Frontier in Chemical Synthesis II: Heterocycle Chemistry

http://moodle.epfl.ch/
http://lcso.epfl.ch/Teaching

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Lecture Structure/Plan

- Introduction on February 22
- End of Introduction: choice of general area for each participant
- Max until April 15: choice of topic and title: the topic has to be more focused than the general fields of research in the introduction!
- April-May: preparation of the talk, please come to us if you need to redefine the topic or just need help preparing the presentation
- May 15+16: presentations (30 min presentation/30 min discussion)
- Presentations will be open access to all interested people!

Lecture Structure: The presentation

- Power point presentation: 30 min (around 30 slides, try not to be too short or too long!). Discussion and exercices: 30 min. 5 min change/break.
- 3 sessions of 3 presentations. One chairman for each.
- Mostly chemdraws, exceptions for complexe models/structures
- Expertise in primary literature expected, not only review
- Each participant has to ask at least one question for each talk
- 2 questions/problems on the talk given to the public
- Open to everybody

Lecture Structure: The presentation

- **Structure of the talk:**
  - Introduction with: position in the field, importance of topic, reason for choice of exact topic, what are related topics
  - Pioneering works in the field
  - Most important works on the topic (try to find the right balance between in-depth and in-breadth insights)
  - Conclusion and future developments

Lecture Structure: The presentation

- **Form of the talk:**
  - Use a simple but clear corporate design for each slide (title, logo…)
  - Do not put too much information on one slide! (No overlong tables, huge synthetic schemes, ….)
  - ChemDraw should be big enough (at least 100%, 125 % is better)
  - Do not use too much text, key words are enough
  - If you use colors, it should be to attract attention to what is important
  - Check your English, eventually ask a friend to help you correct it
  - Check your timing to be at 30 +- 3 min.

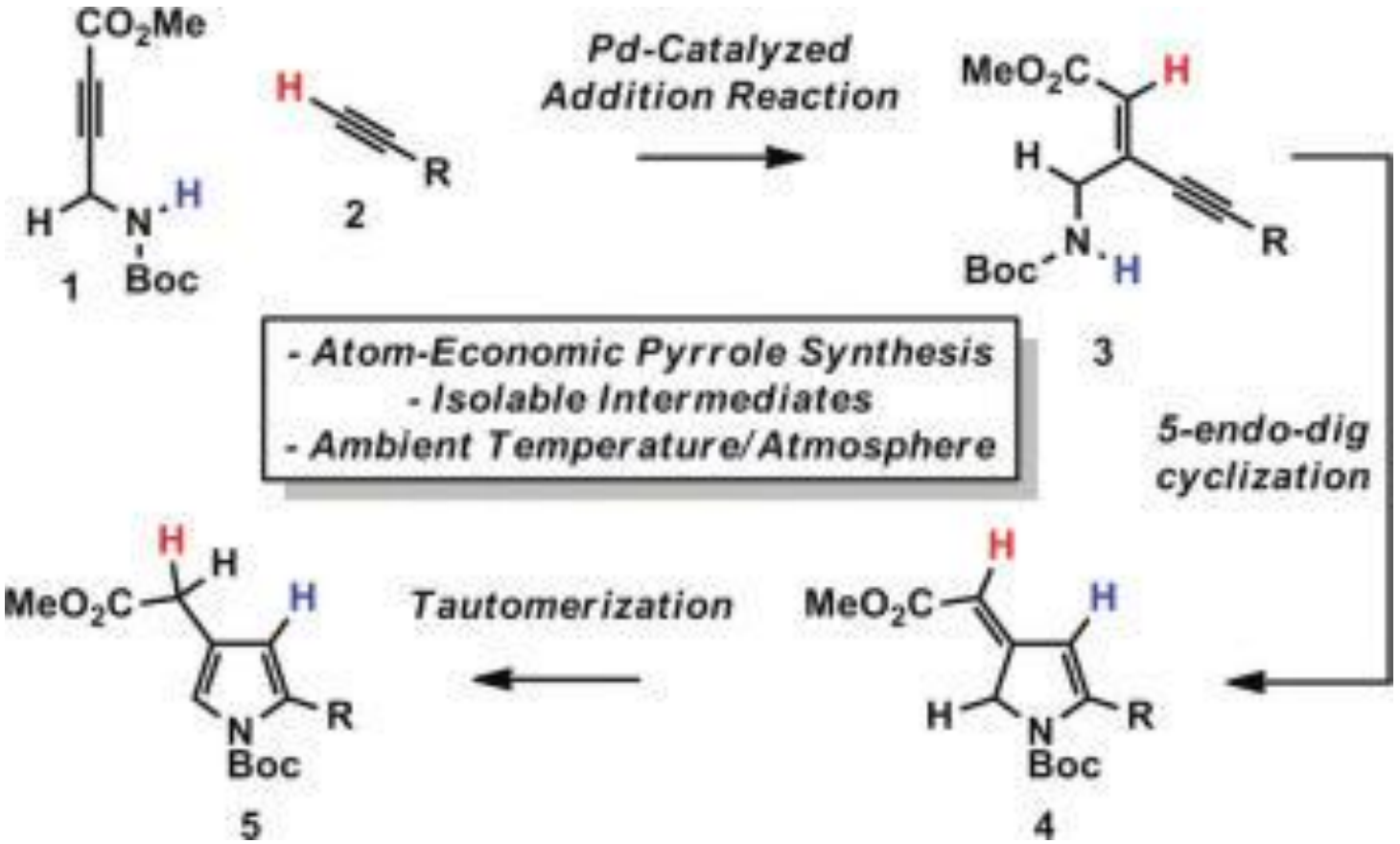
Lecture Structure: Goals of the Lecture

- Become aware of current effort in heterocycle chemistry
- Learn to enter a new topic and understand it
- Using databases and other tools to find all relevant publications
- Recognizing the most relevant works in a field
- Learn to give well-structured presentations
- Public presentation and handling of questions and discussions
- Individual organisation of work

Lecture Structure: Content

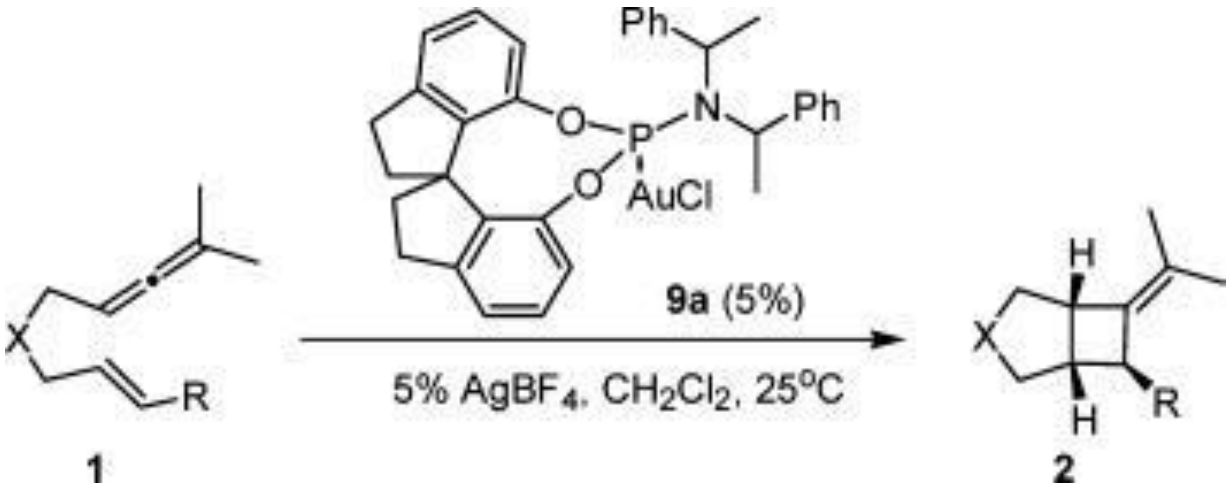
- Synthesis of Heterocycles
  - Small Rings
  - 5-membered Ring
  - 6-membered Ring
  - Indoles
  - Others
- Functionalization of Heterocycles
- Heterocyclic Natural Products
- Heterocycles as Catalysts or as Ligands
- Applications of Heterocycles: Medicinal Chemistry and Materials

Innovative Synthesis: Catalytic Cyclizations

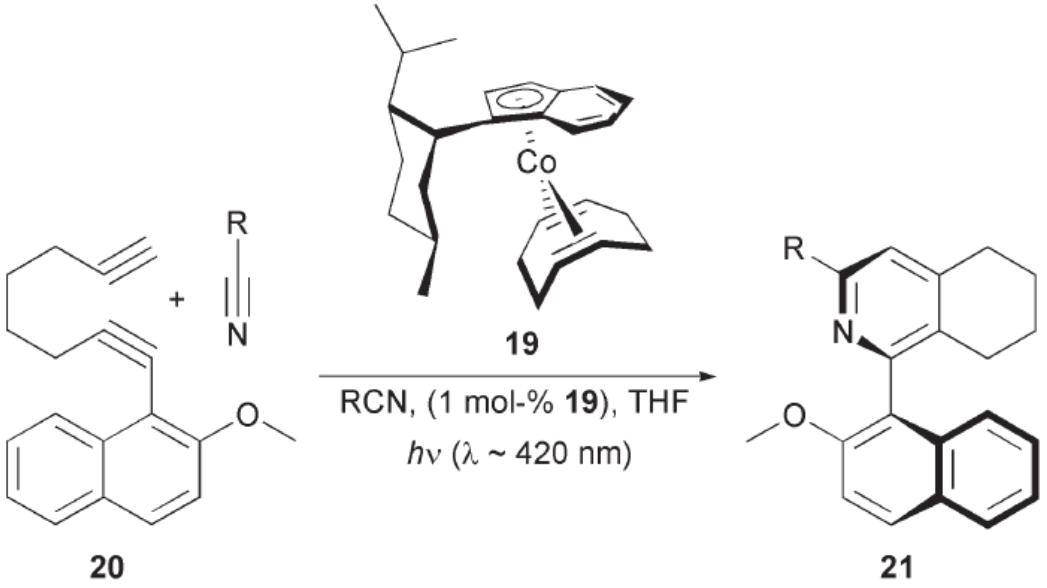


Trost, B. M.; Lumb, J. P.; Azzarelli, J. M., *J. Am. Chem. Soc.* **2011**, *133*, 740-743.

Innovative Synthesis: Annulation Reactions



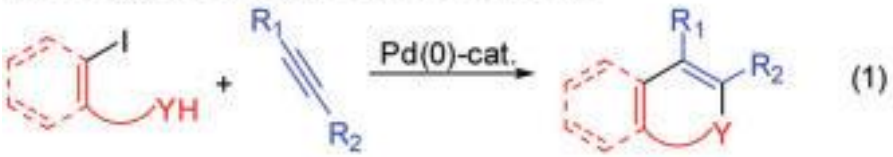
Gonzalez, A. Z.; Benitez, D.; Tkatchouk, E.; Goddard, W. A.; Toste, F. D., *J. Am. Chem. Soc.* **2011**, *133*, 5500-5507.v



Heller, B.; Hapke, M., *Chem. Soc. Rev.* **2007**, *36*, 1085-1094.

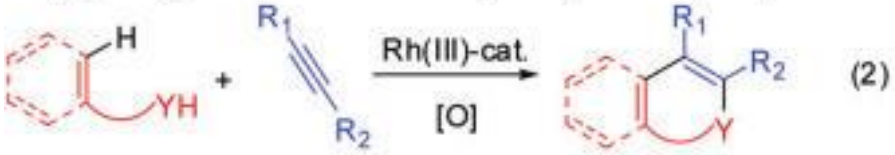
Innovative Synthesis: Annulation Reactions

Larock-type heterocycle synthesis (1991):

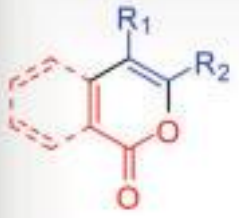


Y = O, $C(CH_3)_2O$, CO_2Me (H not present), NR

Rh(III)-catalyzed oxidative heterocycle synthesis (2007):

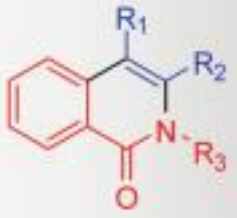


Rh(III)-catalysis applied to the synthesis of:

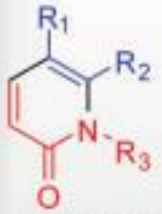


Isocoumarins
(Satoh and Miura)

Isoquinolines
(Satoh and Miura,
Jones, Fagnou)

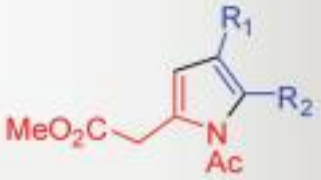


Isoquinolones
(Satoh and Miura,
Fagnou, Rovis, Li)



Pyridones
(Li)

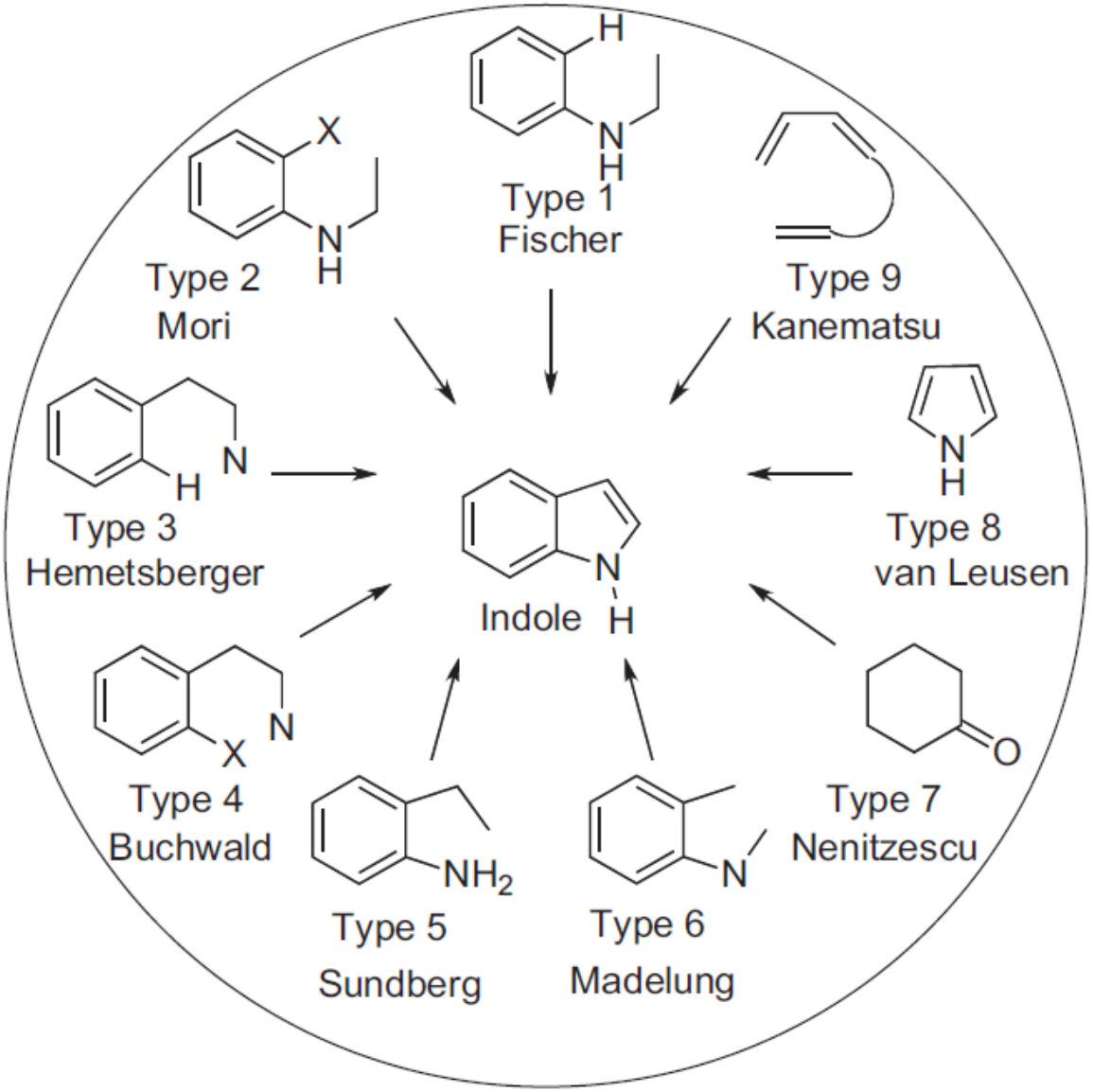
Indoles
(Fagnou)



Pyrroles
(Glorius)

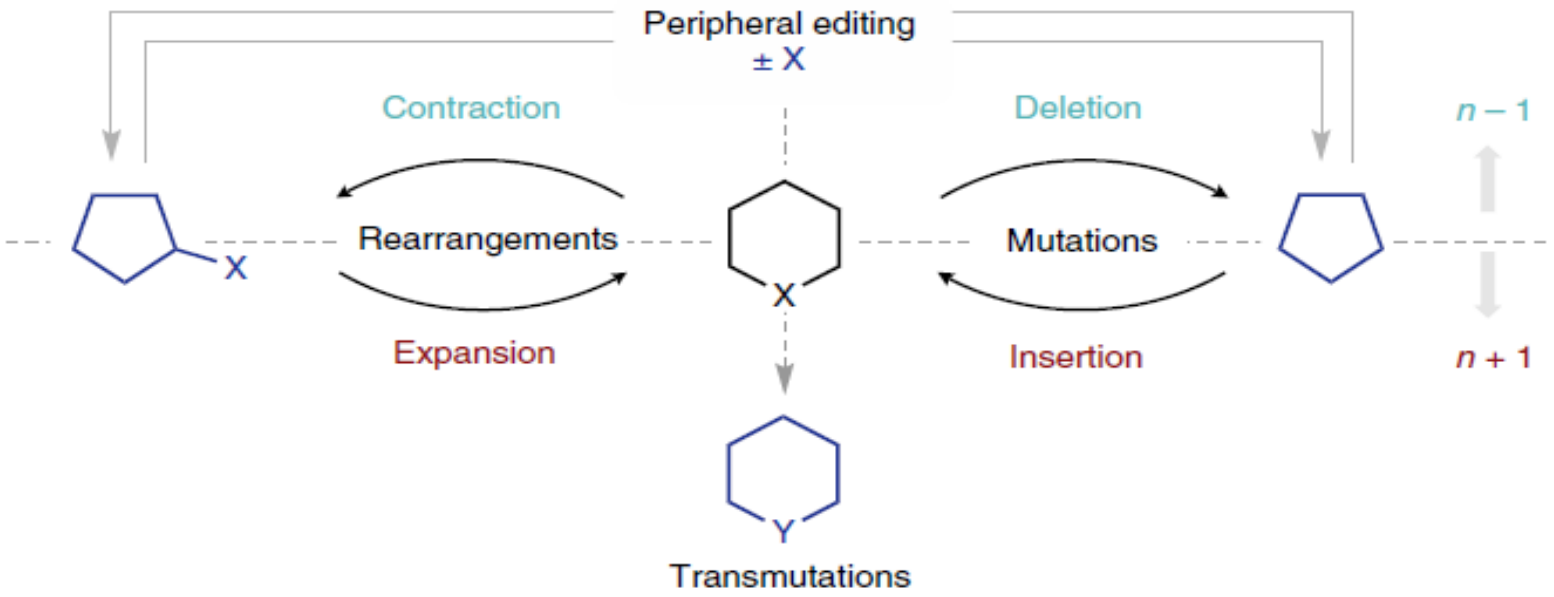
Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K., *J. Am. Chem. Soc.* **2010**, *132*, 18326-18339.

Indole: King of the Rings

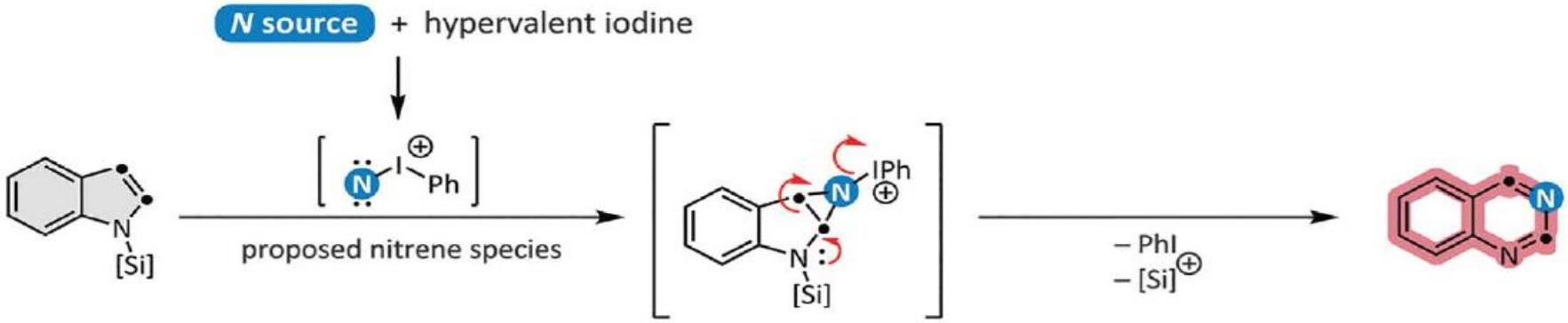


Taber, D. F.; Tirunahari, P. K., *Tetrahedron* **2011**, *67*, 7195-7210.

Current Buzz: skeletal editing

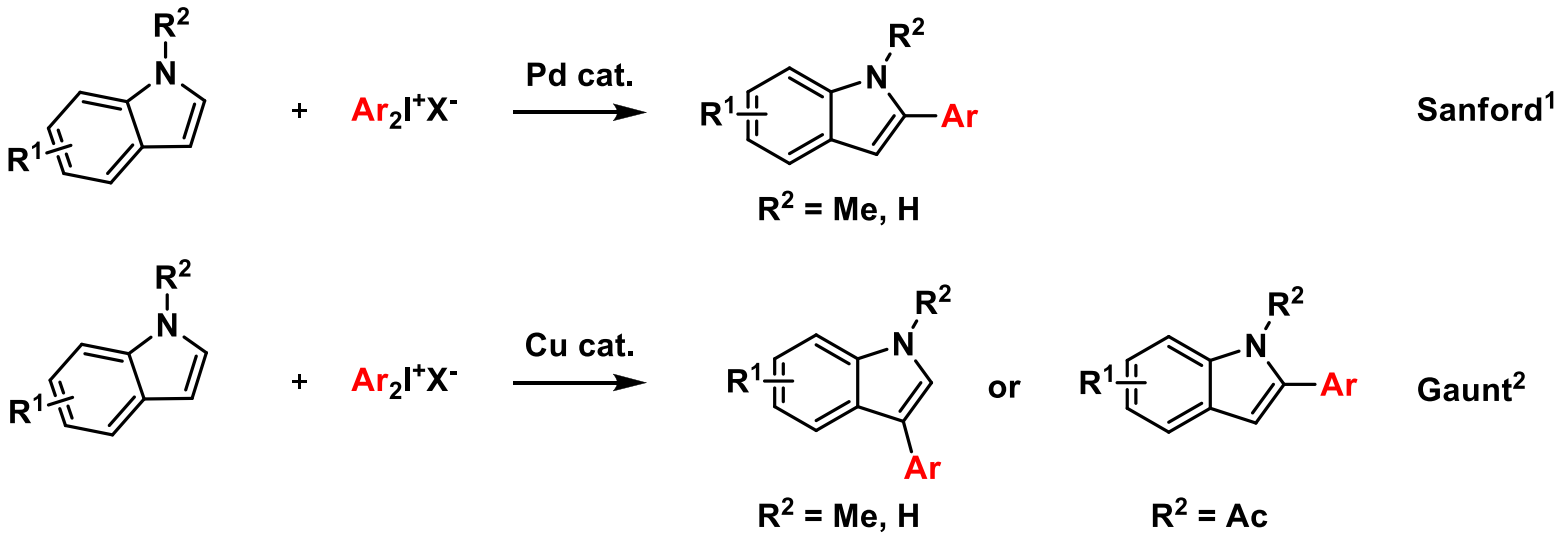


Jurczyk, J.; Woo, J.; Kim, S. F.; Dherange, B. D.; Sarpong, R.; Levin, M. D., *Nat. Synth.* **2022**, *1*, 352-364.
Joynson, B. W.; Ball, L. T., *Helv. Chim. Acta* **2023**, *106*, e202200182.

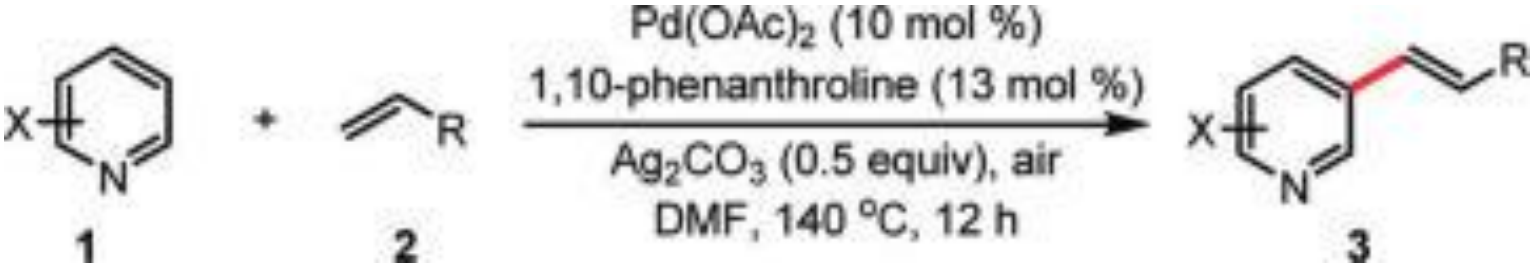


Reisenbauer, J. C.; Green, O.; Franchino, A.; Finkelstein, P.; Morandi, B *Science* **2022,** *377*, 1104.

C-H Functionalization of Heterocycles

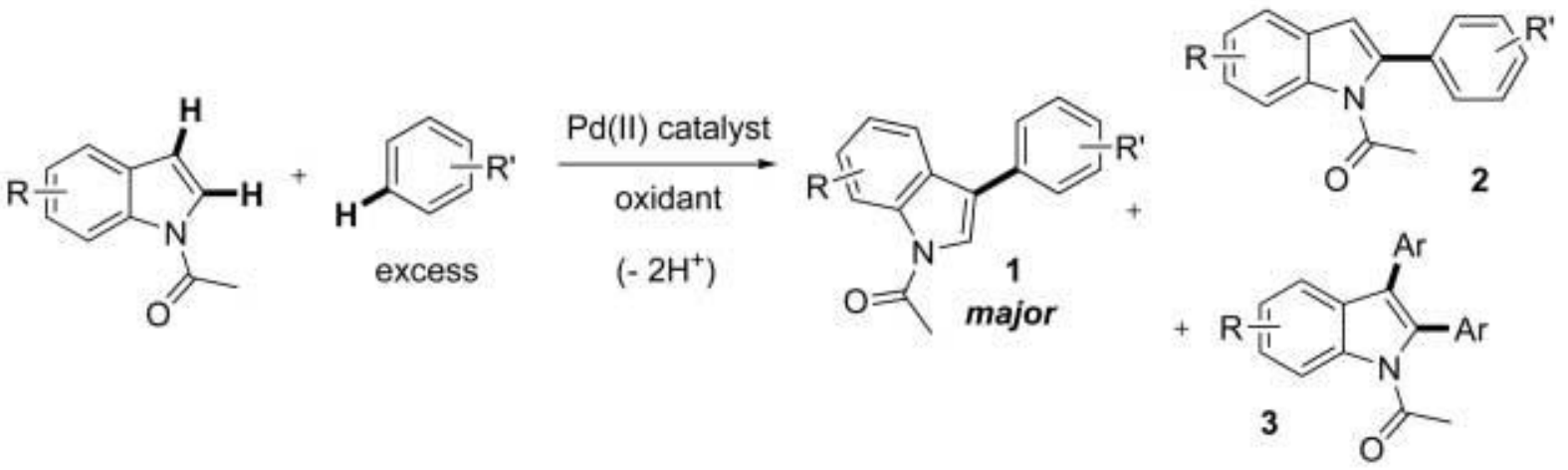


(1) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972. (2) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172..

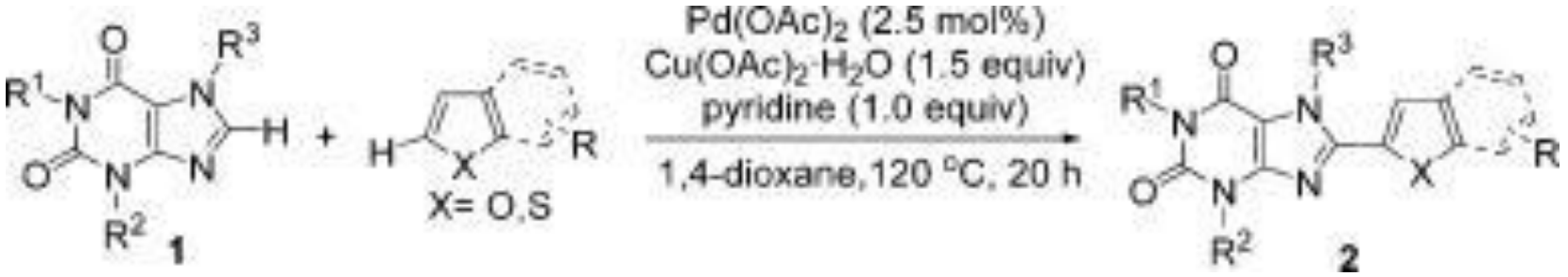


Ye, M. C.; Gao, G. L.; Yu, J. Q., *J. Am. Chem. Soc.* **2011**, *133*, 6964-6967.

C-H Functionalization of Heterocycles

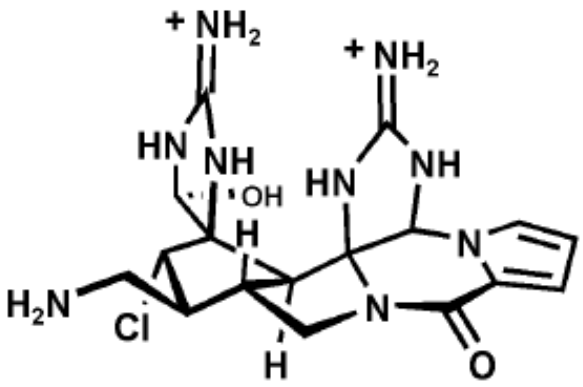


Stuart, D. R.; Fagnou, K., *Science* **2007**, *316*, 1172-1175.



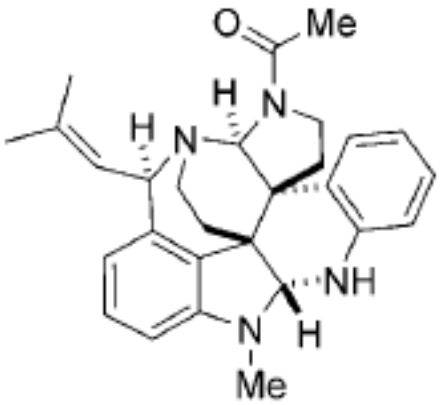
Xi, P. H.; Yang, F.; Qin, S.; Zhao, D. B.; Lan, J. B.; Gao, G.; Hu, C. W.; You, J. S., *J. Am. Chem. Soc.* **2010**, *132*, 1822.

Heterocyclic Natural Products



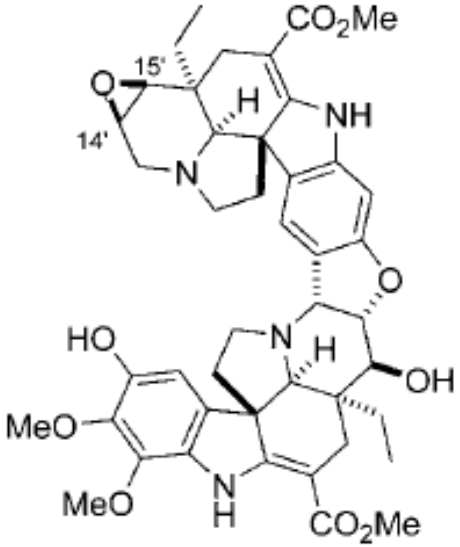
1: palau'amine

Seiple, I. B.; Su, S.; Young, I. S.; Lewis, C. A.; Yamaguchi, J.; Baran, P. S., *Angew. Chem.-Int. Edit.* **2010**, *49*, 1095-1098.



8:communesin F

Liu, P.; Seo, J. H.; Weinreb, S. M., *Angew. Chem.-Int. Edit.* **2010**, *49*, 2000-2003.



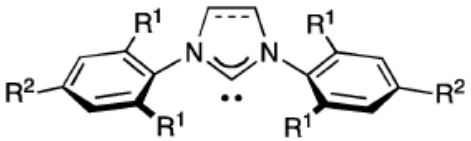
(–)-conophylline (**1**)

Han-ya, Y.; Tokuyama, H.; Fukuyama, T., *Angew. Chem.-Int. Edit.* **2011**, *50*, 4884-4887.

1, Vindoline

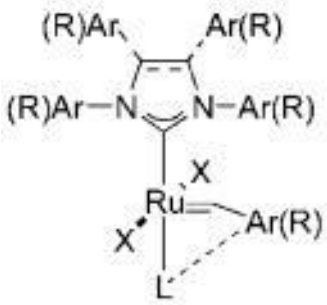
Kato, D.; Sasaki, Y.; Boger, D. L., *J. Am. Chem. Soc.* **2010**, *132*, 3685-+.

Heterocycles as Ligands/Catalysts: Carbenes

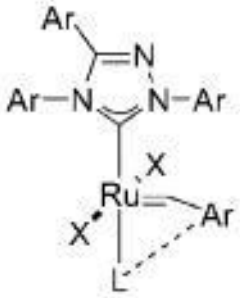


(S)IPr R^1 = ^{i}Pr, R^2 = H
(S)IMes R^1 = R^2 = Me

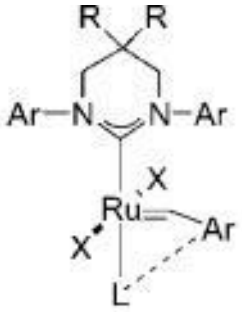
IMe R = Me
ItBu R = ^{t}Bu
ICy R = cyclohexyl
IAd R = 1-adamantyl



imidazol-2-ylidenes
imidazolin-2-ylidenes

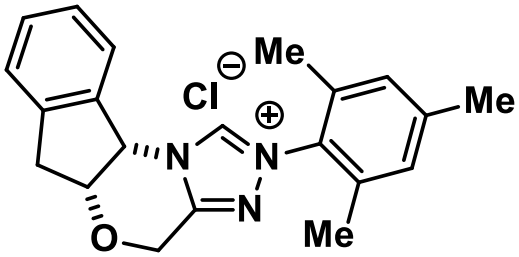


1,2,4-triazol-5-ylidenes

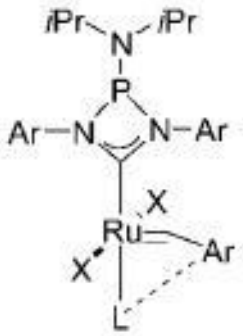


tetrahydropyrimidin
-2-ylidenes

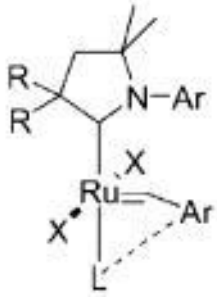
Fortman, G. C.; Nolan, S. P., *Chem. Soc. Rev.* **2011**, *40*, 5151-5169.



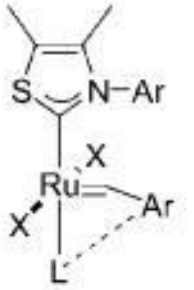
Chiang, P. C.; Kaeobamrung, J.; Bode, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 3520.



four-membered ring
diaminocarbene



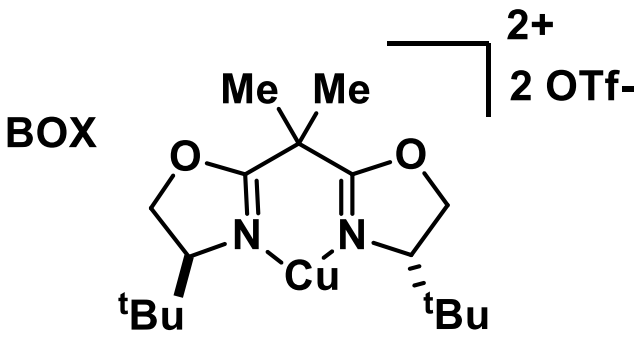
cyclic
(alkyl)(amino)carbenes

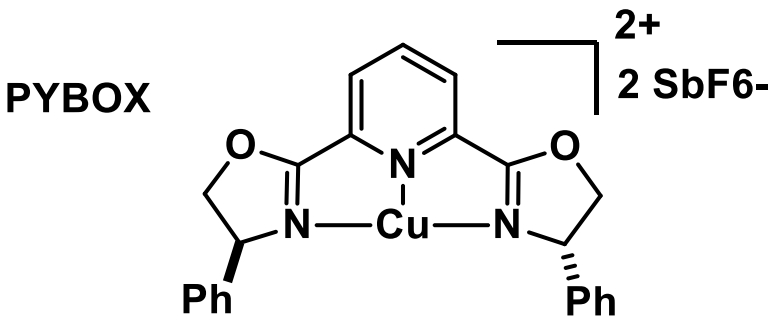


thiazol-2-ylidenes

Vougioukalakis, G. C.; Grubbs, R. H., *Chem. Rev.* **2010**, *110*, 1746-1787.

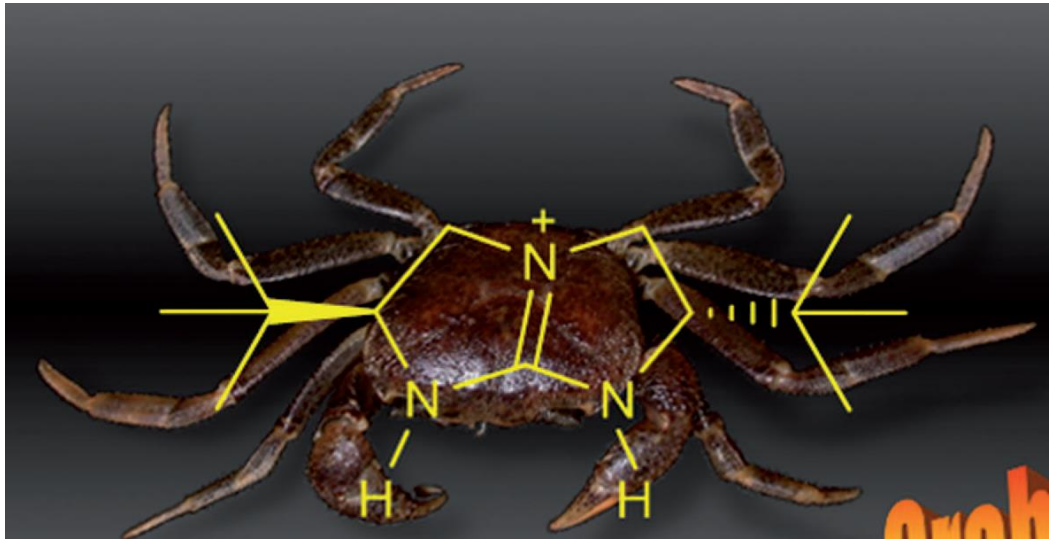
Heterocycles as Ligands/Catalysts





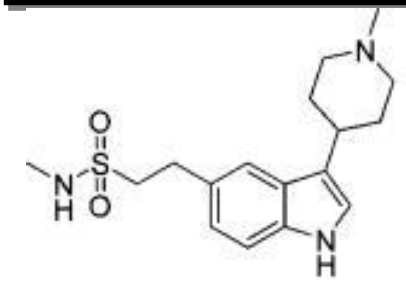
Hargaden, G. C.; Guiry, P. J., *Chem. Rev.* **2009**, *109*, 2505-2550.

Guanidines
Organocatalysts

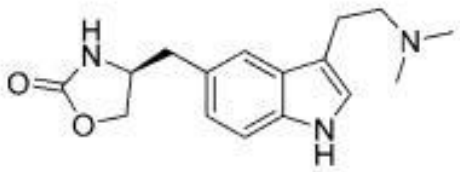


Leow, D.; Tan, C. H., *Chem.-Asian J.* **2009**, *4*, 488-507.

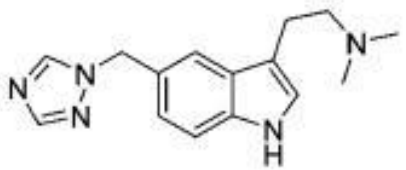
Applications of Heterocycles: Drugs and MedChem



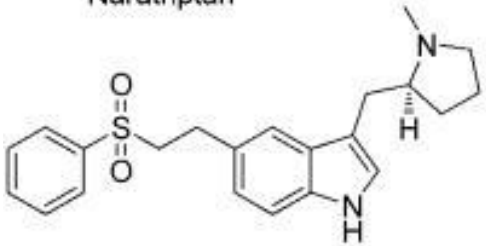
Naratriptan



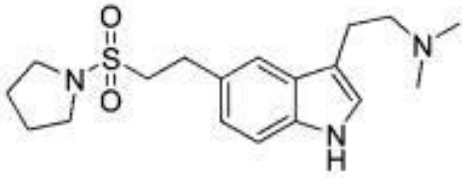
Zolmitriptan



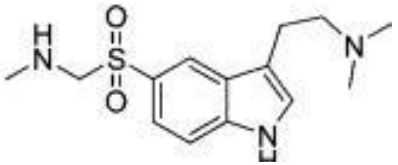
Rizatriptan

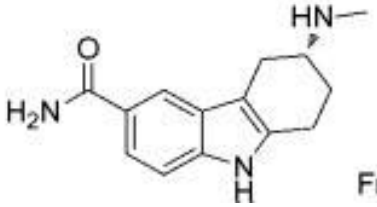


Eletriptan

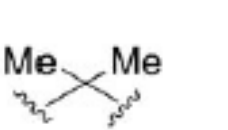


Almotriptan



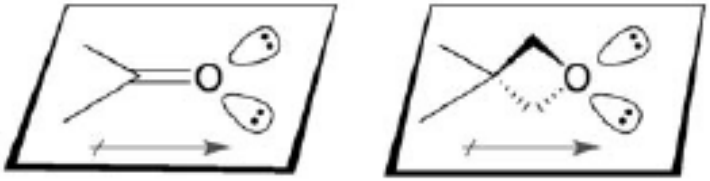


Frovatriptan

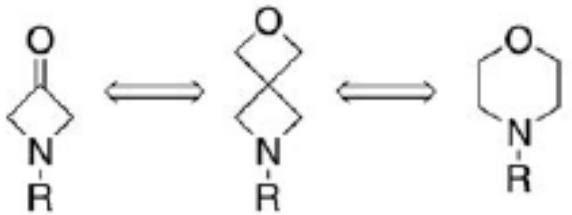


lipophilic
bulk increase

liponeutral
bulk increase



Functional Group and Structural Analogies



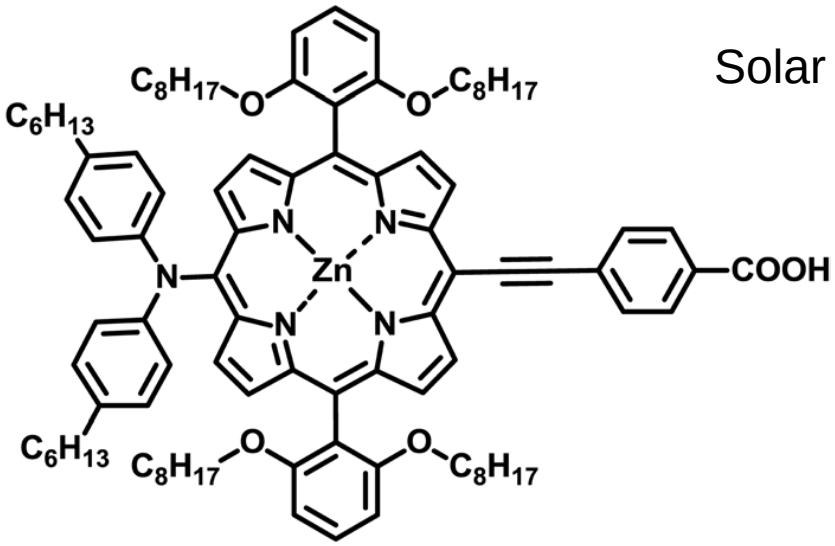
Kochanowska-Karamyan, A. J.; Hamann, M. T., *Chem. Rev.* **2010**, 4489-4497.

Burkhard, J. A.; Wuitschik, G.; Rogers-Evans, M.; Muller, K.; Carreira, E. M., *Angew. Chem., Int. Ed.* **2010**, *49*, 9052-9067.

Top Selling Drugs

http://cbc.arizona.edu/njardarson/group/top-pharmaceuticals-poster

Applications of Heterocycles: Materials



Solar Cells

Yella, A.; Lee, H. W.; Tsao, H. N.; Yi, C. Y.; Chandiran, A. K.; Nazeeruddin, M. K.; Diau, E. W. G.; Yeh, C. Y.; Zakeeruddin, S. M.; Gratzel, M., *Science* **2011**, *334*, 629-634.
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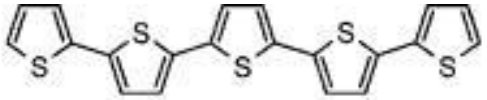
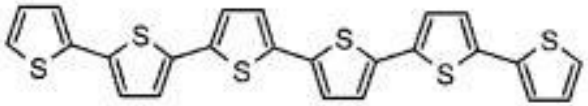
Organic Electronic

Mishra, A.; Ma, C. Q.; Bauerle, P., *Chem. Rev.* **2009**, *109*, 1141-1276.



1.1



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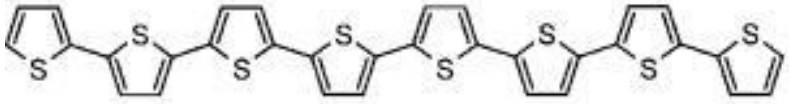
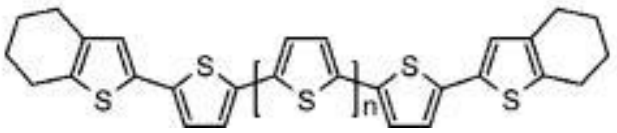


1.3



1.4: n = 1-3