Woollins' Reagent: A Graphical Review of Its Main Synthetic Uses

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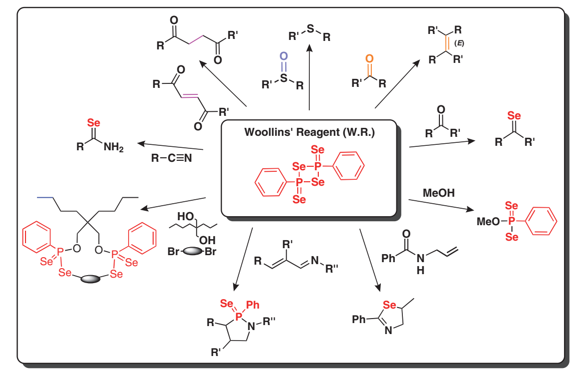


Received: 24.06.2024
Accepted after revision: 23.08.2024
Published online: 07.10.2024 (Version of Record)
DOI: 10.1055/s-0040-1720136; Art ID: SO-2024-06-0025-GR

Abstract Woollins' reagent (W.R.) was initially used for the selenation of carbonyl compounds. However, various synthetic applications utilizing this reagent have since been discovered, making it increasingly useful. Examples include the formation of heterocycles, the stereospecific reduction of olefins, and the synthesis of selenoic acids, among others. Consequently, synthetic studies of W.R. derivatives have become increasingly relevant due to the growing demand for selenated compounds in various applications. Two notable examples are the agricultural sector, with the development of pesticides, and the pharmaceutical sector, with the development of antivirals, antioxidants, and neuroprotectors, among others. Hence, this graphical review aims to address the synthetic diversity that W.R. can provide, presenting examples of its main synthetic uses.

Key words carbonyl selenation, cyclization, stereoselectivity, heterocycles, macrocycles, (*E*)-olefination, regioselective reduction, selenoamide

Woollins' reagent (W.R.; $C_{12}H_{10}P_2Se_4$) is a dark red solid with an unpleasant odor. While this compound poses no inherent risks during handling, it should be stored at approximately 2 °C in an inert environment to maintain its integrity due to its hygroscopic nature.[1a] W.R. has emerged as an analogue to Lawesson's reagent (LR), both functioning as chalcogen-donating agents for carbonyl compounds, with selenium replacing the oxygen and sulfur in LW.[1b,c]

In addition to its role as a selenium donor to carbonyl compounds, W.R. has found applications in various other reactions, including the formation of heterocycles containing phosphorus and/or selenium, macrocycle formation, stereospecific generation of (*E*)-olefins, and regioselective reduction of unsaturated bonds, among others. The synthesis of the reagent employs recent and optimized methodologies, resulting in a high level of purity and excellent yields (96–99%).[1d,e]

It is noteworthy that selenium compounds have diverse applications across various industrial sectors, contributing to their economic value. These applications span multiple fields, such as the pharmaceutical sector,[1f–h] including veterinary pharmacology;[1i] agricultural practices using selenium compounds in fertilizers, pesticides and fungicides;[1j] the synthesis of natural products and their analogs;[1k] modification of the mechanical properties of polymeric materials;[1l] and cosmetics.[1m] Hence, the synthetic exploration of selenium-derived compounds assumes increasing importance and necessity.

Biographical Sketches

João V. X. da Silva is a chemistry student at the Federal University of Rio de Janeiro (UFRJ) and is currently an intern under the supervision of Prof. Sabrina B. Ferreira and Dr. Ingrid C. Chipoline. His work involves the synthesis and evaluation of substances generated by artificial intelligence, which are potentially active against SARS-CoV-2. Additionally, he has experience in medicinal organic synthesis for neglected diseases, focusing on leishmaniasis and tuberculosis.

Ingrid C. Chipoline holds a bachelor's degree in industrial chemistry from the Universidade Federal Fluminense (2016), a master's degree (2018), and a Ph.D. in chemistry (2022) from the same university. She is currently undertaking postdoctoral research in the field of organic synthesis, with an emphasis on the production of molecules generated by artificial intelligence through flow chemistry on a chip.

Sabrina B. Ferreira received her Ph.D. from the Federal University of Rio de Janeiro (UFRJ) in 2008 under the supervision of Prof. Carlos R. Kaiser and Prof. Vitor F. Ferreira. After postdoctoral studies at Fluminense Federal University (UFF) with Prof. Vitor F. Ferreira, she became a professor at UFRJ in 2010, where she is the head of the Laboratory of Organic Synthesis and Biological Prospecting. Her research efforts focus on organic synthesis in the following areas: heterocycles, carbohydrates, natural products, and the search for biologically active compounds.

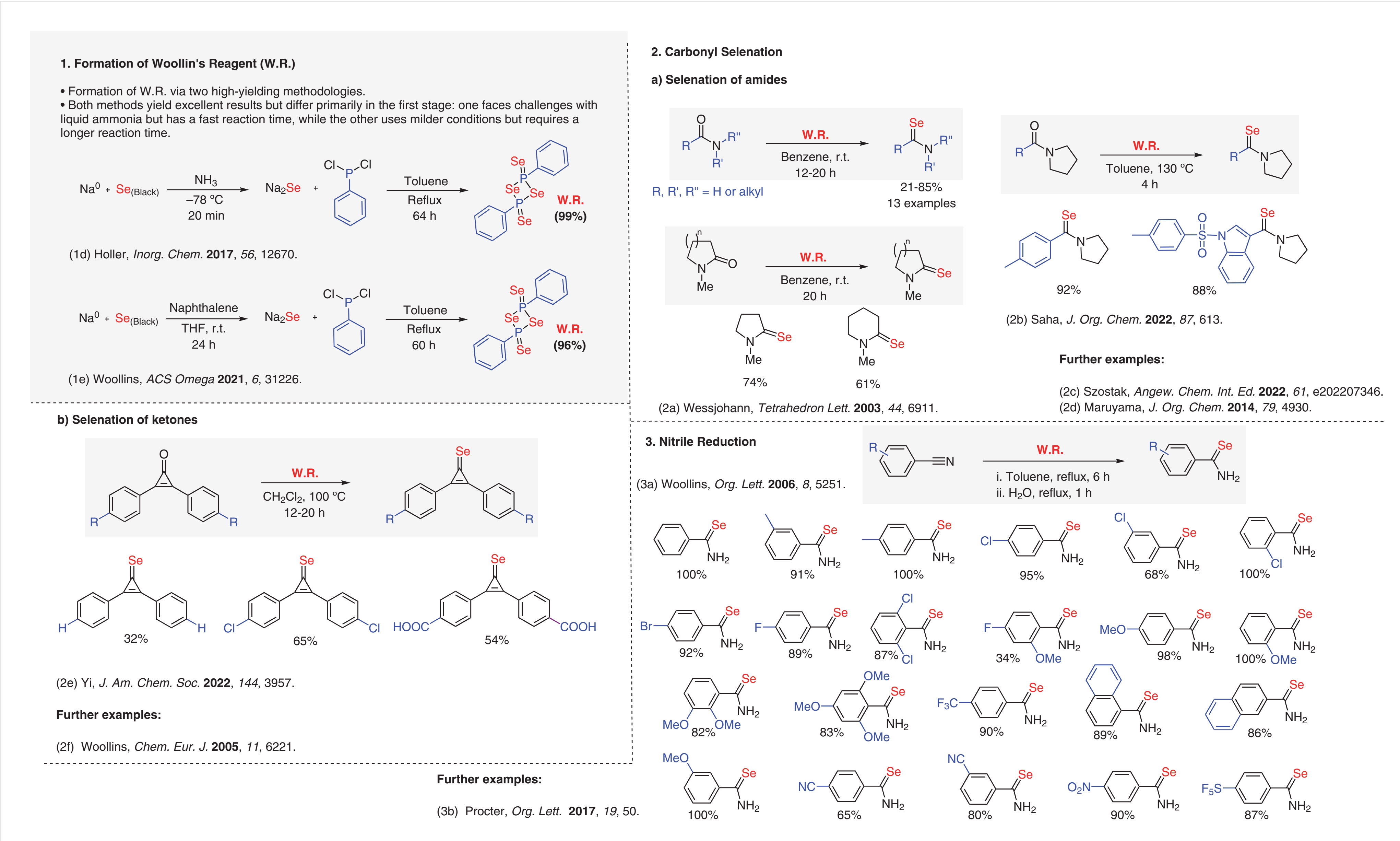


Figure 1 Formation of Woollins' reagent and carbonyl selenylation

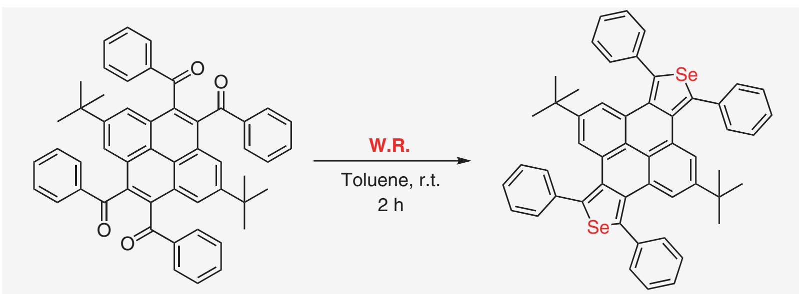
4. Preparation of heterocycles containing Se/N/O from carbonyl compounds

a) Heterocycles containing only selenium

R = H or alkyl

83-99%
7 examples

(4a) Woollins, *Org. Biomol. Chem.* **2010**, *8*, 1655.



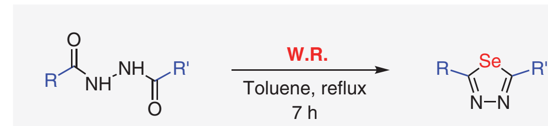
(4b) Zhang, *Asian J. Org. Chem.* **2018**, *7*, 2213. 68%

Further examples:

(4c) Hamura, *Chem. Lett.* **2017**, *46*, 703.
(4d) Takashi, JP Patent 2016160239, **2016**.

b) Heterocycles containing nitrogen and selenium

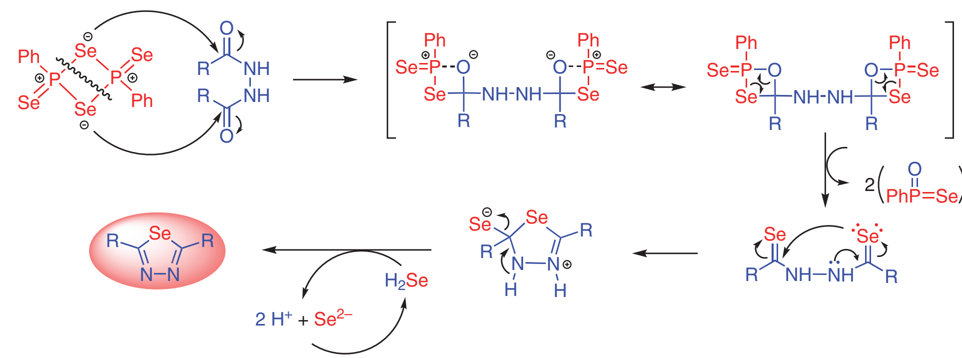
(4e) Woollins, *Eur. J. Org. Chem.* **2009**, 1612.



R, R' = ethoxy, furanyl, pyridyl, thiophenyl, aryl

51-99%
36 examples

Proposed Mechanism:

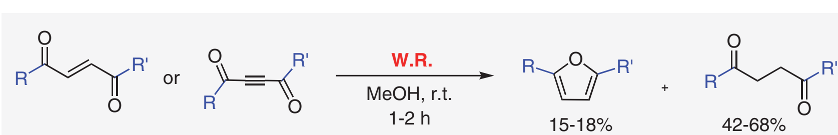


(4f) Rauf, *Arabian J. Chem.* **2018**, *11*, 143.

Further examples:

(4g) Murineddu, *Eur. J. Med. Chem.* **2022**, *238*, 114440.
(4h) Woollins, *Synlett* **2015**, *26*, 839.
(4i) Frański, *J. Heterocycl. Chem.* **2012**, *49*, 1266.

c) Heterocycles containing only oxygen

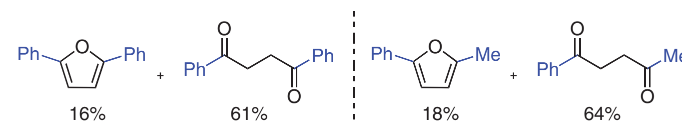


R, R' = Aryl or alkyl

12 examples

(4j) Jaisankar, *Synlett* **2012**, *23*, 2615.

Selected examples:



The expected product, the heterocycle, is formed, but in low yield compared to the co-product of double bond reduction. This issue will be addressed in **Section 5** (Figure 3).

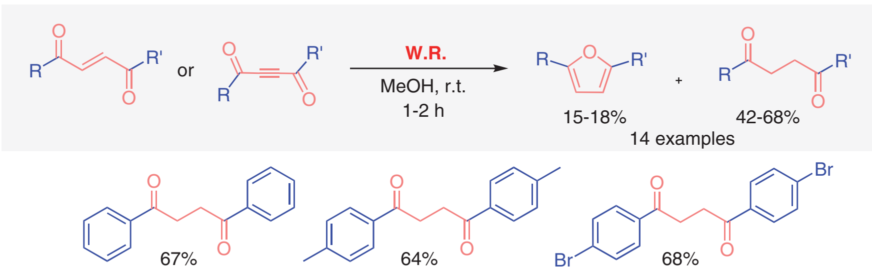
Figure 2 Formation of heterocycles containing selenium, nitrogen, and oxygen atoms

5. Chemoselective reduction of conjugated 1,4-dicarbonyl compounds

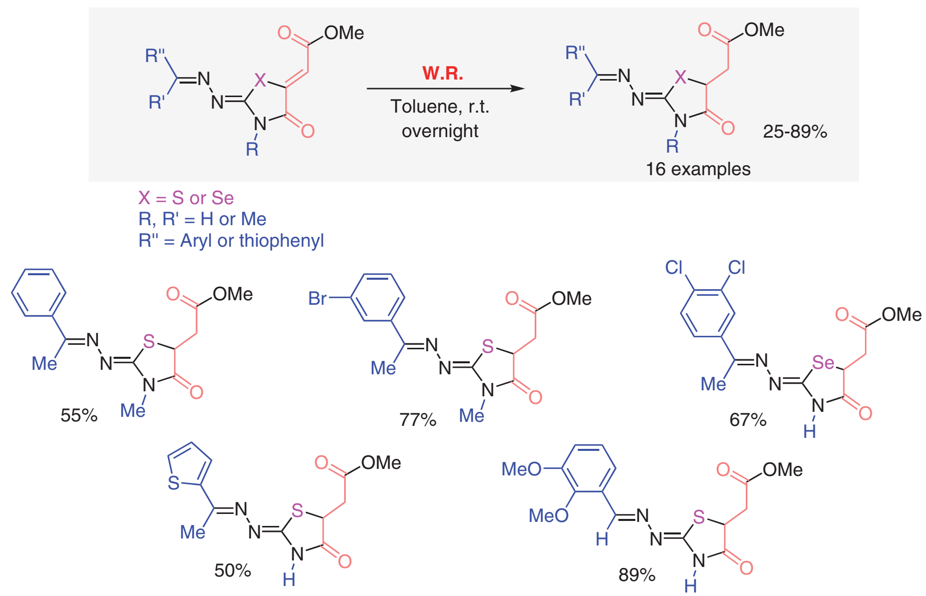
As observed in **Section 4c** (Figure 2), the heterocycle is not the major product when a conjugated dicarbonyl structure is present; rather, a chemoselective reduction product of unsaturation predominates.

This section presents various examples validating this observation and a mechanistic proposal.

Previous reaction: **Section 4c**

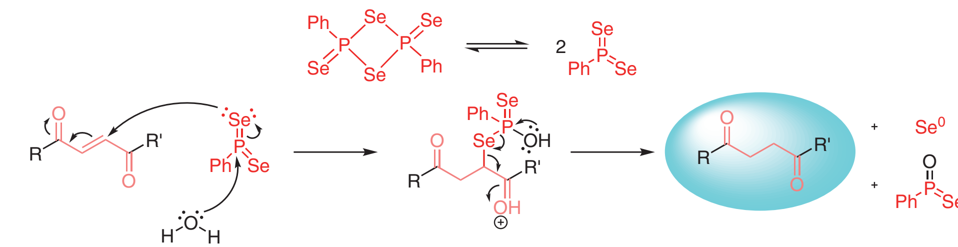


(4j) Jaisankar, *Synlett* **2012**, *23*, 2615.



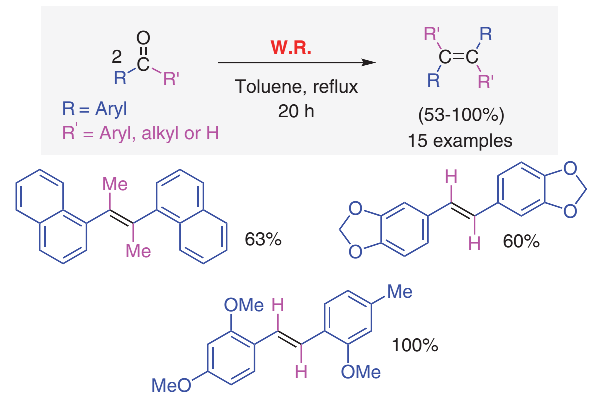
(5) Mahler, *Tetrahedron Lett.* **2017**, *58*, 1445.

Generical mechanistic proposal for this reduction



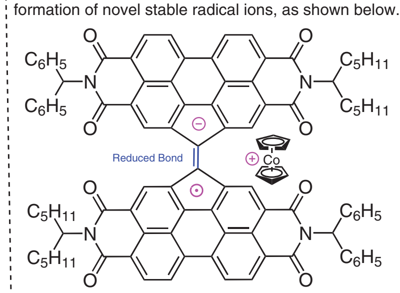
Both references 4j and 5 provide corroborative mechanistic proposals.

6. Stereoselective synthesis of (*E*)-olefins by a reductive coupling reaction



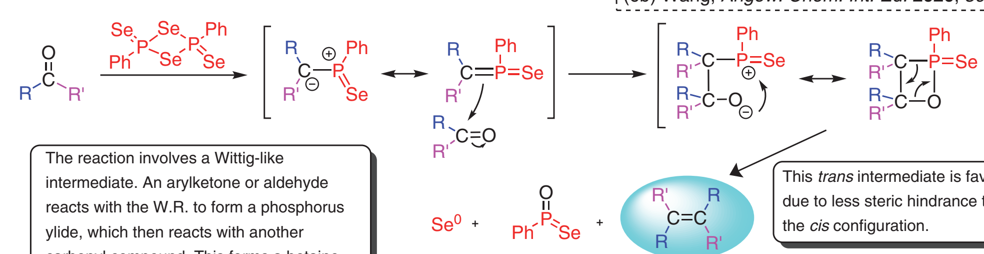
An additional interesting application:

A recent study demonstrated that it is possible to perform coupling (in this case, symmetric) to form highly electron-deficient structures, leading to the formation of novel stable radical ions, as shown below.



(6b) Wang, *Angew. Chem. Int. Ed.* **2020**, *59*, 752.

Proposed mechanism for the formation of (*E*)-olefins



The reaction involves a Wittig-like intermediate. An arylketone or aldehyde reacts with the W.R. to form a phosphorus ylide, which then reacts with another carbonyl compound. This forms a betaine intermediate that rearranges and eliminates PhP(Se)(O), resulting in the olefin.

This *trans* intermediate is favored due to less steric hindrance than the *cis* configuration.

(6a) Woollins, *Dalton Trans.* **2007**, 1477.

Figure 3 Chemoselective reduction of conjugated 1,4-dicarbonyl compounds, stereoselective synthesis of (*E*)-olefins by a reductive coupling reaction and the respective mechanistic proposals

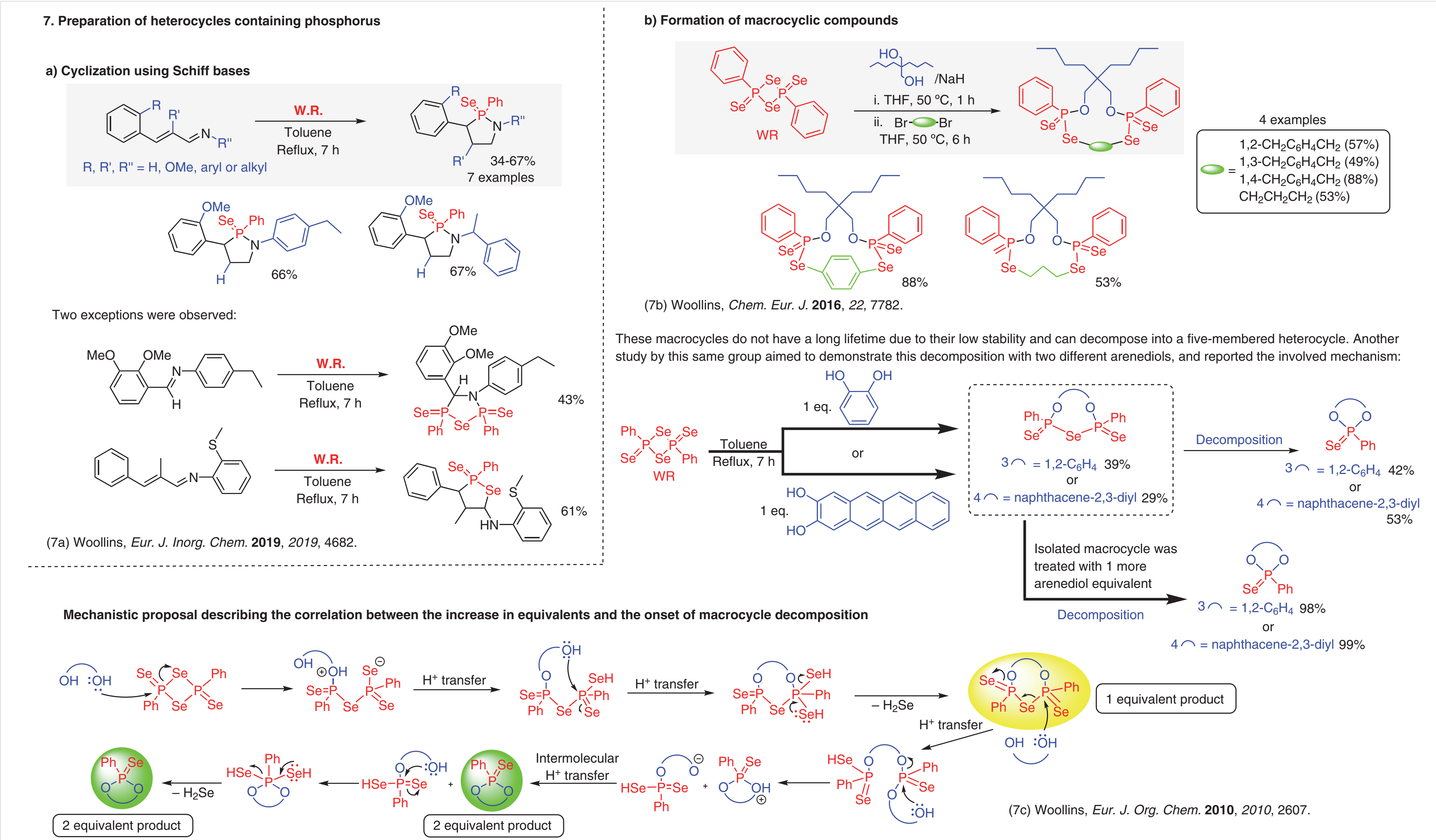
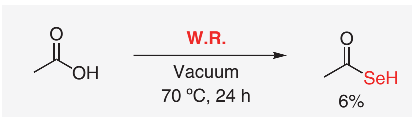


Figure 4 Preparation of heterocycles containing phosphorus, and the formation of macrocyclic compounds along with mechanistic proposals

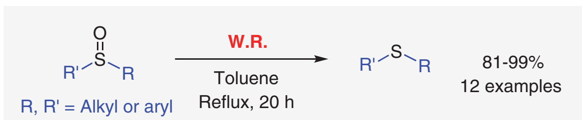
8. Selenoic acid formation

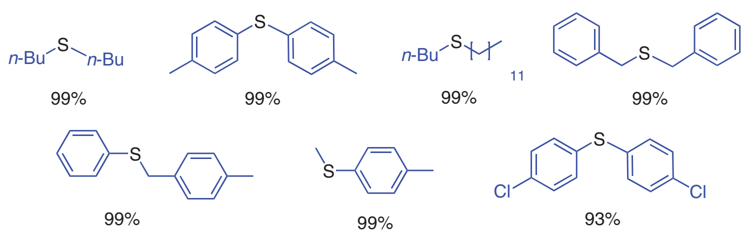


Further examples:
(8b) Yamamoto, *J. Med. Chem.* **2012**, *55*, 7696.
(8c) Yamamoto, *Bioinorg. Chem. Appl.* **2018**, *28*, 2256.
(8d) Ellman, *ACS Cent. Sci.* **2017**, *3*, 1322.

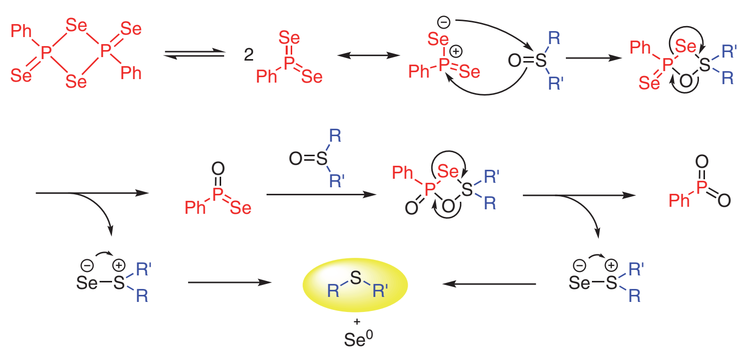
(8a) Védova, *Angew. Chem. Int. Ed.* **2008**, *47*, 10114.

9. Sulfoxide deoxygenation to sulfides





Proposed mechanism:



(9) Woollins, *Tetrahedron Lett.* **2007**, *48*, 3677.

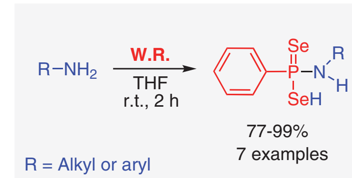
10. Replacement of hydrogen within hydroxy, amino, and/or mercapto groups

a) Alcohol substrate

(10a) Woollins, *Dalton Trans.* **2005**, 2188.

Further examples:
(4a) Woollins, *Org. Biomol. Chem.* **2010**, *8*, 1655.
(10b) Woollins, *Tetrahedron Lett.* **2015**, *71*, 1792.
(10c) Woollins, *Tetrahedron Lett.* **2008**, *64*, 5442.
(10d) Woollins, *Chem. Commun.* **2024**, *50*, 6214.

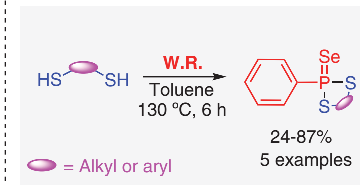
b) Amine substrate



(10e) Woollins, *Z. Anorg. Allg. Chem.* **2011**, *637*, 1800.

Further examples:
(10f) Woollins, *Phosphorus, Sulfur Silicon Relat. Elem.* **2016**, *191*, 341.
(10g) Woollins, *Tetrahedron* **2013**, *69*, 5299.
(10h) Woollins, *Eur. J. Org. Chem.* **2013**, 7402.

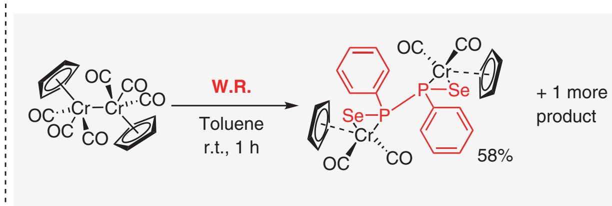
c) Mercapto substrate

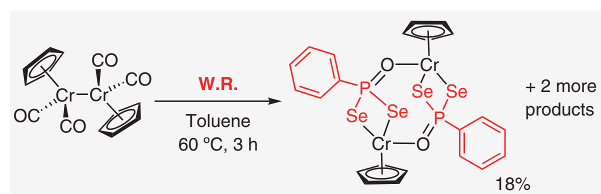


(10i) Woollins, *ARKIVOC* **2016**, *(iii)*, 9.

11. Organometallic transformations

a) Ligand substitution

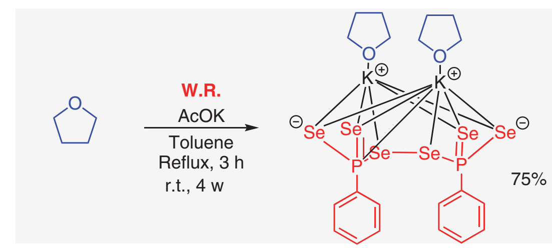


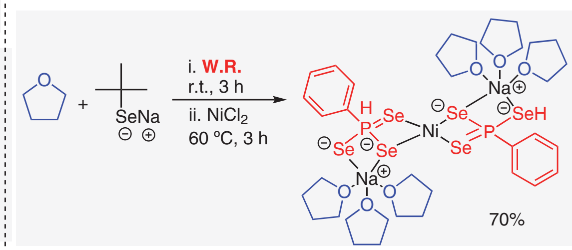


(11a) Ooi, *Inorg. Chim. Acta* **2011**, *366*, 350.

Further examples:
(11b) Robinson, *Inorg. Chim. Acta* **2016**, *440*,1.

b) Organometallic formation





(11c) Rothenberger, *Chem. Eur. J.* **2006**, *13*, 598.

Further examples:
(11d) Rothenberger, *Dalton Trans.* **2007**, 4255.
(11e) Rothenberger, *Z. Anorg. Allg. Chem.* **2007**, *633*, 440.

Figure 5 Selenoic acid formation, sulfoxide reduction (with a mechanistic proposal), hydrogen replacement and organometallic transformations/formation

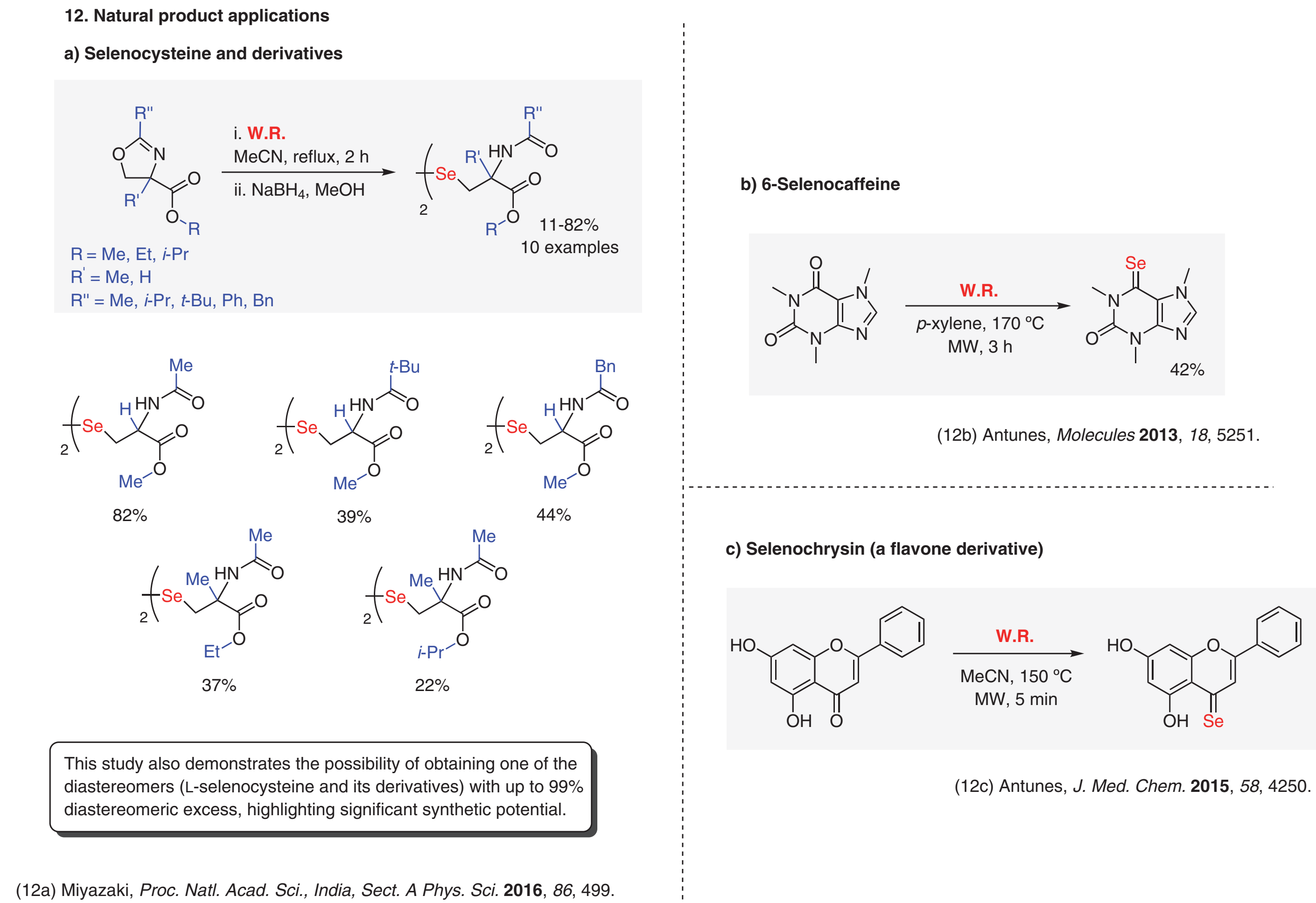


Figure 6 Natural product applications

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

I am grateful to the Fundação Oswaldo Cruz (Fiocruz) (Oswaldo Cruz Foundation) for a scholarship and to Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) (Coordination for the Improvement of Higher Education Personnel) for the institutional financial support.

Acknowledgment

I extend my gratitude to the Institute of Chemistry at the Federal University of Rio de Janeiro (UFRJ) and to Professor Sabrina Ferreira's research group for providing me with the knowledge necessary to realize this work.

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