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 synthesis. 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, Ti, and Hg), accomplished stereoselective syntheses of several natural products, such as strophanthinidin (a cardio-active drug), estrone (a female sexual hormone), tetrahydrocannabinol (an active constituent of marihua), 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.

Over the past 30 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. 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 alkylation 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**


**Rearrangements**


**Fragmentation**


**Stereocontrolled epoxidation**


**Mild deuteration**


**Cyclopropane opening / carboxylation**


**Rearrangements**

1. Selected Reactions Discovered or Developed - Part 2

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

\[
\begin{align*}
\text{Pd(0)} & \quad \text{inv} \quad \text{ret} \\
\text{Mo(0)} & \quad \text{inv} \quad \text{ret} \\
X & \quad \text{Pd} \\
\end{align*}
\]


Pd-catalyzed allylic substitution: Reversal of stereochemistry


Binaphthyl synthesis: highly selective cross-coupling

*CCDC* 1996, 61, 1520.  
*Chem. Rev.* 2003, 103, 3213.

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


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

2. Catalytic Enantioselective Reactions Developed

**Organocatalyzed enantioselective allylation of aldehydes**

\[
\begin{align*}
R_z\text{-}\text{SiCl}_3 + \text{Ar}O & \xrightarrow{L^+ (\leq 5 \text{ mol\%})} \text{CH}_2\text{Cl}_2 \text{ or MeCN} \quad -40 \text{ °C} \\
& \xrightarrow{\text{Cl}_3\text{SiH}} \text{Ar}OH \\
\end{align*}
\]

\(\leq 99\% \text{ ee}\)


**Organocatalyzed enantioselective reduction of imines and ketones**

\[
\begin{align*}
\text{N} \quad \text{Ar} & \xrightarrow{\text{Cl}_3\text{SiH}} \text{HN} \quad \text{Ar} \\
\text{R}^1 \quad \text{R}^2 & \xrightarrow{\text{Toluene, r.t.}} \text{HN} \quad \text{R}^1 \quad \text{R}^2 \\
(\geq 1 \text{ mol\%}) & \leq 97\% \text{ ee} \\
\end{align*}
\]

Org. Lett. 2004, 6, 2253.
Angew. Chem., Int. Ed. 2007, 46, 3722.

**Amino acids via organocatalyzed enantioselective alkylation of glycine**

\[
\begin{align*}
\text{Ph} \quad \text{N} \quad \text{N} & \xrightarrow{\text{RX, NaOH}} \text{Ph} \quad \text{N} \quad \text{N} \\
\text{NOBIN} & \xrightarrow{\text{HCl, H}_2\text{O}} \text{NOBIN} \\
(\leq 98.5\% \text{ ee}) & \\
\end{align*}
\]


**Enantioselective Mo-catalyzed allylic substitution; syn-syn mechanism**

\[
\begin{align*}
\text{Ph} \quad \text{O} \quad \text{CO}_2\text{Me} & \xrightarrow{\text{NaCH(CO}_2\text{Me)}_2} \text{MeO}_2\text{C} \quad \text{CO}_2\text{Me} \\
\text{VALDY} & \xrightarrow{\text{Ph} \quad \text{O} \quad \text{CO}_2\text{Me}} \text{Ph} \quad \text{O} \quad \text{CO}_2\text{Me} \\
(32 : 1; 98\% \text{ ee}) & \\
\end{align*}
\]

3. Catalytic Stereocontrolled Reactions - Part 1

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

![Chemical reaction diagram](image)

**Asymmetric Pd-catalyzed Baeyer-Villiger reaction**

![Chemical reaction diagram](image)

**Pd-Catalyzed carbynylative amidation proceeds as a syn addition**

![Chemical reaction diagram](image)

**Modular approach to aryl-C-ribonucleosides**

![Chemical reaction diagram](image)

**Desymmetrization of meso-epoxides**

![Chemical reaction diagram](image)
3. Catalytic Stereocontrolled Reactions - Part 2

**Trisubstituted tetrahydrofurans via double allylation**


**Enzymatic resolution of 1-arylpropanols**

![J. Org. Chem. 2008, 73, 9148.](image)

**Enantioselective organocatalyzed aldol reaction**


**Novel Pd-catalyzed carbonylation of alkenes**


**Amidopalladation towards polysubstituted tetrahydrofurans**
4. Synthesis of Biologically Significant Molecules

**Strophantidin**


**Estrone**


**Tetrahydrocannabinol**


**Convolatumydine A**


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


**SCH48461**, $X = \text{MeO, } R = \text{Me, } Y = Z = \text{H}$

**SCH58235**, $X = \text{F, } R = \text{H, } Y = \text{OH, } Z = \text{F}$

**Work in progress**

**(+)-Speranskatine A**

**Work in progress**

**(-)-N-Acetylcolchino**

**Work in progress**

And what’s next?
Whatever we do, we keep having fun.