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, Tl, and Hg), 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.

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 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**


**Rearrangements**


**Fragmentation**


**Stereocontrolled epoxidation**


**Mild deuteration**


**Cyclopropane opening / carbonylation**


**Rearrangements**

1. Selected Reactions Discovered or Developed - Part 2

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

![Diagram of Mo-catalyzed allylic substitution]


**Pd-catalyzed allylic substitution: Reversal of stereochemistry**

![Diagram of Pd-catalyzed allylic substitution]


**Binaphthyl synthesis: highly selective cross-coupling**

![Diagram of binaphthyl synthesis]

*Aldrich* 713694

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

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

![Diagram of stereoselective corner opening]


**Solid-state $S_N2$ reaction ($B_{Al2}$ mechanism)**

![Diagram of solid-state $S_N2$ reaction]

2. Catalytic Enantioselective Reactions Developed

**Organocatalyzed enantioselective allylation of aldehydes**

\[
\begin{align*}
\text{R}_E^\text{Z} &\text{SiCl}_3 \\
\text{OR}_E^\text{Z} &\text{ClSiCl}_3 \\
+ &\text{L}^* (\leq 5 \text{ mol}%) \\
\text{CH}_2\text{Cl}_2 \text{ or MeCN} &-40 \text{ °C} \\
\text{Ar} &\text{OH} \\
\rightarrow &\text{Ar} \\
\text{R}_E^\text{Z} &\text{SiCl}_3 \\
\text{ClSiCl}_3 &\text{OH} \\
\text{R}_E^\text{Z} &\text{Cl} \\
\leq 99\% \text{ ee}
\end{align*}
\]


**Organocatalyzed enantioselective reduction of imines and ketones**

\[
\begin{align*}
\text{N} &\text{Ar} \\
\text{R}_1^\text{R}_2 &\text{HN} \\
\text{Sigamide} &\text{HN} \\
\rightarrow &\text{HN} \\
\text{Toluene, r.t.} &\leq 97\% \text{ ee}
\end{align*}
\]

*Org. Lett.* 2004, 6, 2253.  

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

\[
\begin{align*}
\text{RX, NaOH} &\text{N} \\
\text{N} &\text{Ph} \\
\text{NOBIN} &\text{Ph} \\
\rightarrow &\text{Ph} \\
\text{HCl} &\text{H}_2\text{O} \\
\text{H}_2\text{N} &\text{R}_1^\text{R}_2 \\
&\text{OH} \\
\leq 98.5\% \text{ ee}
\end{align*}
\]


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

\[
\begin{align*}
\text{Ph} &\text{CO}_2\text{Me} \\
\text{OCCO}_2\text{Me} &\text{MeO}_2\text{C} \\
\text{Valdy} &\text{Ph} \\
\rightarrow &\text{Ph} \\
\text{NaCH(CO}_2\text{Me)}_2\text{(C}_2\text{H}_3\text{)} &\text{MeO}_2\text{C} \\
\text{Mo(CO)}_3 &\text{CO}_2\text{Me} \\
&\text{Ph} \\
\text{(32 : 1; 98\% ee)}
\end{align*}
\]

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 carbonylative 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-arylprenols**


**Enantioselective organocatalyzed aldol reaction**

Org. Lett. 2007, 9, 5473.

**Novel Pd-catalyzed carbynylation of alkenes**


**Amidopalladation towards polysubstituted tetrahydrofurans**

4. Synthesis of Biologically Significant Molecules

Strophanthidin

Estrone

Tetrahydrocannabinol

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

Work in progress

(−)-N-Acetylocolchino
Work in progress

And what’s next?
5. Current Projects Suitable for MSc, PhD, and Postdoctoral Programs

(1) Novel Pd-Catalyzed Carbonylation of Alkenes

We have recently developed a unique carbonylation of terminal alkenes, catalyzed by Pd\textsuperscript{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 as the key ligand that is an absolute prerequisite 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.

\[
\begin{align*}
PdCl_2 (5 \text{ mol%)}, & \quad \text{CO} + \text{O}_2 (1 \text{ atm}) \\
\text{Cu(OAc)}_2 \cdot 2\text{H}_2\text{O} (1.2 \text{ equiv}) & \rightarrow \\
\text{Bu}_4\text{N}^+\text{Br}^- (10 \text{ mol%)}, & \quad \text{MeOH, MeCN, 60 °C, 48 h} \\
\end{align*}
\]


(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\textsubscript{3}SiH as a reducing agent and the novel valine-derived formamide 5 as a chiral organocatalyst. Although 5, which was commercialized by Aldrich as Sigamide and is still regarded as the champion catalyst, has its limitations. Therefore, this project will be focused on the development of new catalysts with broader scope. In the same time, functional group tolerance will also be explored. There are preliminary 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.

\[
\begin{align*}
\text{R}^1\text{R}^2 & \quad \text{1. H}_2\text{NR}^3 \\
3 & \quad \text{2. Cl}_3\text{SiH, 5 (1 mol%)}, \\
\end{align*}
\]

\textit{Org. Lett. 2004, 6, 2253.}
\textit{Angew. Chem., Int. Ed. 2007, 46, 3722.}
\textit{J. Org. Chem. 2009, 74, 5839.}

(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).
(4) Synthetic Applications

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.

The individual projects will be carried out in collaboration with various groups at Charles University, IOCB (ÚOCHB), Universities of Stockholm, Loughborough, Nijmegen and Rome. Stays at these universities as part of collaboration may be available through Erasmus exchange program. IOCB is expected to contribute to the student stipends.

Some of the funding will come from the multimillion grant recently awarded by the Ministry of Education to the Faculty of Pharmacy at Hradec Králové in which PK participates.
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

Whatever we do, we keep having fun.