Pavel Kočovský – Outline of Research

***Credo:* For those who seek to discover new reactions, the most insightful lessons come from trying to trace important reactivity principles back to their origins.** (K. Barry Sharpless)

General Aims

Our research is focused on organic/organometallic chemistry and mechanisms, includes asymmetric synthesis, transition metal catalysis, organocatalysis, and synthesis of functional molecules and molecular probes. In all our efforts, we aim not just to reach our goals but to do so in an original and chemically interesting manner.

We are mainly interested in the rational design of **novel sustainable synthetic methods**, in particular reactions mediated by transition and non-transition metals and by metal-free organocatalysts. *The primary goal in all our work is to devise and make use of synthetic routes that feature new chemistry and to understand the mechanisms of the chemical reactions we are trying to develop*.

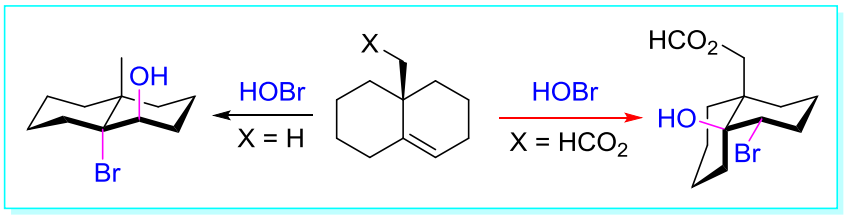
Because of their exceptional steric and electronic properties, transition metal complexes are characterized by tremendous potential for effecting highly selective transformations of organic substrates unattainable by classical organic chemistry. One of the central themes of our research is therefore the utilization of transition and non-transition metals to discover unprecedented reactivity and new transformations for use in organic sysnthesis. This way we are also learning more about the stereochemical and electronic control of the metal-substrate interactions.

Over the years, we have described several novel reactions, using various **metallic reagents and catalysts** (**Pd**, **Mo**, **W**, **Ru**, **Ir**, **Ni**, **V**, **Cu**, **Zn**, **Tl**, **Hg**, and **Au**), accomplished stereoselective syntheses of several **natural products**, such as **strophanthidin** (a cardio-active drug), **estrone** (a female sexual hormone), **tetrahydrocannabinol** (an active constituent of marihuana), and **convolutamydine** (an antileukemia agent). We have also designed a series of new **chiral ligands** for asymmetric, **transition metal-catalyzed reactions**, e.g., **NOBIN**, **MAP**, and **PINDY**, and new electrochemical and mass-spectrometric **sensors** to differentiate enantiomers of biologically significant chiral molecules at very low concentrations. Some of our catalytic methods have been utilized in the synthesis of ***C*-glycosides** with potential anti-viral and anti-cancer activity. Some of our organometallic molecules have been designed as **molecular probes** for studying membrane proteins. Recent interest also includes detection of functional molecules in body fluids by **electrochemical methods**.

Over the past 50 years, transition metal chemistry has revolutionized synthetic methodology and the way chemists think and plan their strategy in the construction of molecules. However, in spite of the tremendous progress and the vast number of unique transformations resulting from these developments, the leaching of the metal and its recovery remain to be the main obstacles that hinder the wider use of transition metal catalysts by pharmaceutical industry in bulk production. Furthermore, the ever increasing cost of the precious metals presents another serious problem. With the advent of the new millennium, we have therefore expanded our activity into the new and exciting area of asymmetric **organocatalysis**, which is now being vigorously pursued in leading laboratories world-wide; in fact, we were among the first groups to launch a systematic investigation in this area. The main goal here is to find small organic molecules that can catalyze those synthetically important reactions, which do not require a metal mediator, and may complement enzymatic transformations. We also hope to learn more about the basic interactions between the catalyst and the substrate by a combination of experimental and **computational methods**. We have focused on the enantioselective allylation of aldehydes with allylsilanes, reduction of ketones and ketimines with trichlorosilane, α-alkylation of amino acid derivatives and, most recently, on aldol reactions. To this end, we have developed several classes of organocatalysts, namely pyridine-type *N*-oxides (**PINDOX**, ***iso*-PINDOX**, **METHOX**, and **QUINOX**, etc.), chiral, binaphthyl-type aminophenols (**NOBIN**, ***iso*-NOBIN**, and their derivatives), and amino acid-derived catalysts, such as **ANGUSOLINE**, **KENAMIDE**, and **SIGAMIDE**. Some of these are commercially available.

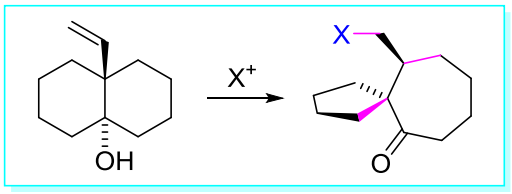
1. Selected Reactions Discovered or Developed - Part 1

Stereocontrol of electrophilic additions by neighboring groups

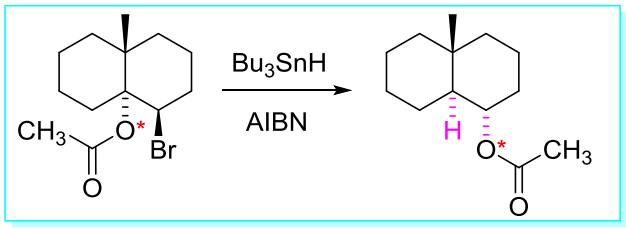


J. Chem. Soc., Perkin Trans. 1 **1987**, 1969.
J. Chem. Soc., Perkin Trans. 1 **1988**, 2297.
Tetrahedron Lett. **1989**, *30*, 4295.
J. Org. Chem. **1990**, *50*, 5580.

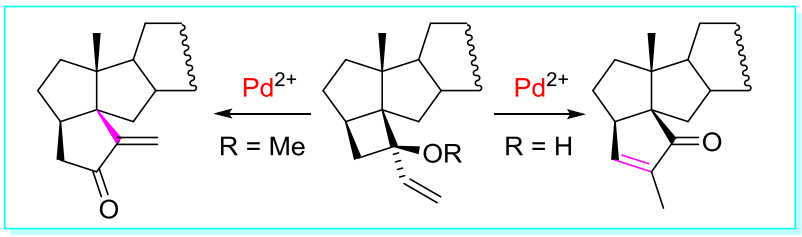
Rearrangements



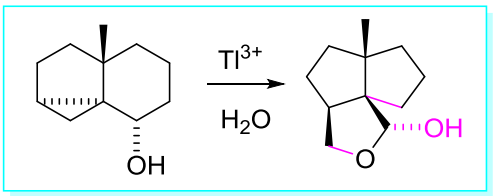
Tetrahedron Lett. **1981**, *22*, 2699.
J. Org. Chem. **1986**, *51*, 4888.



Tetrahedron Lett. **1986**, *27*, 1513.

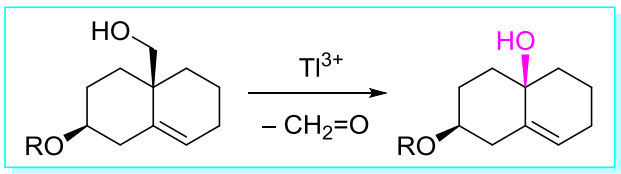


J. Org. Chem. **1999**, *64*, 101.



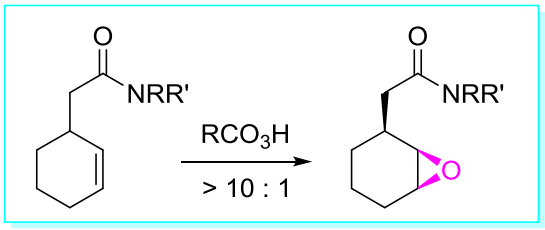
J. Am. Chem. Soc. **1990**, *112*, 6735.
J. Am. Chem. Soc. **1994**, *116*, 186.
J. Org. Chem. **1999**, *64*, 101.

Fragmentation



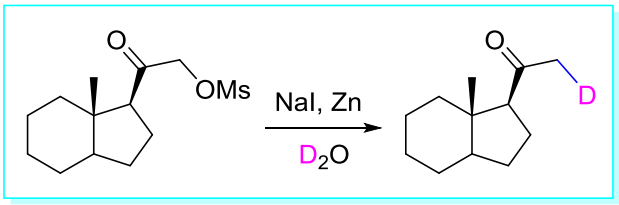
J. Chem. Soc., Chem. Commun. **1990**, 1026.
J. Org. Chem. **1990**, *54*, 5580.
J. Org. Chem. **1994**, *59*, 5439.

Stereocontrolled epoxidation



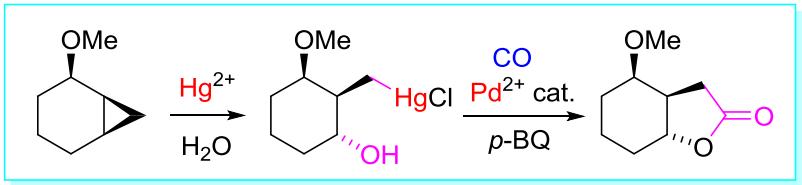
J. Org. Chem. **1990**, *55*, 3236.

Mild deuteration



J. Org. Chem. **1983**, *48*, 2233.

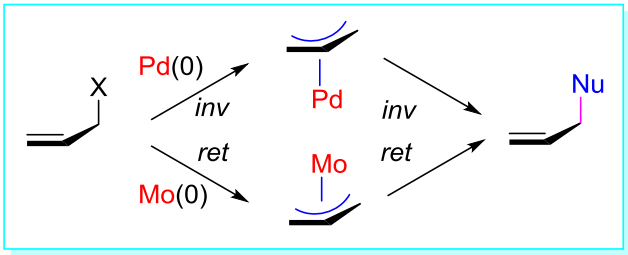
Cyclopropane opening / carbonylation



Tetrahedron Lett. **1996**, *37*, 1125.
Tetrahedron Lett. **1996**, *37*, 5585.

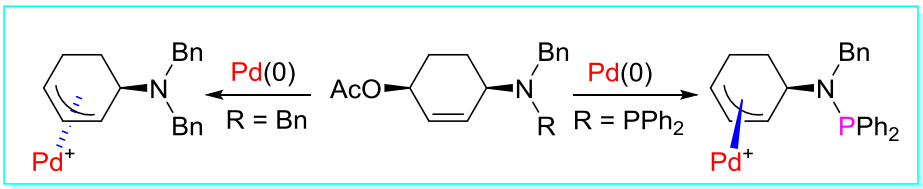
1. Selected Reactions Discovered or Developed - Part 2

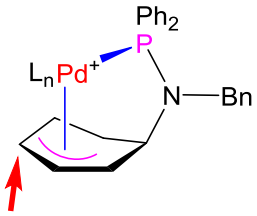
Mo-catalyzed allylic substitution: ret-ret (syn-syn) *Mechanism*



J. Am. Chem. Soc. **1995**, *117*, 6130.
Pure Appl. Chem. **1999**, *71*, 1425.
Chem. Eur. J. **2006**, *12*, 6910.

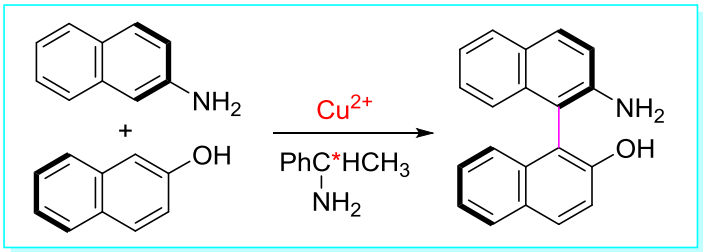
Pd-catalyzed allylic substitution: Reversal of stereochemistry





J. Am. Chem. Soc. **1989**, *111*, 4981 and **1998**, *120*, 6661.

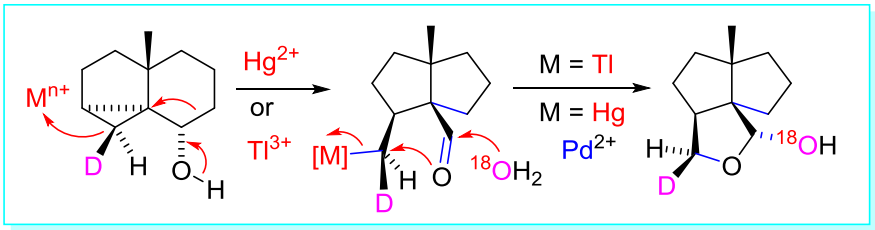
Binaphthyl synthesis: highly selective cross-coupling



Aldrich
713694

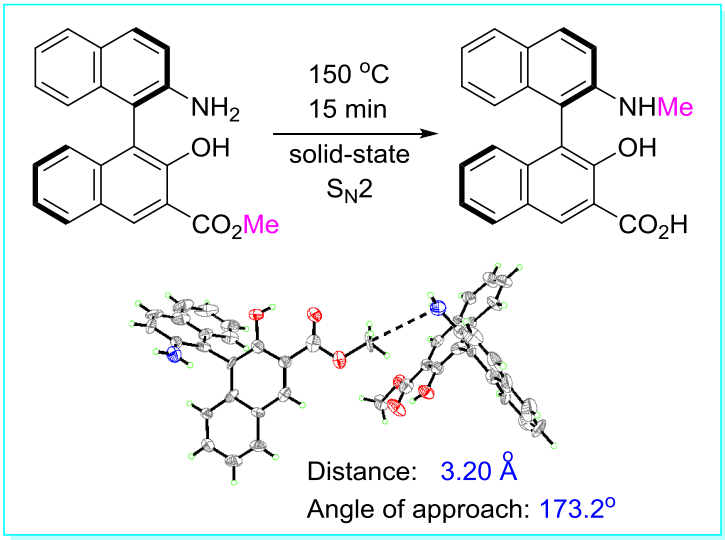
J. Org. Chem. **1992**, *57*, 1917.
J. Org. Chem. **1993**, *58*, 4534.
J. Org. Chem. **1994**, *59*, 2156
CCCC **1996**, *61*, 1520.
Chem. Commun. **1998**, 585.
Chem. Rev. **2003**, *103*, 3213.

Stereoselective corner opening of cyclopropanes by Hg(II) and Tl(III)



J. Am. Chem. Soc. **1990**, *112*, 6735.
J. Am. Chem. Soc. **1994**, *116*, 186.

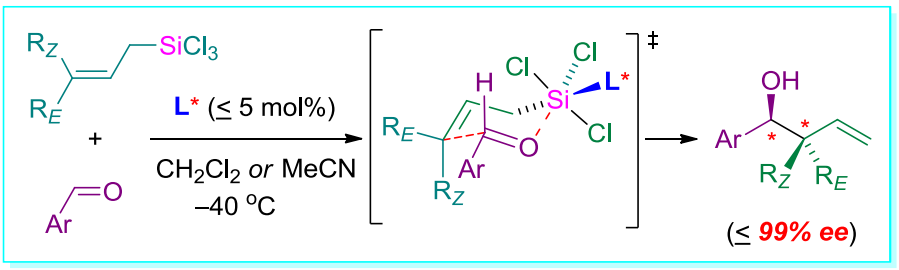
Solid-state S_N2 reaction ($B_{Al}2$ mechanism)

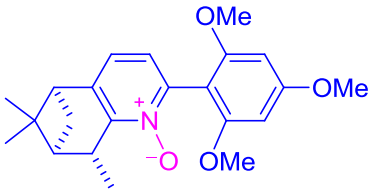


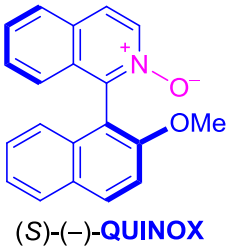
J. Am. Chem. Soc. **1996**, *118*, 487.

2. Catalytic Enantioselective Reactions Developed

Organocatalyzed enantioselective allylation of aldehydes

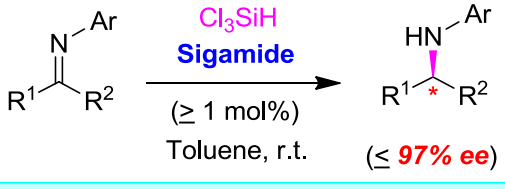


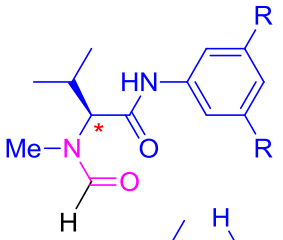




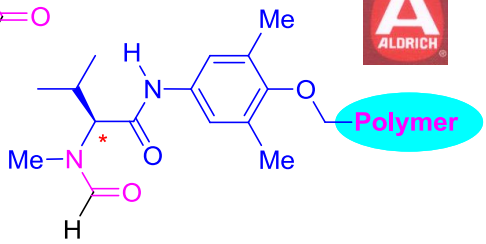
Angew. Chem., Int. Ed. **2003**, *42*, 3674.
J. Org. Chem. **2003**, *68*, 9659.
Org. Lett. **2005**, *7*, 3219.
J. Am. Chem. Soc. **2008**, *130*, 5341.
Pure Appl. Chem. **2008**, *80*, 953 (OMCOS-14).
Chem. Eur. J. **2009**, *15*, 1570.
J. Org. Chem. **2011**, *76*, 4800.
Chem. Eur. J. **2013**, *19*, 9167.

Organocatalyzed enantioselective reduction of imines and ketones





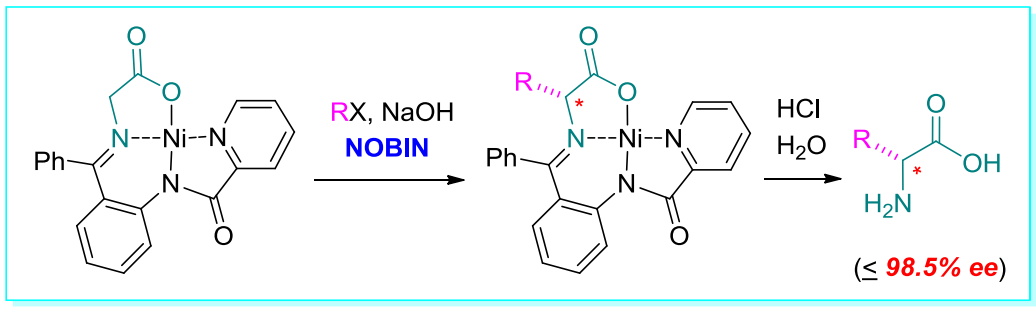
Kenamide, R = Me
Sigamide, R = *t*-Bu
Aldrich 693561 and 693626

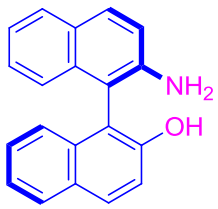


Org. Lett. **2004**, *6*, 2253.
Tetrahedron **2006**, *62*, 264 (Symposium in Print).
Angew. Chem., Int. Ed. **2006**, *45*, 1432.
J. Org. Chem. **2007**, *72*, 1315.
J. Org. Chem. **2008**, *73*, 3985 (Featured Article).
Angew. Chem., Int. Ed. **2007**, *46*, 3722.
Chem. Eur. J. **2008**, *14*, 8082.
Chem. Eur. J. **2009**, *15*, 9651.

J. Org. Chem. **2009**, *74*, 5839 and 8425.
Org. Biomol. Chem. **2010**, *8*, 137.

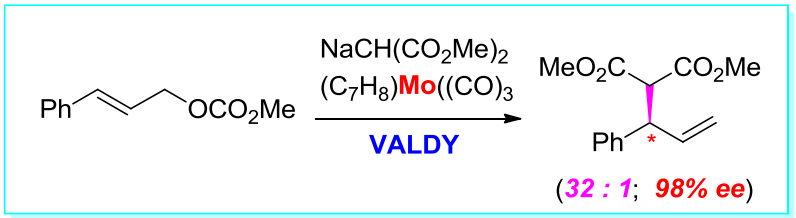
Amino acids via organocatalyzed enantioselective alkylation of glycine

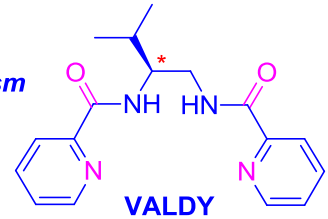




Chem. Eur. J. **2002**, *8*, 4633.
J. Am. Chem. Soc. **2003**, *125*, 12860.
Chem. Rev. **2003**, *103*, 3113.

Enantioselective Mo-catalyzed allylic substitution; syn-syn mechanism

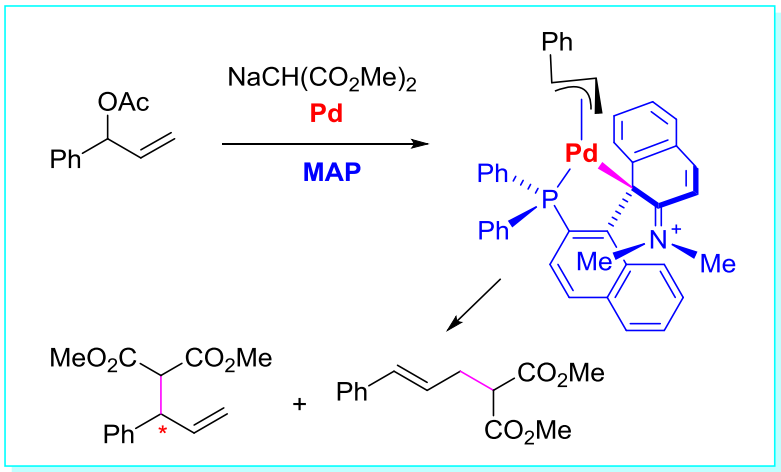


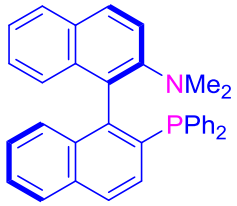


J. Am. Chem. Soc. **1995**, *117*, 6130.
Tetrahedron Lett. **2001**, *42*, 509.
Chem. Eur. J. **2006**, *12*, 6910.

3. Catalytic Stereocontrolled Reactions - Part 1

Enantioselective Pd-catalyzed allylic substitution, memory effect, and unique coordination

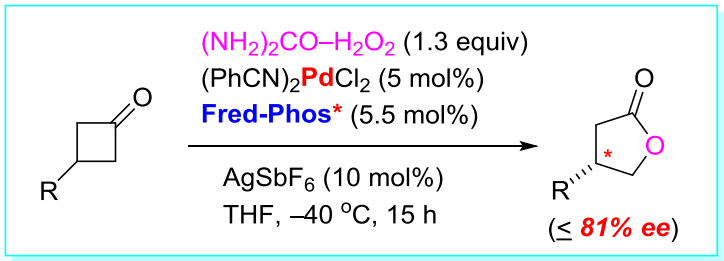


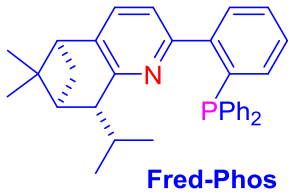


MAP

J. Org. Chem. **1998**, *63*, 7738.
Pure Appl. Chem. **1999**, *71*, 1425.
J. Am. Chem. Soc. **1999**, *121*, 7714.
Chem. Eur. J. **2000**, *6*, 4348.
Chem. Eur. J. **2002**, *8*, 4443.
Chem. Rev. **2003**, *103*, 3113.
J. Organomet. Chem. **2003**, *687*, 256.

Asymmetric Pd-catalyzed Baeyer-Villiger reaction

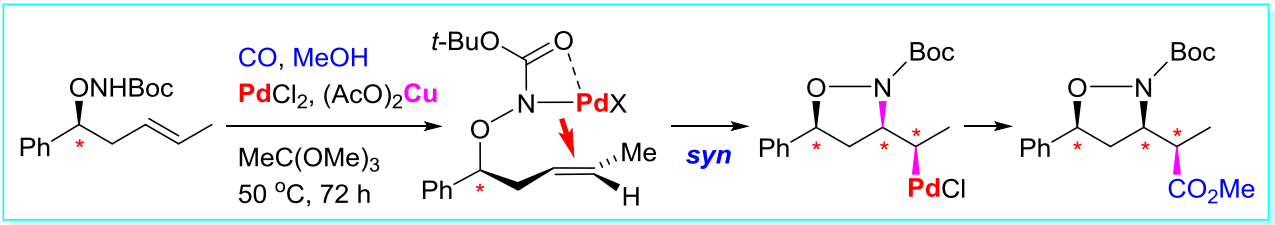




Fred-Phos

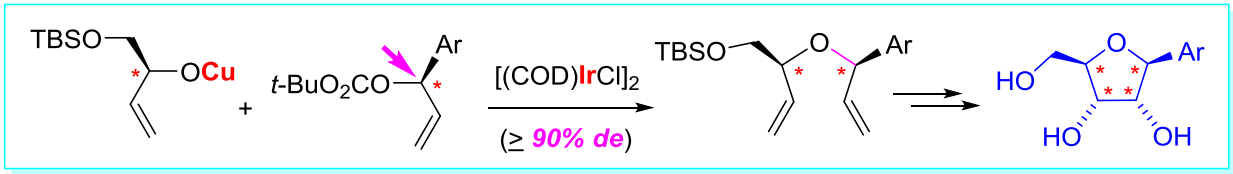
J. Org. Chem. **2008**, *73*, 3996.

Pd-Catalyzed carbonylative amidation proceeds as a syn addition



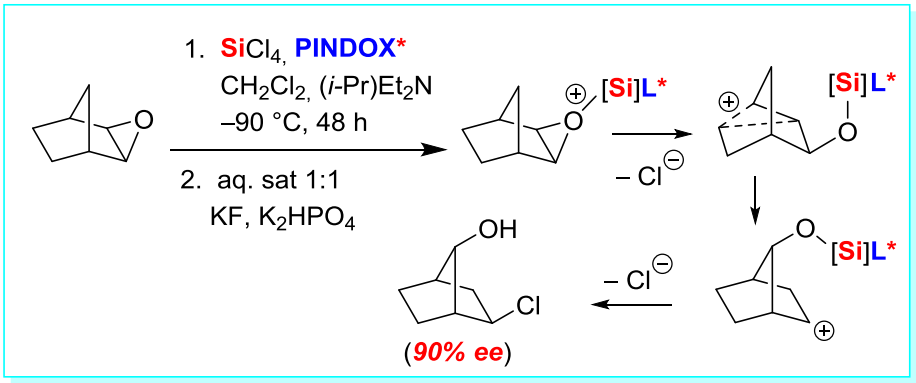
Chem. Eur. J. **2012**, *18*, 6873.
Chem. Eur. J. **2015**, *21*, 36.

Modular approach to aryl-C-ribonucleosides



J. Org. Chem. **2011**, *76*, 7781.
Chem. Rev. **2009**, *109*, 6729.

Desymmetrization of meso-epoxides

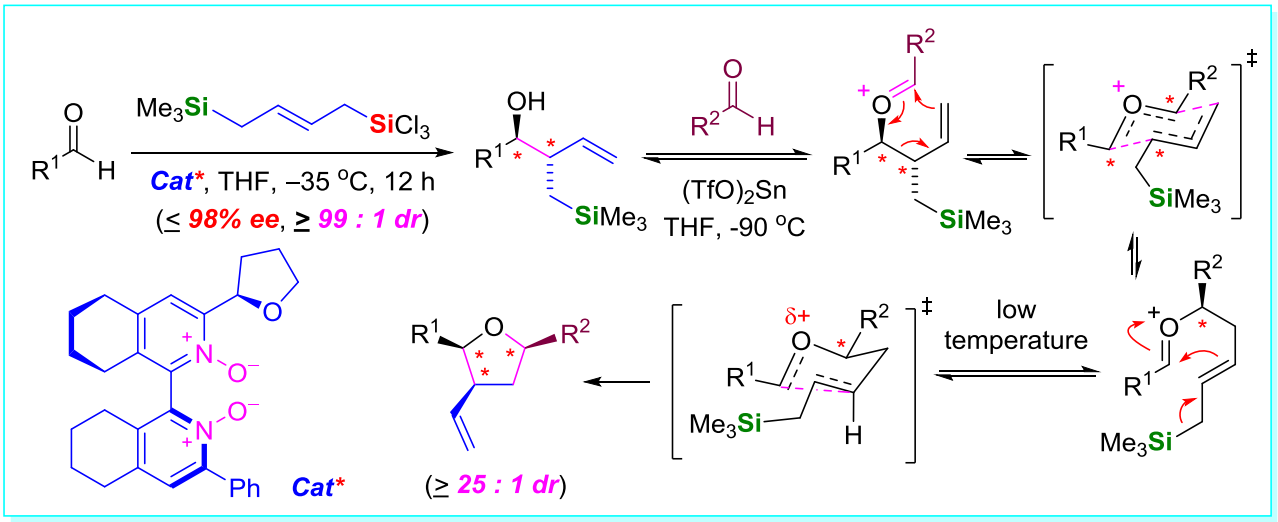


PINDOX

Org. Lett. **2009**, *11*, 5390.

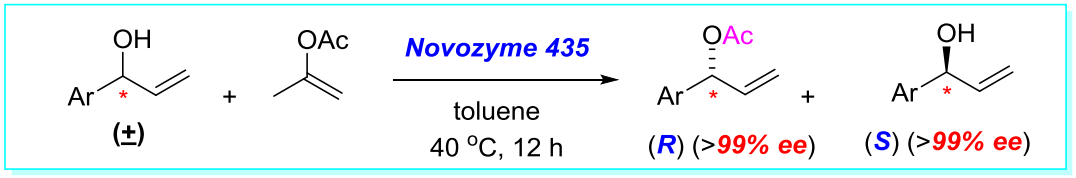
3. Catalytic Stereocontrolled Reactions - Part 2

Trisubstituted tetrahydrofurans via double allylation



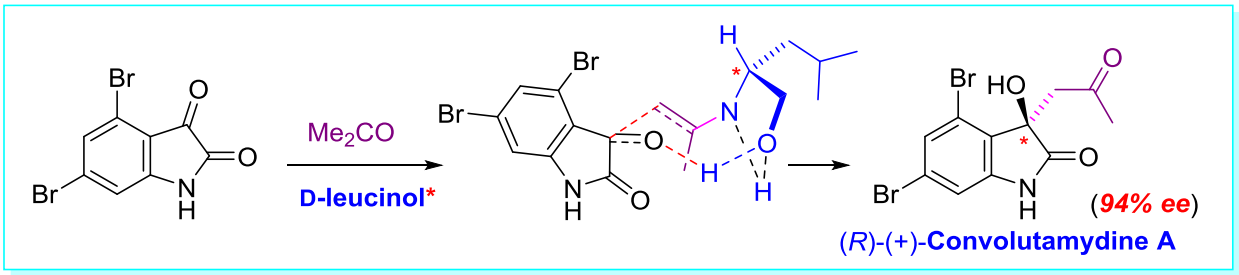
Chem. Eur. J. **2009**, *15*, 1570.
Chem. Eur. J. **2011**, *17*, 7162.

Enzymatic resolution of 1-arylpropenols



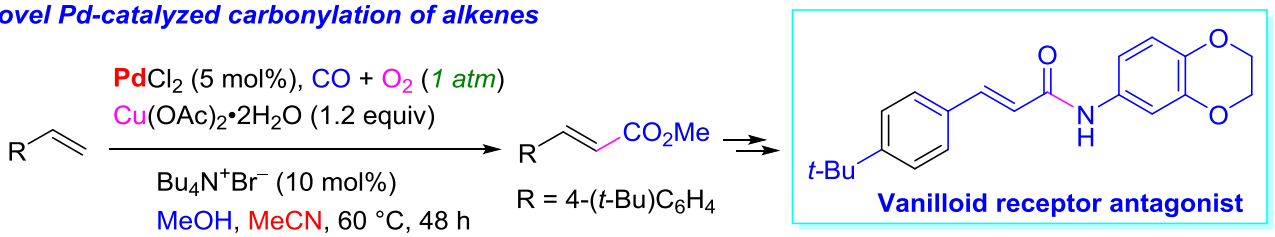
J. Org. Chem. **2008**, *73*, 9148.

Enantioselective organocatalyzed aldol reaction



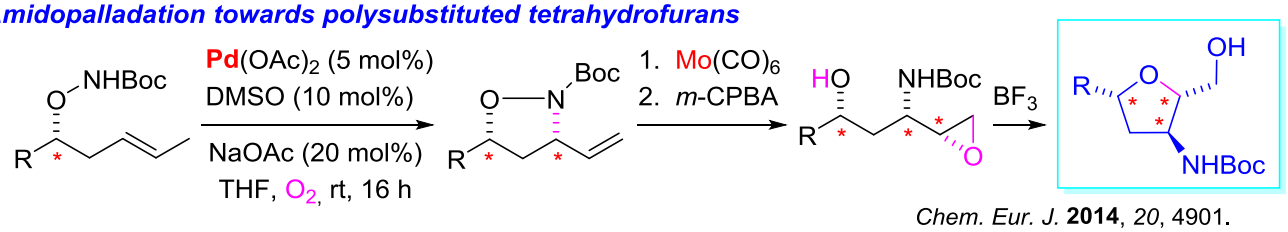
Org. Lett. **2007**, *9*, 5473.
Chem. Eur. J. **2015**, *21*, 12026.

Novel Pd-catalyzed carbonylation of alkenes



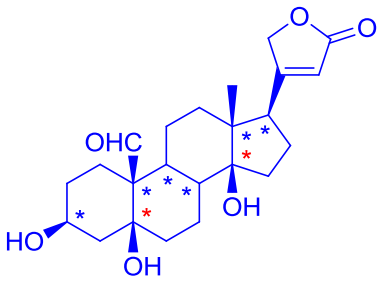
Chem. Eur. J. **2014**, *20*, 4542.

Amidopalladation towards polysubstituted tetrahydrofurans



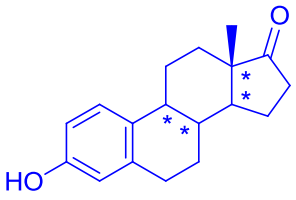
Chem. Eur. J. **2014**, *20*, 4901.

4. Synthesis of Biologically Significant Molecules



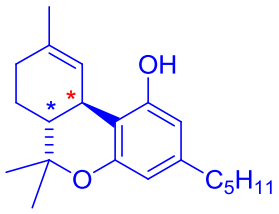
Strophanthidin

Tetrahedron Lett. **1989**, *30*, 4295.



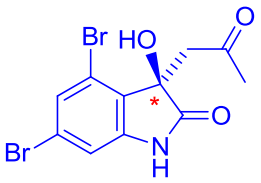
Estrone

J. Org. Chem. **1994**, *59*, 5439.



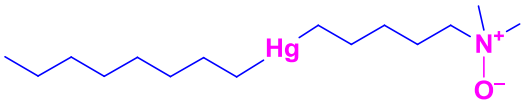
Tetrahydrocannabinol

Collect. Czech. Chem. Commun. **2001**, *66*, 1257.



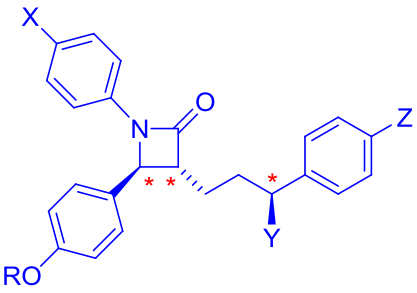
Convolutamydine A

Org. Lett. **2007**, *9*, 5473.



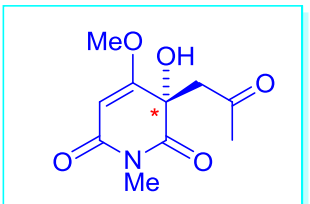
Molecular probes for mapping lipid binding sites on the surface of membrane proteins by X-ray crystallography

Biochem. Soc. Trans. **2011**, *39*, 775.



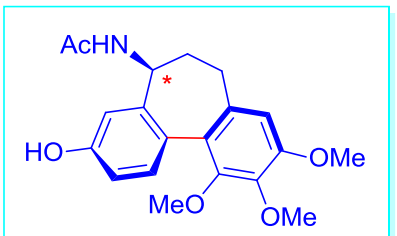
SCH48461, X = MeO, R = Me, Y = Z = H
SCH58235, X = F, R = H, Y = OH, Z = F

Work in progress



(+)-Speranskatine A

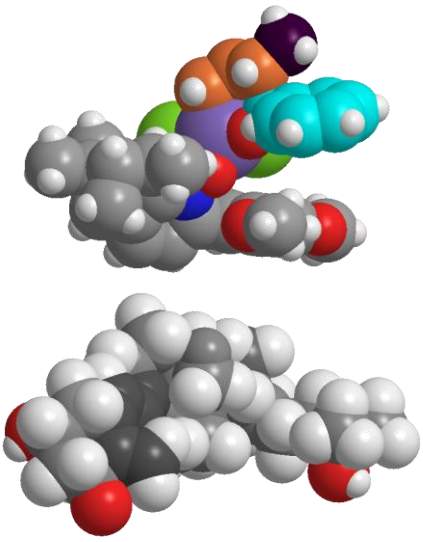
Work in progress

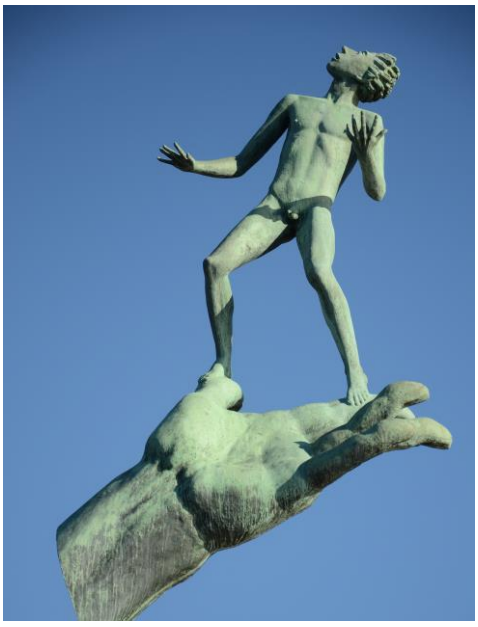


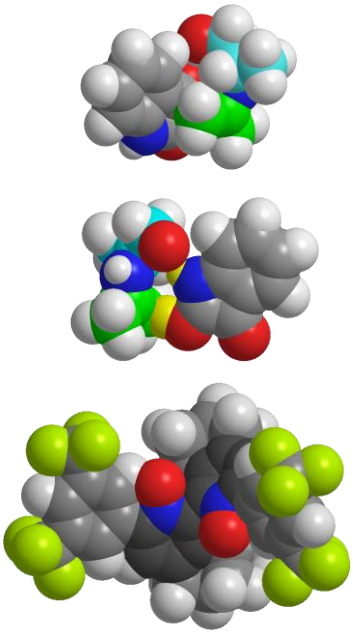
(–)-*N*-Acetylcolchinol

Work in progress

And what's next?



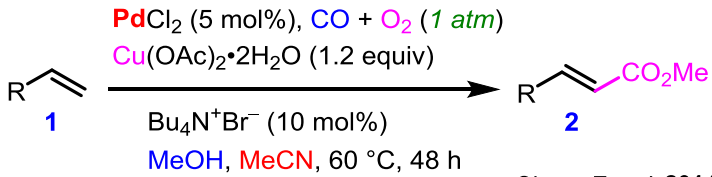




5. Current Projects

(1) Novel Pd-Catalyzed Carbonylation of Alkenes

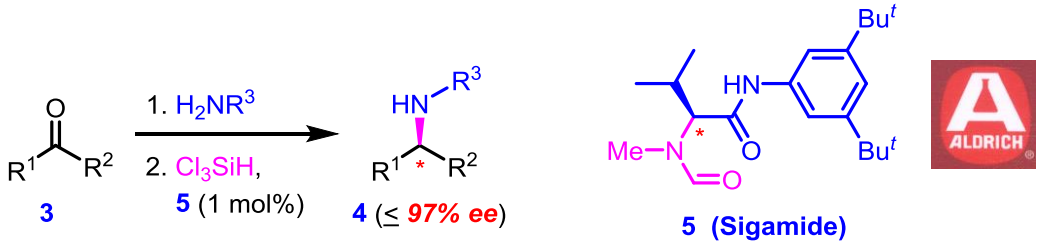
We have recently developed a unique carbonylation of terminal alkenes, catalyzed by Pd^{II} (**1** → **2**). The goal now is to establish its scope, increase the catalytic turnover, and work out the mechanism (both experimentally and computationally), in particular the intriguing role of MeCN and the oxidant that are both essential for the reaction to proceed this way. Note that this new and simple approach to α,β-unsaturated esters has the promise of replacing the much less atom-economic classics, such as the Wittig-type reactions and/or the metathesis methodology that requires more elaborate transition metal catalysts. Furthermore, the related direct synthesis of the corresponding amides has never been achieved and will now be attempted as part of the project.



Chem. Eur. J. **2014**, *20*, 4542.

(2) Reductive Amination of Aldehydes and Ketones

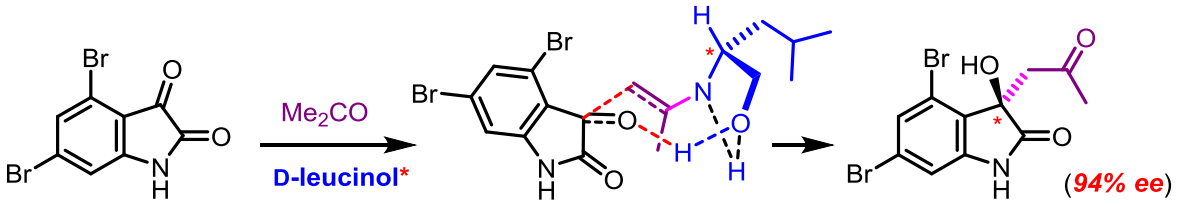
Reductive amination of aldehydes and ketones **3** constitutes one of the most popular methods for the synthesis of amines **4**. Over the years, we have developed its enantioselective version that employs the readily available but largely neglected Cl_3SiH as a reducing agent and the novel valine-derived formamide **5** as a chiral organocatalyst, which was commercialized by Aldrich as ***Sigamide***. This project will be focused on further applications, including click chemistry, isotopic labeling, and functional group tolerance. There are indications that the scope of this methodology will be considerably broader than that of the existing reactions, such as hydrogenation, borane reduction, and transfer hydrogenation of imines.



Org. Lett. **2004**, *6*, 2253.
Angew. Chem., Int. Ed. **2007**, *46*, 3722.
Chem. Eur. J. **2008**, *14*, 8082.
J. Org. Chem. **2009**, *74*, 5839.
J. Org. Chem. **2022**, *87*, 920.

(3) Organocatalyzed Aldol Reaction

We have recently found that chiral primary amino alcohols, such as leucinol, can act as efficient organocatalysts for the cross-aldol reaction of two different ketones. Thus, the isatin derivative **6** was successfully coupled with acetone to afford Convolutamidine A (**7**), a potent anti-cancer marine natural product. The mechanism of this key reaction was established by isotopic labeling in conjunction with in situ NMR experiments and high-level quantum chemistry calculations. The simplicity of this method calls for establishing its scope and for further target syntheses, e.g., that of Speranskatine A (vide infra).



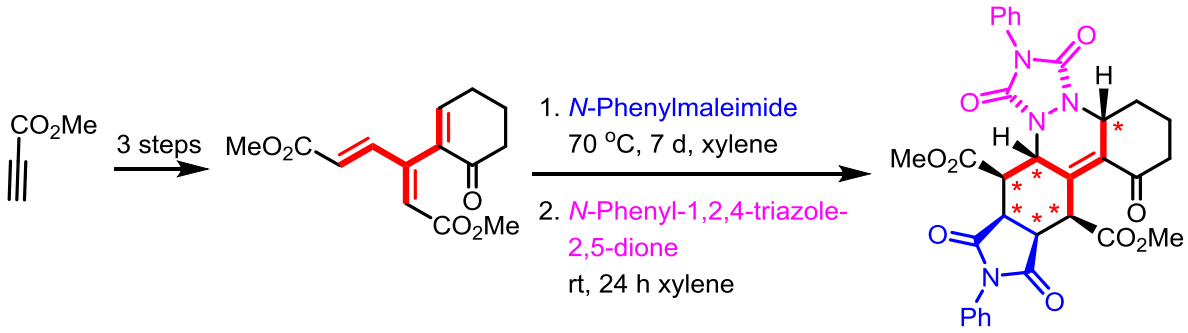
6

7, (*R*)-(+)-**Convolutamydine A**

Org. Lett. **2007**, *9*, 5473.
Chem. Eur. J. **2015**, *21*, 12026.

(4) Dendralenes

Dendralenes stand out as a distinct class of cross-conjugated entities with an extraordinary potential owing to their ability to perform two or more consecutive Diels-Alder reactions in an interconnected manner (Diene Transmissive Diels-Alder Reactions, DTDA). Here, the first D-A addition generates a new diene system that undergoes another D-A reaction, potentially with a different dienophile. In collaboration with the Pharmaceutical Faculty and IOCB, we are currently studying the reactivity of electron-defficient dendralenes with electron-poor dienophiles; the goal is to identify suitable combinations of the reactants and construct polycyclic systems with multiple chiral centers in one-pot.

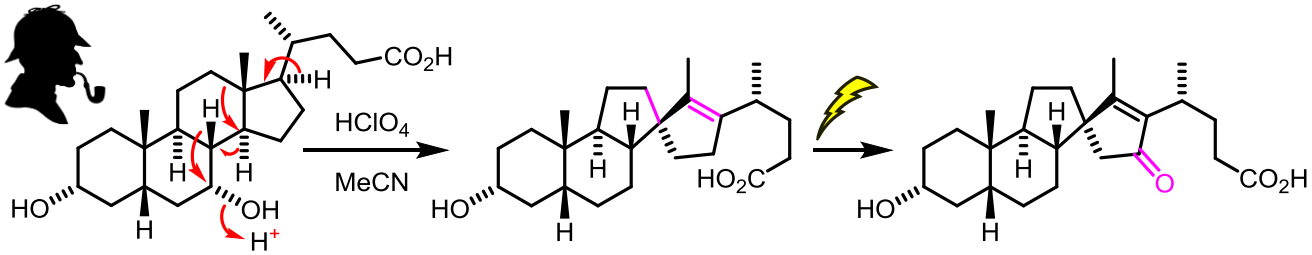


Org. Chem. Front. **2023**, *10*, 5568.

60% after 2 steps

(5) Electrochemical Detection of Steroids in Body Fluids

Steroids constitute a ubiquitous group of biologically active substances with a number of functions in living organisms. Their importance justifies development of new simple techniques suitable for their detection in biological and environmental matrices. Inexpensive electrochemical methods are being developed in collaboration with colleagues at this University, Palacký University (Olomouc), and Comenius University (Bratislava) to detect sterols and bile acids and their conjugates in body fluids to diagnose various conditions, such as Smith-Lemni-Opitz syndrome, Crohn disease, colorectal cancer, etc. Thus, for example, recent detective work enabled us to unveil the mechanism of transformation of chenodeoxycholic acid in an electrochemical cell. This biomolecule was found to undergo a fascinating back-bone rearrangement, followed by allylic oxidation, which can be monitored by changes in voltammetric curves and in UV spectra.



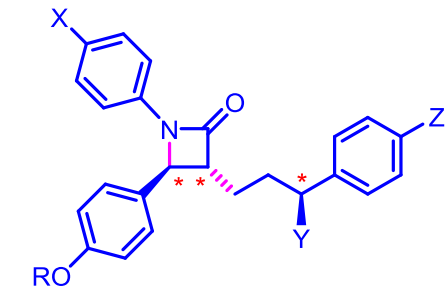
Chenodeoxycholic acid

Electrochem. Commun. **2018**, *86*, 99.
Bioelectrochem. **2020**, *134*, 107539.

Talanta **2021**, *229*, 122260.
Food Chem. **2022**, *393*, 133278.

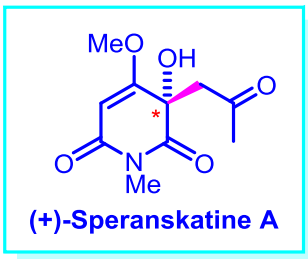
(6) Synthesis of Functional Molecules

The methodology developed under 1-3 will be applied for the synthesis of selected biologically significant compounds, such as **SCH58235**, ***N*-Acetylcolchinol**, **TRPV-1**, and **Speranskatine A**. Chiral elements and the strategic bonds to be constructed by using our methodology are highlighted in all these targets. The synthesis of *N*-acetylcolchinol will require, in addition to the utilization of reductive amination (vide supra), development of a specific arene-arene oxidative coupling to construct the chiral axis in a stereocontrolled manner, which we hope to attain via C-H activation.



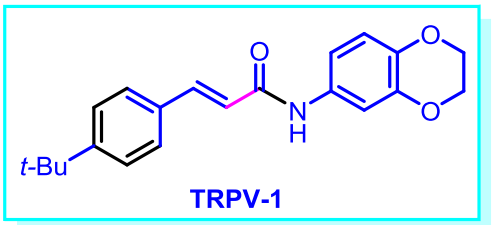
SCH48461, X = MeO, R = Me, Y = Z = H
SCH58235, X = F, R = H, Y = OH, Z = F

Drugs inhibiting cholesterol intake from food



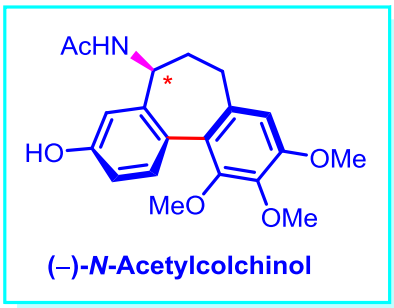
(+)-Speranskatine A

Ackne treatment and other effects (Chinese folk medicine)



TRPV-1

Vanilloid receptor-1 antagonist



(–)-*N*-Acetylcolchinol

Anticancer agent with a similar mode of action as that of taxol

The individual projects are being carried out in collaboration with various groups at Charles University, IOCB (ÚOCHB), and Universities of Stockholm, Nijmegen, Olomouc, and Bratislava.

Multidisciplinary projects

The researchers in our group benefit from joining multidisciplinary projects, which include:

- **Organocatalysis**
- **Transition metal catalysis**
- **Reaction mechanisms**
- **Organometallics**
- **Stereochemistry**
- **Organic synthesis**
- **Natural products**
- **Electrochemistry**
- **Molecular probes**
- **Theoretical calculations**

Freddie-the-Ant

(Jack of all trades)

Whatever we do, we keep having fun.

"Oh nothing much. Just experimenting with some rabbits"