

Science of Synthesis

Houben–Weyl Methods of Molecular Transformations

Getting Started Manual

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Science of Synthesis

Houben–Weyl Methods of Molecular Transformations

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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.

Georg Thieme Verlag KG
Rüdigerstraße 14
D-70469 Stuttgart
Germany

New Features: Release Version 3.6

This new release includes:

New Content

- Three new content volumes have been added in Category 5 (Compounds with One Carbon—Heteroatom bond), as follows:
 - Volume 36 (Alcohols – Clayden/Thomas, 1294 pages in total).
 - Volume 37 (Ethers – Forsyth/Jacobsen, 992 pages in total).
 - Volume 39 (Sulfur, Selenium, and Tellurium – Kambe/Noyori, 1384 pages in total).

- One new content volume has been added in Category 6 (Compounds with All-Carbon Functions), as follows:
 - Volume 44 (Cumulenes and Allenes – Krause/Bellus, 508 pages in total).

This brings the number of volumes online to 38.

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.

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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).

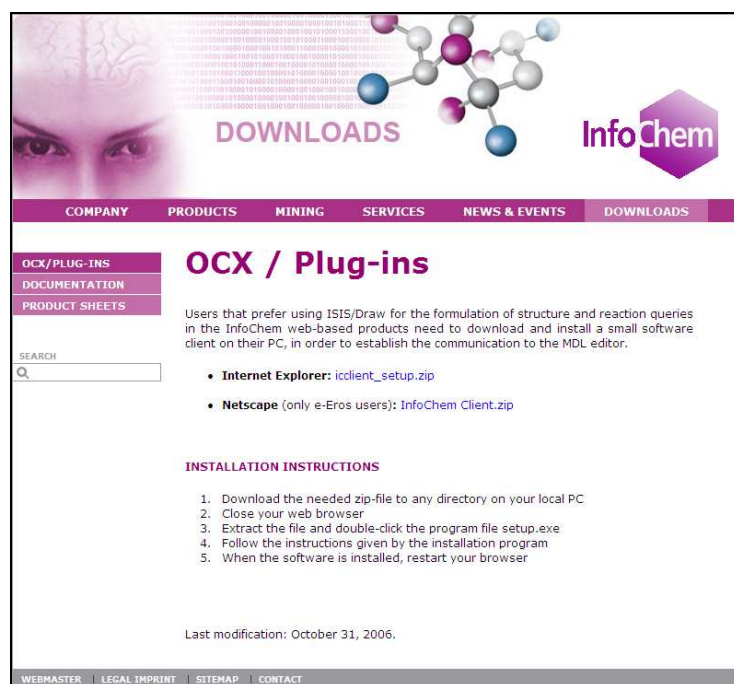
ISIS/Draw:

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.



The screenshot shows the 'Downloads' page for OCX / Plug-ins on the InfoChem website. The page features a navigation menu with 'COMPANY', 'PRODUCTS', 'MINING', 'SERVICES', 'NEWS & EVENTS', and 'DOWNLOADS'. The main content area is titled 'OCX / Plug-ins' and includes a search bar, a list of download links for Internet Explorer and Netscape, and installation instructions. The footer contains links for 'WEBMASTER', 'LEGAL IMPRINT', 'SITEMAP', and 'CONTACT'.

OCX / Plug-ins

Users that prefer using ISIS/Draw for the formulation of structure and reaction queries in the InfoChem web-based products need to download and install a small software client on their PC, in order to establish the communication to the MDL editor.

- **Internet Explorer:** [icclient_setup.zip](#)
- **Netscape** (only e-Eros users): [InfoChem Client.zip](#)

INSTALLATION INSTRUCTIONS

1. Download the needed zip-file to any directory on your local PC
2. Close your web browser
3. Extract the file and double-click the program file setup.exe
4. Follow the instructions given by the installation program
5. When the software is installed, restart your browser

Last modification: October 31, 2006.

WEBMASTER | LEGAL IMPRINT | SITEMAP | CONTACT

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

There are two methods of accessing **Science of Synthesis** from this front page:

Click on the blue "Reference Works" button contained within the "Electronic Products" graphic to be taken directly to the login page

Click on the orange "Login" button contained within the "Electronic Products" graphic to go to a summary page for all Thieme Chemistry electronic products, including journals and monographs (see below).

A variety of links may be followed from this page including:



Product specific information on the Thieme Chemistry Web site.



Information regarding system requirements and plugins.



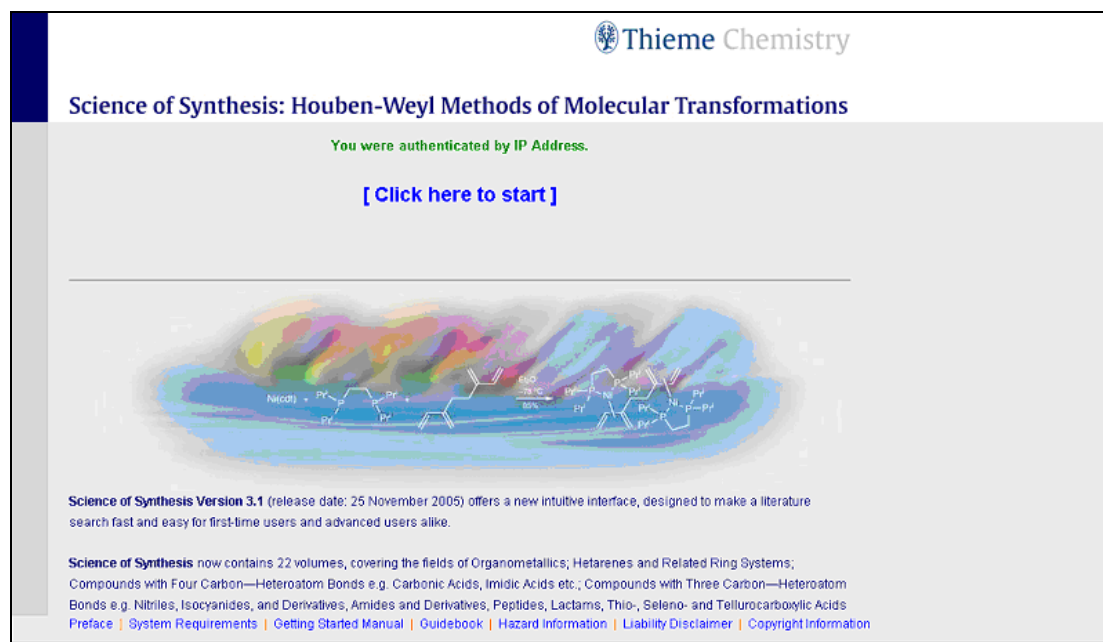
Immediate access to the login page.

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

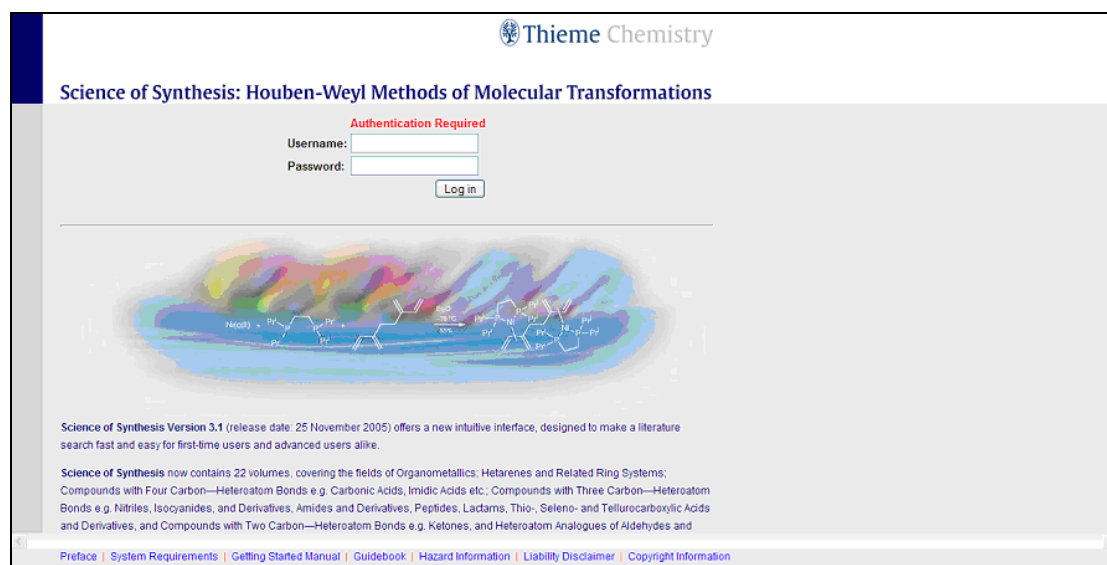
Having arrived at the **Science of Synthesis** Login Page (see Section 1.2) there are two possible ways to proceed:

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



The screenshot shows the login page for Science of Synthesis. At the top right is the Thieme Chemistry logo. Below it, the title "Science of Synthesis: Houben-Weyl Methods of Molecular Transformations" is displayed. A green message states "You were authenticated by IP Address." Below this is a blue button labeled "[Click here to start]". In the center is a large, colorful chemical reaction scheme. At the bottom, there is a paragraph about Science of Synthesis Version 3.1 and a list of navigation links: Preface | System Requirements | Getting Started Manual | Guidebook | Hazard Information | Liability Disclaimer | Copyright Information.

- 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).



The screenshot shows the login page with an authentication form. At the top right is the Thieme Chemistry logo. Below it, the title "Science of Synthesis: Houben-Weyl Methods of Molecular Transformations" is displayed. A red message states "Authentication Required". Below this are two input fields: "Username:" and "Password:". To the right of the password field is a "Log in" button. In the center is a large, colorful chemical reaction scheme. At the bottom, there is a paragraph about Science of Synthesis Version 3.1 and a list of navigation links: Preface | System Requirements | Getting Started Manual | Guidebook | Hazard Information | Liability Disclaimer | Copyright Information.

- 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

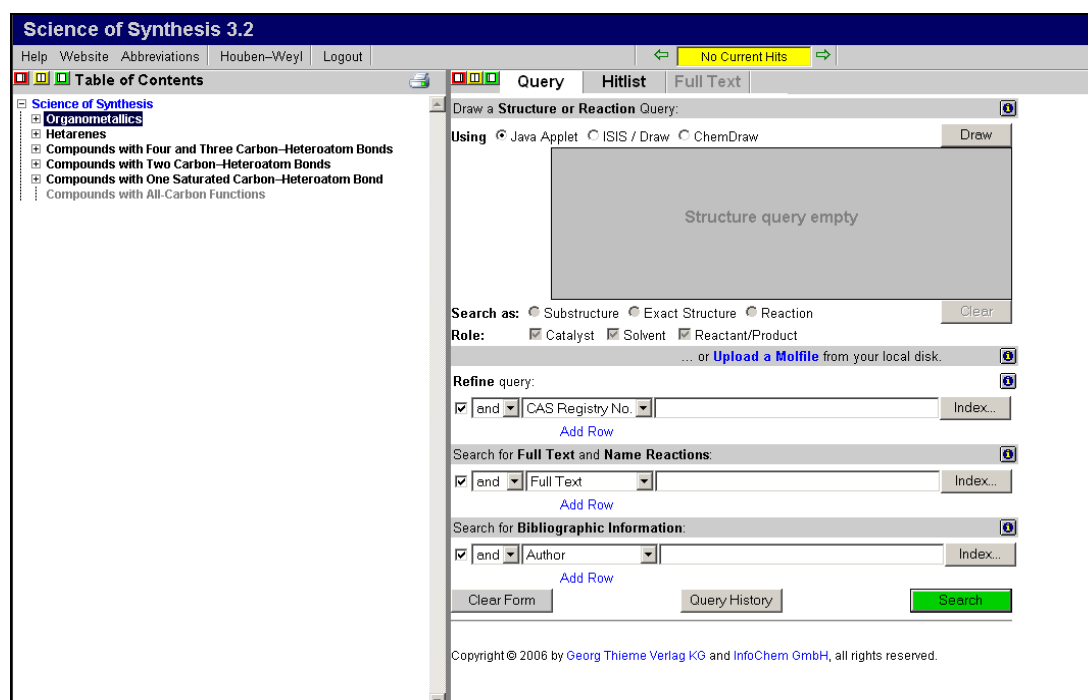
Thieme Institutional Sales
Tel: +49-711-8931-407
Fax: +49-711-8931-797
eproducts@thieme.de

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.

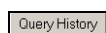
Full Text Display: Displays the full text of a selected hit.



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.

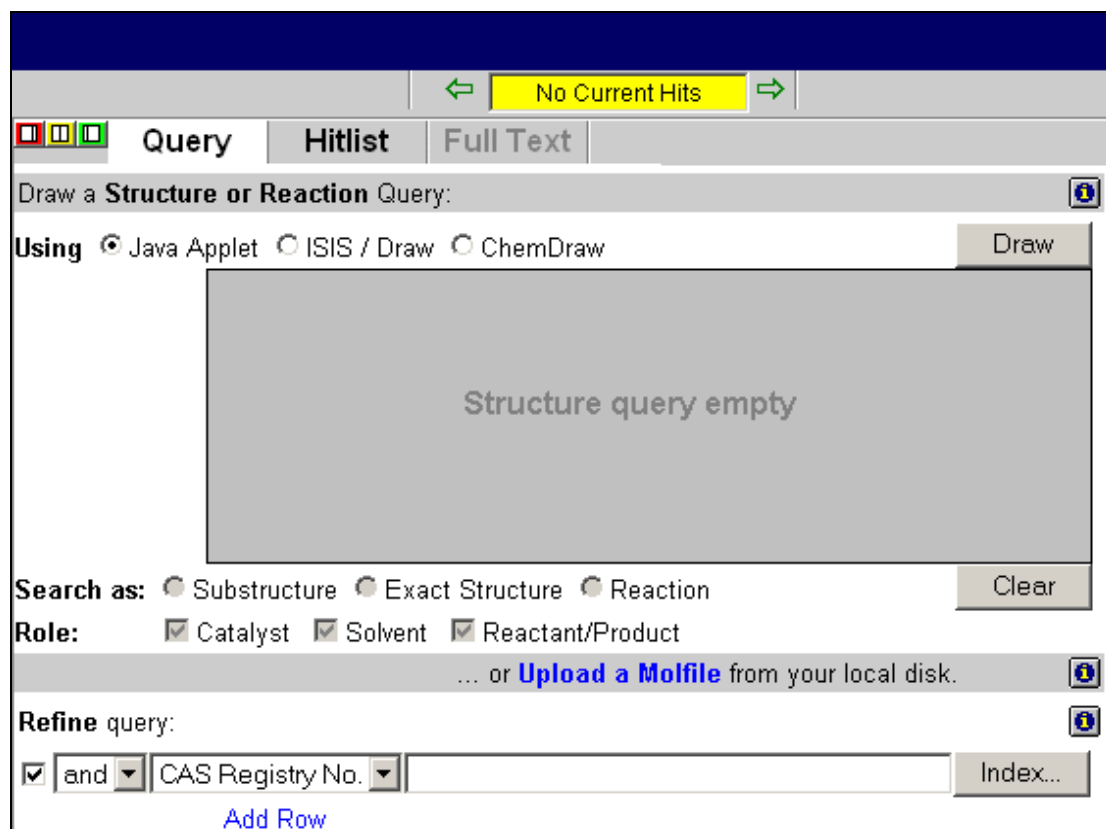
Website: Provides a link to the Thieme Chemistry web page for information about **Science of Synthesis**.

- 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 .



The screenshot displays the search interface with the following elements:

- Navigation: Back and forward arrows flanking a yellow box labeled "No Current Hits".
- Tabs: "Query", "Hitlist", and "Full Text".
- Instruction: "Draw a Structure or Reaction Query:" with an information icon.
- Drawing Options: Radio buttons for "Java Applet" (selected), "ISIS / Draw", and "ChemDraw", with a "Draw" button.
- Canvas: A large grey area containing the text "Structure query empty".
- Search Criteria: Radio buttons for "Substructure", "Exact Structure", and "Reaction", with a "Clear" button.
- Role Selection: Checkboxes for "Catalyst", "Solvent", and "Reactant/Product".
- File Upload: "... or Upload a Molfile from your local disk." with an information icon.
- Refinement: "Refine query:" section with a checked "and" dropdown, a "CAS Registry No." dropdown, an input field, and an "Index..." button.
- Footer: "Add Row" link.

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 $A \rightarrow B \rightarrow C$ is not searchable. However, it is, of course, possible to search for the reactions $A \rightarrow B$, $A \rightarrow C$, or $B \rightarrow C$.

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.

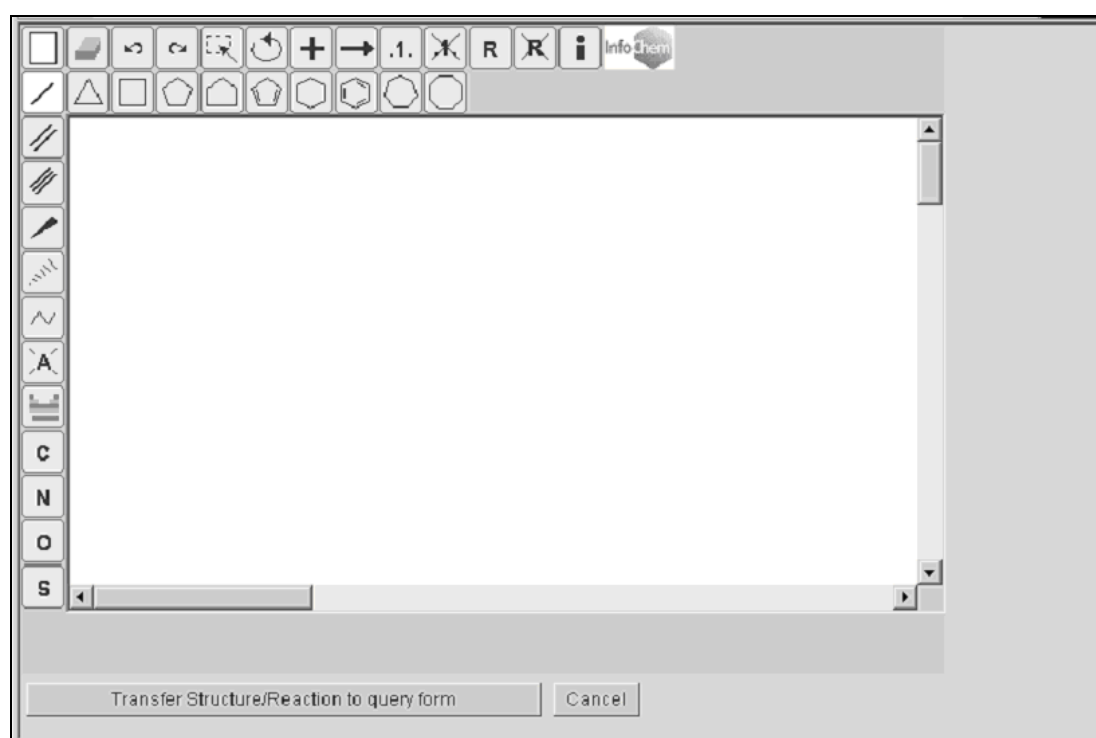
The default search setting is for all options to be active.

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 , 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
	edit query atom	opens the define query atom window, which allows the user to change atom properties
	open periodic table	opens a periodic table to select any atom and specify its charge, valence, isotope etc

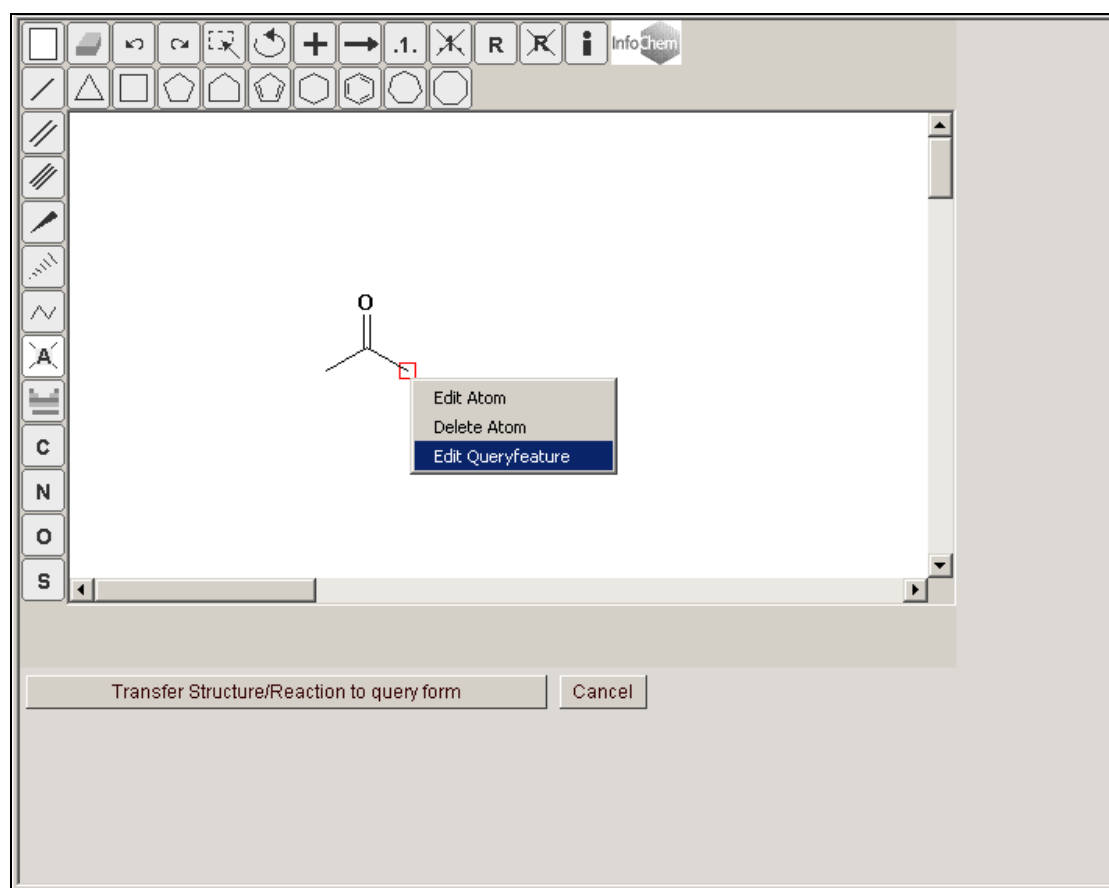
	draw C atom	draws a C atom or converts an existing atom
	draw N atom	draws a N atom or converts an existing atom
	draw O atom	draws a O atom or converts an existing atom
	draw S atom	draws a S atom or converts an existing atom
	cyclopropane	draws a cyclopropane ring
	cyclobutane	draws a cyclobutane ring
	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
	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

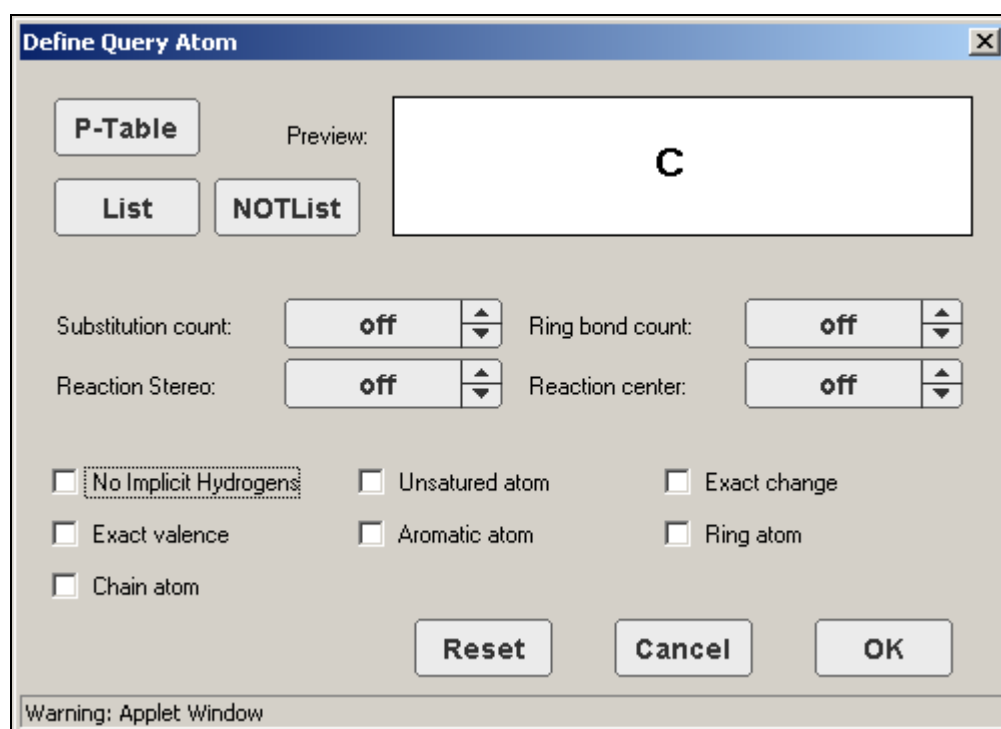
The button panels within the ICedit drawing window may be used to draw simple structures. However, the ICedit drawing tool contains several functions by which additional information may be added to a structure. This is especially useful in that it allows detailed searches without the need to explicitly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

2.2.1.2.1 Using the Define Atom Query 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 Queryfeature" from the available list.



This gives access to the define query atom page 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.

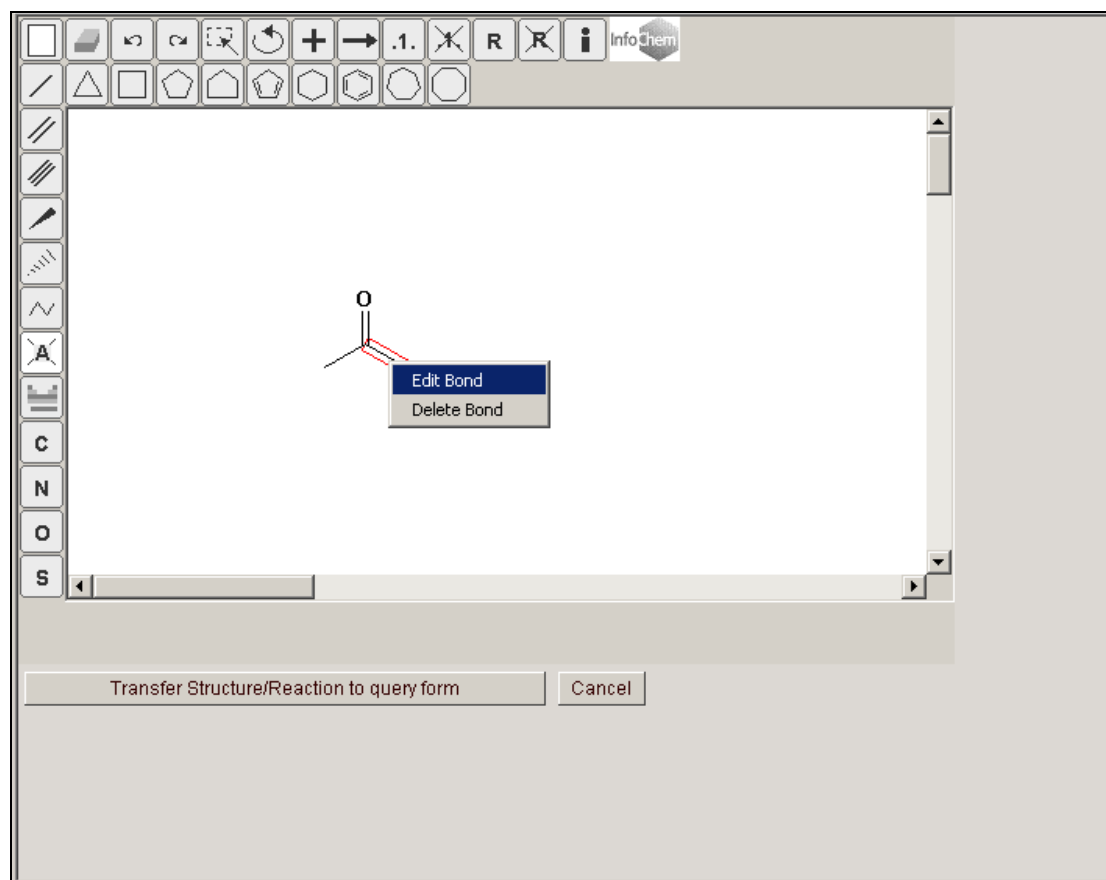
Chain atom: The atom is part of a chain.

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.

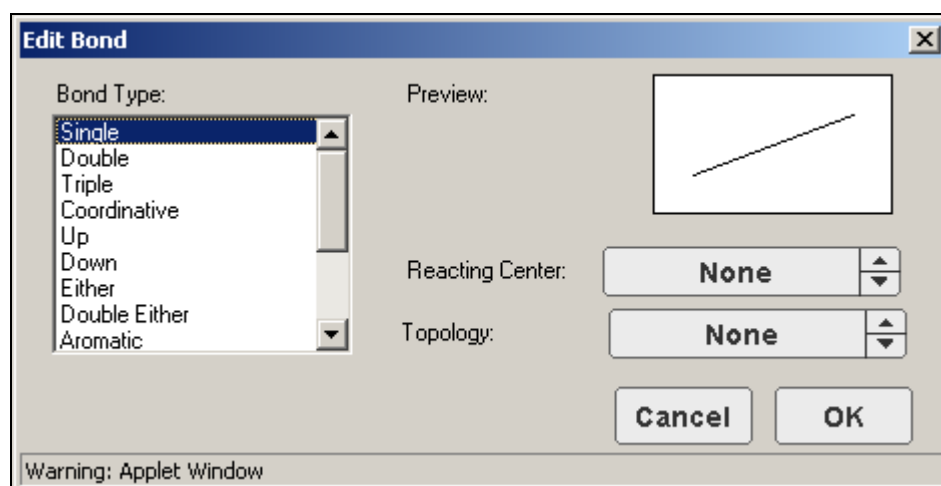
The define atom query window may also be accessed by clicking on  in the drawing window button panel.

2.2.1.2.2 Using the Define Bond Query 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.

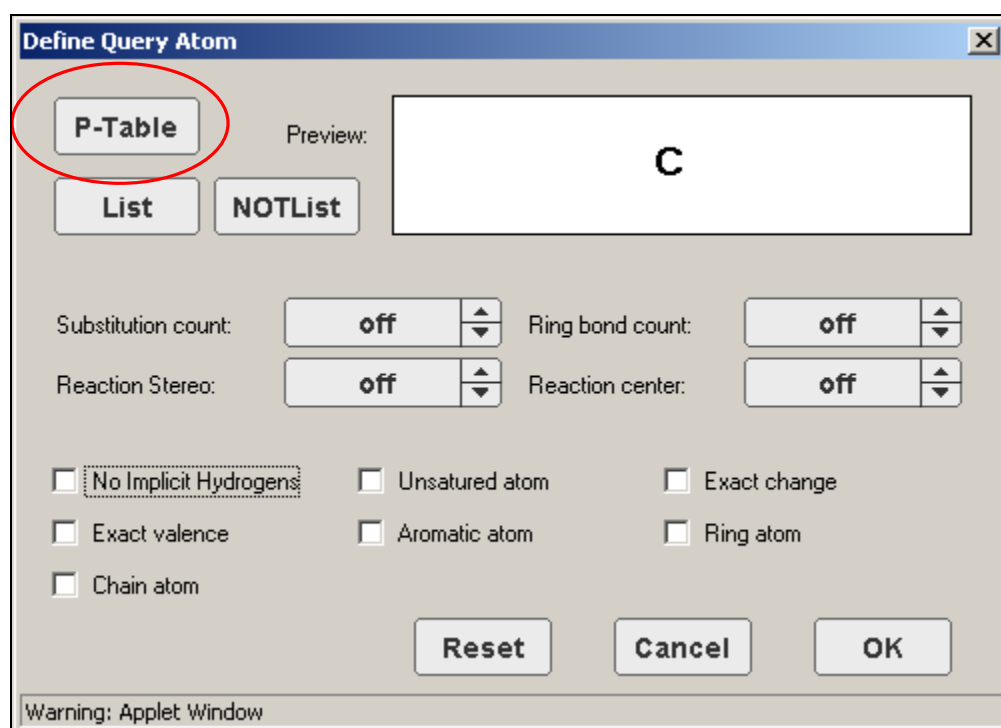


- Bond Type:** Allow the user to specify the type of bond.
- Preview:** A graphical display of the type of bond currently selected.
- Reacting Center:** Allows the user to assign a bond as being unchanged, made, broken, or otherwise altered.

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 Define Query Atom window loads a periodic table identical in most respects to that available using the periodic table button in the drawing window (see [Section 2.2.1.1](#)).



However, this periodic table also 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 (not currently available)

Periodic Table: Select Atom

H																			He
Li	Be										B	C	N	O	F				Ne
Na	Mg										Al	Si	P	S	Cl				Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br			Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I			Xe
Cs	Ba		Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At			Rn
Fr	Ra		Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg									
La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu					
Ac	Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr					

Query atoms: **A Q X R**

Charge: 0 Isotope: off Radical: off Valence: off

Reset Cancel OK

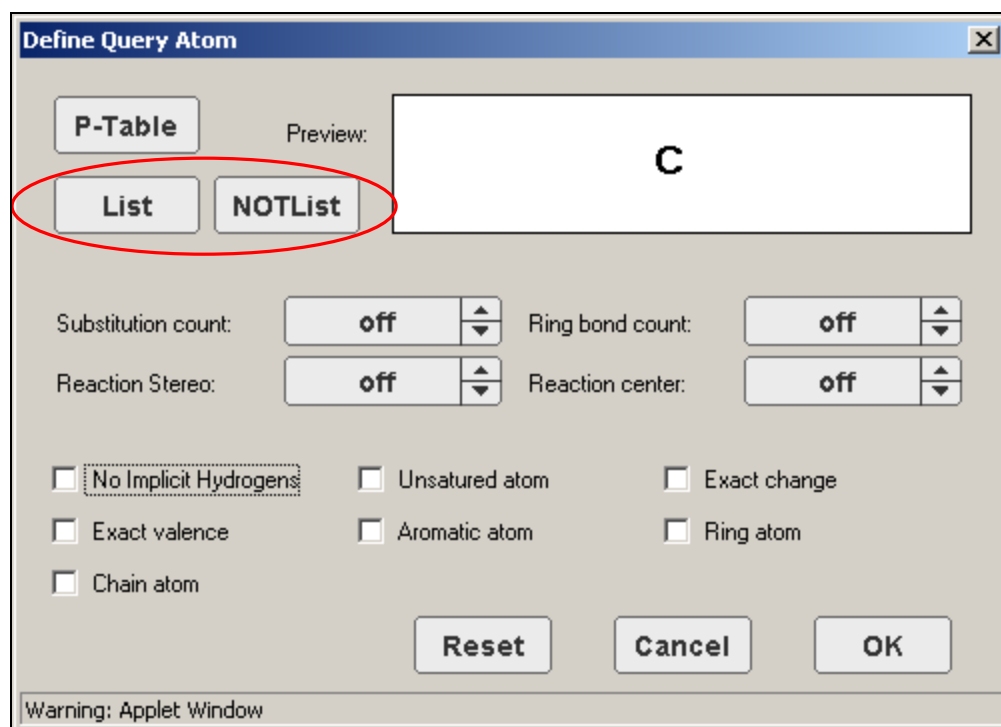
Warning: Applet Window

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

- Select a highlighted atom with the right mouse button.
- Select the Edit Queryfeature 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).

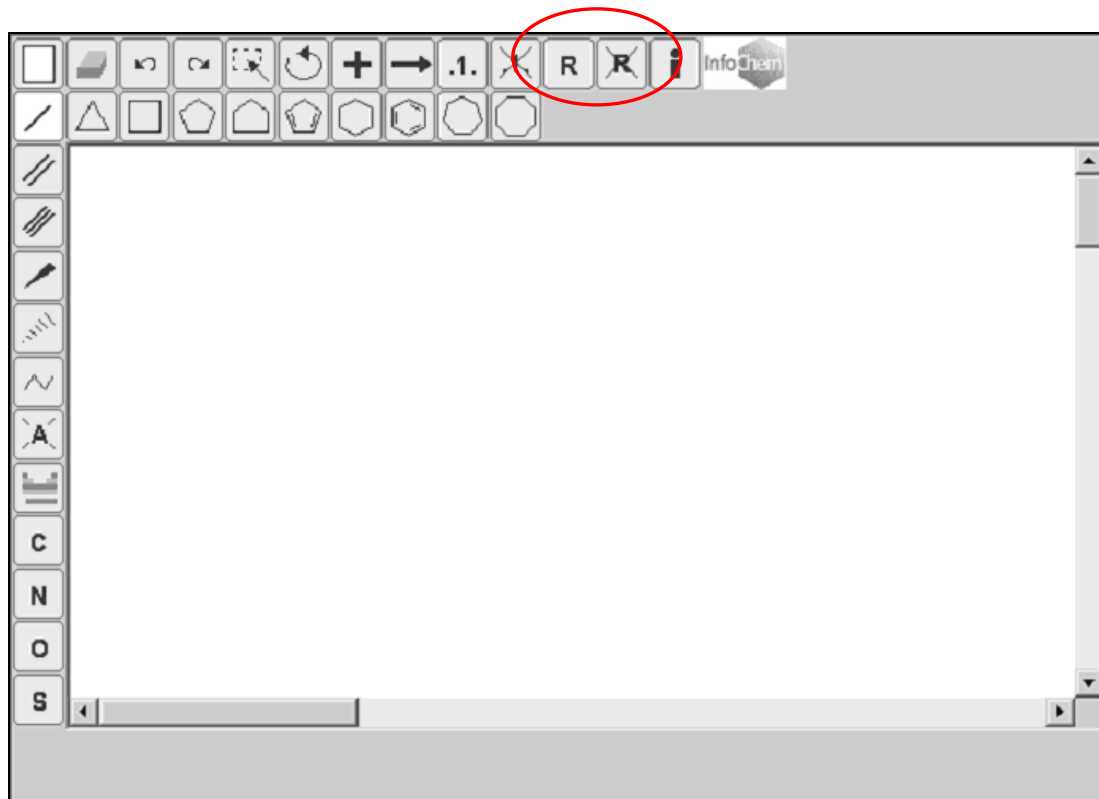


The following procedure is thus required to introduce a list:

- Select a highlighted atom with the right mouse button.
- Select the Edit Queryfeature 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

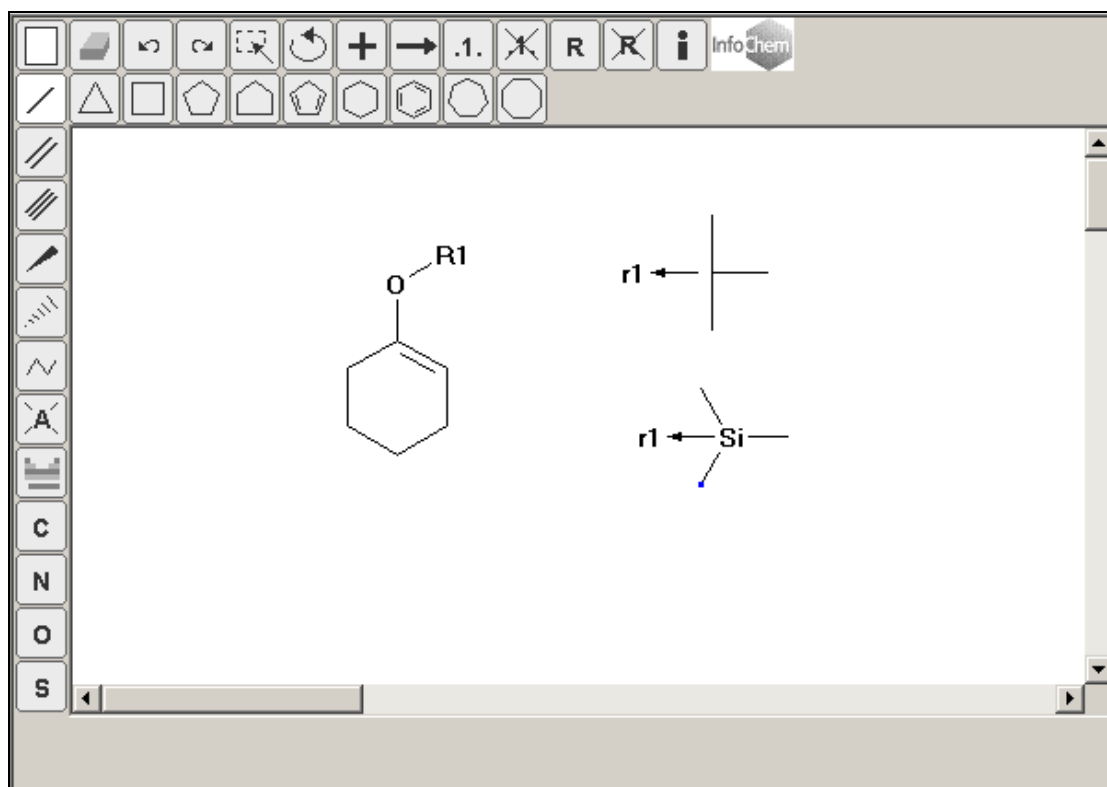
2.2.1.2.5 User Specified R-groups

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.

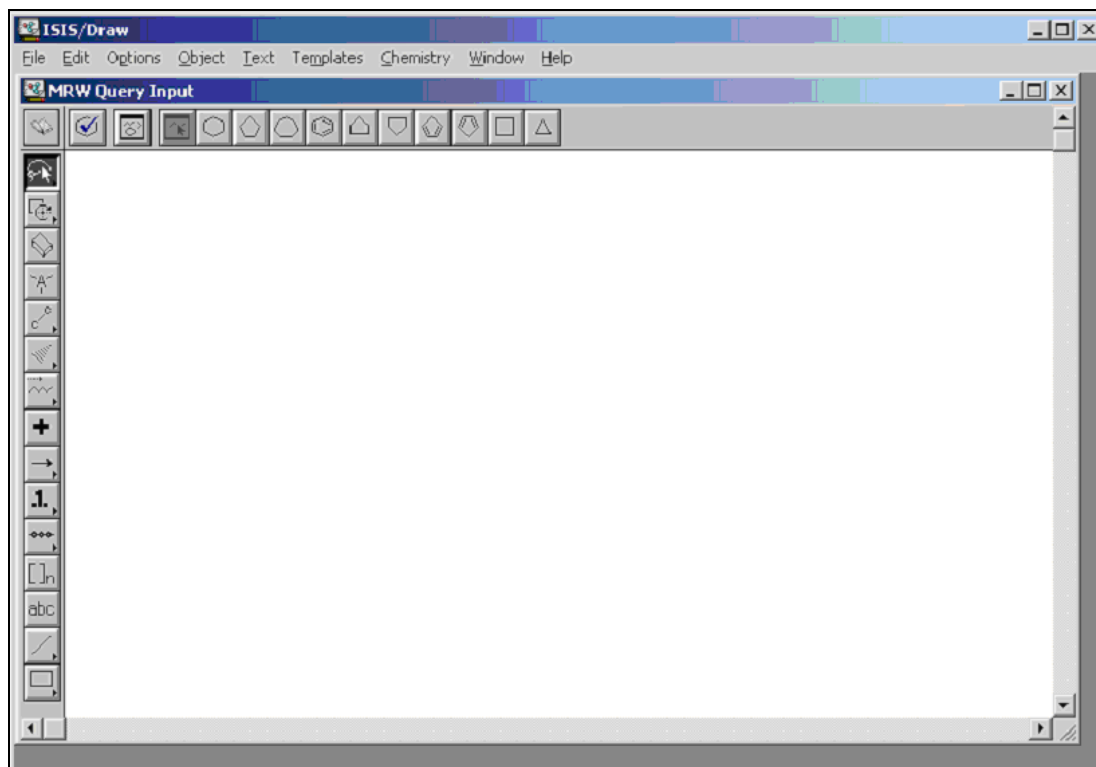



2.2.1.3 Transferring a Structure to the Search Window

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

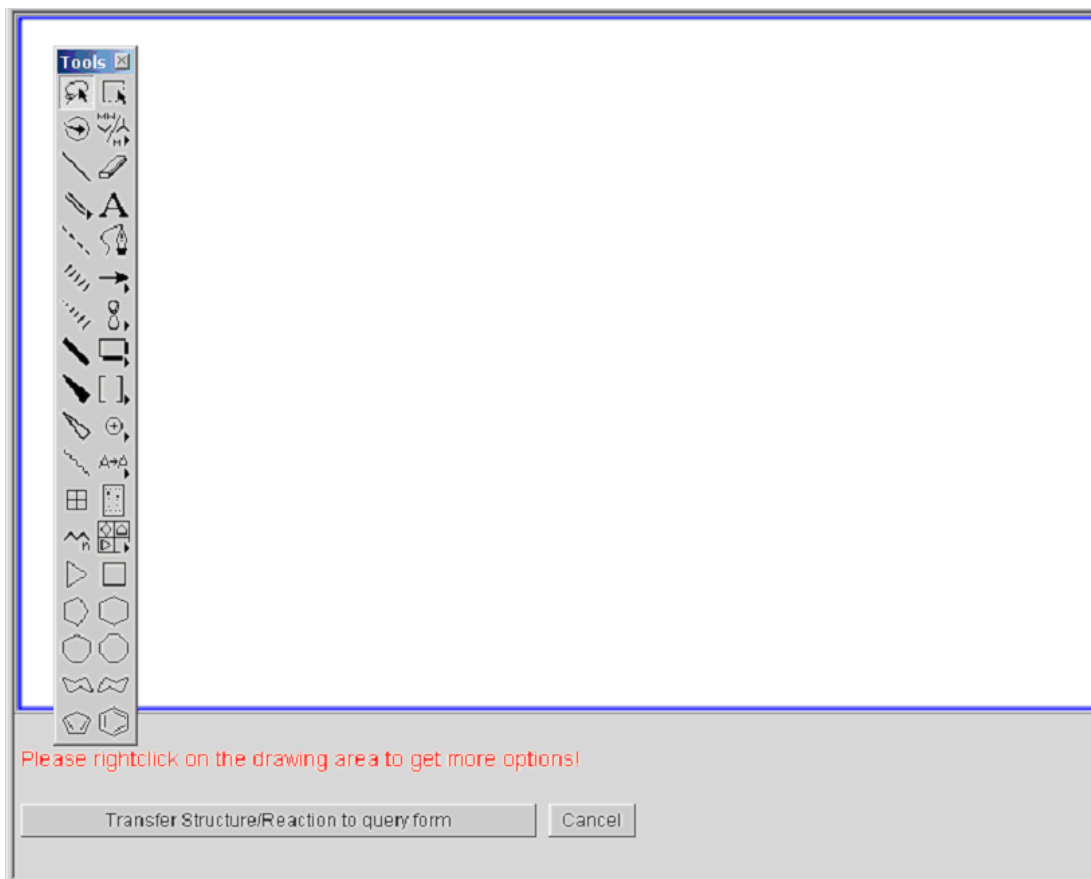
Select the ISIS/Draw drawing package. Then click , or click on the structure window. The drawing software will start automatically, and the drawing window will be displayed.



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.



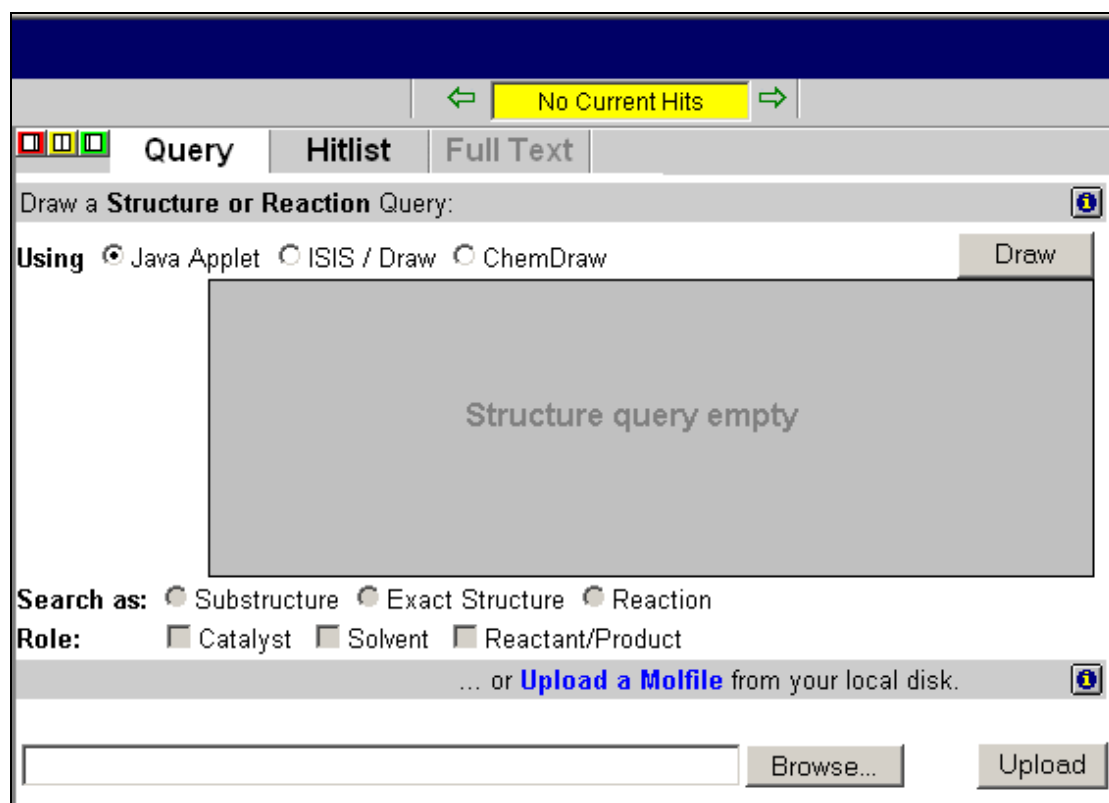
The initial window is featureless. The main tool bar used in ChemDraw can be activated by the following procedure:

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

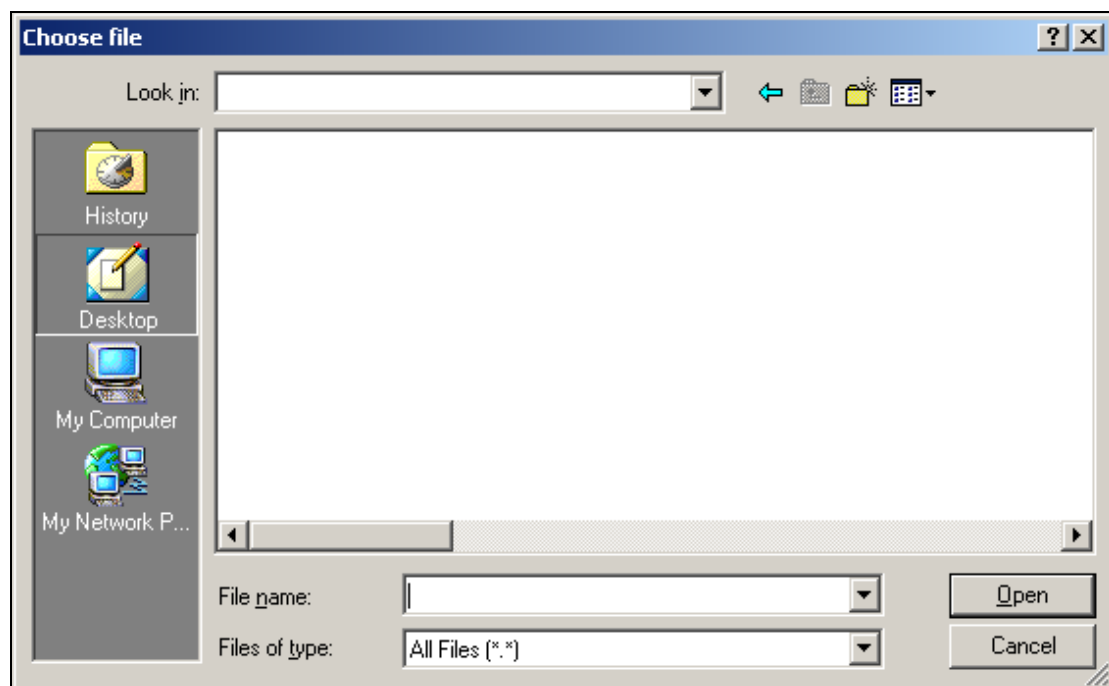
Once drawing is complete the button on the bottom left hand corner of the window may be used to transfer the structure to the search window.

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 to find the directory where your Molfiles are saved.



Select the Molfile you want (name.mol), click on , and then on 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.

← No Current Hits →

Query Hitlist Full Text

Draw a **Structure or Reaction** Query: ⓘ

Using Java Applet ISIS / Draw ChemDraw Edit

CC(=O)C

Search as: Substructure Exact Structure Reaction Clear

Role: Catalyst Solvent Reactant/Product

... or [Upload a Molfile](#) from your local disk. ⓘ

- 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 . If you wish to edit the structure, you can return to the drawing window by clicking on .

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.

The screenshot shows a 'Refine query' window with two rows of search criteria. The first row has a checked checkbox, a dropdown menu set to 'and', a dropdown menu set to 'CAS Registry No.', an empty text input field, and an 'Index...' button. The second row has a checked checkbox, a dropdown menu set to 'and', a dropdown menu with a list of options: 'CAS Registry No.', 'Catalyst', 'Solvent', 'Reaction Temp.', and 'Reaction Yield', an empty text input field, and an 'Index...' button. Below the second row is a blue 'Add Row' link. The window also features a 'Search for' label and a 'Full Text and Name Reactions:' label.

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.

The screenshot shows the 'Refine query' window with the first row of search criteria. Below the first row, a dropdown menu is open, showing the options 'and', 'or', and 'not'. The 'and' option is selected. Below the dropdown menu is a blue 'Add Row' link. The window also features a 'Search for' label and a 'Full Text and Name Reactions:' label.

2.4.1 CAS Registry Number

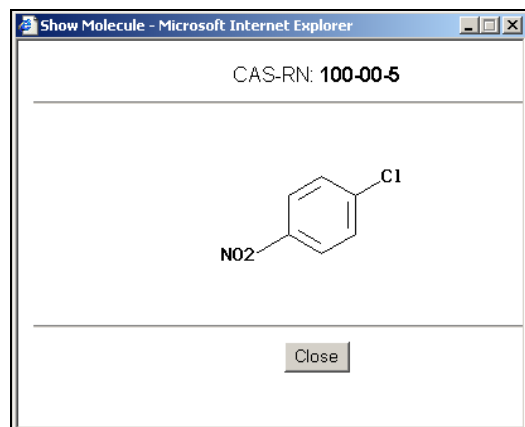
The CAS registry number search field enables you to search exact structures without using the Structure or Reaction query. Clicking on [Index...](#) will give all available registry numbers. Alternatively a partial CAS number may be entered, and those entries from the index containing the relevant fragment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

The screenshot shows the Science of Synthesis 3.2 interface. On the left, the 'Index' tab is active, displaying a table of 109408 terms (1-50 shown). The table has columns for '#', 'Terms', and 'Term'. The first few rows are:

#	Terms	Term
1	19	100-00-5
2	40	100-01-6
3	20	100-02-7
4	1	100-04-9
5	16	100-05-0
6	69	100-06-1
7	45	100-07-2
8	20	100-09-4
9	57	100-10-7
10	16	100-11-8
11	1	100-12-9
12	1	100-13-0
13	5	100-14-1
14	2	100-15-2
15	34	100-16-3
16	5	100-17-4
17	24	100-19-6
18	4	100-20-9

On the right, the 'Query' tab is active. It shows a search interface with options for 'Using' (Java Applet, ISIS / Draw, ChemDraw) and 'Search as' (Substructure, Exact Structure, Reaction). The 'Role' section includes Catalyst, Solvent, and Reactant/Product. There are search fields for 'CAS Registry No.', 'Full Text', and 'Bibliographic Information', each with an 'Index...' button. A 'Search' button is at the bottom right.

Clicking on [Index...](#) 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 to find the correct name

#	Terms	Term
1	1	Dibromo(1,4,8,11-tetraazacyclotetradecane)nickel(II)
2	1	dibromobis(tributylphosphine)nickel
3	32	dibromobis(triphenylphosphine)nickel(II)
4	1	dibromobis(triphenylphosphine)palladium
5	3	dibromobis(triphenylphosphine)palladium(II)
6	3	dibromoborane
7	12	dibromomethane
8	1	Dibromotetakis(butylamine)nickel(II)
9	1	dibromotriphenylantimony(V)
10	7	dibromotriphenylphosphorane
11	1	dibromotriphenylstibane

Refine query: and Catalyst

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 .

#	Terms	Term
1	5	1,2-dibromo-1,1,2,2-tetrachloroethane
2	1	1,2-dibromo-1,1,2,2-tetrafluoroethane
3	53	1,2-dibromoethane
4	23	1,3-dibromo-5,5-dimethylhydantoin
5	4	1,3-dibromo-5,5-dimethylhydantoin
6	1	1,3-Dibromo-5,5-dimethylhydantoin
7	28	1,3-dibromo-5,5-dimethylimidazolidine-2,4-dione
8	2	1,3-dibromopropane
9	2	1,6-dibromohexane
10	7	2-(3,5-Dibromo-2-hydroxybenzylideneamino)-3,3-dimethyl-(S)-butanoyl-O-tert-butyl-(L)-threonylglycin methylester
11	1	5,5-dibromo-2,2-dimethyl-1,3-dioxane-4,6-dione
12	2	(6,6'-dibromo-1,1'-bi-2-naphtholato)dibromotitanium

Refine query: and Catalyst

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 .

The screenshot shows the Science of Synthesis 3.2 web interface. On the left, there is a table titled "6 Terms" with the following data:

#	Terms	Term
1	292	cyclohexane
2	10	cyclohexanol
3	17	cyclohexene
4	2	cycloocta-1,5-diene
5	4	cyclooctane
6	15	cyclopentane

On the right, the "Query" tab is active, showing a search interface with the following elements:

- Buttons: "Query", "Hitlist", "Full Text", "No Current Hits", "Draw"
- Search as: Substructure Exact Structure Reaction
- Role: Catalyst Solvent Reactant/Product
- Refine query: and Solvent 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.

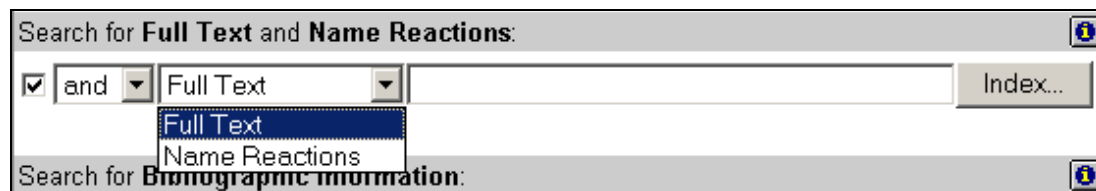
The screenshot displays the Science of Synthesis 3.2 search interface. On the left, the 'Index' panel shows a table with 2 terms and their respective hit counts. The main 'Query' panel on the right features a drawing area with a chemical structure of a cyclohexene ring with a hydroxyl group. Below the drawing area are various search options, including 'Search as' (Substructure, Exact Structure, Reaction), 'Role' (Catalyst, Solvent, Reactant/Product), and 'Refine query' options for CAS Registry No., Full Text, and Bibliographic Information. A 'Query History' button is visible at the bottom of the query panel.

2 Terms		
#	Hits	Term
1	77	query2
2	11	query1

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:

The screenshot shows the Science of Synthesis 3.2 web interface. On the left, the 'Index' panel displays a list of 135 terms, with the first 16 shown. The terms are listed in a table with columns for '#', 'Terms', and 'Term'. The first few terms are: 10 ACYLINDOLE, 33 ACYLINDOLES, 2 ACYLOXYINDOLES, 1 ALKENYLINDOLE, 2 ALKENYLINDOLES, 3 ALKOXYINDOLES, 1 ALKOXYINDOLE, 1 ALKYLINDOLE, 13 ALKYLINDOLES, 1 ALKYLISOINDOLES, 1 ALLYLINDOLE, 2 AMINOINDOLE, 2 ARYLINDOLE, 14 ARYLINDOLES, 1 ARYLISOINDOLE, and 2 AZAINDOLE. The 'Term' column contains the same text as the 'Terms' column. On the right, the 'Query' panel is active, showing a search interface. The 'Search as:' section has radio buttons for 'Substructure', 'Exact Structure', and 'Reaction'. The 'Role:' section has checkboxes for 'Catalyst', 'Solvent', and 'Reactant/Product'. The 'Refine query:' section has a dropdown menu set to 'and' and a text box containing 'CAS Registry No.'. The 'Search for Full Text and Name Reactions:' section has a dropdown menu set to 'and' and a text box containing 'Full Text' and 'indole*'. There are 'Index...' buttons next to the dropdown menus and text boxes.

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

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 screenshot shows a close-up of the 'Search for Full Text and Name Reactions:' field. It features a dropdown menu with 'and' selected, a text box containing 'Full Text', and an 'Index...' button. A dropdown menu is open below the text box, showing 'Full Text' and 'Name Reactions' (highlighted in blue). Below this, there is another section labeled 'Search for Biographic information:' with an 'Index...' button.

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

The screenshot displays the Science of Synthesis 3.2 web interface. The top navigation bar includes links for Help, Website, Abbreviations, Houben-Weyl, and Logout. A status bar shows "No Current Hits". The main interface is divided into several sections:

- Index:** A table with 6 terms related to the Simmons-Smith reaction.
- Query:** A section for drawing a structure or reaction query, currently empty.
- Search as:** Radio buttons for Substructure, Exact Structure, and Reaction.
- Role:** Checkboxes for Catalyst, Solvent, and Reactant/Product.
- Refine query:** A section for adding search criteria, including a dropdown for "CAS Registry No." and a search for "Name Reactions" with the term "*smith*".

#	Terms	Term
1	1	Simmons-Smith conditions
2	4	Simmons-Smith cyclopropanation
3	14	Simmons-Smith reaction
4	1	Simmons-Smith reaction, diastereoselective
5	2	Simmons-Smith reagent
6	3	Smith-Hoehn reaction

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 .

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

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 .

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  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  may be used to check journal abbreviations.
- Click on "Add Row".
- Select "Publication Year" and enter the date of publication.
- Click on .

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:


The screenshot displays the Science of Synthesis 3.5 interface. On the left is a 'Table of Contents' tree with categories like 'Organometallics', 'Organometallic Complexes of Nickel', and 'Organometallic Complexes of Palladium'. The main area shows search results for '2 Hits'. The first hit is titled 'Nickel Complexes of 1,3-Dienes - Diene-Aldehyde Reductive Cyclizations - Triethylborane-Mediated Reactions' by Montgomery, J. in *Science of Synthesis*, (2001) 1. 16. Below the title is a 'Reactions:' section with a chemical scheme showing a nickel complex as a catalyst for the reaction of a diene and an aldehyde to form a chiral alcohol. The second hit is titled 'Nickel Complexes of 1,3-Dienes - 1,4-Dialkylation of Dienes' by Montgomery, J. in *Science of Synthesis*, (2001) 1. 16. Below the title is another 'Reactions:' section with a chemical scheme showing a nickel complex as a reactant and product in a reaction between a diene and a cyclic enone.

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				
<input type="button" value="Unselect All Hits"/>		<input type="button" value="Select All Hits"/>		<input type="button" value="View Marked Hitlist"/>
<input type="button" value="Hide Overview"/>		<input type="button" value="Previous Hits"/>		<input type="button" value="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 Heteroarenes with One Heteroatom
10	2000	1657	243	Fused Five-Membered Heteroarenes with One Heteroatom
11	2001	1900	298	Five-Membered Heteroarenes with One Chalcogen and One Additional Heteroatom
12	2002	2198	178	Five-Membered Heteroarenes with Two Nitrogen or Phosphorus Atoms
13	2003	2376	128	Five-Membered Heteroarenes with Three or More Heteroatoms
14	2003	2504	461	Six-Membered Heteroarenes with One Chalcogen
15	2004	2965	416	Six-Membered Heteroarenes with One Nitrogen or Phosphorus Atom
16	2003	3381	341	Six-Membered Heteroarenes with Two Identical Heteroatoms
17	2003	3722	320	Six-Membered Heteroarenes with Two Unlike or More Than Two Heteroatoms and Larger Hetero-Rings
18	2005	4042	146	Four Carbon—Heteroatom Bonds: $X-C\equiv X$, $X=C=X$, $X_{2C}=X$, 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	5853	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	8454	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 will load the next 50 entries of the hit list. To view a hit on a previous page, click on

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 . 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 button. Once the list has been refined to the users satisfaction the altered hitlist may be viewed using the 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.

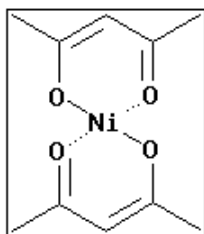
[[Top](#)]: Moves to the top of the hitlist.

Hit 1 of 2 [Table of Contents] [Top]

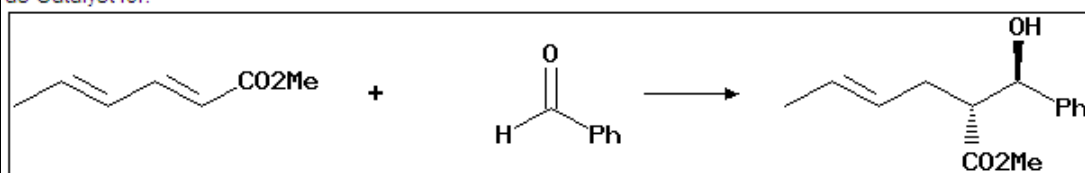
Nickel Complexes of 1,3-Dienes –
Diene–Aldehyde Reductive Cyclizations –
Triethylborane-Mediated Reactions

Montgomery, J. in *Science of Synthesis*, (2001) **1**, 16.

Reactions:



as Catalyst for:



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.

Search Result: 418 Hits		
Unselect All Hits	Select All Hits	View Marked Hitlist
Show Overview	<< Previous Hits	Next Hits >>
<input checked="" type="checkbox"/> Hit 1 of 418 [Table of Contents] [Top] Palladium–Diene Complexes – 1,3-Dienes: The 1,4-Addition of Nucleophiles – The Addition of Nitrogen Nucleophiles Takacs, J. M.; Jiang, X.; Vayalakkada, S. in <i>Science of Synthesis</i>, (2001) 1, 78.		
<input checked="" type="checkbox"/> Hit 2 of 418 [Table of Contents] [Top] Palladium–Alkyne Complexes – Addition of Nitrogen Nucleophiles – Intramolecular Addition of Nitrogen Nucleophiles Followed by Protonation Takacs, J. M.; Vayalakkada, S.; Jiang, X. in <i>Science of Synthesis</i>, (2001) 1, 288.		
<input checked="" type="checkbox"/> Hit 3 of 418 [Table of Contents] [Top] Palladium–Alkyne Complexes – Addition of Nitrogen Nucleophiles – Intramolecular Addition of Nitrogen Nucleophiles Followed by Allylation Takacs, J. M.; Vayalakkada, S.; Jiang, X. in <i>Science of Synthesis</i>, (2001) 1, 291.		
<input checked="" type="checkbox"/> Hit 4 of 418 [Table of Contents] [Top] Palladium–Alkyne Complexes – Addition of Nitrogen Nucleophiles – Intramolecular Addition of Nitrogen Nucleophiles Followed by Vinylation or Arylation Takacs, J. M.; Vayalakkada, S.; Jiang, X. in <i>Science of Synthesis</i>, (2001) 1, 294.		
<input checked="" type="checkbox"/> Hit 5 of 418 [Table of Contents] [Top] Palladium–Alkyne Complexes – Addition of Nitrogen Nucleophiles – Intramolecular Addition of Nitrogen Nucleophiles Followed by Vinyl or Aryl Carbonylation Takacs, J. M.; Vayalakkada, S.; Jiang, X. in <i>Science of Synthesis</i>, (2001) 1, 297.		
<input checked="" type="checkbox"/> Hit 6 of 418 [Table of Contents] [Top] Palladium–Alkene Complexes – Palladium-Catalyzed Heterocyclization: Intramolecular Addition of Nitrogen Nucleophiles – Intramolecular Addition of Amine Followed by β -Hydride Elimination Takacs, J. M.; Vayalakkada, S. in <i>Science of Synthesis</i>, (2001) 1, 358.		

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.

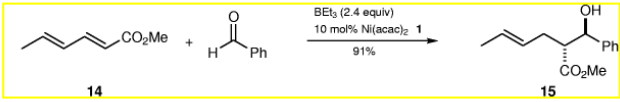
1.1.1.4.2 Variation 2:
Triethylborane-Mediated Reactions

Montgomery, J., in *Science of Synthesis*, 1 (2001), p. 16

Information on *Science of Synthesis* Volume 1
Feedback

The intermolecular process between simple dienes and aldehydes is reported by Tamaru.^[31] Triethylborane is employed as the reducing agent, and yields are good for a variety of substituted electron-rich and electron-poor dienes. Interestingly, reactions employing triethylborane and bis(acetylacetonato)nickel(II) (**1**) produce 4,5-unsaturated alcohols (Scheme 9), whereas reactions employing bis(η^4 -cycloocta-1,5-diene)nickel(0) (**2**), triphenylphosphine, and triethylsilane produce 3,4-unsaturated silyl ethers. The mechanistic basis for this reversal of regioselectivity has not been established.

Scheme 9 Reductive Coupling with Triethylborane^[31]



Methyl (2*R*,4*E*)-2-[(*R*)-Hydroxy(phenyl)methyl]hex-4-enoate (**15**).^[31]

Into a N_2 -purged flask containing $[Ni(acac)_2]$ (**1**; 12.8 mg, 0.05 mmol) were introduced successively freshly dried (Na benzophenone ketyl) THF (3 mL), methyl (2*E*,4*E*)-hexa-2,4-dienoate (**14**; 2.52 g, 20 mmol), PhCHO (530 mg, 5 mmol), and 1 M BEt_3 in hexane (12.0 mL) via a syringe. The homogeneous mixture was stirred at rt for 66 h until the PhCHO disappeared completely. After dilution with EtOAc (50 mL), the mixture was washed successively with 2 M HCl, sat. $NaHCO_3$, and sat. NaCl, and then dried ($MgSO_4$), and concentrated in vacuo. The residual oil was subjected to column chromatography (silica gel, hexanes/EtOAc 16:1) to give an analytically pure sample of **15**; yield: 1.07 g (91%).

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.

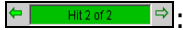
All sections of Science of Synthesis loaded in full text view show the section title and the volume reference. Two links are provided at the start of the document:


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

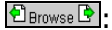
Feedback: Allows the user to report errors or send queries related to the document to the Science of Synthesis helpdesk.

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.

The screenshot displays the Science of Synthesis 3.5 web interface. On the left is a navigation tree under 'Science of Synthesis' with categories like 'Organometallics' and 'Applications'. The main content area shows 'Scheme 9 Reductive Coupling with Triethylborane^[31]'. The reaction scheme depicts the reductive coupling of methyl (2E,4E)-hexa-2,4-dienoate (14) with benzaldehyde (PhCHO) to form methyl (2R*,4E)-2-[(R*)-hydroxy(phenyl)methyl]hex-4-enoate (15) in 91% yield. The reagents are BEt₃ (2.4 equiv) and 10 mol% Ni(acac)₂. Below the scheme is the full name of product 15 and a detailed experimental procedure. A 'References' section at the bottom lists reference [31] from the *J. Am. Chem. Soc.* (1998) 120, 4033. The footer includes copyright information for Georg Thieme Verlag KG and the DOI: 10.1055/tcsos-001(2005.1)-00011.


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


Thieme Chemistry Literature Crossover	
	Reference details: Kimura, M.; Ezoe, A.; Shibata, K.; Tamaru, Y., <i>J. Am. Chem. Soc.</i> , (1998) 120 , 4033.
 CROSSREF.ORG THE CITATION LINKING BACKBONE	DOI: 10.1021/ja973847c
Last CrossRef Update: 05/28/2006	
	Order from FIZ Autodoc
Copyright © 2008 by Georg Thieme Verlag KG, all rights reserved Document Identifier SR-001-00051 http://www.science-of-synthesis.com	

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.

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.

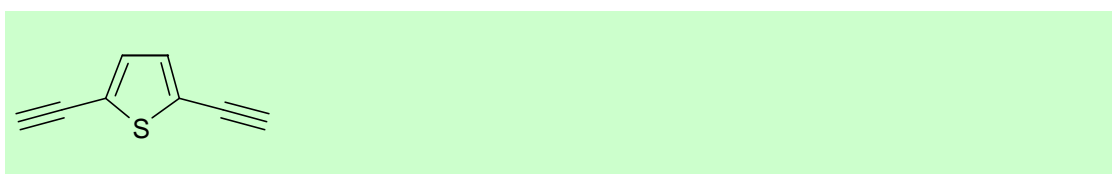
6 Science of Synthesis Worked Examples

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:

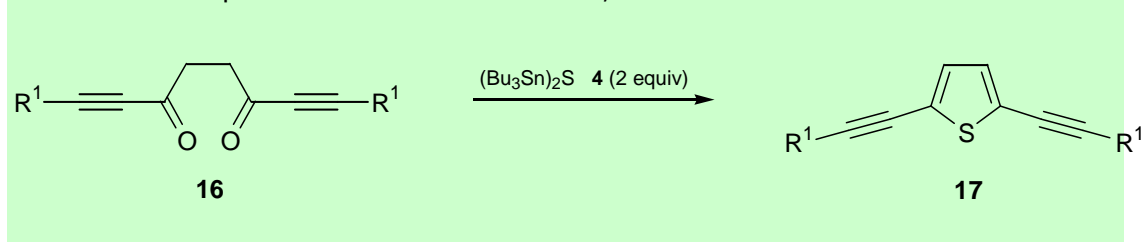
Heaney, H.; Christie, S. in *Science of Synthesis*, (2003) **3**, 412

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]



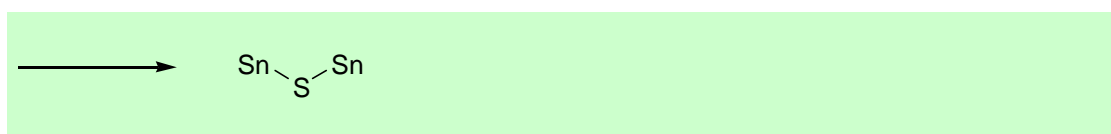
Clicking on the reference citation at this point will give you the following reference:

[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

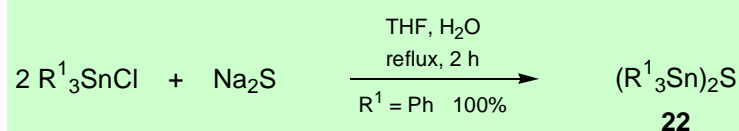
Carry out a **Reaction Search** for:



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 $(\text{Bu}_3\text{Sn})_2\text{S}$ reagents will be included in your answer set.

The **Hitlist** will give you one hit: Jousseume, 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]



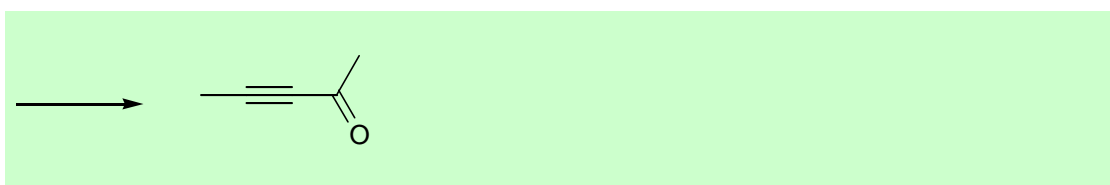
Hexaphenyldistannathiane (22, R¹ = Ph); Typical Procedure:^[10]

A 50-mL flask was charged with Ph_3SnCl (10.53 g, 2.73 mmol) and reagent grade THF (27 mL). A soln of $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$ (6.56 g, 2.73 mmol) in H_2O (8 mL) 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 $\text{Ph}_6\text{Sn}_2\text{S}$, 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** ($\text{R}^1 = \text{Ph}$) 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

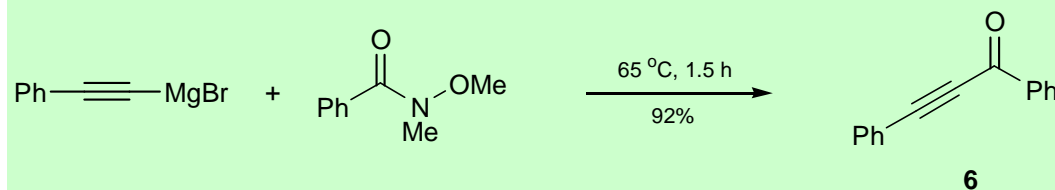
Carry out a **Reaction Search** for:



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 alkylation 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]

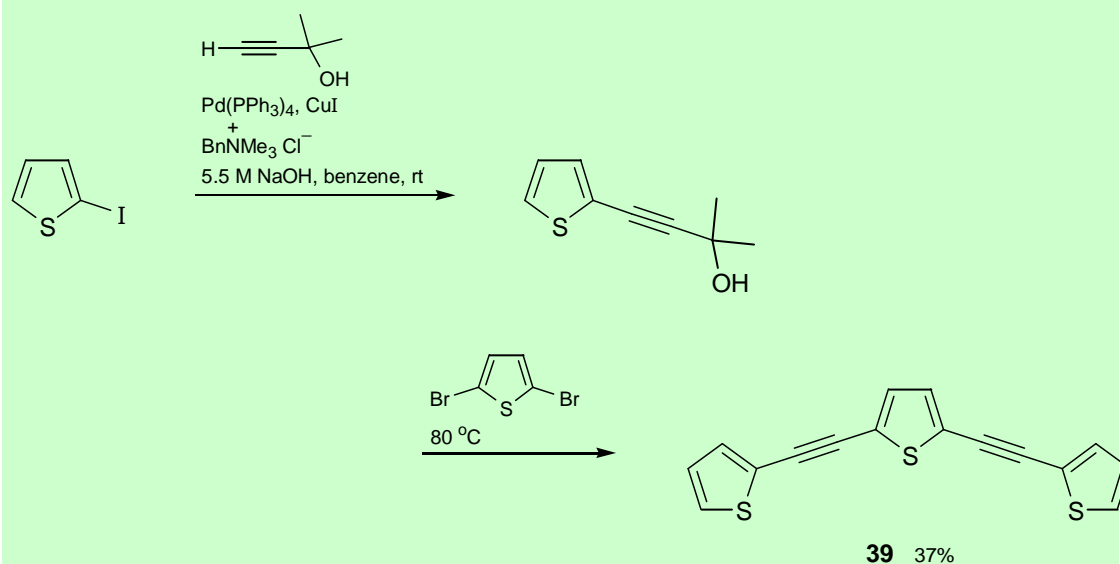


Clicking on the reference citation number gives the full reference.

[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]



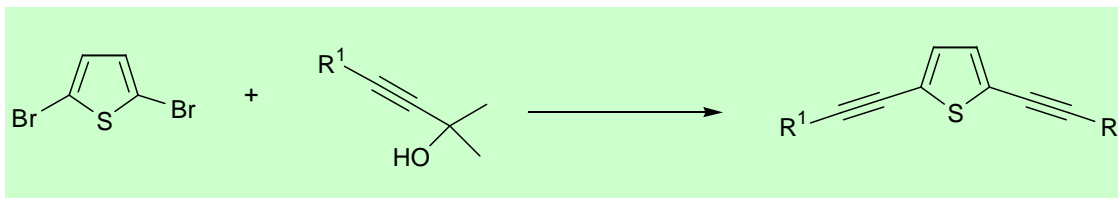
2,5-Bis(2-thienylethynyl)thiophene (39); Typical Procedure:^[740]

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 N₂ and added to a mixture of CuI (0.324 g, 1.7 mmol), Pd(PPh₃)₄ (1.37 g, 1.19 mmol), and BnMe₃NCl (0.24 g, 1.19 mmol) under N₂. An O₂-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 N₂ and added to the mixture, which was then stirred at 70–80 °C for 50 h. A sat. aq soln of NH₄Cl (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.

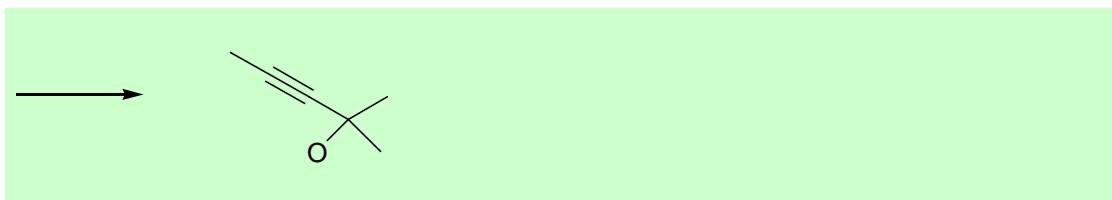
So we are basically looking at the following transformation:



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

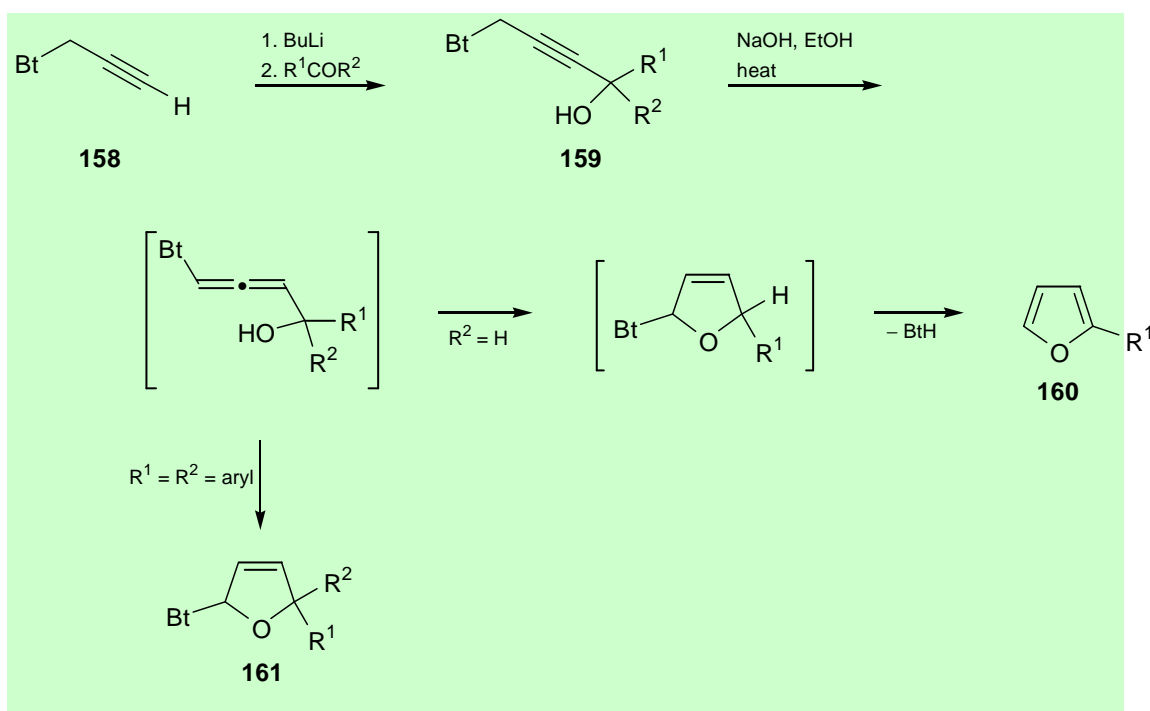
1) The Preparation of the Alkynol

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.

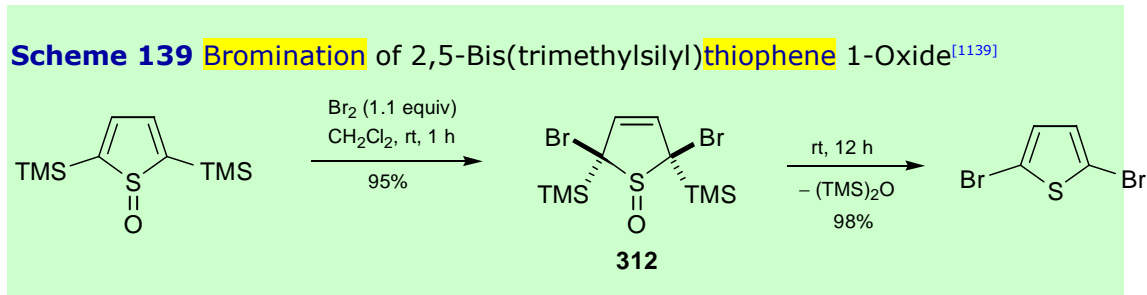
2) The Preparation of the 2,5-Dibromothiophene

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

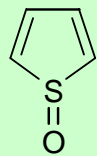
You will get 5 hits. Go to Volume 9 and the second hit, Schatz, J. in *Science of Synthesis*, (2000) **9**, 396 (Section 9.10.3).



The reference given for this bromination reaction is:

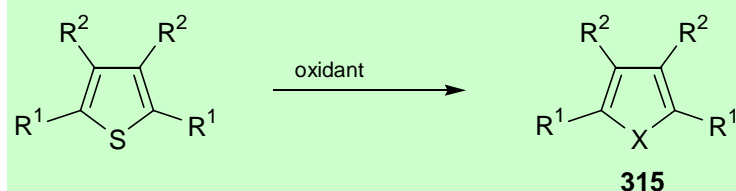
[1139] Zhang, S. Z.; Sato, S.; Horn, E.; Furukawa, N., *Heterocycles*, (1998) **48**, 227.

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

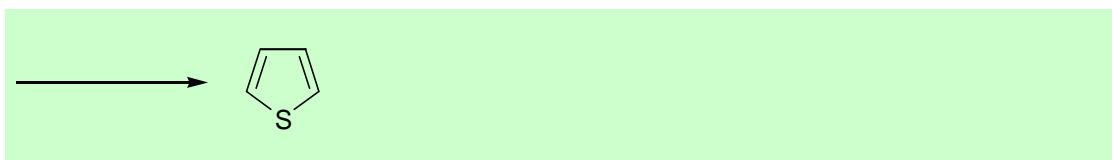


You will get eight hits. Choose Volume 9 and Schatz, J. in *Science of Synthesis*, (2000) **9**, 398 (Section 9.10.3.1.2.1, Hit 7). You will get the following result along with a table of derivatives, a typical procedure and a number of useful references:

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



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:

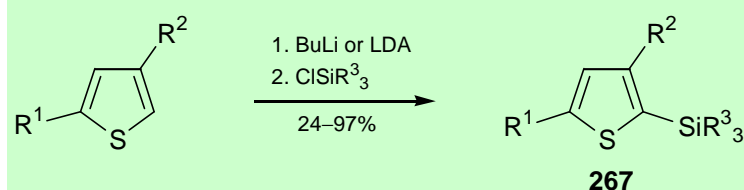


together with a **Fulltext Search** for:

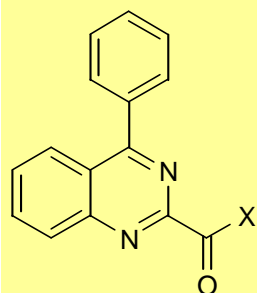
silylation

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]

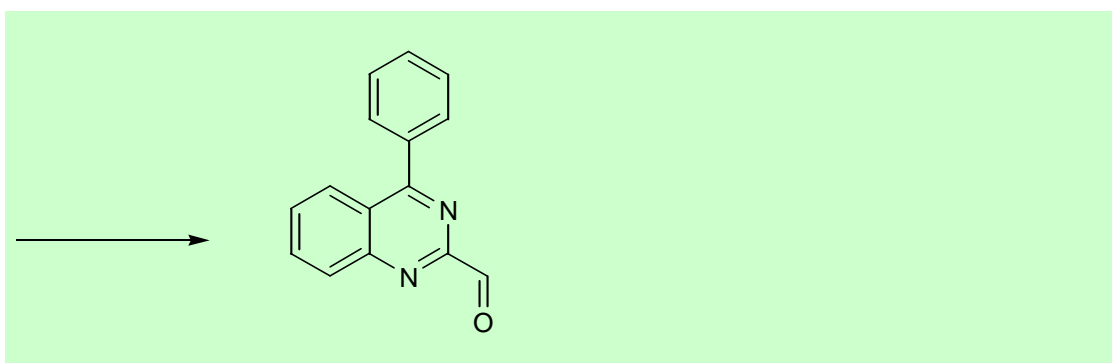


A table with a list of substituents, two procedures and a series of useful references are cited.

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

X=OH, OEt, NHAc, NPh

Carry out a **Reaction Search** for:



You will get five hits in total.

Synthesis is possible via:

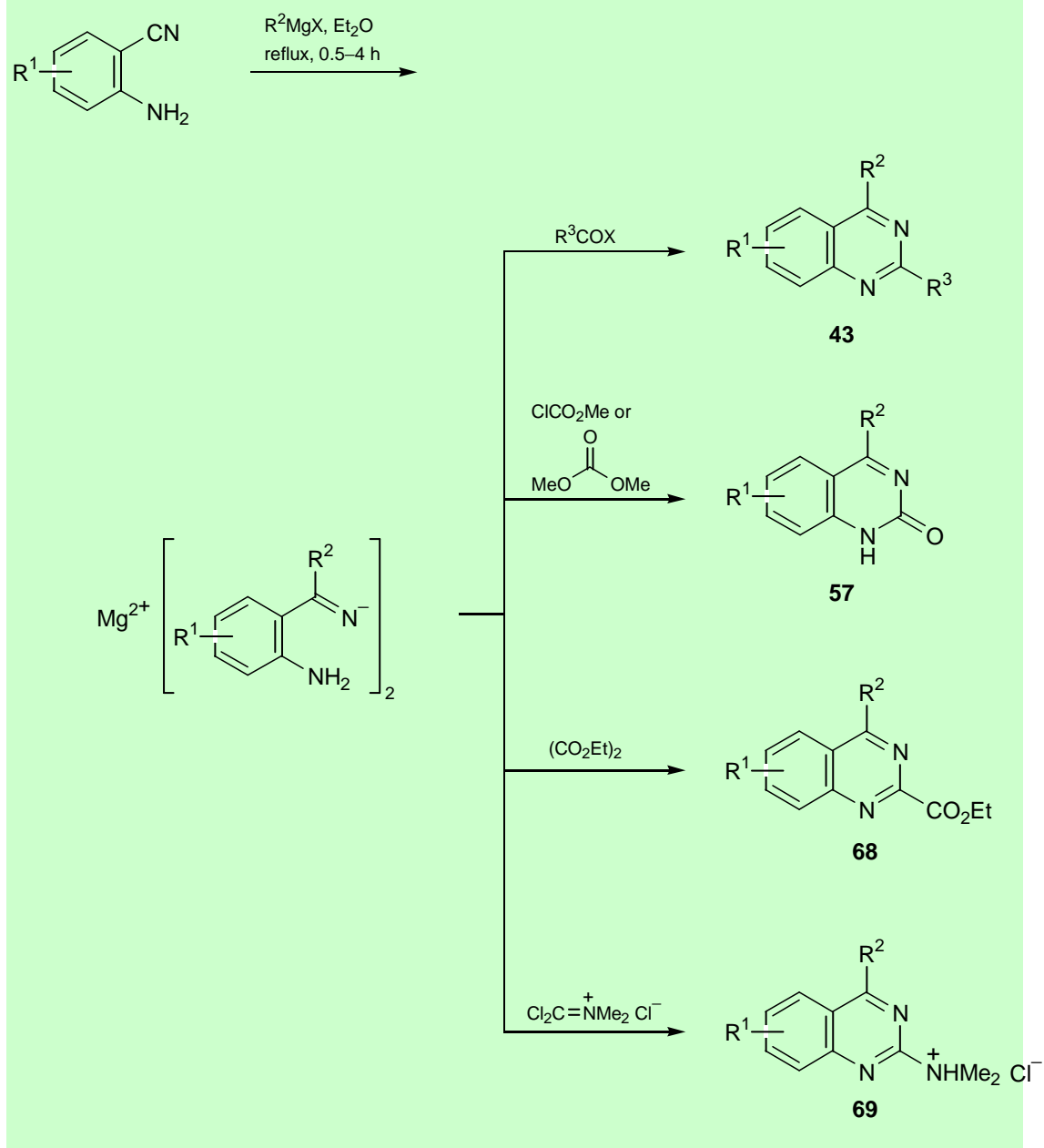
- a)** The Cyclization of 2-Aminobenzonitriles: Kikelj, D. in *Science of Synthesis*, (2003) **16**, 614 (Section 16.13.1.1.2.6.10).
- b)** The Cyclization of 3-Phenyl-2,1-benzioxazole: Kikelj, D. in *Science of Synthesis*, (2003) **16**, 655 (Section 16.13.2.1.4).
- c)** Ring Contraction Reactions: 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).

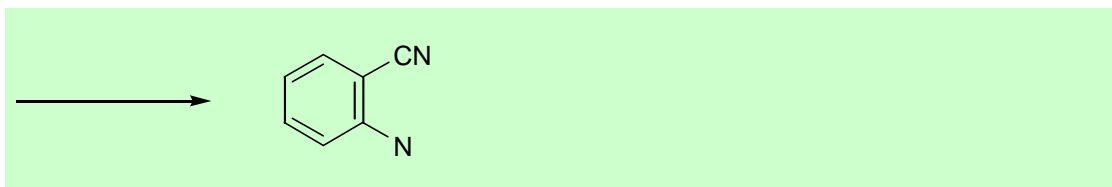
Clicking on this hit gives you the following information:

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.



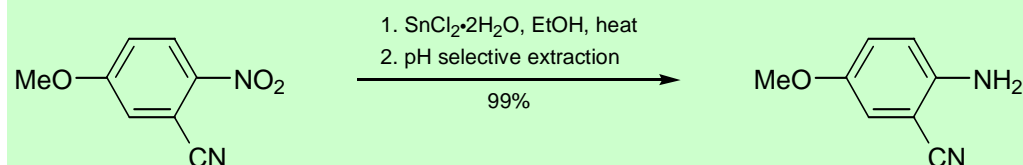
Now search using exactly the same query together with the following term in the **Full Text** field:

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]



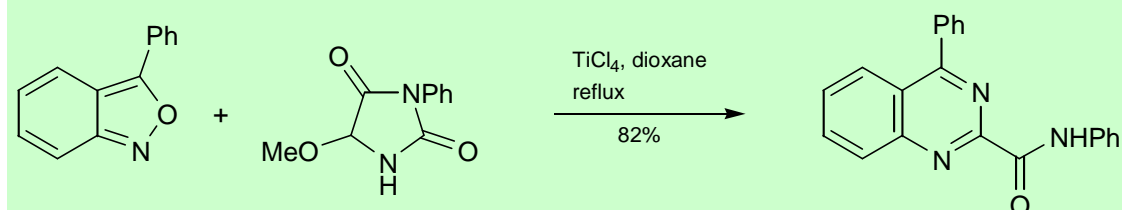
A reference for this type of reaction is available:

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

b) The Cyclization of 3-Phenyl-2,1-benzisoxazole: 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-Diphenylquinazoline-2-carboxamide from 3-Phenyl-2,1-benzisoxazole^[588]



Together with the following reference:

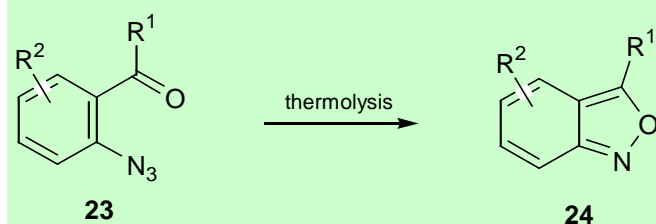
[588] Ohta, K.; Nakamura, Y.; Iwaoka, J.; Nomura, Y., *Nippon Kagaku Kaishi*, (1990), 72; *Chem. Abstr.*, (1990) **113**, 6272.

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]



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, R¹ = Ph; R² = H):^[89]

A soln of 2-azidoaryl ketone **23** (R¹ = Ph; R² = 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.