Meggers Laboratory – *Research Accomplishments*

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Over the past 20 years, the Meggers laboratory focused on ***exploiting metal-centered stereochemistry for applications in medicine, chemical biology, and asymmetric catalysis***. The research program started with the design of metal-based protein kinase inhibitors, the subsequent design of chiral organocatalysts based on inert metal complexes ("metal-templated organocatalysis"), and finally arrived at the current focal point of developing chiral transition metal catalysts featuring exclusively metal-centered chirality ("chiral-at-metal" catalysts).

For the evolution of this research program, see the following essay: *Angew. Chem. Int. Ed.* **2017**, *56*, 5668.

- **"Chiral-at-Metal" Transition Metal Catalysts: Stereogenic Metal Center & Achiral Ligands**

We developed a **novel class of chiral transition metal complexes** for applications in asymmetric catalysis. The conventional approach relies on using carefully tailored chiral ligands whereas our strategy exploits the stereogenicity of the central metal upon an asymmetric assembly of the organic ligands around a central metal (Figure 1). Our group has pioneered the general use of such "chiral-at-metal" catalysts in which the metal center both serves as the exclusive stereogenic center and at the same time acts as the reactive center for catalysis. This chiral-at-metal approach has the appeal of structural simplicity and, most importantly, provides access to unexplored chemical space for novel transition metal catalyst architectures with potentially novel overall properties.

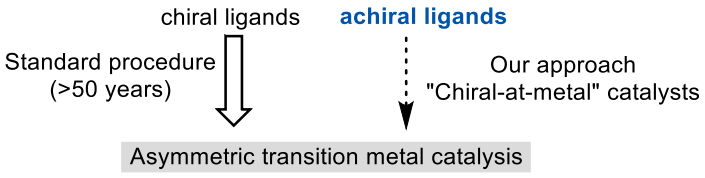


Figure 1. Chiral transition metal catalysis: Chiral ligands *versus* achiral ligands. Note that this scheme refers to *reactive* transition metal catalysts as opposed to catalysts in which a metal plays solely a structural role.

Our initial design consisted of bis-cyclometalated iridium(III) or rhodium(III) complexes. More recently, we expanded the family of chiral-at-metal catalyst to ruthenium and even iron bis-(pyridyl-NHC) complexes (Figure 2). All these propeller-type complexes feature C_2-symmetry with either a Λ- (left-handed screw of the propeller) or Δ-configuration (right-handed screw of the propeller).

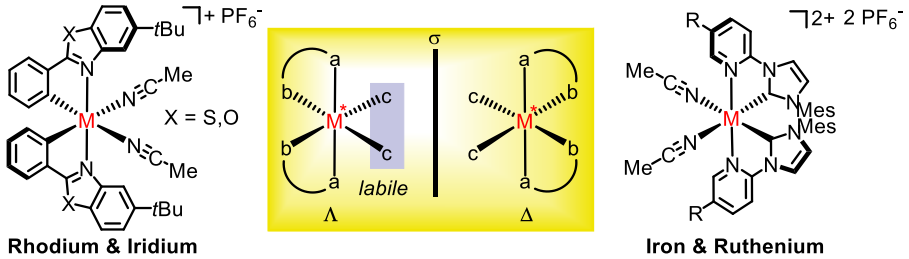


Figure 2. Novel chiral transition metal catalysts with exclusively achiral ligands developed in the Meggers group.

Key references for the design of chiral-at-metal catalysts: *JACS* **2014**, *136*, 2990 (our first report, Ir, 108 citations); *JACS* **2017**, *139*, 4322 (Ru); *JACS* **2019**, *141*, 4569 (Fe); *Nat. Catal.* **2019**, *2*, 34 (asymmetric electrochemistry with Rh); *Acc. Chem. Res.* **2017**, *50*, 320; *Acc. Chem. Res.* **2023**, *56*, 1128; *Chem. Soc. Rev.* **2025**, *54*, 1986.

The chiral-at-metal catalysts developed in our group had significant impact in the following two areas:

(1) Asymmetric photocatalysis: Bis-cyclometalated iridium(III) or rhodium(III) complexes have been demonstrated by us to be highly suitable for **intertwining photoactivation with asymmetric catalysis**. In 2014, we reported the first example of a visible-light-induced asymmetric catalysis in

which a single chiral metal complex served both as the photoredox catalyst and the asymmetric catalyst (Figure 3).

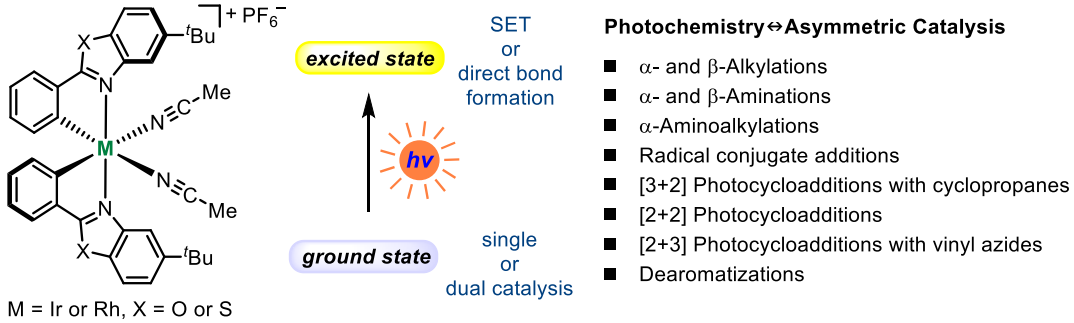


Figure 3. Bis-cyclometalated Rh^{III} and Ir^{III} complexes for intertwining photochemistry with asymmetric catalysis.

Some highlights:

- Catalytic enantioselective radical trichloromethylation
- Enantioselective C(sp^3)-H functionalization via radical translocation
- Efficient catalytic enantioselective radical conjugate additions through photoredox catalysis
- Direct visible-light-excited catalytic asymmetric intermolecular [2+2] photocycloadditions
- Catalytic asymmetric dearomatizations by visible-light-activated [2+2] photocycloaddition
- Chiral 1-pyrrolines by stereocontrolled direct photoreaction from electronically excited state
- Catalytic deracemization of ketones
- Photoelectrochemical asymmetric dehydrogenative [2+2] cycloaddition

Key references for asymmetric photocatalysis: *Nature* **2014**, *515*, 100 (our first report); *Acc. Chem. Res.* **2017**, *50*, 320; *Acc. Chem. Res.* **2019**, *52*, 833; *J. Am. Chem. Soc.* **2021**, *143*, 13393; *Nat. Catal.* **2023**, *6*, 1186.

(2) Asymmetric Nitrene-Mediated C-H Aminations and Oxygenations: Recently, we disclosed the chiral-at-metal ruthenium complexes are highly suitable for catalyzing **enantioselective intramolecular C(sp^3)-H aminations**. We provided the first example of a highly enantioselective ring-closing C(sp^3)-H amination of primary aliphatic azides to provide chiral pyrrolidines by combining of chiral transition metal catalysis with nucleophilic phosphine catalysis (Figure 4). In this unique dual catalysis system, the phosphine activates the organic azide and transfers a nitrene to the ruthenium complex, which then executes the enantioselective C-H amination. Interestingly, we also discovered that nitrene chemistry can be used to implement **enantioselective C(sp^3)-H oxygenations** instead of aminations. Finally, in our newest work, we developed a **stereocontrolled 1,3-migratory nitrene C(sp^3)-H insertion** for the catalytic asymmetric synthesis of α-amino acids.

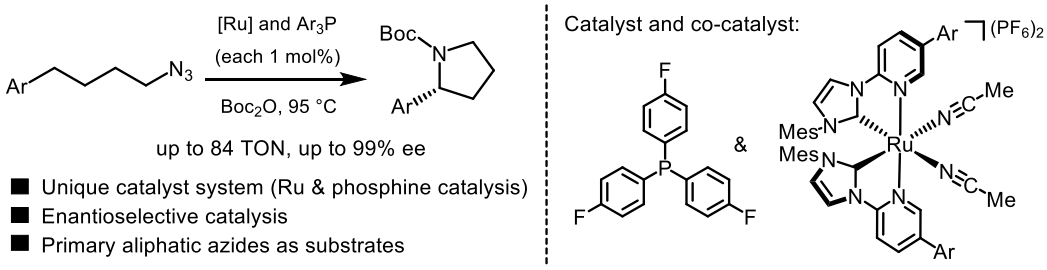


Figure 4. Enantioselective intramolecular C(sp^3)-H amination of aliphatic azides by dual chiral-at-ruthenium and phosphine catalysis.

Key references for asymmetric C(sp^3)-H amination: *Angew. Chem. Int. Ed.* **2019**, *58*, 1088; *Chem. Sci.* **2019**, *10*, 3202. *J. Am. Chem. Soc.* **2019**, *141*, 19048; *Chem* **2020**, *6*, 2024 (highlighted in *Chem* **2020**, 6, 1851), *Angew. Chem. Int. Ed.* **2020**, *59*, 21706; *Nat. Chem.* **2022**, *14*, 566.

For a recent nitrene-mediated C(sp^3)–H amination, see: *Angew. Chem. Int. Ed.* **2026**, *65*, e4041858.

• Metal-Templated Asymmetric Organocatalysis

Our group developed a series of highly effective "metal-based organocatalysts" in which catalysis is exclusively mediated through the organic ligand sphere, while the central metal plays a purely structural role. By doing so, we gained additional control over the proper arrangement of functional groups and thereby providing catalysts with higher turnover numbers and asymmetric inductions compared to structurally more simple chiral organocatalysts (Figure 5). In a key proof-of-principle study we demonstrated that a fine-tuned cooperativity of hydrogen bond formation and van der Waals interactions implemented within a rigid metal complex template can provide an extremely active catalyst achieving remarkable rate accelerations of k_{cat}/k_{uncat} = 2.5 x 10^5 with catalyst loadings down to 0.004 mol% and up to 20250 TON while retaining high enantioselectivity (>90% ee), all this just orchestrated by weak interactions!

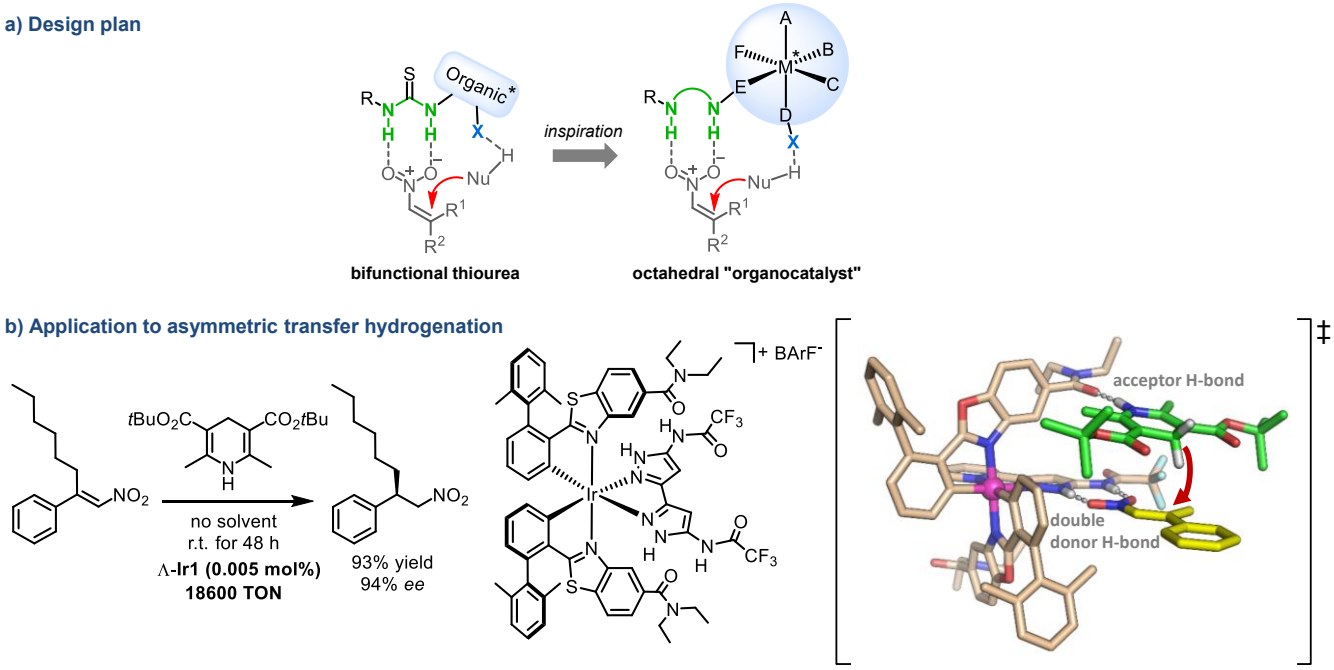


Figure 5. Metal-templated low-loading asymmetric organocatalysis. Shown is a representative reaction and the putative transition state. BArF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

Key references: *JACS* **2013**, *135*, 10598 (our first report), *JACS* **2016**, *138*, 8774 (highest turnover numbers).

• Inert Metal Complexes as Enzyme Inhibitors

Complementing organic elements with a metal center provides new opportunities for building three dimensional structures with unique and defined shapes. We demonstrated that such unexplored chemical space can lead to the discovery of molecules with unprecedented biological properties. This strategy was applied to the design of highly potent and selective protein kinase inhibitors (Figure 6). One organometallic complex is commercially available as selective inhibitor of the protein kinase GSK-3: EMD Millipore, catalog number 361558, "GSK-3 Inhibitor XV".

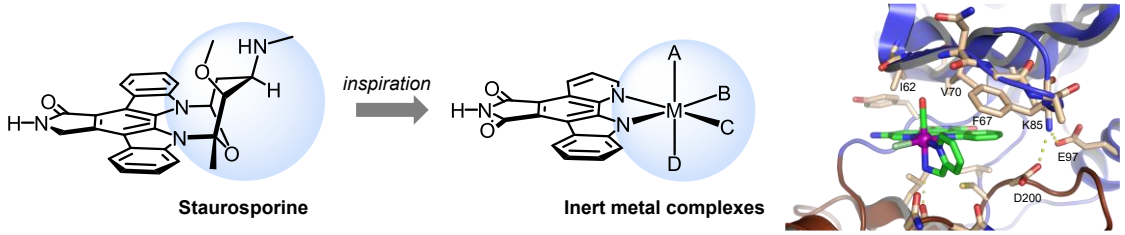


Figure 6. Inert metal complexes as protein kinase inhibitors using staurosporine as the lead structure.

Key references: *JACS* **2004**, *126*, 13594 (our first report); *Angew. Chem. Int. Ed.* **2006**, *45*, 1580 (our first co-crystal structure) *JACS* **2011**, *133*, 5976 (our most sophisticated design); *Chem. Commun.* **2009**, 1001 (feature article about this topic).

- **Other Previous Projects**

(1) **Asymmetric coordination chemistry:** Development of new strategies for the asymmetric synthesis of chiral octahedral metal complexes by employing temporarily coordinated chiral bidentate ligands as chiral auxiliaries (*Acc. Chem. Res.* **2013**, *46*, 2635; first report: *JACS* **2009**, *131*, 9602). We also reported the first example of a catalytic asymmetric synthesis of a chiral octahedral metal complex (*Angew. Chem. Int. Ed.* **2010**, *49*, 7955).

(2) **Hypervalent silicon complexes with bioactivity:** Hydrolytically surprisingly stable octahedral silicon complexes as potent DNA intercalators (*Chem. Commun.* **2012**, *48*, 7131).

(3) **Bioorthogonal catalysis:** Pioneering work on organometallic complexes for bioorthogonal catalysis in living mammalian cells (first report: *Angew. Chem. Int. Ed.* **2006**, *45*, 5645; 177 citations).

(4) **Minimal acyclic nucleic acid:** Discovery and development of the minimal nucleic acid GNA containing an acyclic three-carbon propylene glycol phospodiester backbone (*Acc. Chem. Res.* **2000**, *43*, 1092; first report: *JACS* **2005**, *127*, 4174; 249 citations). The acyclic three-carbon backbone is the most simplified backbone of a phosphodiester containing nucleic acid but displays duplex stabilities that exceed the stabilities of duplex DNA. It might have implications as an early genetic system during the evolution of life on Earth.

(5) **Metal-mediated base pairing (postdoctoral research):** First example of an artificial metal-mediated base pair in DNA (first report: *JACS* **2000**, *122*, 10714; 330 citations; crystal structure: *JACS* **2001**, *123* 12364; 209 citations).

(6) **Long-range charge transport in DNA (PhD research):** Unraveling the mechanism of long-range charge transport in duplex DNA through a guanine-hopping mechanism (PhD research, *JACS* **1998**, *120*, 12950; 615 citations).