

Tandem allylic isomerization – IMDAF reaction in the synthesis 5,6,7-substituted indoles



***Research Topic Seminar
Jie Xu
06.04.11***

Contents

- ***Introduction of indoles***
- ***Preparation and functionalization of indoles***
- ***Amino furan cycloaddition***
- ***Summary and acknowledgement***

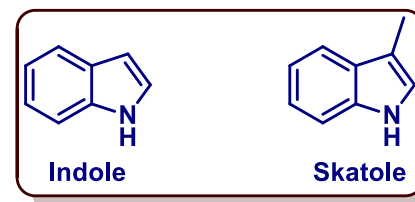
Contents

- ***Introduction of indoles***
- *Preparation and functionalization of indoles*
- *Amino furan cycloaddition*
- *Summary and acknowledgement*

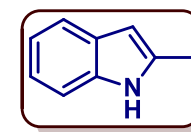
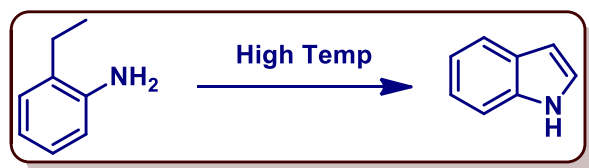
General Properties



Indole and the simple alkyl indoles are colorless crystalline solids



With a range of odours from naphthalene-like to faecal

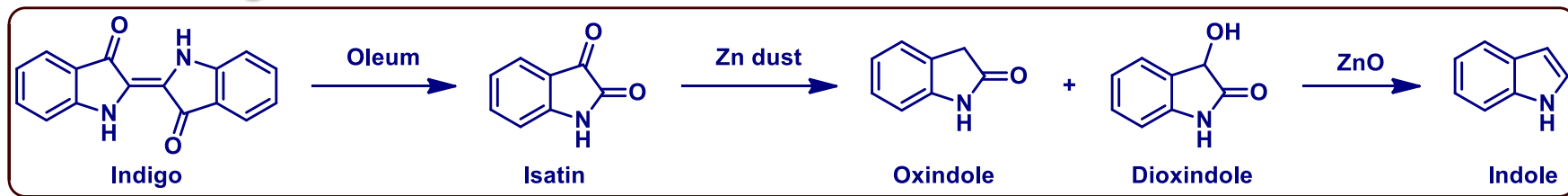


*Many simple indoles are available commercially and produced by **synthesis***

*Most indoles are quite stable in air with the exception of those which carry a simple alkyl group at **C-2***

Joule, J.A.; Mills, K. in *Heterocyclic Chemistry* (5th Edition), Wiley, Hoboken, N.J., 2009.

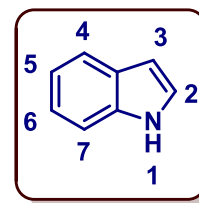
History



Adolf von Baeyer

The Nobel Prize in Chemistry 1905

Indole = indigo + oleum



1869: Propose the formula of indole
Which is generally accepted today

“In recognition of his services in the advancement of organic chemistry and the chemical industry, through his work on **organic dyes and hydroaromatic compounds”.**

http://nobelprize.org/nobel_prizes/chemistry/laureates/1905/

Baeyer, A. *Chem. Ber.* **1868**, 1, 17. Bayer, A. *Chem. Ber.* **1869**, 2, 679.

Reserpine



Isolated in 1952
India snake root *R. serpentina* Benth.



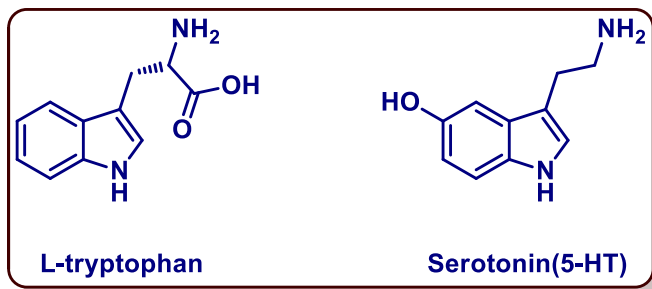
One of the first drugs for the treatment of diseases of the **central nervous system (CNS) such as anxiety and mental disorders.**

Approved: June 20, 1960

Chen, F. R; Huang, J. *Chem. Rev.* **2005**, *105*, 4671 – 4706

Bioactive Indole

- **Tryptophan, tryptamine, auxins,**

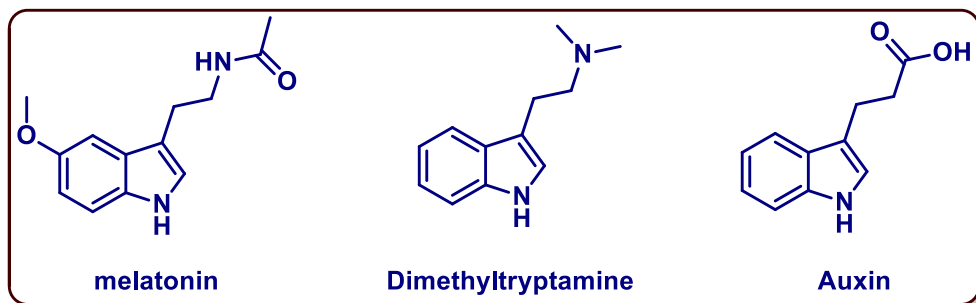


L-tryptophan

Serotonin(5-HT)

Essential Amino Acid

Neurotransmitter



melatonin

Dimethyltryptamine

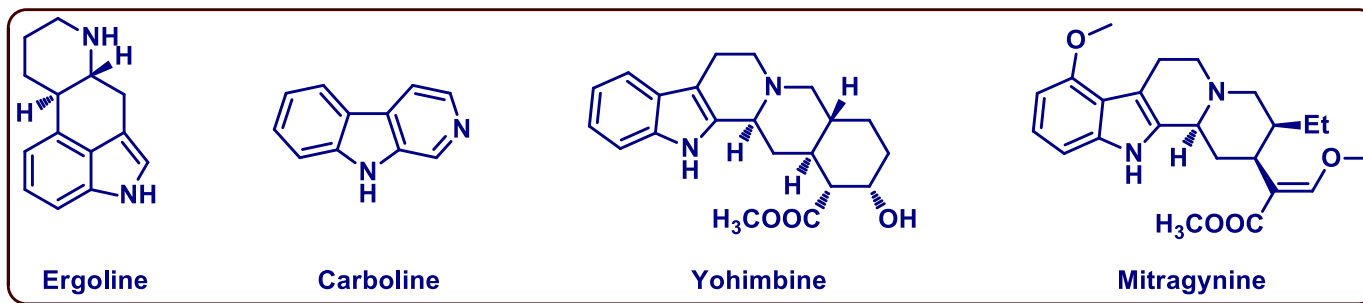
Auxin

Neurotransmitter

Hallucinogen

Plant hormone

Natural Indole Alkaloid

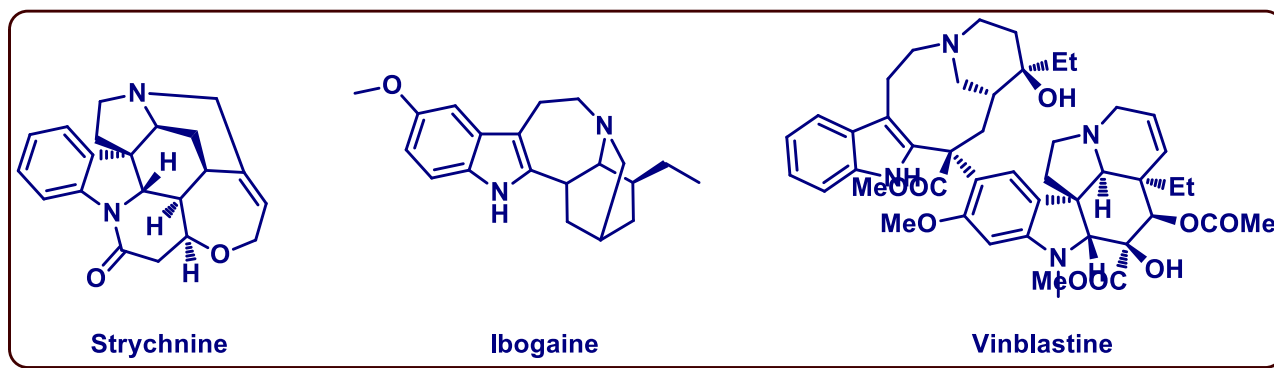


Ergolines
Psychedelic drugs

β -carbolines
CNS drugs

Yohimbine
Stimulant drugs

Kratom alkaloids
Psych stimulant



Strychnos nux-vomica alkaloids
Toxic pesticide

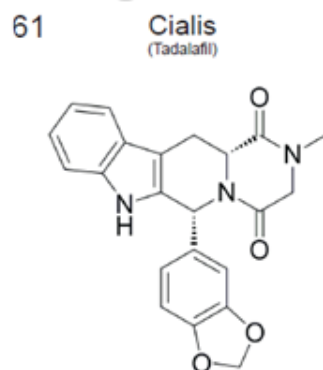
Iboga alkaloids
Psychoactive drugs

Vinca alkaloids
Anti-mitotic & anti-microtubule agents

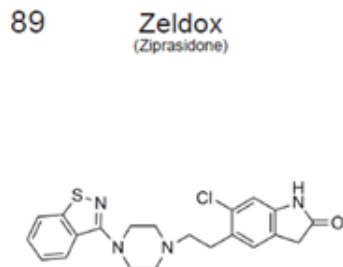
Kawasaki, T.; Higuchi, K. *Nat. Prod. Rep.* **2005**, 22, 761.

Ishikura, M.; Yamada, K. *Nat. Prod. Rep.* **2009**, 26, 803.

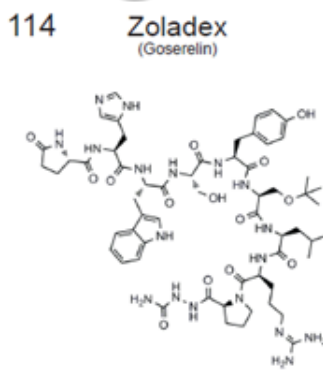
Top 200 brand-name drugs in 2009



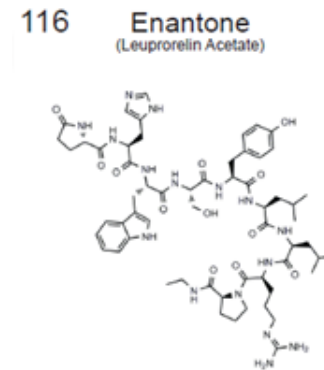
\$1599 Million
Erectile Dysfunction Prd



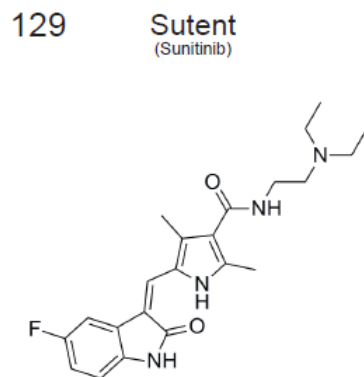
\$1287 Million
Antipsychotics



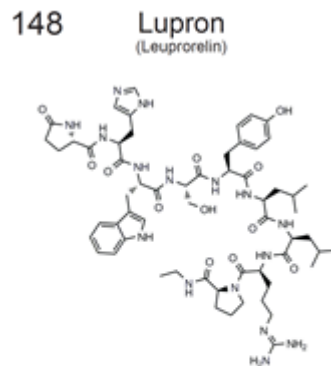
\$962 Million
Cytostatic Hormones



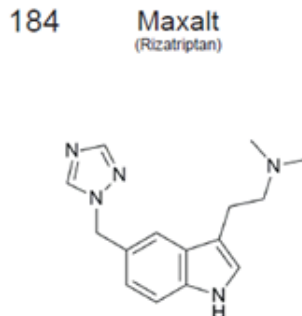
\$957 Million
Cytostatic Hormones



\$881 Million
All Oth. Antineoplastics



\$768 Million
Cytostatic Hormones



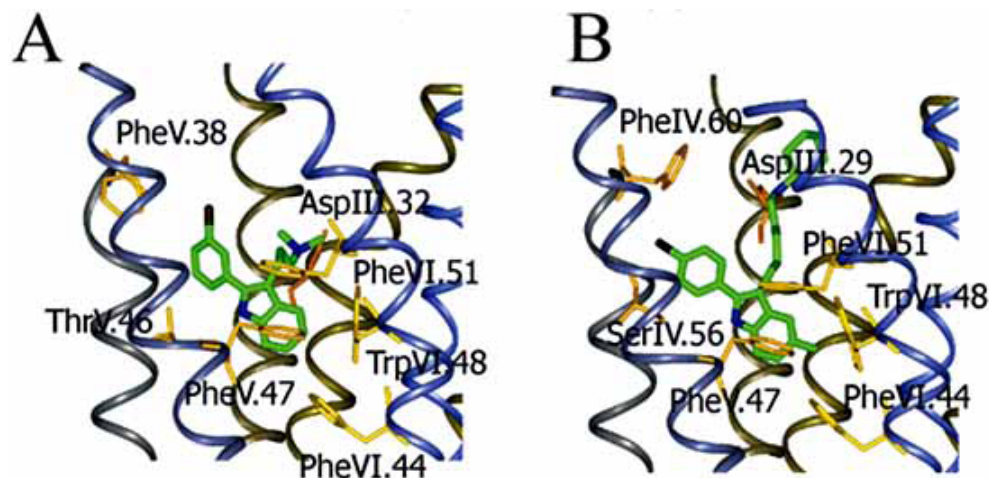
\$641 Million
Anti-Migraine Preps

**Drugs with indole
or indoline cores**

<http://cbc.arizona.edu/njardarson/group/sites/default/files/Top200PharmaceuticalProductsByWorldwideSalesin2009.pdf>

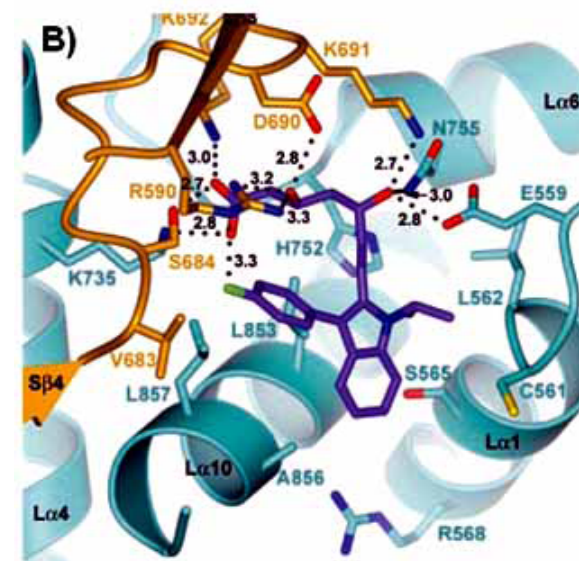
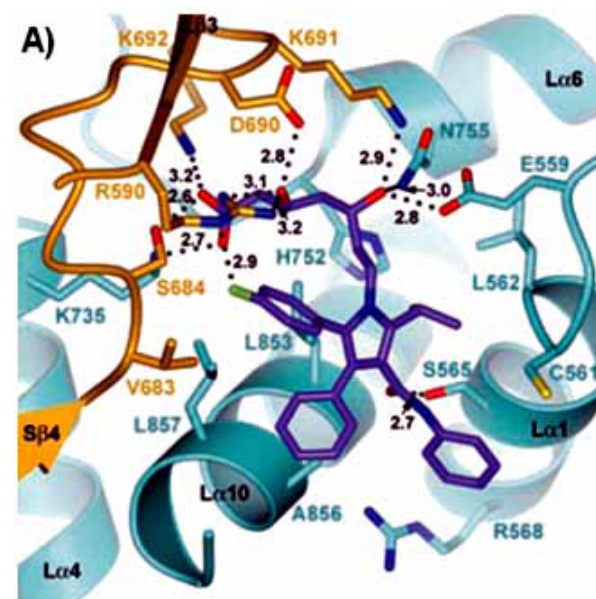
Biological Activity

- **Enzyme inhibitors**
 - HMG-CoA Reductase Inhibitors
 - Cyclooxygenase Inhibitors
 - Phosphodiesterase (PDE) Inhibitors
- **Bio receptor Modulators**
 - 5-Hydroxytryptamine (5-HT) Receptors
 - Cannabinoid Receptors



Representative interactions of indole ligands respectively at serotonin 5-HT₆ (A) and melanocortin-4 (B) receptors.

Fraga, C. *et al. Mini-Rev. in Med. Chem.* 2009, 9, 782.

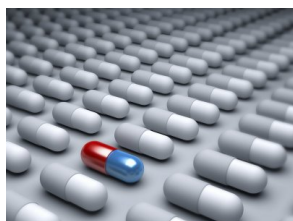


HMG-CoA Reductase Inhibitors

Broad Spectrum of Application



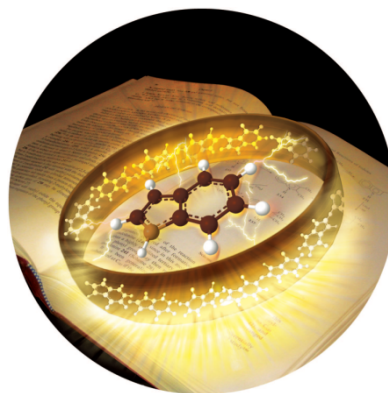
Agrochemicals



Pharmaceuticals



Pigments

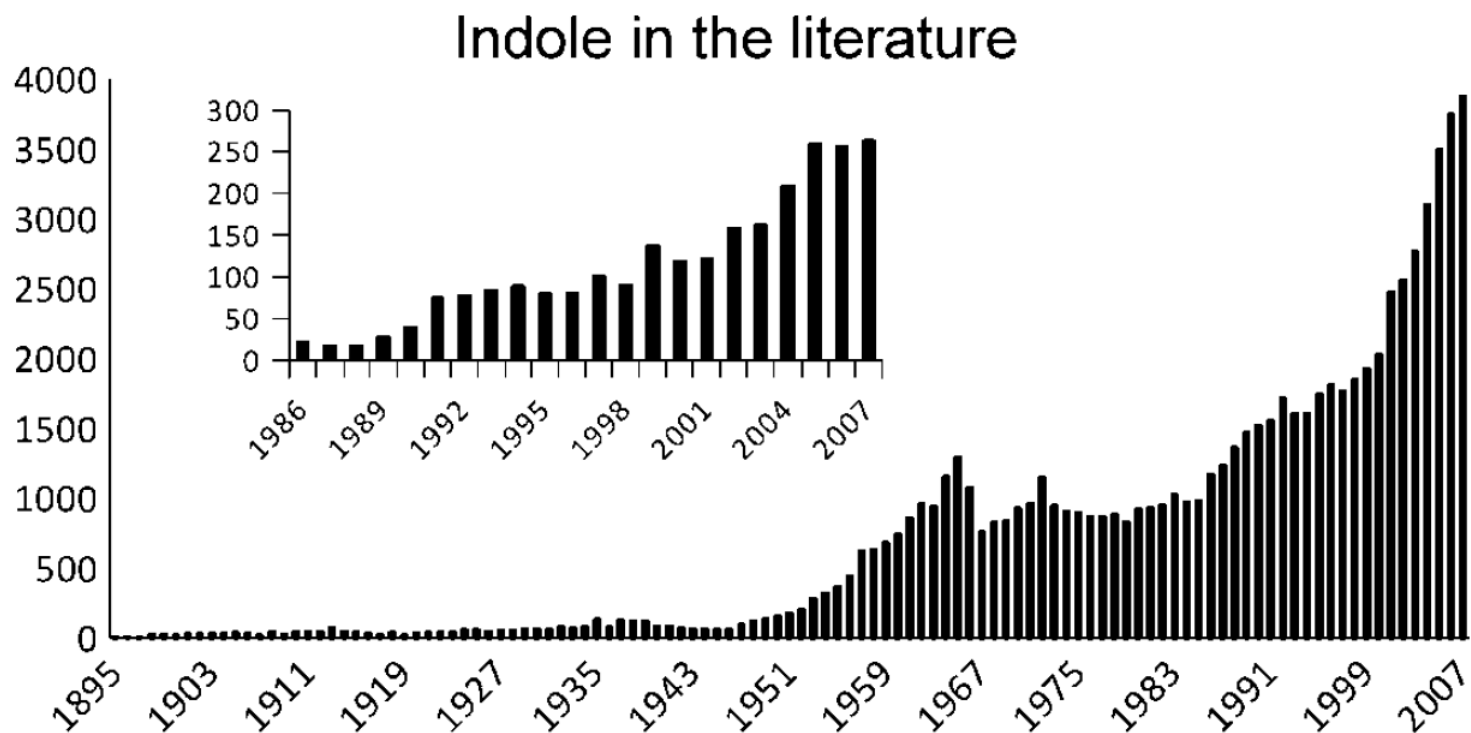


Material Science



Fragrances

Statics



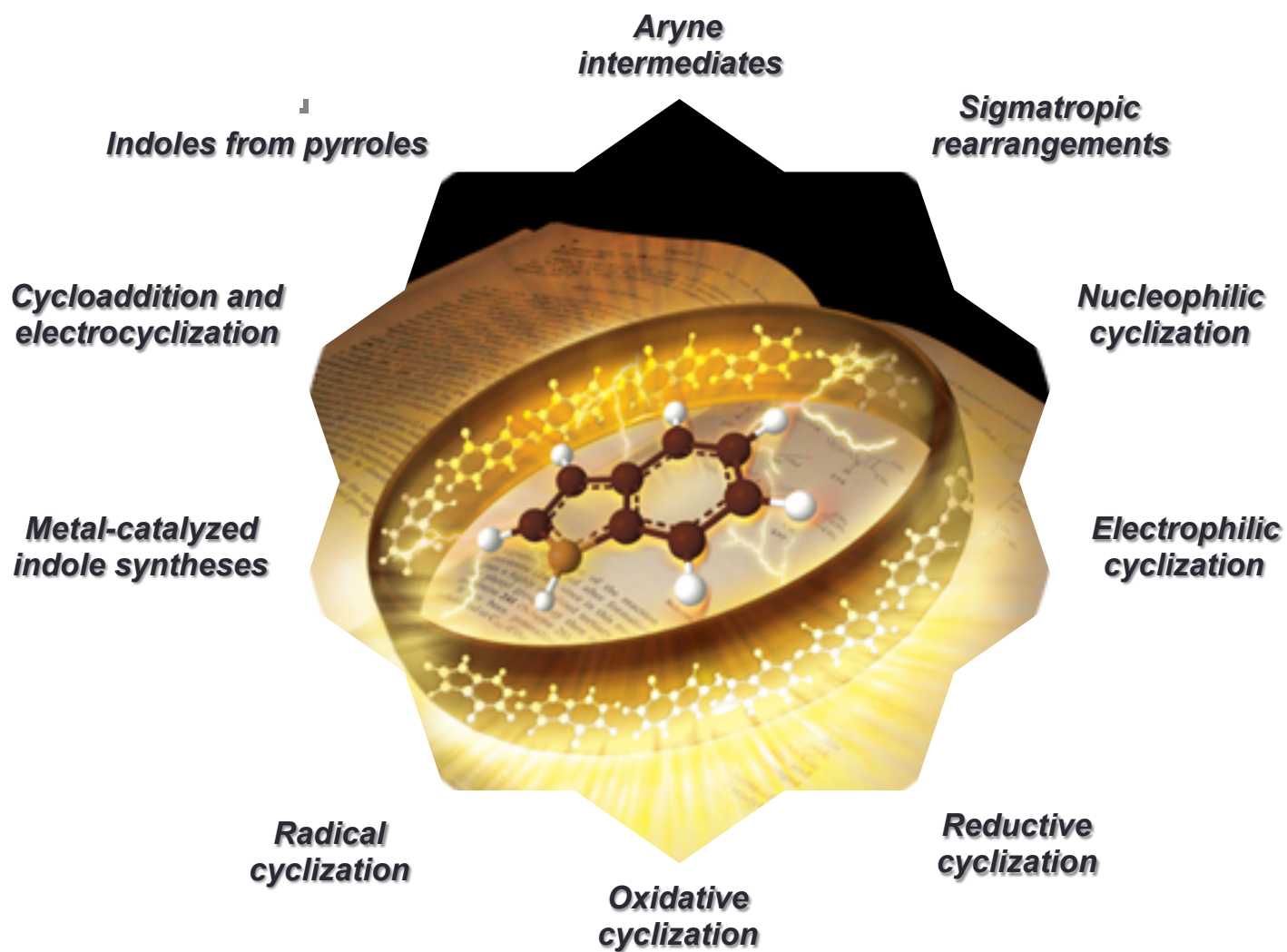
- **Number of publications (limited to letters and review articles) focusing on indole (SciFinder Scholar). The inset shows the number of publications dealing with the synthesis or functionalization of indoles (1986–2007).**

Bandini, M.; Eichholzer, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 9608.

Contents

- *Introduction to indoles*
- ***Preparation and functionalization of indoles***
- *Amino furan cycloaddition*
- *Summary and acknowledgement*

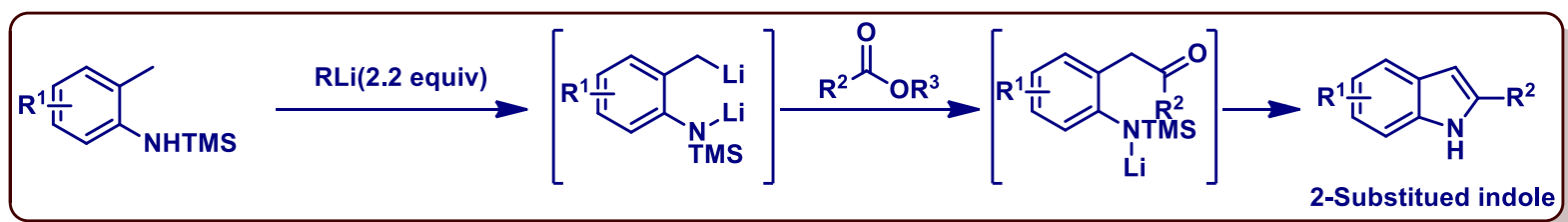
Syntheis



Cyclization

● Nucleophilic

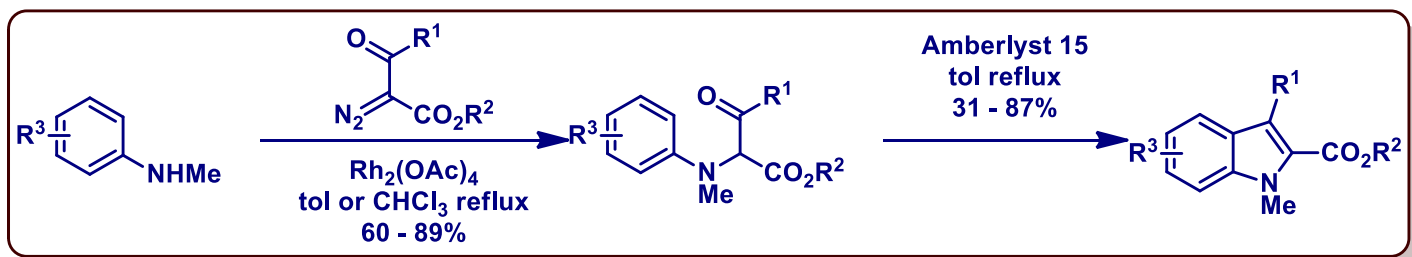
Madelung, Schmid, Wender, Couture, Smith, Kihara
Nenitzescu, Engler, Bailey–Liebeskind, Wright, Saegusa



Madelung, W. *Ber*, **1912**, 45, 1128.

● Electrophilic

Bischler, Nordlander, Cadogan–Sundberg, Sundberg,
Hemetsberger, Quéguiner, Iwao, Magnus, Feldman



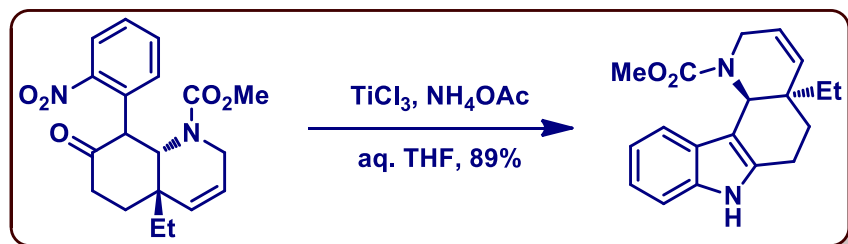
R¹ = Me, Et, Ph; R² = Me, Et; R³ = H, 7-Br, 7-OMe, 5-Cl, 5-NO₂, 5-OMe, 5,7-diOMe

Moody, C. J.; Swann, E. *Synlett*, **1998**, 135.

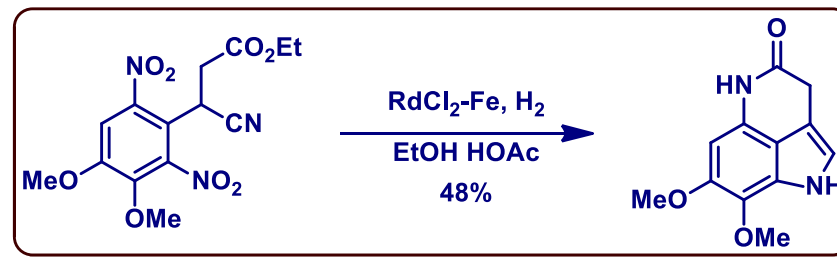
Cyclization

● Reductive

Reissert, **Leimgruber-Batcho, Makosza**



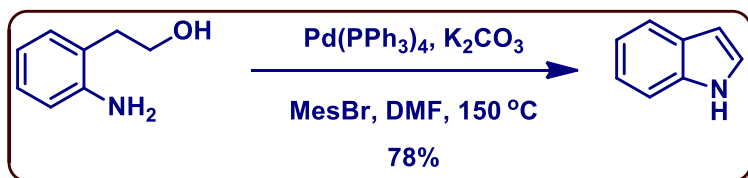
Lobachevsky, P. *et al. Aust. J. Chem.* **1998**, 51, 243.



Makosza, M.; Stalewski, J. *Synthesis*, **1997**, 1131

● Oxidative

Watanabe, Knölker



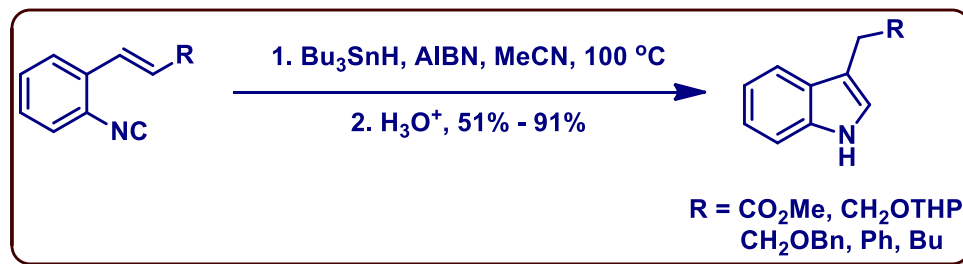
Ohta, A. *et al. Tetrahedron Lett.* **1996**, 37, 9203.

● Radical

Tin-mediated cyclization

Samarium-mediated cyclization

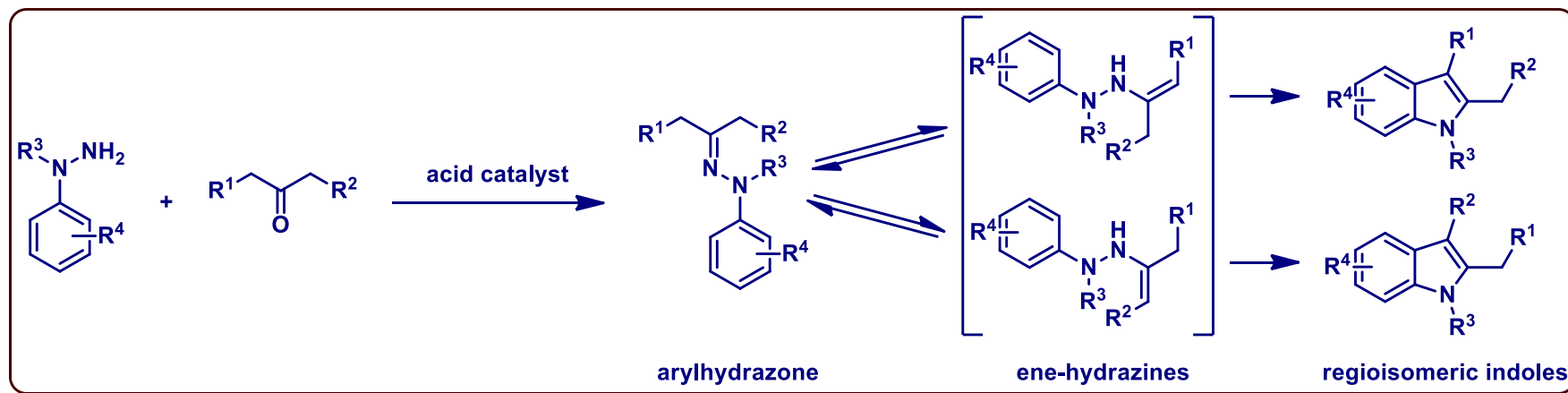
Murphy indole-indoline synthesis



Kobayashi, S. *et al. Tetrahedron Lett.* **1999**, 40, 1519.

Sigmatropic Rearrangements

- Fischer, Gassman, Bartoli, Thyagarajan, Julia



Fischer indole synthesis

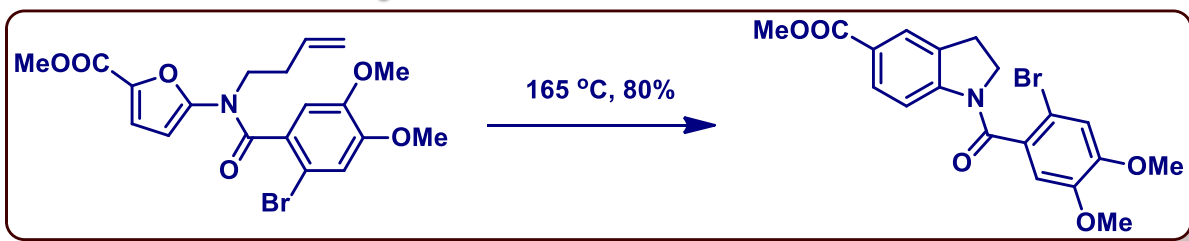
Prominent role as a route to indoles, both new and old, and to the large-scale production of indole pharmaceutical intermediates.

Gribble, G. J. *Chem. Soc., Perkin Trans. 1*, **2000**, 1045.

Robinson, B., *The Fischer Indole Synthesis*, Wiley-Interscience, New York, 1982.

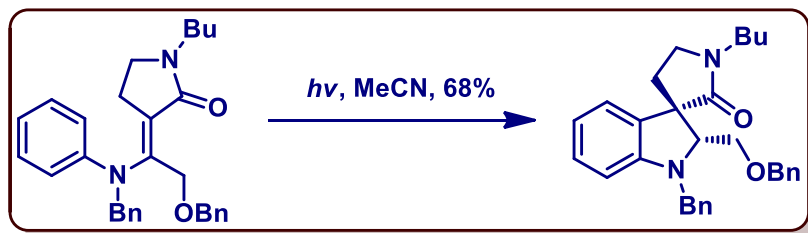
Cycloaddition and Electrocyclization

● Diels–Alder cycloaddition



Padwa, A.; Dimitroff, M.; Waterson, A. G.; Wu, T. *J. Org. Chem.* **1998**, 63, 3986.

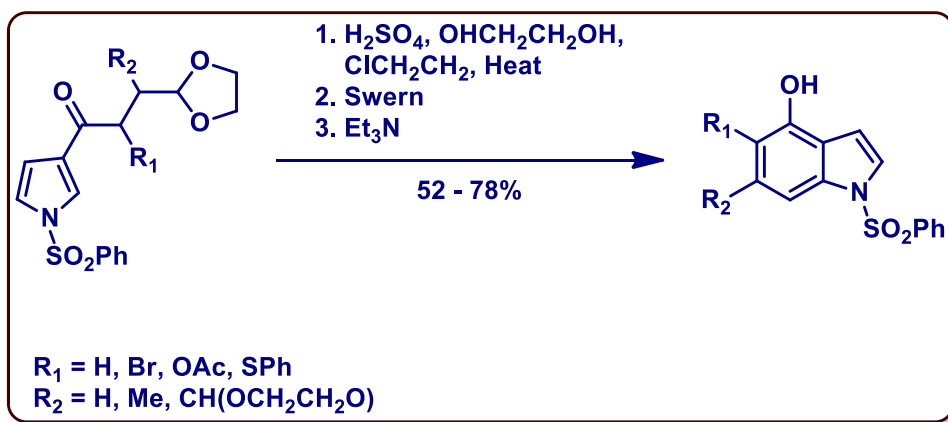
● Chapman photocyclization



Ibrahim-Ouali, M.; Sinibaldi, M. E.; Troin, Y.; Guillaume D.; Gramain, J. C. *Tetrahedron*, **1997**, 53, 16083.

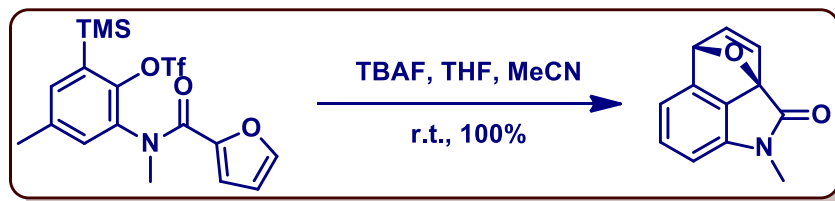
Indoles from Pyrroles

Natsume indole synthesis



Utsunomiya, I.; Muratake, H.; Natsume, M. *Chem. Pharm. Bull.* **1995**, 43, 37.

Aryne intermediates



Hardcastle, I. R.; Hunter, R. F.; Quayle, P.; Edwards, P. N. *Tetrahedron Lett.*, **1994**, 35, 3805.

Metal-catalyzed indole syntheses

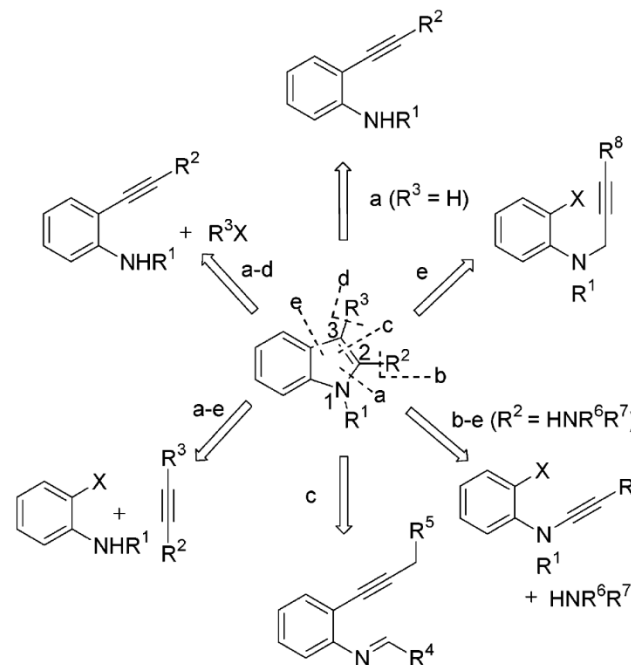
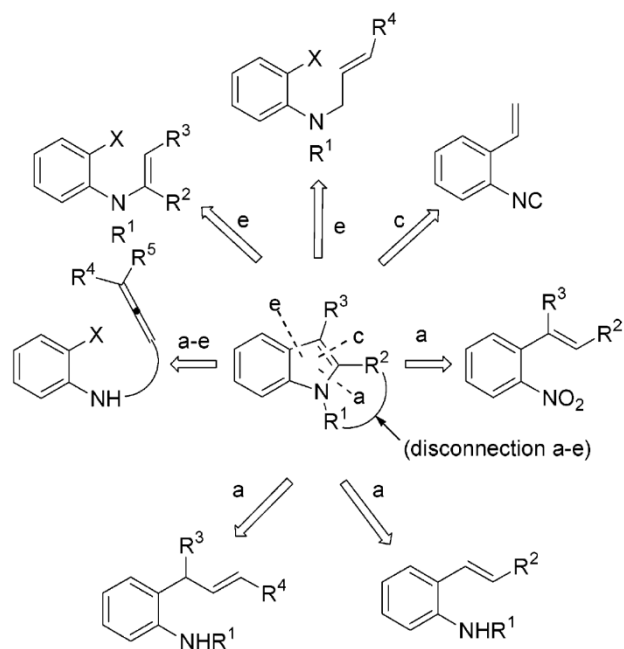
● Pd

Hegedus–Mori–Heck indole synthesis

Yamanaka–Sakamoto indole synthesis

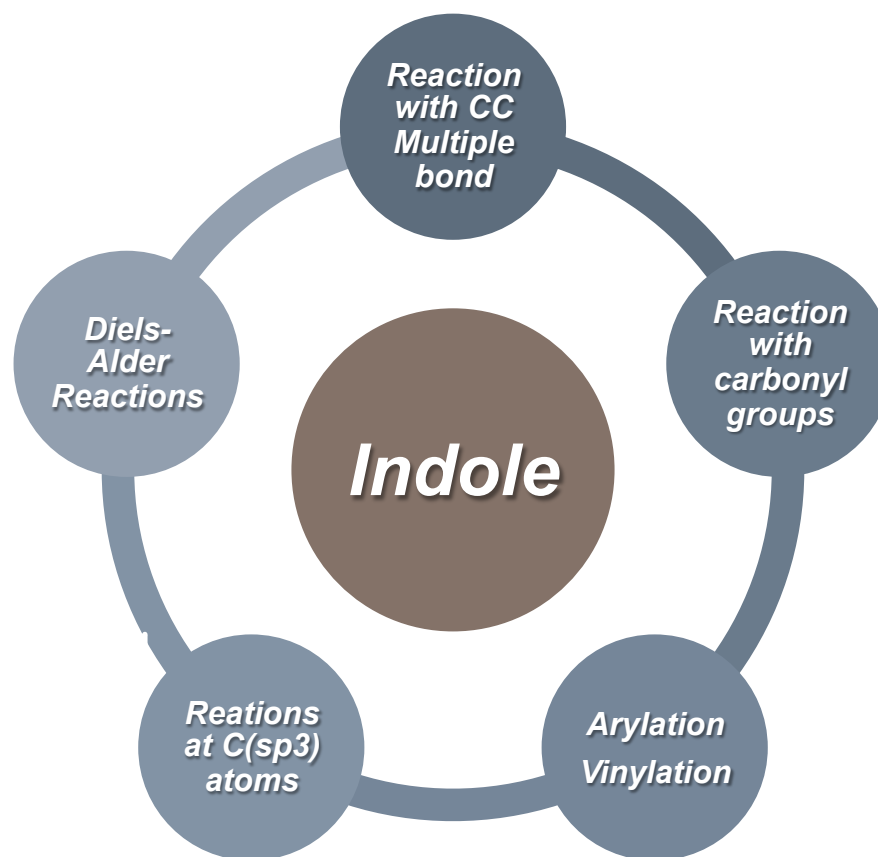
Larock indole synthesis

● Rh, Ru, Ti (Fürstner), Zr, Cu (Castro), Cr, Mo



Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873.
Gribble, G. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 1045.

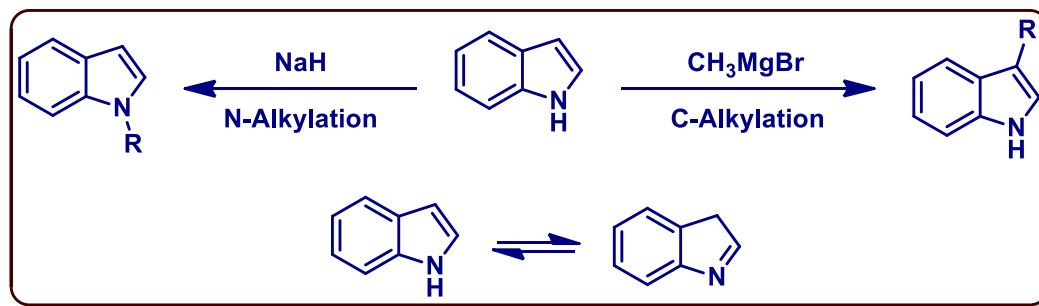
Functionalization of indole



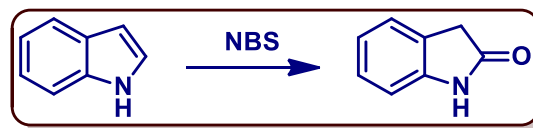
Bandini, M.; Eichholzer, A. *Angew. Chem. Int. Ed.* **2009**, 48, 9608

Chemical Properties

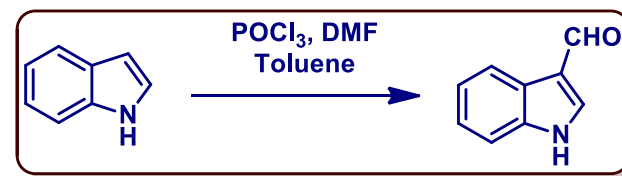
Basicity
 $pK_a (H_2O) = 12.36 - 19.50$
 $K_{eq} = 10^{-6}$



Oxidation of indole
Electron rich nature

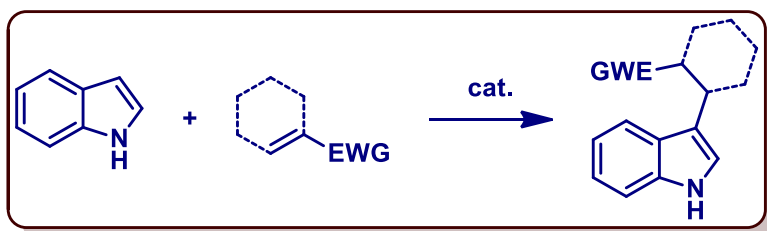


Electrophilic substitution
C3 10^{13} times reactive than benzene

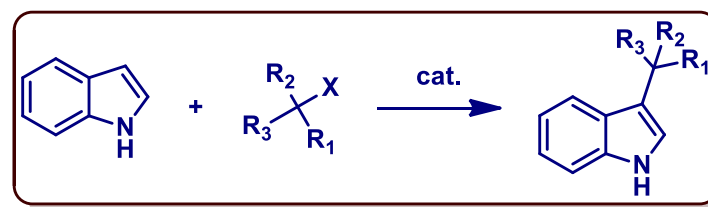


Functionalization of indole

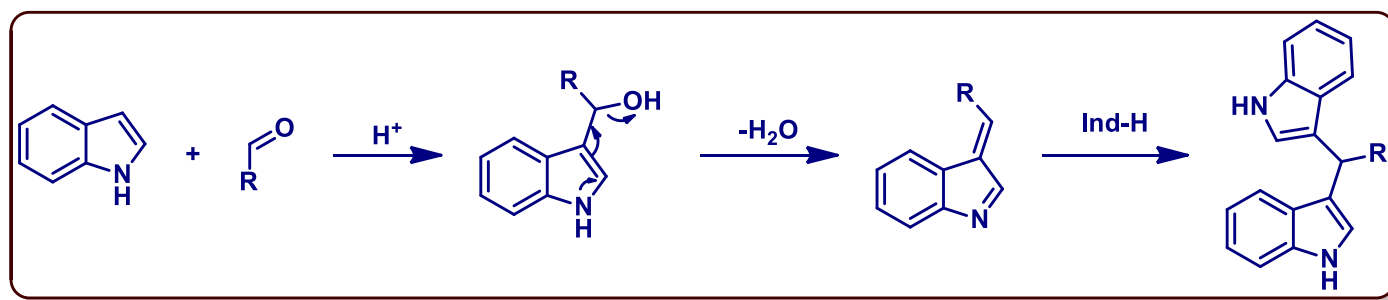
● Reaction with CC Multiple bond



● Reactions at C(sp³) atoms



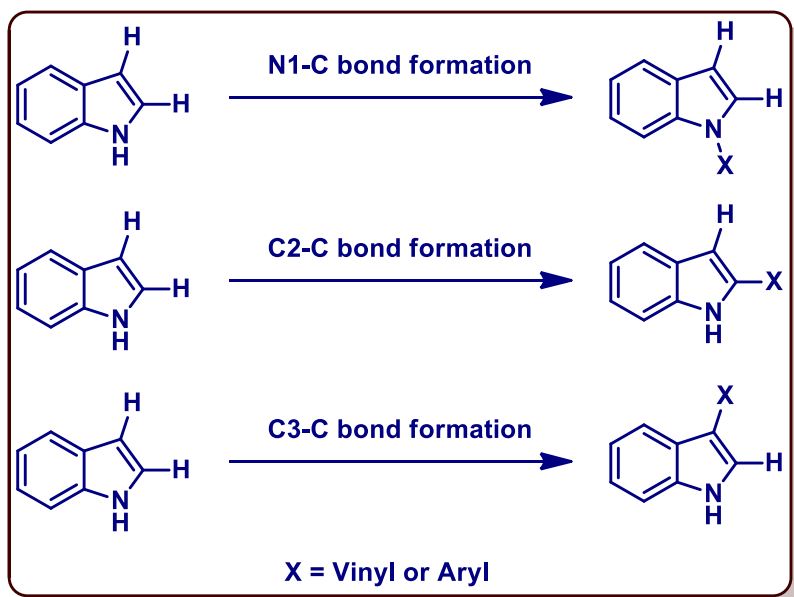
● Reaction with carbonyl groups



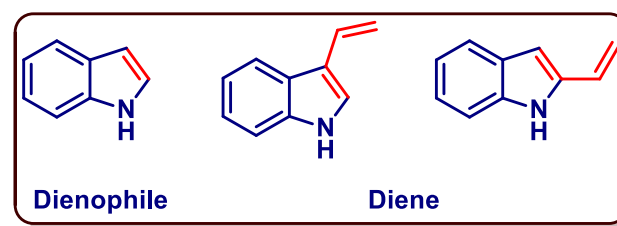
Bandini, M.; Eichholzer, A. *Angew. Chem. Int. Ed.* **2009**, 48, 9608

Functionalization of indole

● Arylation Vinylation



● Diels-Alder Reactions



● Reactive in N1, C2, C3

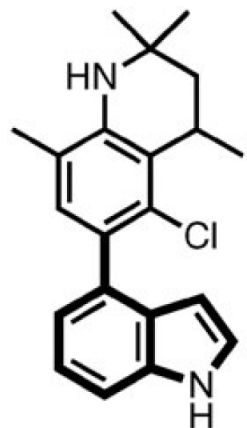
Bandini, M.; Eichholzer, A. *Angew. Chem. Int. Ed.* **2009**, 48, 9608

Contents

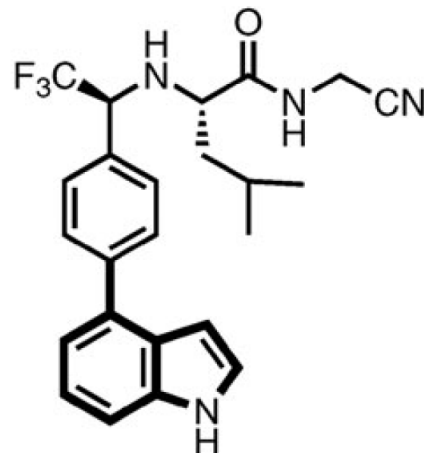
- *Introduction to indoles*
- *Preparation and functionalization of indoles*
- ***Amino furan cycloaddition***
- *Summary and acknowledgement*

Background

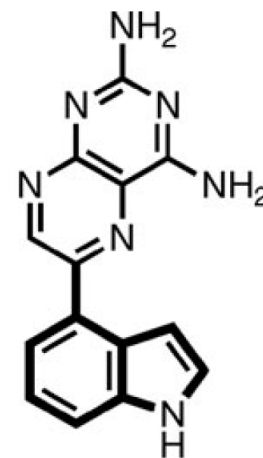
- Presence of 4-substitued natural indole compound
- Lack of effective ways to synthesis 4-substitued indole



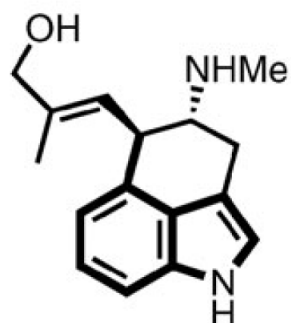
*glucocorticoid
receptor ligand*



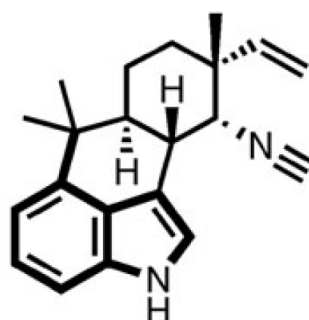
cathepsin K inhibitor



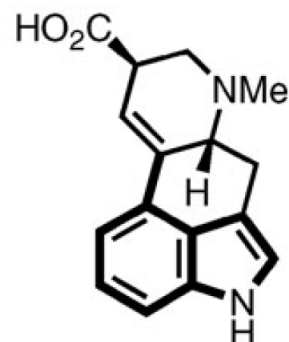
*phosphoinositide
3-kinase inhibitor*



fumigaclavine A



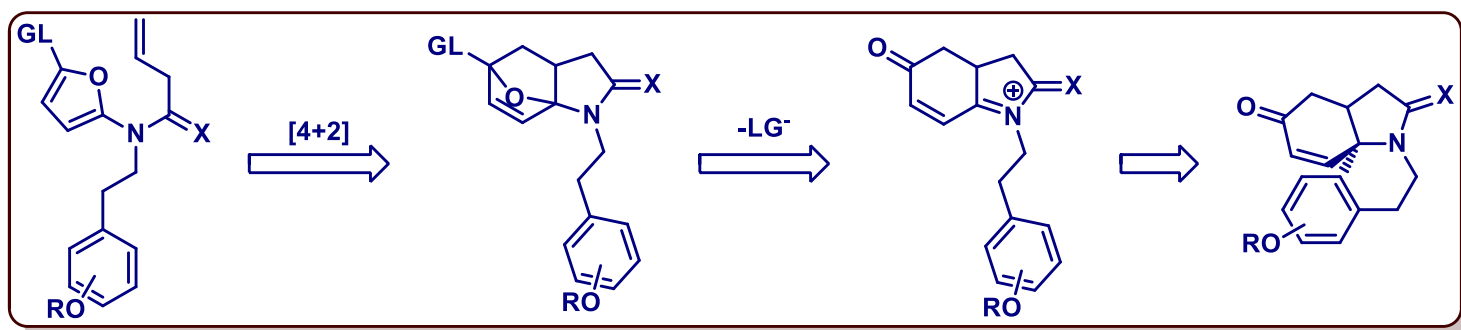
ambiguine A isonitrile



lysergic acid

Petronijevic, F.; Timmons, C.; Cuzzupey, A.; Wipf, P. *Chem. Commun.* **2009**, 104.

Amino furan cycloaddition



Prof. Albert Padwa
Emory University

For reviews of *IMDAF*

Kappe, C. O.; Murphree, S. S.; Padwa, A.,
Tetrahedron, **1997**, *53*, 14179;



Pergamon

Tetrahedron, Vol. 53, No. 42, pp. 14179-14233, 1997
© 1997 Elsevier Science Ltd
All rights reserved. Printed in Great Britain
0040-4020/97 \$17.00 + 0.00

PII: S0040-4020(97)00747-3

TETRAHEDRON REPORT NUMBER 430

Synthetic Applications of Furan Diels-Alder Chemistry

C. Oliver Kappe[†], S. Shaun Murphree[‡], and Albert Padwa^{**}

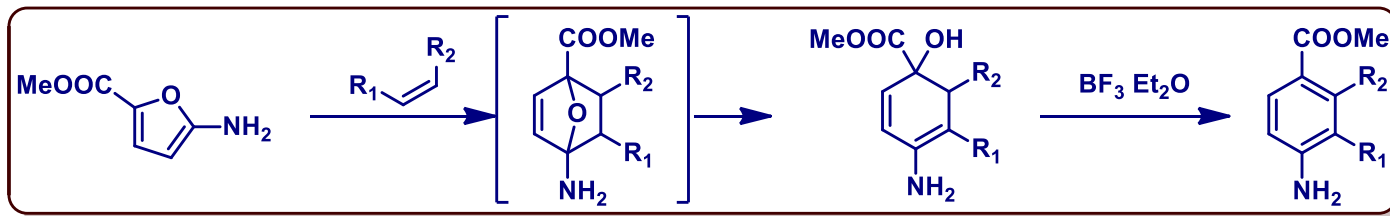
[†]Institute of Organic Chemistry, Karl-Franzens University, Graz, Austria

[‡]Bayer, Corp., PO Box 118088, Charleston, South Carolina 29423 USA

^{**}Department of Chemistry, Emory University, Atlanta, Georgia 30322 USA

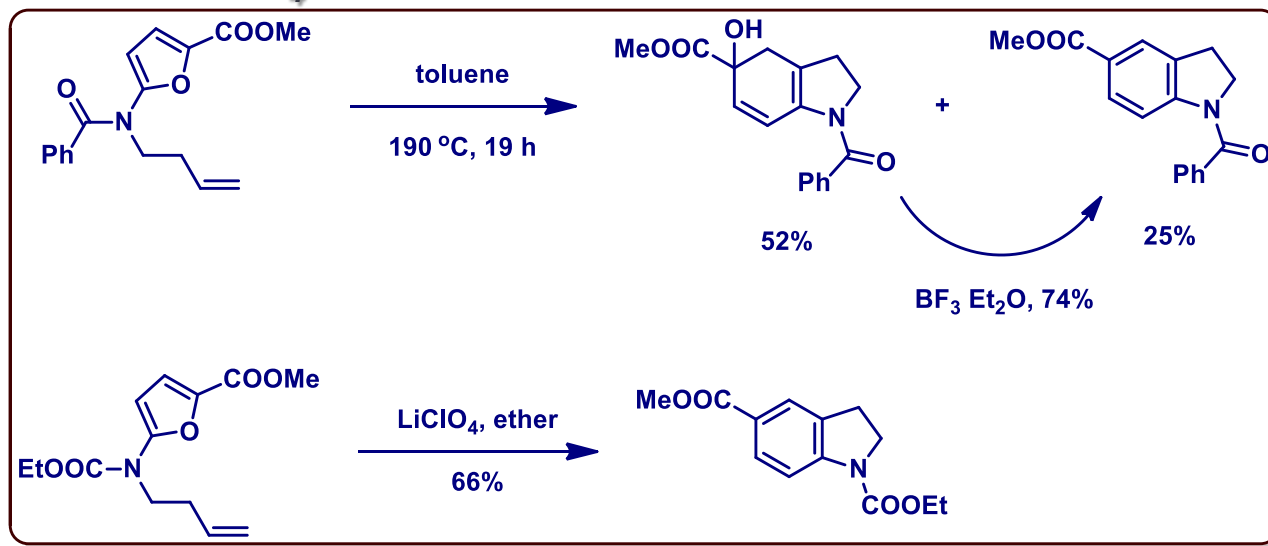
Amino furan cycloaddition to indoline

● Amino Furan Diels Alder Reaction



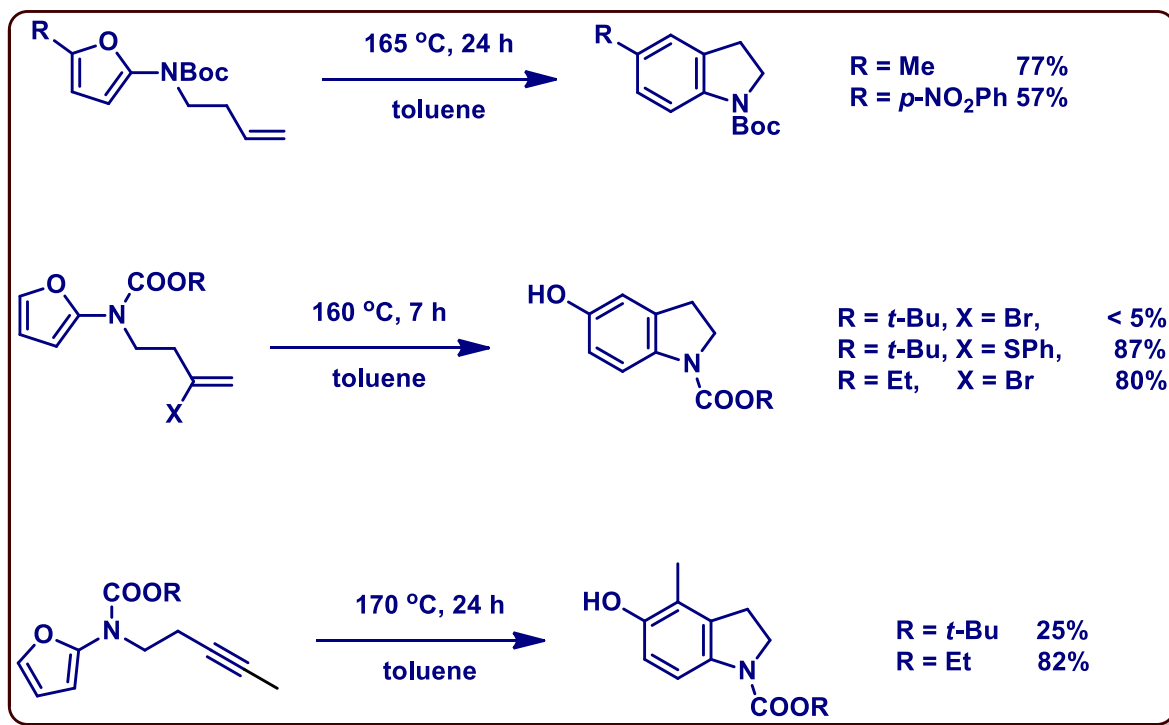
Padwa, A., et. al., *J. Org. Chem.*, **1997**, 62, 2786 ; Padwa, A., et. al., *J. Org. Chem.*, , **1997**, 62, 4088

● Thermal or LiClO₄ in ether



Padwa, A. et al. *J. Org. Chem.* **1998**, 63, 3986 .

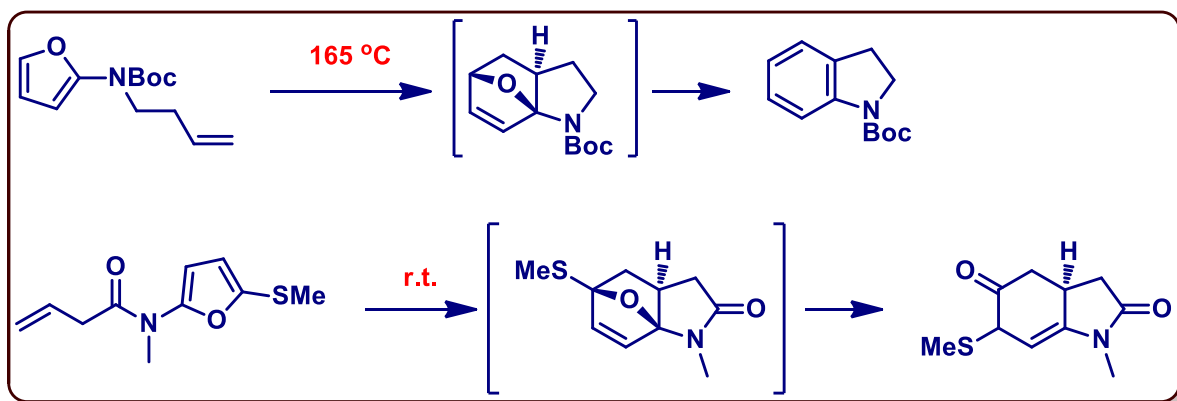
Amino furan cycloaddition to indoline



- **COOEt more stable than Boc**
- **Br, SPh as leaving group**
- **Alkyne IMDAF**
- **Indoline synthesis**

Padwa, A. *et al. J. Org. Chem.* **1999**, *64*, 3595.

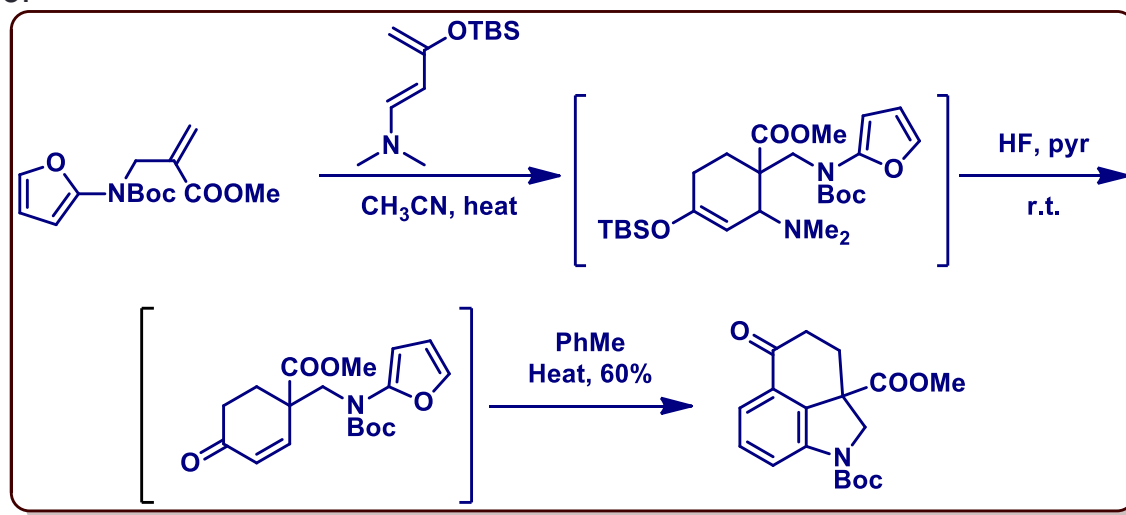
Amino furan cycloaddition to indoline



- DFT calculation of IMDAF with Becke3LYP/6-31G* model

Padwa, A. *et al. Org. Lett.*, 2002, 4, 473.

- Danishefsky diene to synthesis the precursor
- Carbomethoxy group to activate the olefin
- Ergoline intermediate



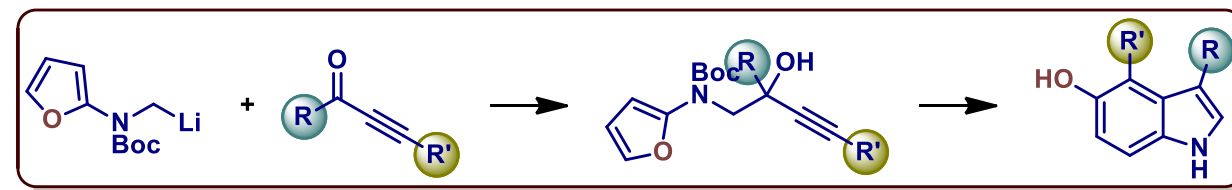
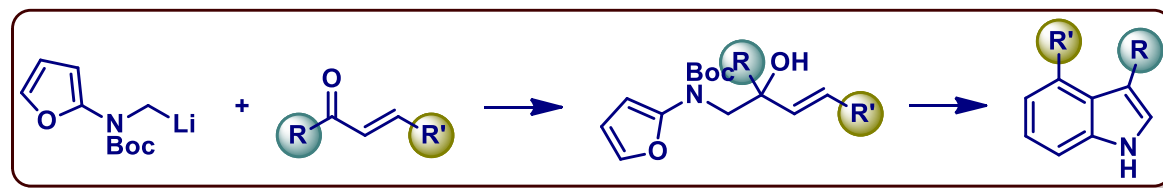
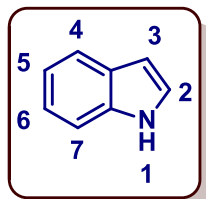
Padwa, A. *et al. J. Org. Chem.* 2005, 70, 6833.

Previous Work

- **Microwave assisted IMDAF**

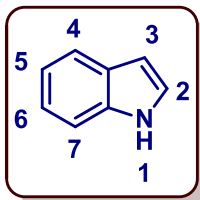
- *Much fast heating process and less reaction times*
- *Higher temperatures in the pressurized reactor vial*

- **Deprotected indole product rather than protected indoline**

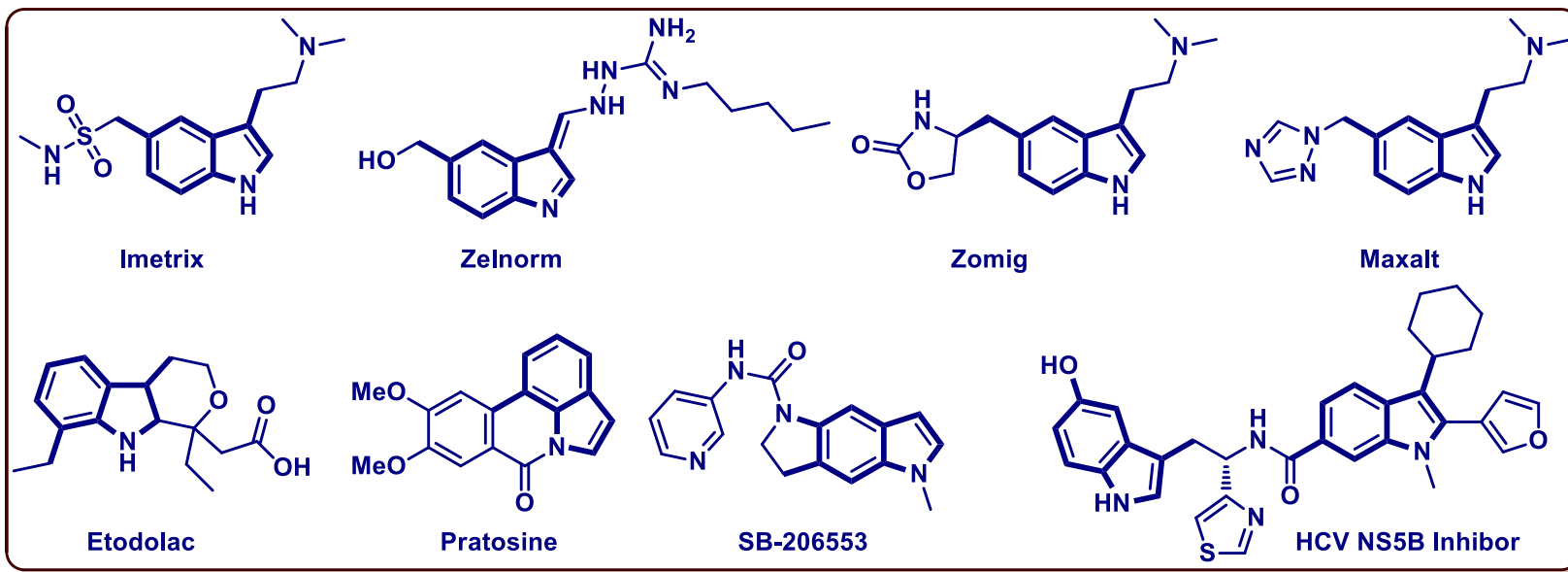


Petronijevic, F.; Timmons, C.; Cuzzupey, A.; Wipf, P. *Chem. Commun.* **2009**, 104.

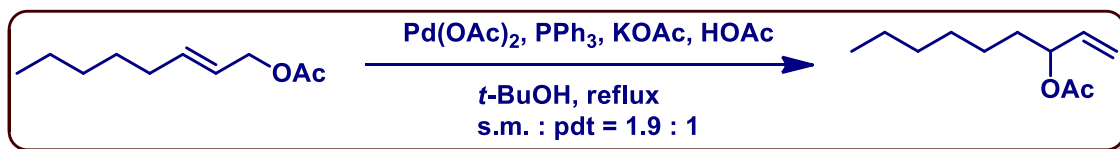
Methodologies in our group



- 3, 4-sustitued by Filip
- 5-hydroxy substituted by Ki Bum
- 5,6,7-substitued indole

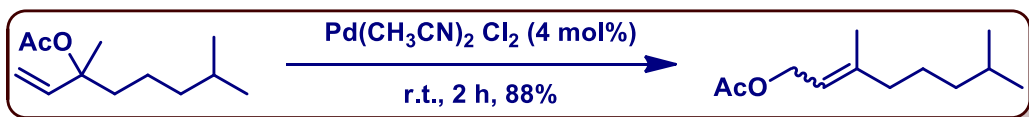


Allylic Isomerization



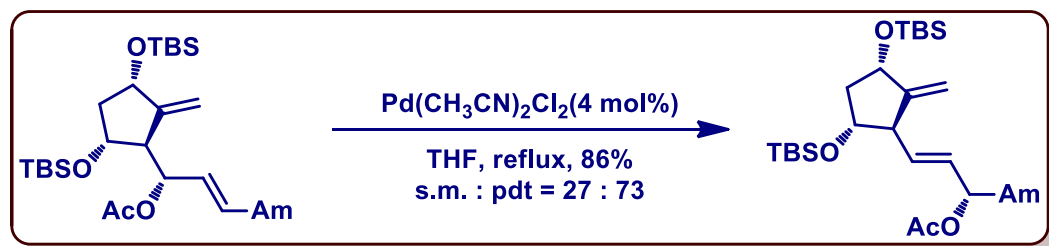
- $\text{Pd}(\text{OAc})_2$ catalyst
- Internal olefin favored

Tsuji, J. *et al. Bull. Chem. Soc. Jp.* **1976**, *49*, 1701.



- $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$ catalyst
- 100% conversion of terminal olefin

Overman, L. E.; Knoll, F. M. *Tetrahedron Lett.* **1979**, 321.



- $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$ catalyst
- Equilibrium of two internal olefins

Nakai, T. *et al. Tetrahedron Lett.* **1993**, *34*, 5923.

Contents

- *Introduction to indoles*
- *Preparation and functionalization of indoles*
- *Amino furan cycloaddition*
- ***Summary and acknowledgement***

Acknowledgement

- *Dr. Wipf*
- *Wipf group members past & present*
- *NMR & MS facilities*
- *NIH, University of Pittsburgh Arts & Science Fellowships*

