

Several functions have been included to help navigation of the Full Text Screen:



: Allows the user to view hits in sequential fashion (forwards or backwards) by clicking on the green arrows.


: Allows the user to move between previously displayed (non-sequential) hits (similar to the back/forward buttons on internet browsers).

: Allows the user to view documents in numerical order (as if leafing through the pages of a book).

Furthermore, the content of the Full Text screen is internally cross-linked to aid navigation. For example:

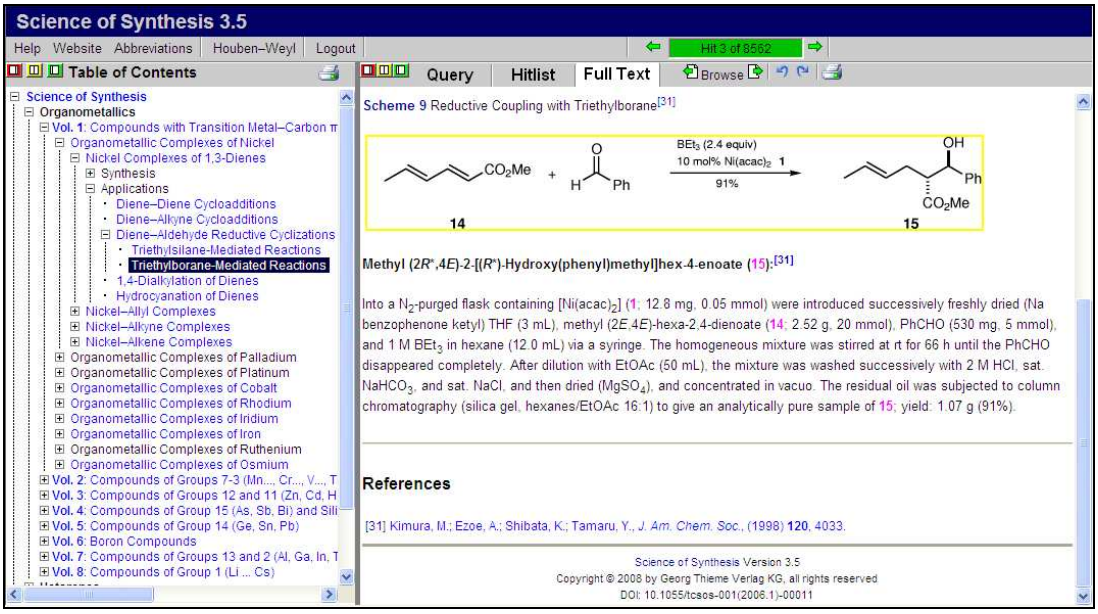
[references]: Clicking on references within the text will centre on the screen a list of all references contained in that document.

Scheme/Table Links: Clicking on a Scheme or Table will centre that Scheme/Table on the screen

Compound Numbers: Clicking on a compound number in a document will centre that compound on the screen. Compounds from different documents are shown in popup windows.

5.2.2 Linking to Other Information Sources

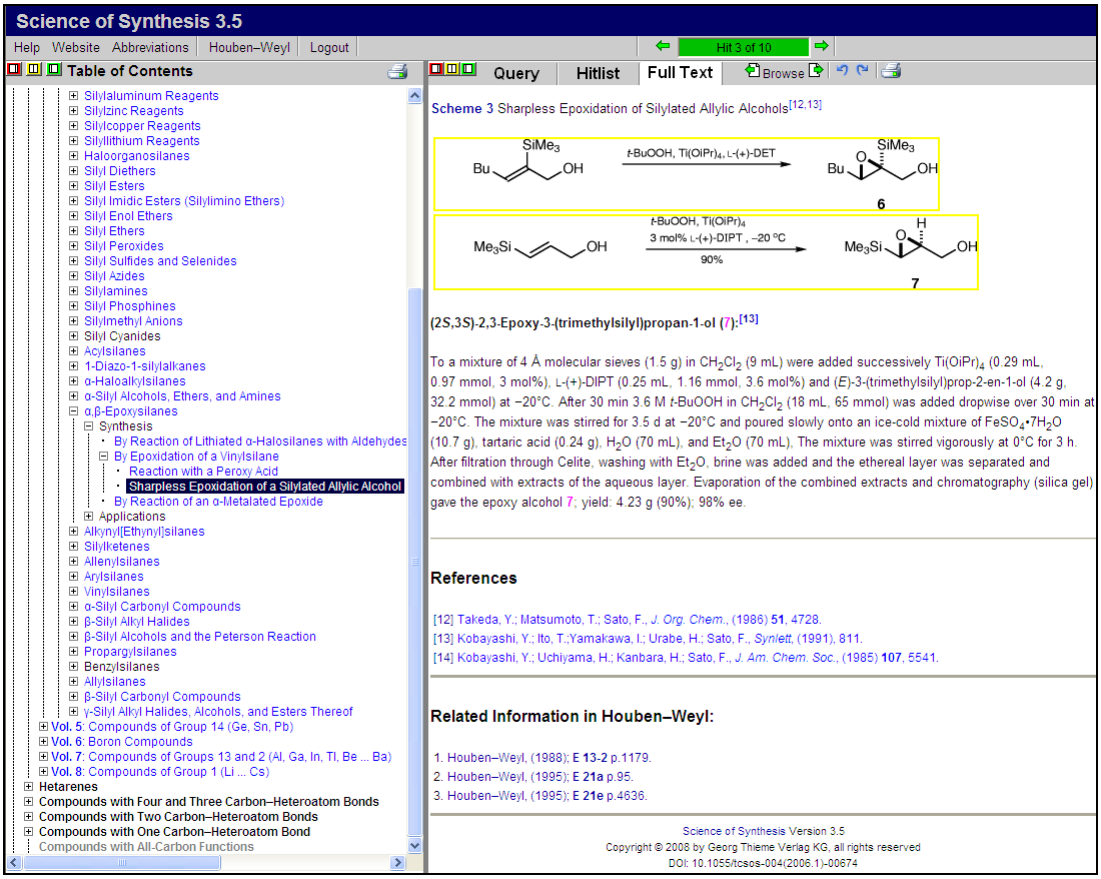
It is possible to follow links from Science of Synthesis to other sources of information. These links are contained at the bottom of each document in the full text view.



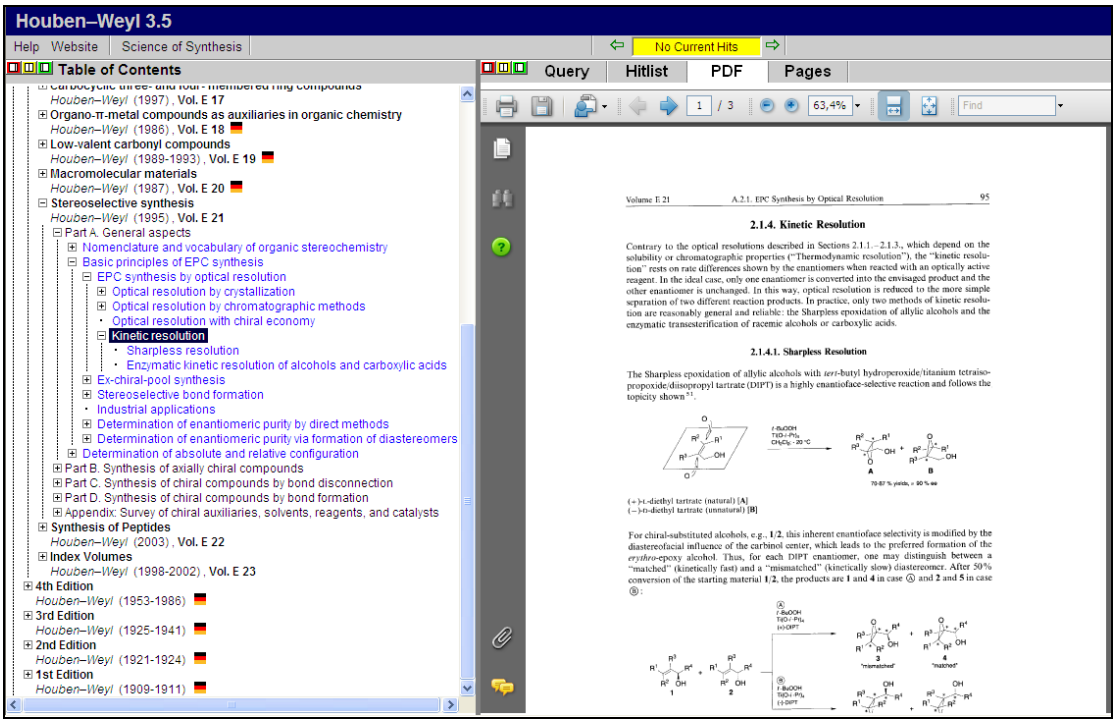
Clicking on a reference brings up the following pop-up window:

Clicking on the DOI of the reference allows the user to obtain the information directly from the publisher (dependant upon approved access or payment of a download fee).

If related information is available in *Houben–Weyl*, it can be accessed by clicking on the relevant cross-links, which feature below the references in each full text document.



Clicking on a *Houben–Weyl* link will automatically open that product at the correct page.



More information upon *Houben–Weyl* is available in the *Houben–Weyl Getting Started Manual*.

5.2.3 Printing

To print the document currently in the full text view click on the printer icon  in the top right-hand corner of the full text screen.

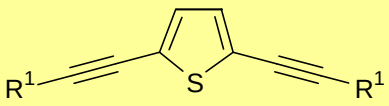
Multiple documents may be printed from the table of contents using the printer icon  in the top right-hand corner of the table of contents screen.

Hit lists may be printed by right-clicking on the hitlist and selecting the print option.

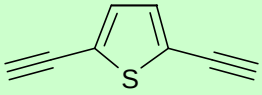
6 Science of Synthesis Worked Examples

Practical examples of the use of *Science of Synthesis* in resolving organic synthetic queries.

Example 1 The Synthesis of 2,5-Dialkynylthiophenes



Carry out a **Substructure Search** in *Science of Synthesis* for:

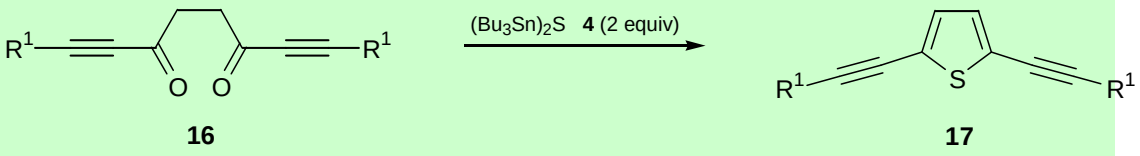


and look at the **Hitlist**. It displays the following three hits:

Heaney, H.; Christie, S. in *Science of Synthesis*, (2003) **3**, 412
Jousseaume, B. in *Science of Synthesis*, (2002) **5**, 383
Gabel, D. in *Science of Synthesis*, (2004) **6**, 1282

A) Clicking on the result from Volume 5 (Jousseaume), Section 5.2.12, we can see that this is a cyclization reaction. You should see the following reaction, which appears surrounded by a yellow box i.e. it is marked up as a hit.

Scheme 6 Thiophenes from Thionation of 1,4-Diketones[30]



16 **17**

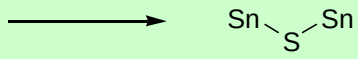
Clicking on the reference citation at this point will give you the following reference:

[30] Freeman, F.; Kim, D. S. H. L.; Rodriguez, E., *J. Org. Chem.*, (1992) **57**, 1722.

The next step is to determine how to make the starting materials so that you can carry out the thionation reaction.

1) The Preparation of a Hexasubstituted Distannathiane

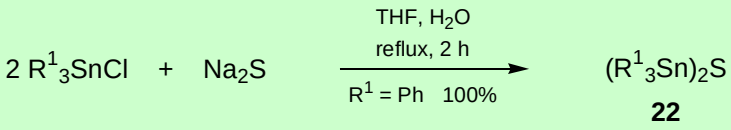
Carry out a **Reaction Search** for:



It is important to include the reaction arrow in order to define the distannathiane as a product otherwise if you carry out a simple Substructure Search all the $(Bu_3Sn)_2S$ reagents will be included in your answer set.

The **Hitlist** will give you one hit: Jousseaume, B. in *Science of Synthesis*, (2002) **5**, 388, Section 5.2.12.2.2. By clicking on this hit you will get the following result:

Scheme 10 Hexaphenyldistannathiane from Chlorotriphenylstannane[10]

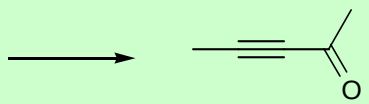


Hexaphenyldistannathiane (22, R^1 = Ph); Typical Procedure:[10]
A 50-mL flask was charged with Ph_3SnCl (10.53 g, 2.73 mmol) and reagent grade THF (27 mL). A soln of $Na_2S•9H_2O$ (6.56 g, 2.73 mmol) in H_2O (8mL) was then added in one portion, and the mixture was stirred vigorously and heated at reflux for 2 h at 65 °C (THF/H_2O 3.3:1). The progress of the reaction was followed by TLC (UV detector) and when complete THF was evaporated and EtOAc (150 mL) was added. Then the mixture was stirred for a few min to completely dissolve the Ph_6Sn_2S, which had separated. The organic phase was separated, washed with H_2O (2 x 30 mL), and dried (Na_2SO_4). The mixture was filtered and the solvent was evaporated under reduced pressure. Crude **22** (R^1 = Ph) was obtained as colorless crystals (hexanes); yield: 10.05 g (100%); mp 144–145 °C.

The full reference citation and electronic backfile links are available in addition to the typical procedure.

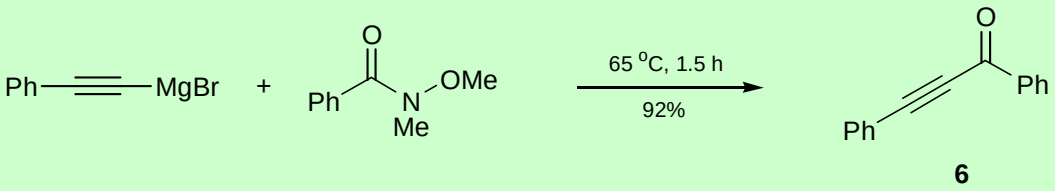
2) The Preparation of the Alkynone

Carry out a **Reaction Search** for:



Please ensure to include the reaction arrow in order to define the alkynone as a product. You will get 48 hits spread across 12 volumes. You could try an alkynylation of a succinic acid derivative thus making the diketone in one step. Choose the following hit: Yanagisawa, A. in *Science of Synthesis*, (2004) **7**, 524, Section 7.6.4.4 (Hit 13).

Scheme 4 Reaction of Phenylethynylmagnesium Bromide with *N*-Methoxy-*N*-methylbenzamide[16]



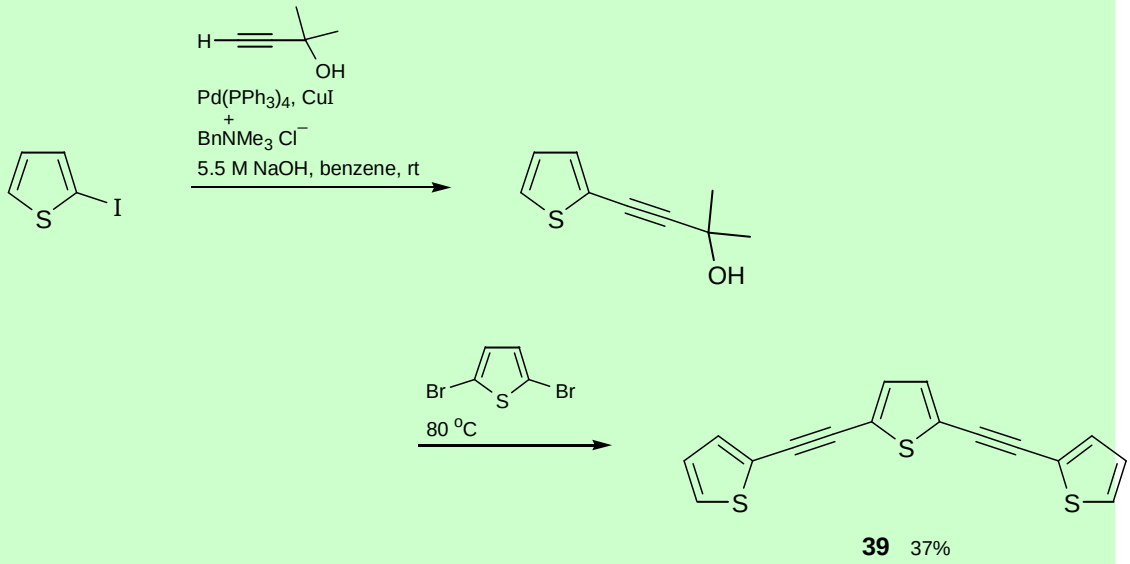
6

Clicking on the reference citation number gives the full reference.

[16] Nahm, S.; Weinreb, S. M., *Tetrahedron Lett.*, (1981) **22**, 3815.

B) If you now click on the result in the original **Hitlist** which cites Heaney, H.; Christie, S. in *Science of Synthesis*, (2003) **3**, 412.(Section 3.4.2.6.1) you will see an alternative to the cyclization reaction described previously i.e. a substitution reaction.

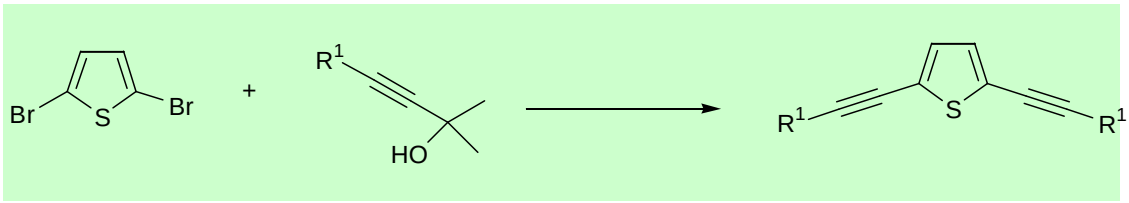
Scheme 146 Synthesis of 2,5-Bis(2-thienylethynyl)thiophene from 2-Methylbut-3-yn-2-ol, Tetrakis(triphenylphosphine)palladium(0), and Copper(I) Iodide in the Presence of Benzyltrimethylammonium Chloride in Benzene/Aqueous Sodium Hydroxide[740]



39 37%

2,5-Bis(2-thienylethynyl)thiophene (39); Typical Procedure:[740]
A mixture of 2-iodothiophene (7.16 g, 34 mmol) and 2-methylbut-3-yn-2-ol (2.86 g, 34 mmol) in benzene (**CAUTION:** *carcinogen*) (24 mL) was purged with N_2 and added to a mixture of CuI (0.324 g, 1.7 mmol), $Pd(PPh_3)_4$ (1.37 g, 1.19 mmol), and $BnMe_3NCl$ (0.24 g,1.19 mmol) under N_2. An O_2-free soln of 5.5M NaOH (24.5 mL) was added and the mixture was stirred at rt. After 50 h, GC analysis of an aliquot showed that the first stage of the reaction was complete. A soln of 2,5-dibromothiophene (4.11 g, 17 mmol) in benzene (5 mL) was purged with N_2 and added to the mixture, which was then stirred at 70–80 °C for 50 h. A sat. aq soln of NH_4Cl (200 mL) was then added and the mixture was extracted
into benzene, filtered, and concentrated to leave a solid residue. Purification by chromatography (silica gel, hexane) gave **39**; yield: 1.86 g (36%); mp 116–118 °C.

The full reference citation is available in addition to the typical procedure. So we are basically looking at the following transformation:



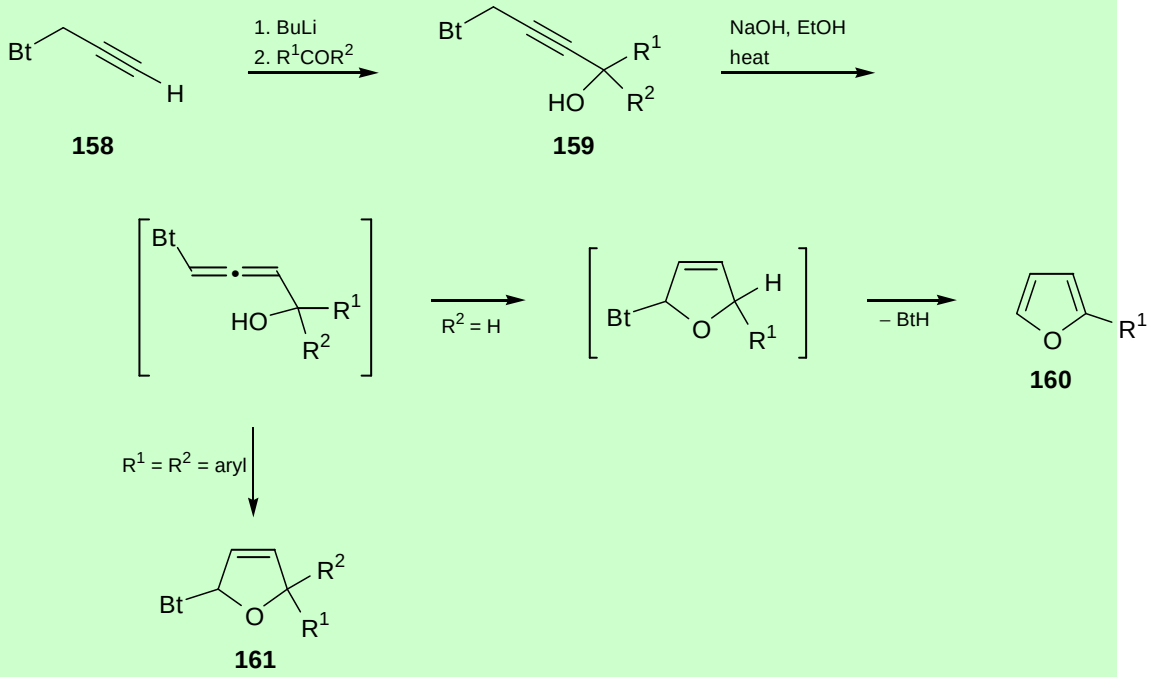
Once again we now need to look at the preparation of the starting materials.

1) The Preparation of the Alkynol

Carry out a **Reaction Search** for:

You will get 40 hits. Choose Volume 9 and hit number 23 i.e. König, B., *Science of Synthesis*, (2000) **9**, 216 (Section 9.9.1.3.1.2.5), and you will get the following result:

Scheme 54 Synthesis of Furans and Dihydrofurans from 1-(4-Hydroxyalkynyl)benzotriazoles[275,276]



The first step is the one of interest i.e. the lithiation reaction and two useful references are available:

[275] Katritzky, A. R.; Li, J.; Gordeev, M. F., *J. Org. Chem.*, (1993) **58**, 3038.

[276] Katritzky, A.; Li, J., *J. Org. Chem.*, (1995) **60**, 638.

2) The Preparation of the 2,5-Dibromothiophene

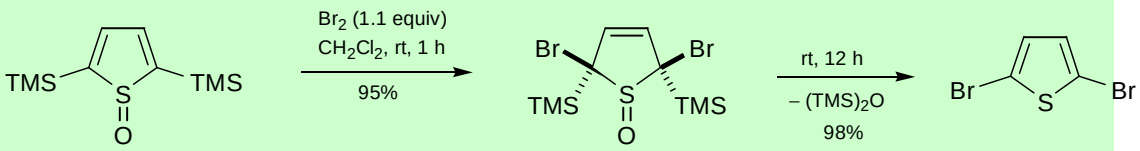
The regiospecific bromination of thiophene is not easy to achieve. Therefore you need to take the following approach:

Carry out a **Full Text Search** (using the Add Row option) for:

AND Full Text thiophene
NEAR Full Text bromination

You will get 5 hits. Go to Volume 9 and the second hit, Schatz, J. in *Science of Synthesis*, (2000) **9**, 396 (Section 9.10.3).

Scheme 139 Bromination of 2,5-Bis(trimethylsilyl)thiophene 1-Oxide[1139]

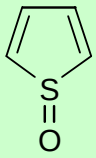


312

The reference given for this bromination reaction is:

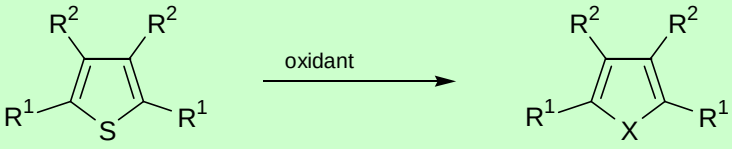
[1139] Zhang, S. Z.; Sato, S.; Horn, E.; Furukawa, N., *Heterocycles*, (1998) **48**, 227.

In order to prepare the parent thiophene *S*-oxide do a **Substructure Search** for:



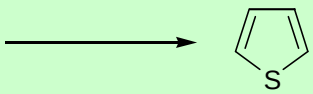
You will get eight hits. Choose Volume 9 and Schatz, J. in *Science of Synthesis*, (2000) **9**, 398 (Section 9.10.3.1.2.1, Hit 7). You will get the following result along with a table of derivatives, a typical procedure and a number of useful references:

Scheme 141 Stepwise Oxidation of Thiophene to Thiophene 1-Oxides and Thiophene 1,1-Dioxides[127,857,1116,1133,1134,1141-1143]



315

The synthesis of the 2,5-bis(trimethylsilyl)thiophene itself is not given but silylations in the 2-position are possible e.g.
Carry out a **Reaction Search** for:

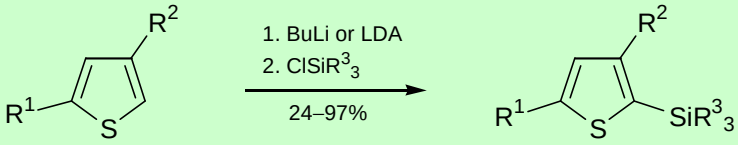


together with a **Fulltext Search** for:

silylation

You will get seven hits. Please choose Schatz, J. in Science of Synthesis, (2000) 9, 375 (Section 9.10.1.4.2.4.2, Hit 3). You will get the following result:

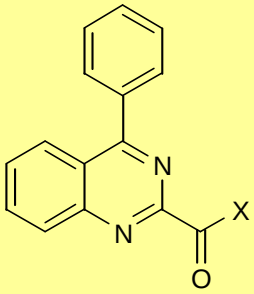
Scheme 110 2-Silylation of Thiophenes[114,942-946]



267

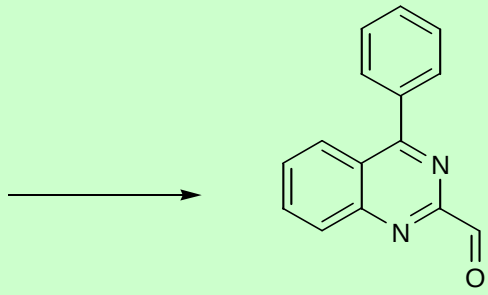
A table with a list of substituents, two procedures and a series of useful references are cited.

Example 2 Synthesis of 4-Phenylquinazoline-2-carboxylic Acid Derivatives



X=OH, OEt, NHAc, NHPh

Carry out a **Reaction Search** for:



You will get five hits in total.

Synthesis is possible via:

a) The Cyclization of 2-Aminobenzonitriles: Kikelj, D. in *Science of Synthesis*, (2003) **16**, 614 (Section 16.13.1.1.2.6.10).

b) The Cyclization of 3-Phenyl-2,1-benziosoxazole: Kikelj, D. in *Science of Synthesis*, (2003) **16**, 655 (Section 16.13.2.1.4).

c) Ring Contraction Reactions: Kikelj, D. in *Science of Synthesis*, (2003) **16**, 665 (Section 16.13.2.3.2) and Kikelj, D. in *Science of Synthesis*, (2003) **16**, 669 (Section 16.13.2.3.4).

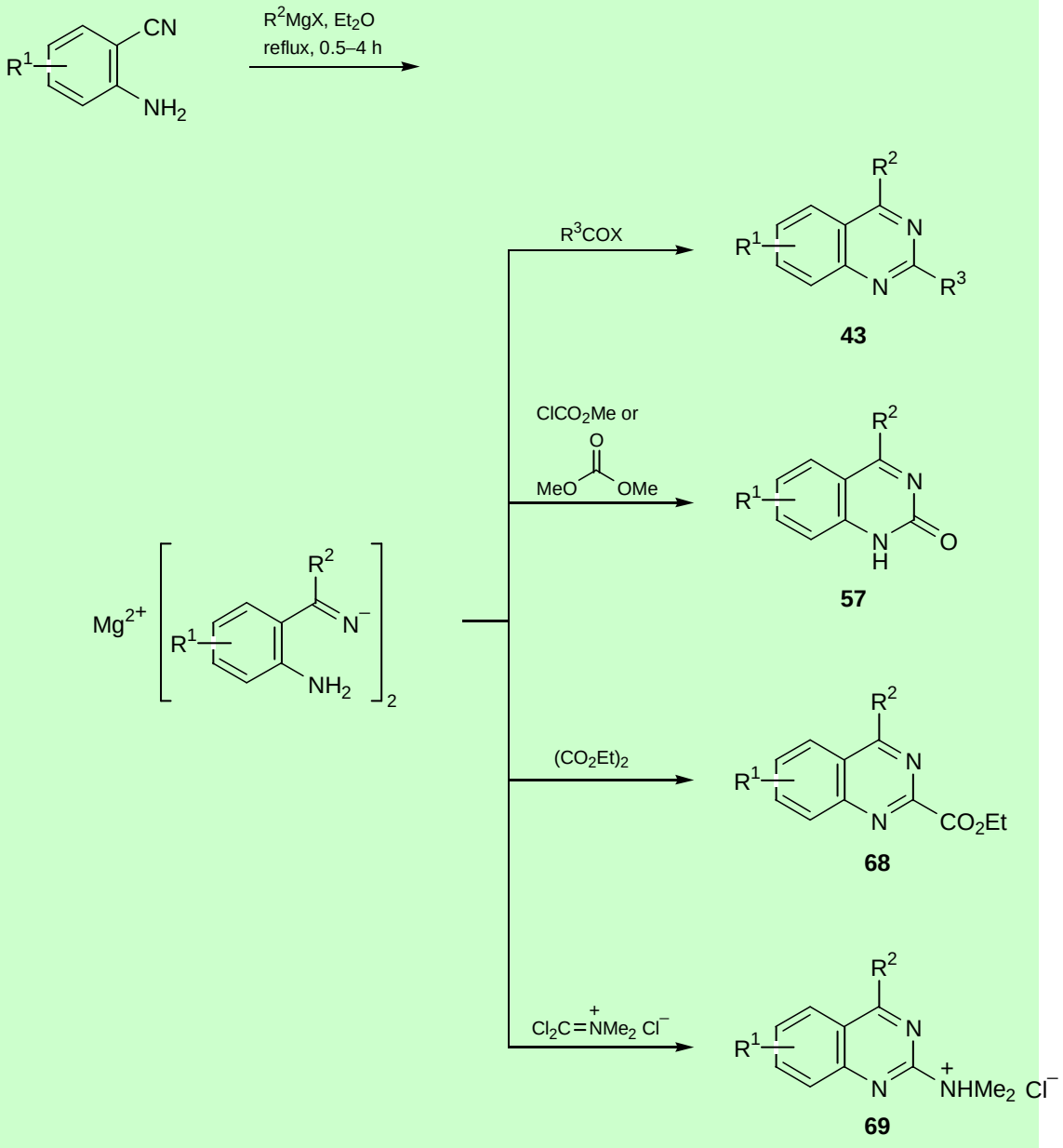
d) Elimination Reactions: Kikelj, D in *Science of Synthesis*, (2003) **16**, 670 (Section 16.13.3.1.1).

Let us take a look at the first two of these in more detail.

a) The Cyclization of 2-Aminobenzonitriles: Kikelj, D. in *Science of Synthesis*, (2003) **16**, 614 (Section 16.13.1.1.2.6.10).

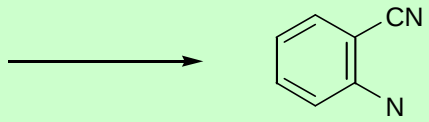
Clicking on this hit gives you the following information:

Scheme 49 Quinazolines from 2-Aminobenzonitriles, Grignard Reagents, and Carbonyl Compounds or Phosgene Iminium Chlorides[377,378]



The reaction of interest is the third reaction down.

Carrying out a **Reaction Search** for the substructure given below gives a total of 16 different hits.



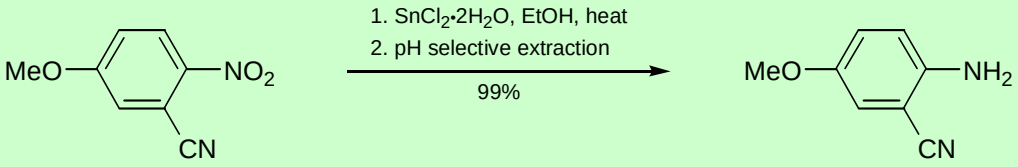
Now search using exactly the same query together with the following term in the **Full Text** field:

reduction

In this case you get three hits so you have managed to narrow down your hit list considerably.

The result of interest is: Wood, M. E. in *Science of Synthesis*, (2002) **5**, 344 (Section 5.2.8) i.e. the preparation of the required starting material through selective nitro group reduction with tin(II) chloride.

Scheme 55 Selective Nitro Group Reduction with Tin(II) Chloride[130]



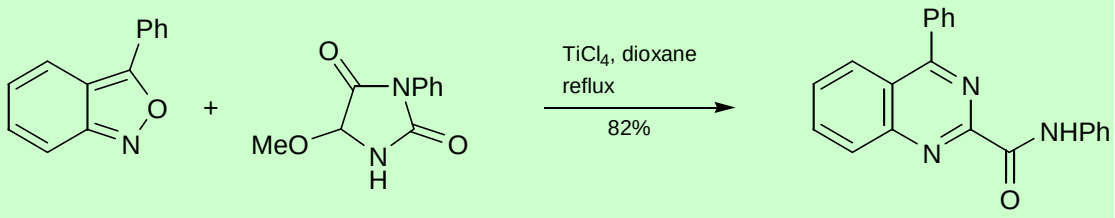
A reference for this type of reaction is available:

[130] Bellamy, F. D. ; Ou, K., *Tetrahedron Lett.*, (1984) **25**, 839.

b) The Cyclization of 3-Phenyl-2,1-benziosoxazole: Kikelj, D. in *Science of Synthesis*, (2003) **16**, 655 (Section 16.13.2.1.4).

Clicking on this hit gives you the following information:

Scheme 114 *N*,4-Diphenyquinazoline-2-carboxamide from 3-Phenyl-2,1-benzisoxazole[588]



Together with the following reference:

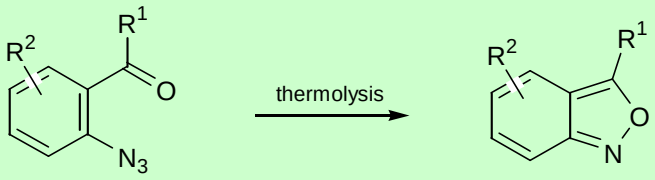
[588] Ohta, K.; Nakamura, Y.; Iwaoka, J.; Nomura, Y., *Nippon Kagaku Kaishi*, (1990), 72; *Chem. Abstr.*, (1990) **113**, 6272.

In order to find out how to prepare the benzisoxazole you can do an **Exact Structure Search** for the 3-phenyl-2,1-benzisoxazole and this will give a total of eight hits. Those hits are located in:

- Smalley, R. K. in *Science of Synthesis*, (2001) **11**, 343 (Section 11.11.1.1.2.1)
- Smalley, R. K. in *Science of Synthesis*, (2001) **11**, 346 (Section 11.11.1.1.2.2)
- Smalley, R. K. in *Science of Synthesis*, (2001) **11**, 348 (Section 11.11.1.1.3.1)
- Smalley, R. K. in *Science of Synthesis*, (2001) **11**, 353 (Section 11.11.1.1.3.3)
- Smalley, R. K. in *Science of Synthesis*, (2001) **11**, 360 (Section 11.11.1.1.3.6)
- Brown, D. W.; Sainsbury, M. in *Science of Synthesis*, (2001) **11**, 615 (Section 11.16.2.2.1)
- Surman, M. D.; Hutchings, R. H. in *Science of Synthesis*, (2003) **17**, 771 (Section 16.13.2.1.4)
- Kikelj, D. in *Science of Synthesis*, (2003) **16**, 655 (Section 17.4.5.2.1.3.4)

If we just take a look at one example i.e. Smalley, R. K. in *Science of Synthesis*, (2001) **11**, 343 (Section 11.11.1.1.2.1), the first hit, we can see that the desired benzisoxazole is formed via a cyclization reaction:

Scheme 7 2,1-Benzisoxazoles by Thermolysis of 2-Azidoaryl Aldehydes and Ketones[15,74,76,80,84,85]



23 **24**

A range of different possible substituents are given together with varying reaction conditions. A detailed experimental procedure for the preparation of 3-phenyl-2,1-isoxazole is given.

3-Phenyl-2,1-benzisoxazole (24, R^1 = Ph; R^2 = H):[89]

A soln of 2-azidoaryl ketone **23** (R^1 = Ph; R^2 = H; 3.5 g, 16 mmol) in chlorobenzene (40 mL) was added dropwise over 10 min to boiling chlorobenzene (160 mL) and the resulting soln was heated under reflux for 1 h. The excess of solvent (ca. 190 mL) was removed under reduced pressure, and the residual oil was cooled and then triturated with petroleum ether (bp 40-60 °C, 50 mL) until the residue solidified. The product was collected by filtration and crystallized (50% aq EtOH) as colorless prisms; yield: 2.5-2.8 g (82-92%); mp 54 °C.