

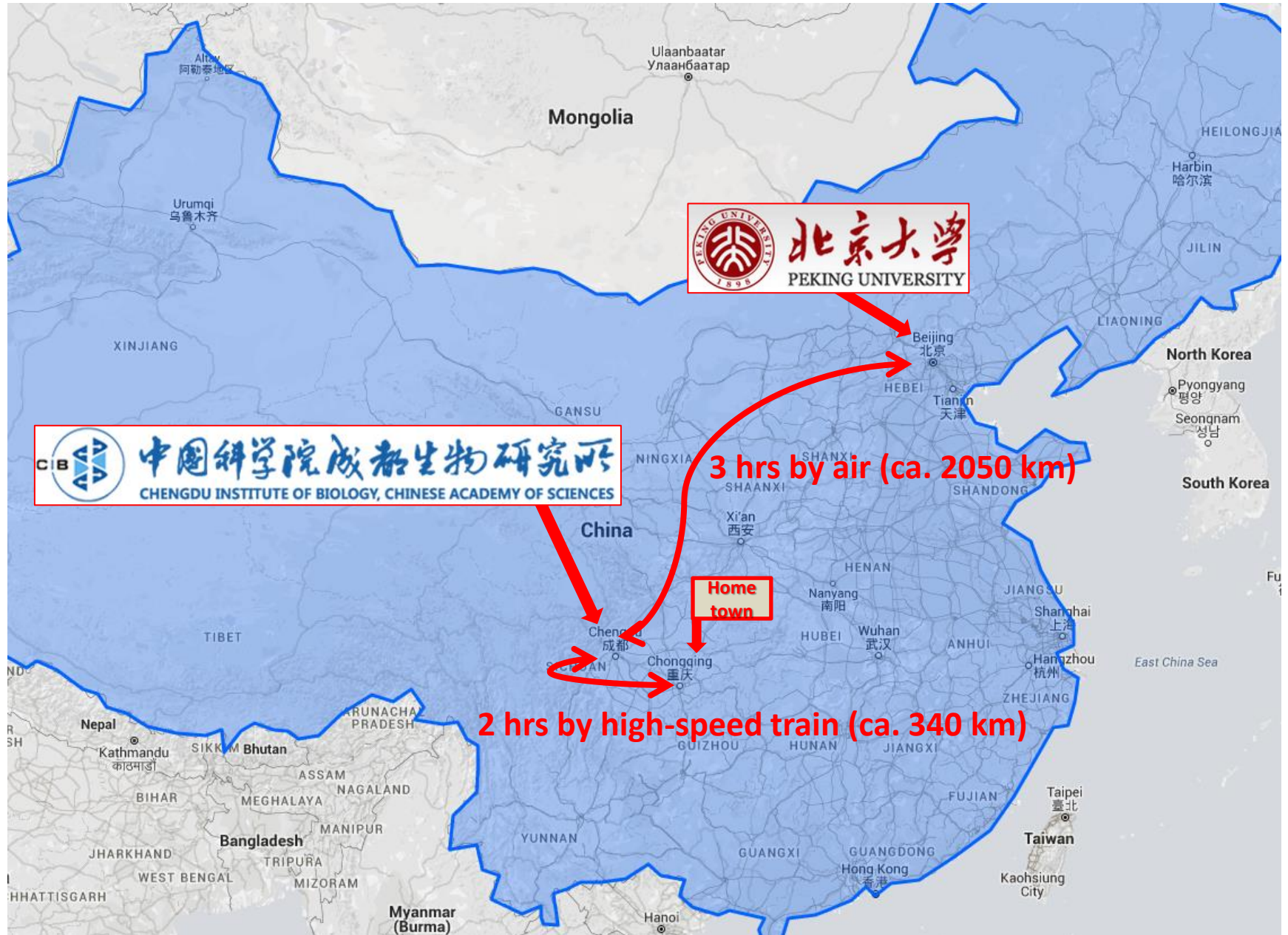
A Short Journey in
Asymmetric Organocatalysis
and
Transition Metal Catalysis

Xiang-Wei Liu

刘祥伟

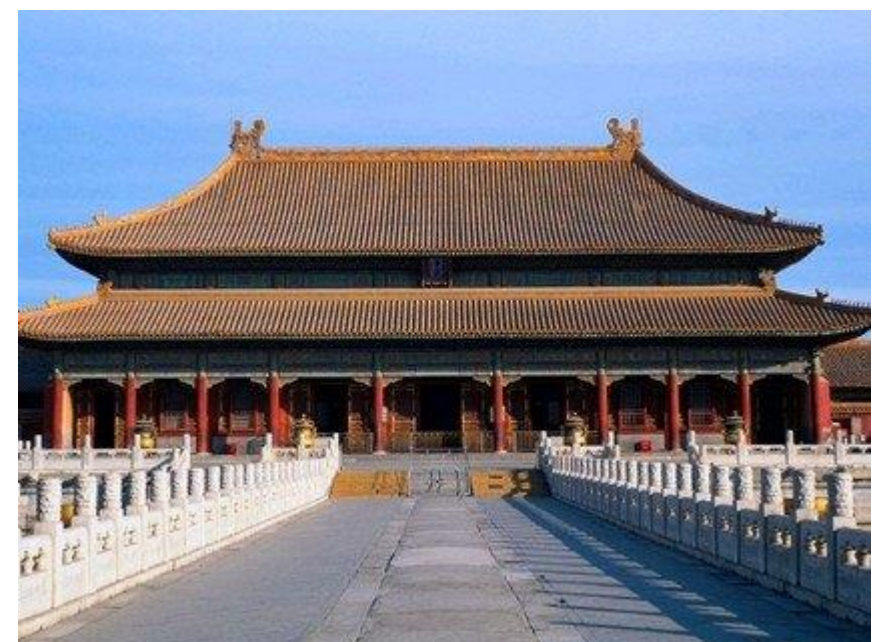
Feb 11th, 2017

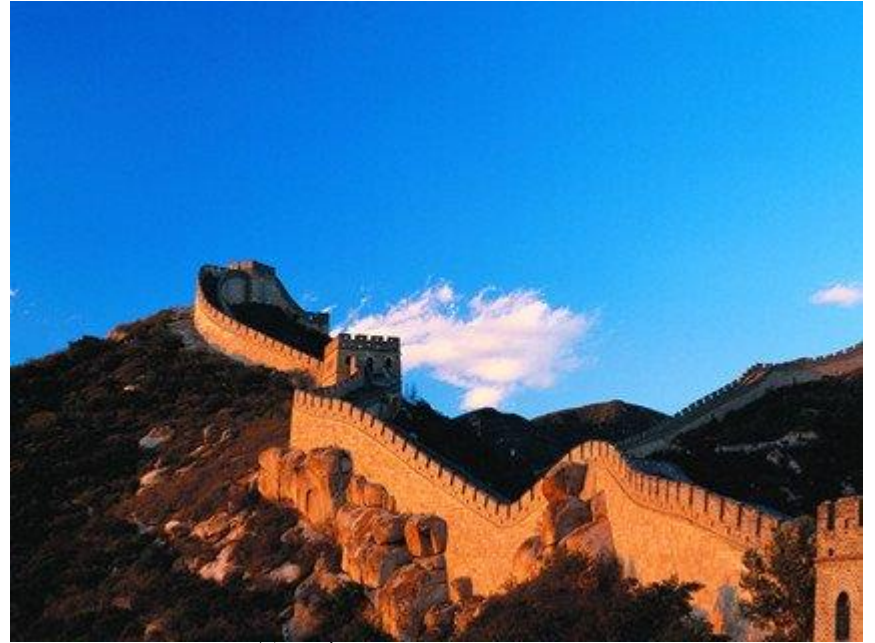
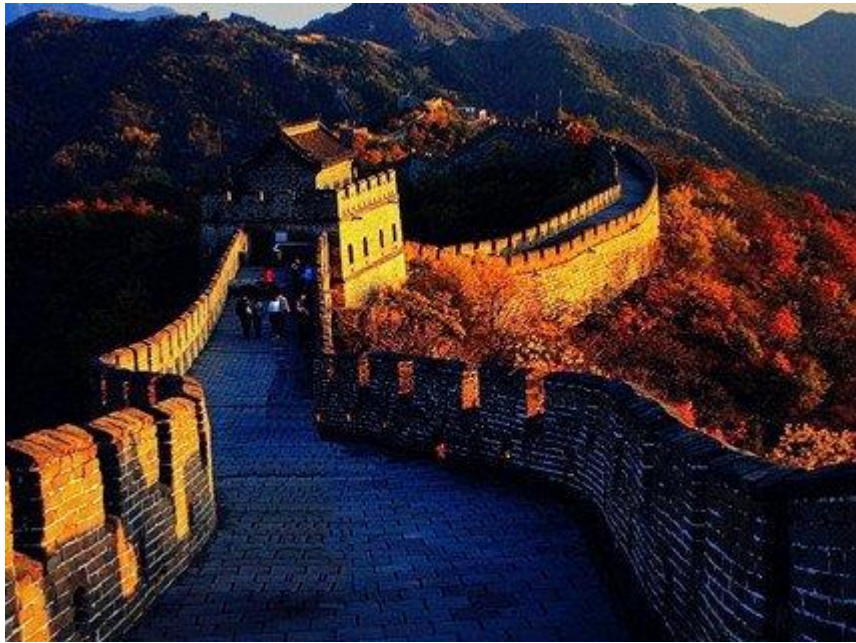
*Institut Català d'Investigació Química (ICIQ), Tarragona,
Spain*





Forbidden city (Beijing, 北京)





Great wall (Beijing, 北京)





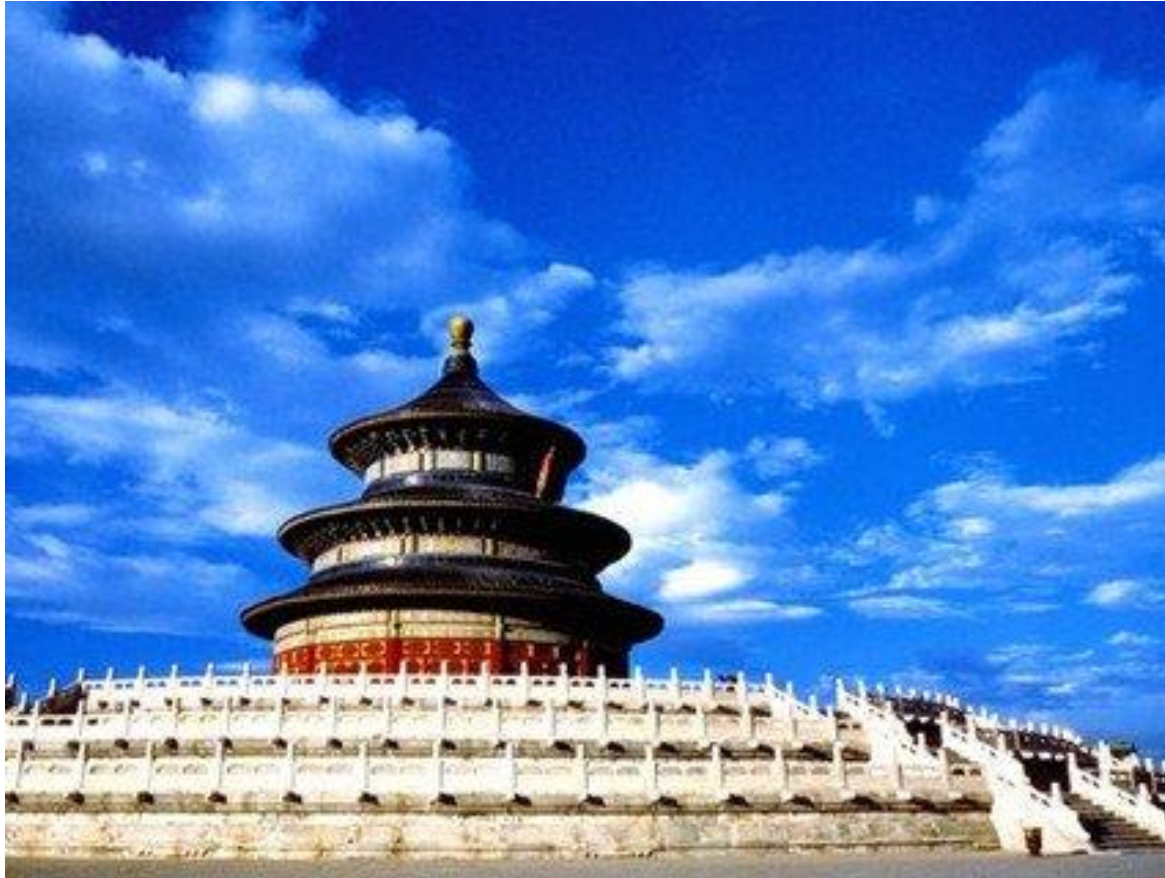
Bird's Nest

Olympic Stadiums (Beijing, 北京)



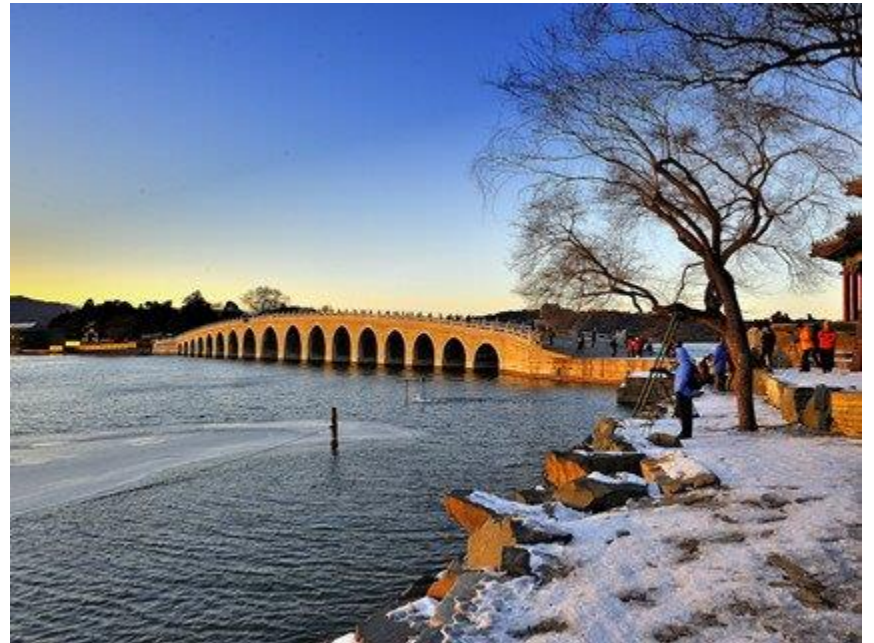
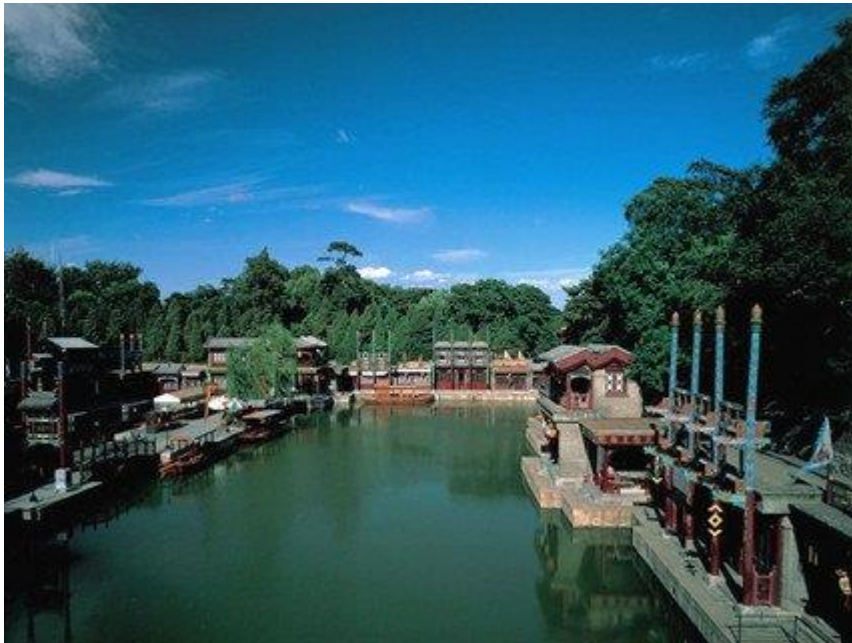
Water Cube

Temple of Heaven (Beijing)





Summer Palace (Beijing, 北京)





Emei Mountain (Chengdu, 成都)



Chengdu Research Center of Giant Panda Breeding



The Giant Stone Buddha at Leshan



Jiuzhaigou Valley (Chengdu, 成都)



Delicious foods

Beijing (北京) Duck



Chongqing (重庆)



Chongqing (重庆)



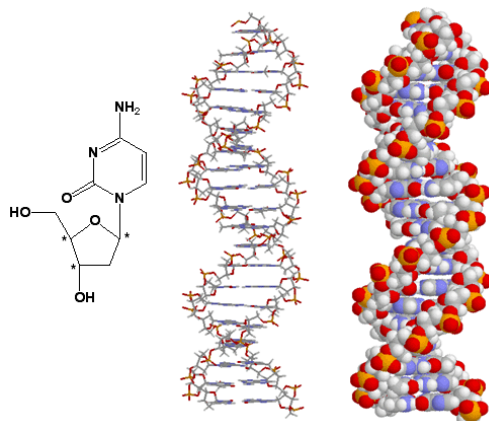
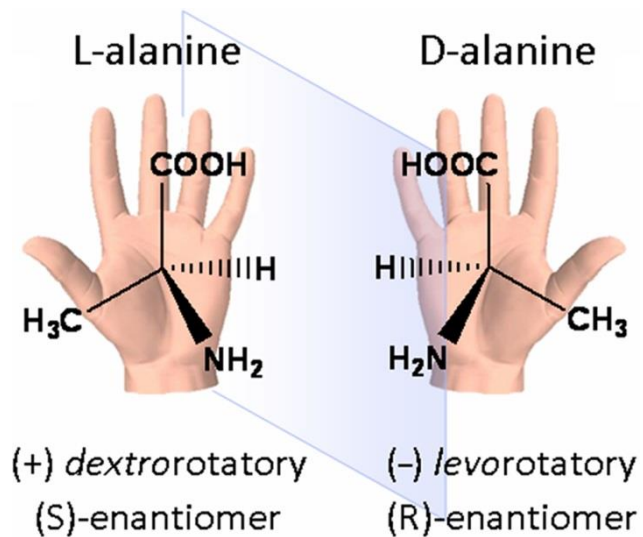
Chengdu (成都)



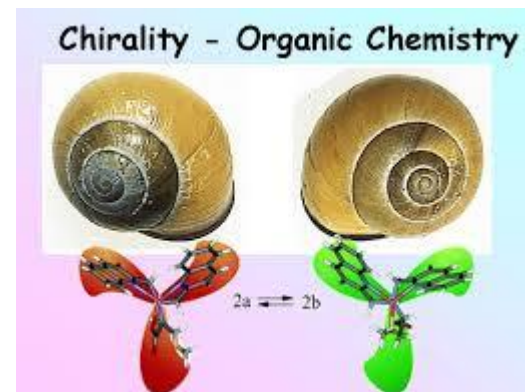
Chongqing (重庆)



The Ubiquity of Chirality



Snail



Storm



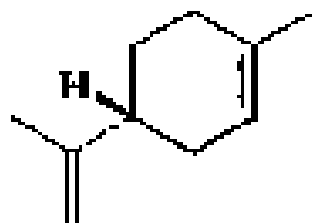
Spring



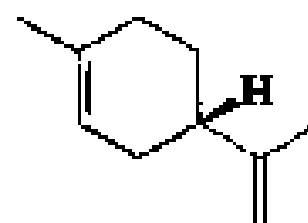
Screw



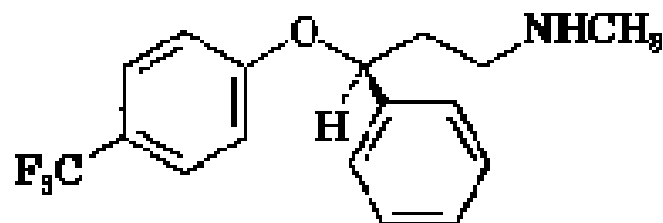
Chirality In Nature



(+)-Limonene
(in oranges)



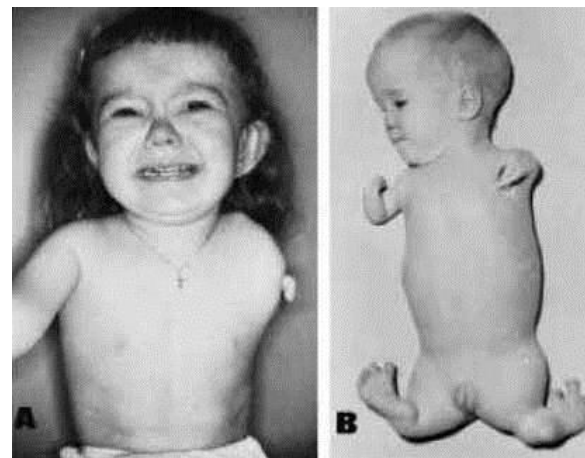
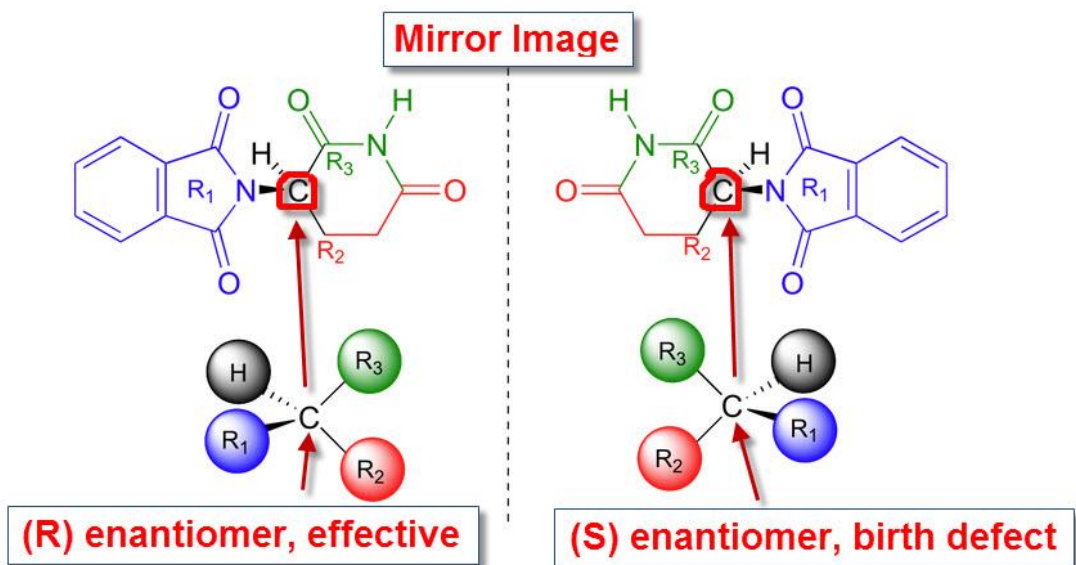
(-)-Limonene
(in lemons)



(S)-Fluoxetine
(prevents migraine)

The Importance of Chirality

---Thalidomide disaster---



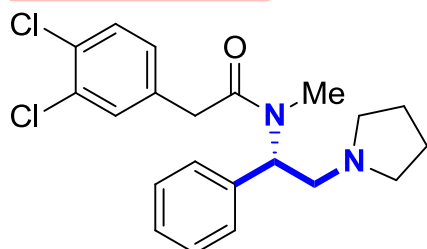
- Thalidomide was first marketed in 1957 in West Germany under the trade-name **Contergan**. The German drug company Chemie Grünenthal developed and sold the drug. Primarily prescribed as a sedative or hypnotic, thalidomide also claimed to cure "anxiety, insomnia, gastritis, and tension".
- Afterwards, it was used against nausea and to alleviate morning sickness in **pregnant women**. Thalidomide became an **over-the-counter** drug in West Germany on October 1, 1957. *Shortly after the drug was sold in West Germany, between 5,000 and 7,000 infants were born with phocomelia (malformation of the limbs). Only 40% of these children survived. Throughout the world, about 10,000 cases were reported of infants with phocomelia due to thalidomide; only 50% of the 10,000 survived.* Those subjected to thalidomide while in the womb experienced limb deficiencies in a way that the long limbs either were not developed or presented themselves as stumps. Other effects included deformed eyes and hearts, deformed alimentary and urinary tracts, blindness and deafness. The negative effects of thalidomide led to the development of more structured drug regulations and control over drug use and development.

phocomelia

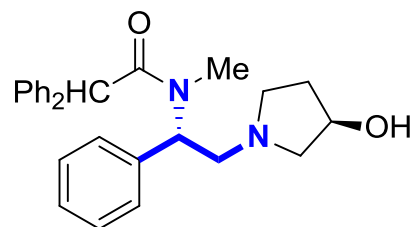


Importance of chiral vicinal diamines...

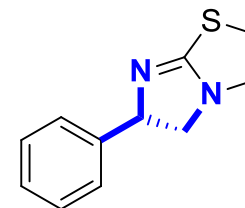
Pharmaceuticals



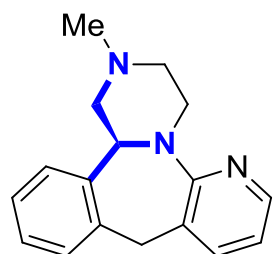
ICI-199441



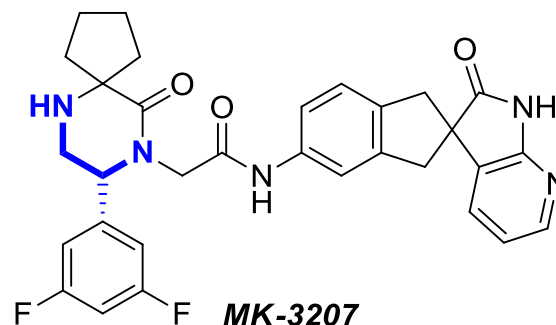
asomalodine



(S)-levamisole

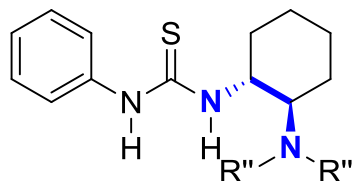


(S)-esmirtazipine

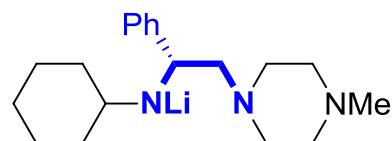


MK-3207

Organocatalyst



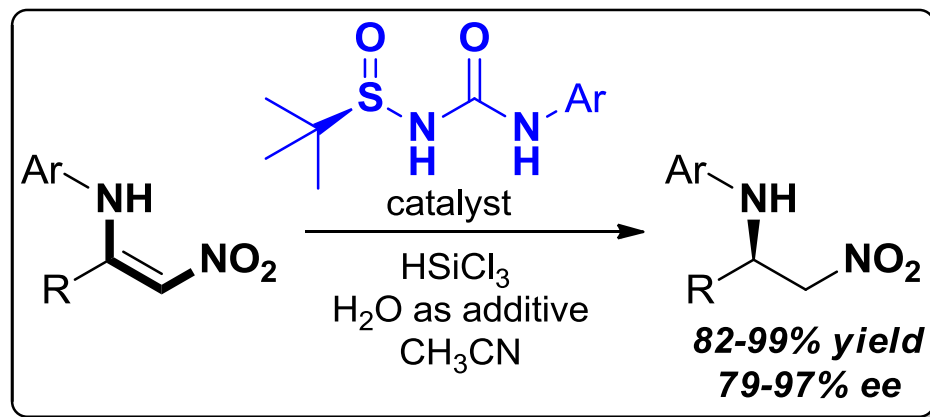
Chiral base



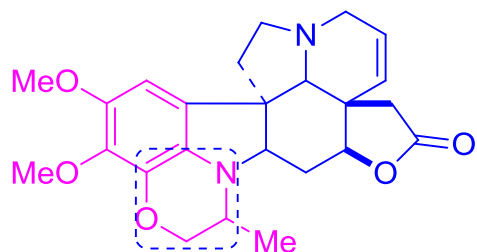
Lithium amide

A. Pasini and F. Zunino, et al., *Angew. Chem. Int. Ed. Engl.* **1987**, 26, 615; M. Ohno, et al. *J. Am. Chem. Soc.* **1990**, 112, 838; J. Reedijk, *Chem. Commun.* **1996**, 801; K. Soai and S. Niwa, *Chem. Rev.* **1992**, 92, 833; H. U. Blaser, *Chem. Rev.* **1992**, 92, 935; K. B. Sharpless, et al. *Chem. Rev.* **1994**, 94, 2483.

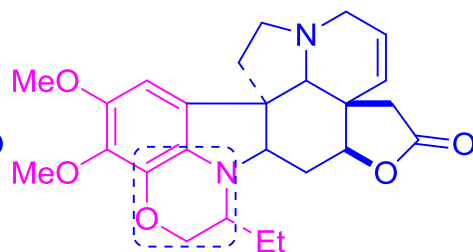
■ Lewis base catalyzed asymmetric reduction of β -nitro enamines



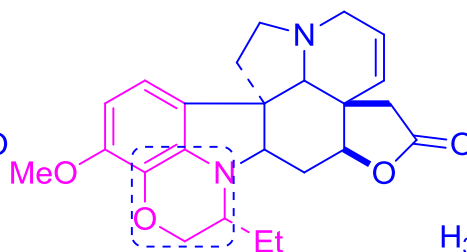
Importance of chiral quinoxazines...



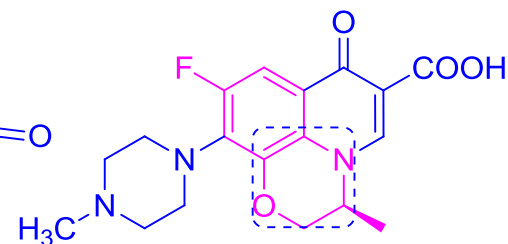
Obscurinervidine



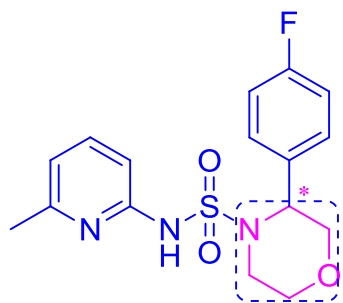
Obscurinervine



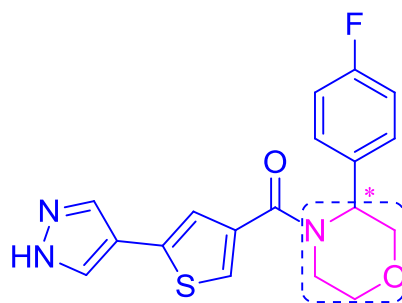
Neblinine



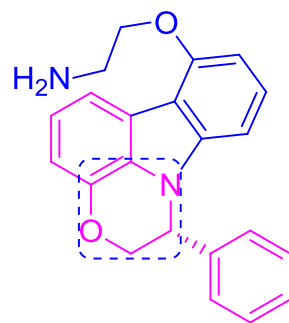
Levofloxacin



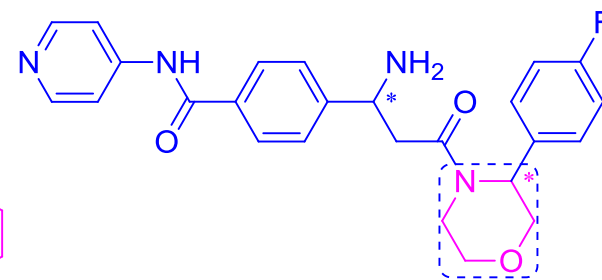
**11β-Hydroxysteroid
dehydrogenase type 1
modulator**



**11β-Hydroxysteroid
dehydrogenase type 1
inhibitor**



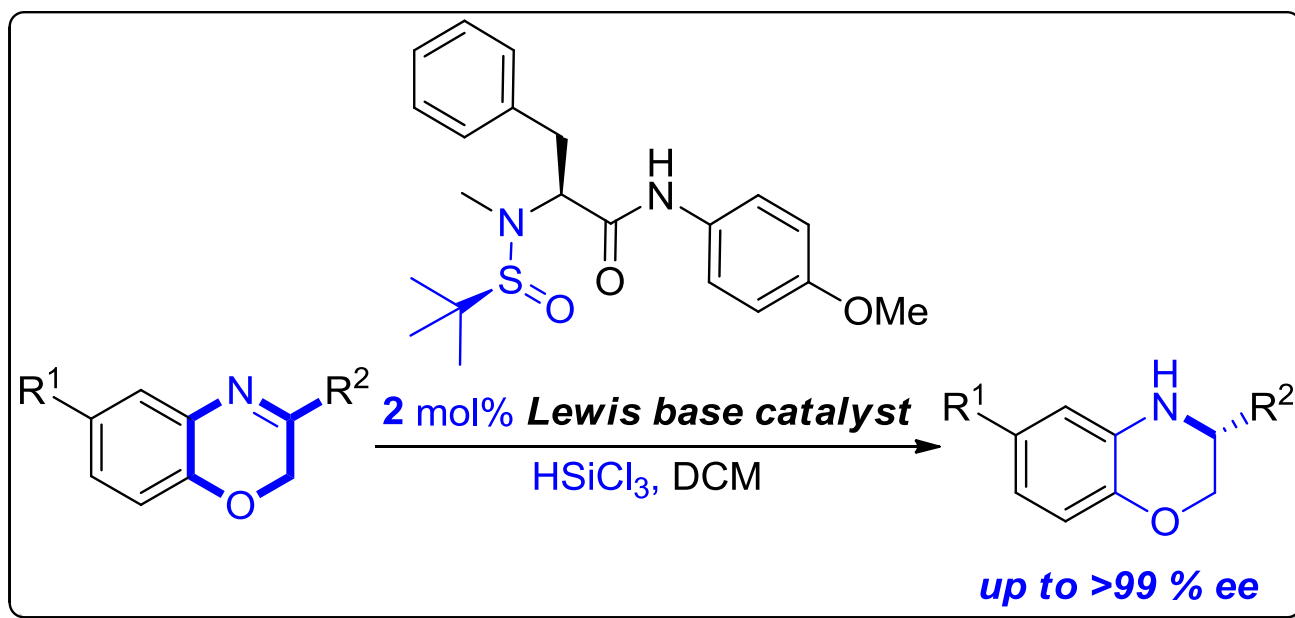
**5-HT6 serotonin
receptor modulator**



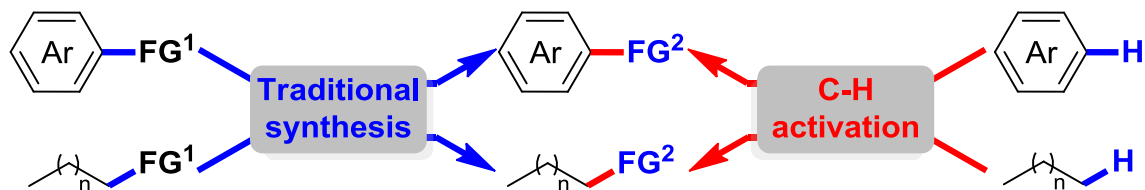
AGC kinase inhibitor

K. S. Brown, C. Djerassi, *J. Am. Chem. Soc.* **1964**, *86*, 2451; A. Belattar, J. E. Saxton, *J. Chem. Soc., Perkin trans. 1* **1992**, 679; bJ. Ilaš, P. Š. Anderluh, M. S. Dolenc, D. Kikelj, *Tetrahedron* **2005**, *61*, 7325; Y.-G. Zhou, P.-Y. Yang, X.-W. Han, *J. Org. Chem.* **2005**, *70*, 1679; L. A. Mitscher, P. N. Sharma, D. T. W. Chu, L. L. Shen, A. G. Pernet, *J. Med. Chem.* **1987**, *30*, 2283.

■ Lewis base catalyzed asymmetric reduction of benzoxazines



C-H activation *versus* traditional synthesis



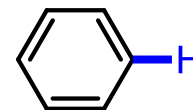
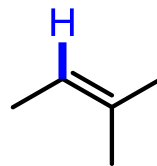
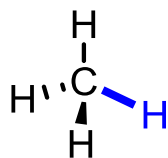
Traditional methods:

- *Pre-functionalization is needed*
- *Low atom-economy*
- *Low step-economy*

Advantage of C-H activation :

- *Ubiquity of C-H Bonds*
- *Avoidance of Prefunctionalization*
- *High atom-economy*
- *High step-economy*

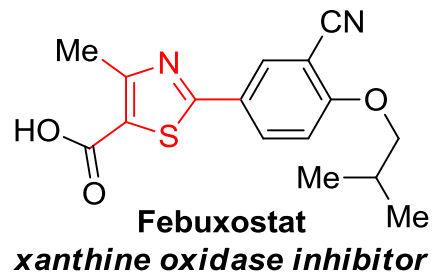
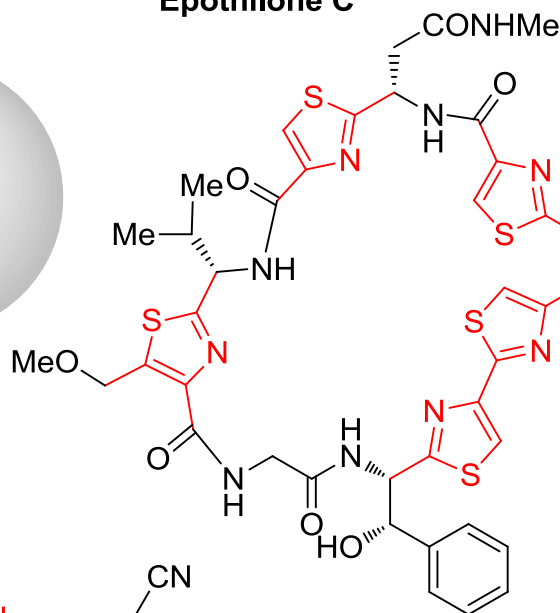
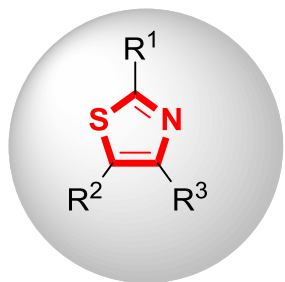
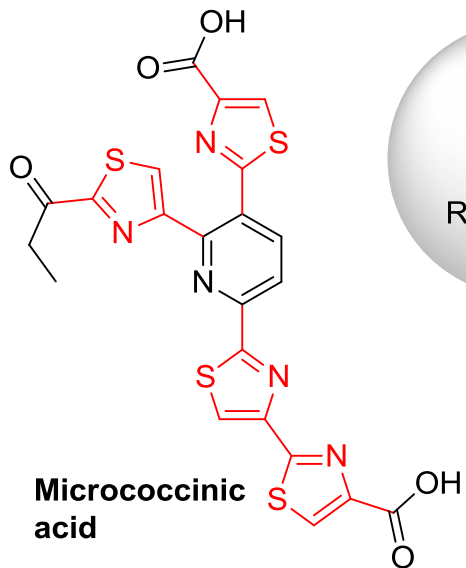
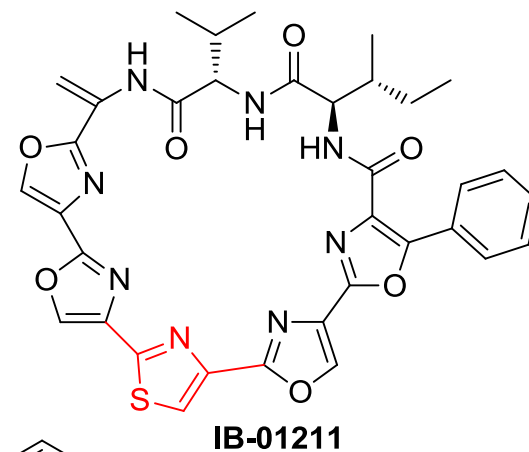
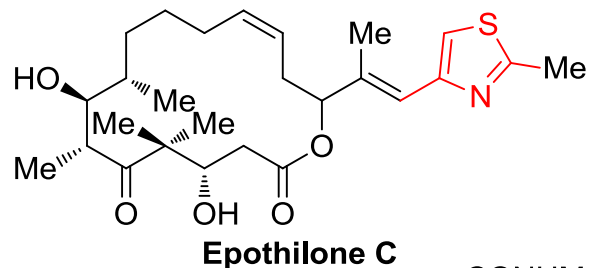
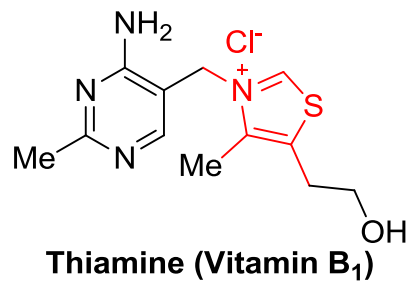
Various Unreactive C-H Bonds



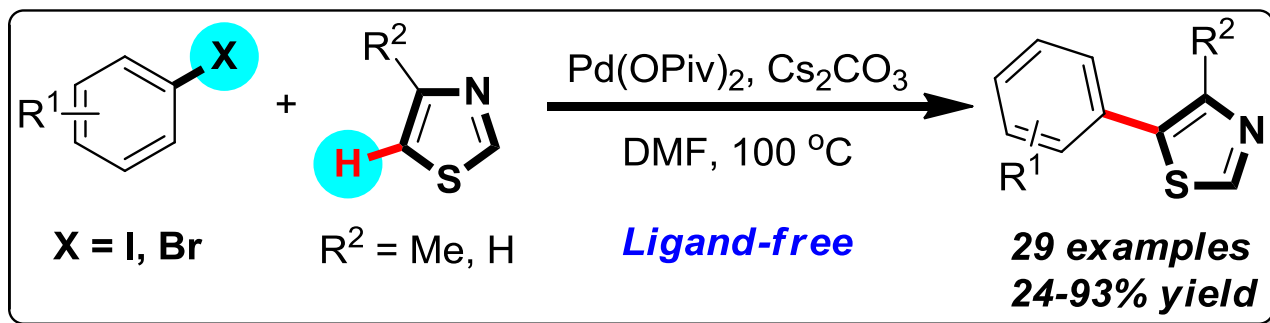
Emerging Synthetic Tool for Natural Products and Pharmaceuticals

X. Chen, K. M. Engle, D. -H. Wang, J. -Q. Yu, *Angew. Chem. Int. Ed.*, **2009**, 48, 5094; T. W. Lyons, M. S. Sanford, *Chem. Rev.*, **2010**, 110, 1147; L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem. Int. Ed.*, **2009**, 48, 9792; H. Li, B. -J. Li, Z. -J. Shi, *Catal. Sci. Technol.*, **2011**, 1, 191; Yamaguchi, J.; Yamaguchi, A. D.; Itami, K., *Angew. Chem. Int. Ed.* **2012**, 51, 8960.

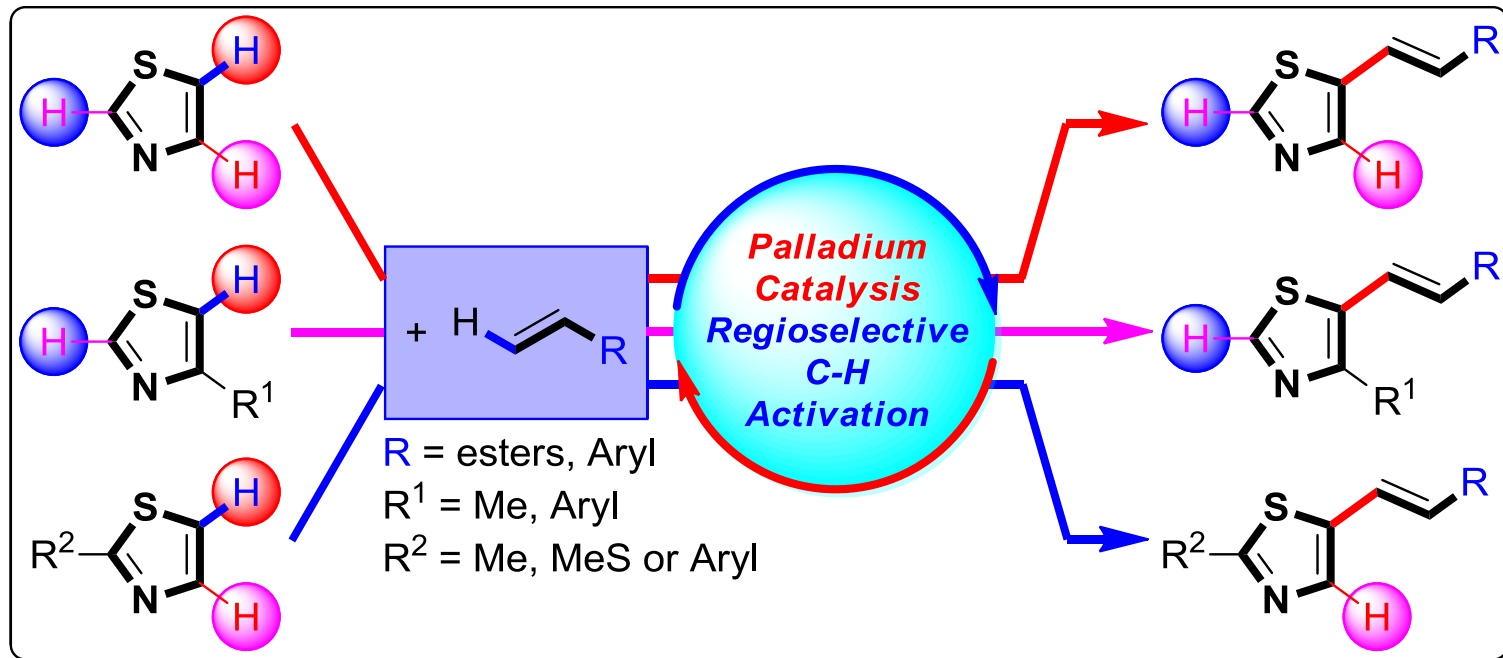
Importance of thiazole-containing molecules



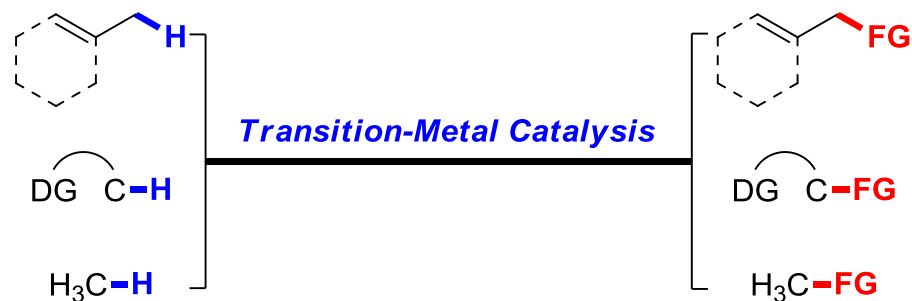
■ Regioselective arylation of thiazole derivatives



■ Regioselective alkenylation of thiazole derivatives



C(sp³)-H Activation



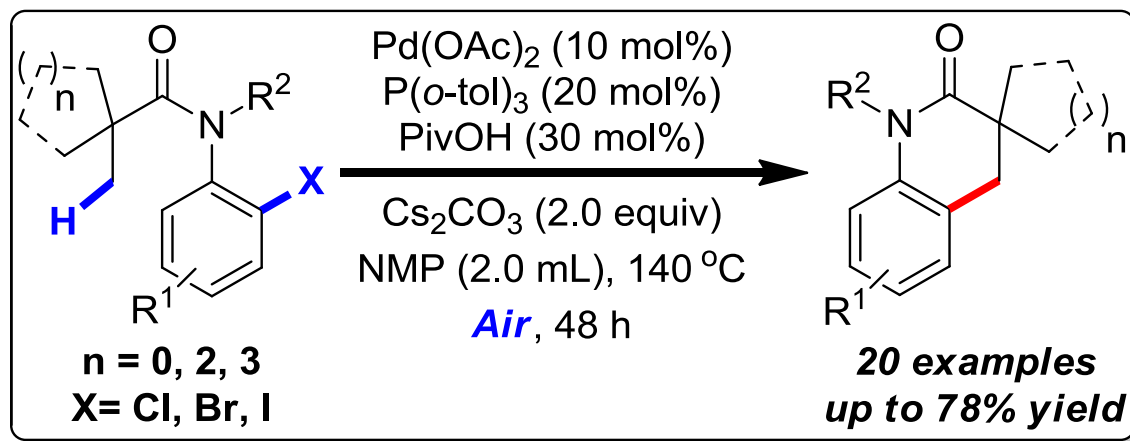
- I. Allylic/Benzylic sp³ C-H activation
- II. Directing group-oriented sp³ C-H activation
- III. Direct activation of sp³ C-H bonds in methane

Challenges for C(sp³)-H activation:

- *High bond dissociation energy required*
- *Lack of effective HOMO or LUMO to interact with catalytic centers*
- *Difficult to control regioselectivities*

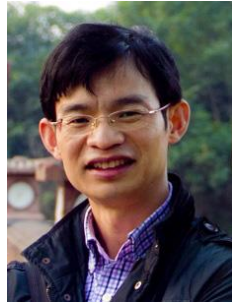
M. S. Chen, M. C. White, *J. Am. Chem. Soc.*, **2004**, *126*, 1346; A. R. Dick, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.*, **2004**, *126*, 2300; V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.*, **2005**, *127*, 13154; Z. An, X. Pan, X. Liu, X. Han, X. Bao, *J. Am. Chem. Soc.*, **2006**, *128*, 16029.

■ *De Novo* synthesis of 3,4-Dihydroquinolinone Derivatives *via* Palladium-Catalyzed C(sp³)-H Activation



Acknowledgement

Prof. Jian Sun



Prof. Zhang-Jie Shi

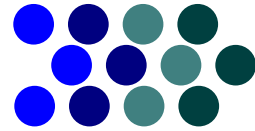


Prof. Ruben Martin



And all colleagues from these three groups!

- \$ China Postdoctoral Science Foundation**
- \$ Porton Fine Chemicals Ltd & DSM (China) Ltd**
- \$ National Natural Science Foundation of China (NSFC)**
- \$ Ministry of Science and Technology of the People's Republic of China (MOST)**
- \$ Marie Curie Fellowship (702563-NOVOCAT-H2020-MSCA-IF-2015)**



Thanks for your attention!

